Dose recommendations for anticancer drugs in patients with renal or hepatic impairment

Version: 1

Issued: July 2024

The National Strategic Clinical Network for Cancer (Cancer Network) is part of the NHS Wales Executive, working to improve outcomes and care for cancer patients in Wales.

Under the non-Surgical Oncology Work stream (comprising Systemic Anti-Cancer Therapy, Acute Oncology, Genomics and Cancer Outcome and Services Dataset (COSD), the Cancer Network works to develop areas of best practice and align priorities and processes in SACT delivery across Wales.

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Document Approval

Title:	**Dose recommendations for anticancer drugs in patients with renal or hepatic impairment**		
Version Number:	1.0	**Date of last update:**	July 2024
Lead Editor(s):	Diana Matthews, Tracy Parry, Gail Povey SACT Lead Pharmacists, National Strategic Clinical Network for Cancer		
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	Medicines Management Group, Cancer Network	Endorsed	
	All Wales SACT Nurse Forum, Cancer Network	Endorsed	
	All Wales SACT Group, Cancer Network	Endorsed	

Change History

Version Number	Date	Author	Status	Comment/Reason for Issue
0.0	May 2024	Gail Povey	Draft	Peer reviewed guidance, issued for endorsement as best practice.
1	July 2024	Gail Povey	Issued	

THE LANCET
Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. *Lancet Oncol* 2023; **24:** e229.

Supplementary Figure 1: Search strategy used for PubMed

("Renal Insufficiency, Chronic"[MeSH] OR "Renal Insufficiency"[MeSH:noexp] OR "Renal Insufficiency"[ti] OR "Renal Impairment"[ti] OR "Renal Dysfunction"[ti] OR "impaired renal function"[ti] OR “renal function”[ti] OR “haemodialysis”[ti] OR "Hepatic insufficiency"[MeSH] OR "Liver failure"[MeSH] OR "hepatic insufficiency"[ti] OR "liver failure"[ti] OR "liver impairment"[ti] OR "hepatic dysfunction"[ti] OR "impaired liver function"[ti] OR "liver dysfunction"[ti] OR "impaired hepatic function"[ti] OR “hepatic impairment” [ti]) AND (“XX” [Supplementary Concept *or* MeSH] OR "XX"[Tiab])

XX indicates the anticancer drug to be evaluated with its corresponding MeSH term or Supplementary Concept

Supplementary Table 1: Dose recommendations for anticancer drugs in patients with renal or hepatic impairment

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
1	**Abemaciclib**	Abemaciclib is primarily metabolised in the liver to active metabolites (M2, M18 and M20) which contribute to the clinical effect. Abemaciclib and its metabolites are excreted in feces (81%), predominantly as metabolites. Approximately 3% is excreted in urine.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A: 1·2 fold increase in AUC Child-Pugh B: 1·1-fold increase in AUC Child-Pugh C: 2·4-fold increase in AUC, reduce dose frequency to QD **EMA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: decrease in dosing frequency to QD is advised	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: reduce dose frequency to QD	Verzenio label[1] SPC Verzenios[2]
2	**Abiraterone**	Abiraterone acetate is hydrolysed to abiraterone, which is then metabolised in the liver to metabolites which contribute to the clinical effect. Abiraterone and its metabolites are predominantly excreted in feces (81%) and to a lesser extent in urine (5%).	**EMA/FDA:** Renal impairment: no dose adjustment HD: dose after dialysis, no dose adjustment **Marbury *et al.*** ESRD requiring haemodialysis: $AUC_{0\text{-}inf}$: 65·0% (90% CI 34.3-123·2%)	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA/FDA:** Child-Pugh A: no dose adjustment Child-Pugh B: 25% of the dose, 250 mg QD (FDA) / caution (EMA) Child-Pugh C: not recommended **Marbury *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$: 111% (90% CI 59·6-208·4%) Child-Pugh B: $AUC_{0\text{-}inf}$: 357% (90% CI 190·9-667·5%) Child-Pugh C with 16 fold dose reduction: $AUC_{0\text{-}inf}$: 43·6% (90% CI 18·4-103·5%)	Child-Pugh A: no dose adjustment is needed Child-Pugh B: 25% of the original dose Child-Pugh C: avoid	Zytiga label[1] SPC Zytiga[2] Marbury *et al.*[3]
3	**Acalabrutinib**	Acalabrutinib is primarily metabolised by CYP3A enzymes. Its major metabolite, ACP-5862, is 50% less potent than acalabrutinib. Acalabrutinib is mainly excreted in feces (84%) and minorly in urine (14%, < 2% unchanged).	**EMA/FDA:** eGFR ≥ 30 ml/min/1 ·73m^2: no dose adjustment eGFR < 30 ml/min/1 ·73m^2: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Child-Pugh A/B or mild/moderate no dose adjustment Child-Pugh C or severe: not recommended **FDA:** Child-Pugh A and B: no dose adjustment Child-Pugh C: no data available	Child-Pugh A/B or mild/moderate: no dose adjustment is needed Child-Pugh C or severe: not recommended	Calquence label[1] SPC Calquence[2] Xu *et al.*[4]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					Xu *et al.* Child-Pugh A: AUC0-inf: 146·2% (90% CI 84·0-254·5%) Child-Pugh B: $AUC_{0\text{-}inf}$: 130·5% (90% CI 74·9-227·1%) Child-Pugh C: $AUC_{0\text{-}inf}$: 467·3% (90% CI 282·1-774·1%)		
4	**Adagrasib**	Adagrasib is metabolised primarily by CYP3A4 and inhibits its own CYP3A4 metabolism following multiple dosing to steady-state which permits CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2D6 to contribute to its metabolism at steady-state. 75% of the dose was recovered in feces (14% as unchanged) and 4·5% recovered in urine (2% as unchanged).	**FDA:** CLcr 15-90 mL/min: no clinically significant differences in the pharmacokinetics are expected. CLcr < 15 mL/min: not studied HD: not studied	GFR ≥ 15 ml/min: no need for dose adjustment is expected GFR < 15 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh classes A to C or mild to severe: no clinically significant differences in the pharmacokinetics are expected.	Child-Pugh A to C or mild to severe: no need for dose adjustment is expected. Monitor closely for liver toxicity	Adagrasib label[1]
5	**Afatinib**	Afatinib metabolism is minimal. Afatinib is predominantly excreted unchanged in feces (85%). Renal excretion is minimal (4%).	**FDA:** eGFR ≥ 30 ml/min 1·73m^2: 40 mg QD eGFR 15-29 ml/min/1 ·73m^2: 30 mg QD eGFR < 15 ml/min/1 ·73m^2: not studied **EMA:** eGFR ≥ 15 ml/min/1·73m^2: 40 mg QD eGFR < 15 ml/min/1·73m^2: not recommended HD: not recommended **Wiebe *et al.*** eGFR 30-59 ml/min/1·73m^2: $AUC_{0\text{-}inf}$: 122 ·4% (90% CI 96·1-155·9) eGFR 15-29 ml/min/1 ·73 m^2: $AUC_{0\text{-}inf}$: 150·1 (105·6–213·3) **Imai *et al.*** HD: 30 mg QD was tolerated and effective.	eGFR ≥ 15 ml/min: no dose adjustment is needed eGFR < 15 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: not studied **Schnell *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$: 92·6% (90% CI 68 ·0-126 ·3%) Child-Pugh B: $AUC_{0\text{-}inf}$: 94 ·9% (90% CI 72 ·3-124 ·5%) Child-Pugh C: not studied	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: no need for dose adjustment is expected	Gilotrif label[1] SPC Giotrif [2] Wiebe *et al*.[5] Schnell *et al*.[6] Imai *et al*.[7]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
6	**Aflibercept**	Aflibercept is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** Renal impairment: no dose adjustment HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild and moderate: no dose adjustment Severe: not studied	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Zaltrap label[1] SPC Zaltrap[2]
7	**Alectinib**	Alectinib is metabolised in the liver. The major metabolite M4 contributes to the clinical effect. Alectinib and its metabolites are predominantly excreted in feces (98%). Excretion in urine is minimal (<1%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: 75% of the original dose (450 mg BID) **Morcos *et al.*** Alectinib and M4 combined exposure: Child-Pugh A: not studied Child-Pugh B: $AUC_{0\text{-}inf}$: 136% (90% CI 94·7-196) Child-Pugh C: $AUC_{0\text{-}inf}$: 176% (90% CI 98 ·4-315)	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 75% of the original dose (450 mg BID)	Alecensa label[1] SPC Alecensa[2] Morcos *et al.* [8]
8	**Alpelisib**	Alpelisib is primarily metabolised by systemic (non-hepatic) amid hydrolysis in the pharmacological inactive metabolite BZG791, followed by a minor contribution of CYP3A4. Alpelisib and its metabolites are mainly excreted in feces (81%). Approximately 13·5% is excreted in urine (2% unchanged alpelisib).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild, moderate or severe or Child-Pugh A, B or C: no dose adjustment	Hepatic impairment: no dose adjustment is needed.	Piqray label[1] SPC Piqray[2]
9	**Amivantamab**	Amivantanab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA:** CLcr ≥ 30 ml/min: no clinically meaningful effect on PK CLcr < 30 ml/min: not studied **FDA:** CLcr ≥ 30 ml/min: no clinically meaningful differences in PK CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no clinically meaningful effect in PK Moderate and severe: no data available	Mild: no dose adjustment is needed. Moderate and severe: no need for dose adjustment is expected.	Rybrevant label[1] SPC Rybrevant[2]
10	**Amsacrine**	Amsacrine is extensively metabolised in the liver to inactive metabolites. Amsacrine and its metabolites are predominantly excreted in	**MHRA:** Renal impairment: 70-80% of the original dose (60-75mg/m^2) HD: not studied	GFR < 60 ml/min: 70-80% of the original dose HD: 70-80% of the original dose may be considered	**MHRA:** Hepatic impairment: 70-80% of the original dose (60-75mg/m^2)	Mild and moderate: 70-80% of the original dose Severe: not recommended.	SPC Amsidine[9]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		feces (bile) and to a lesser extent in urine (42%).					
11	**Anastrozole**	Anastrozole is metabolised in the liver. Anastrozole and its metabolites are mainly excreted in urine (10% unchanged) and to a lesser extent in feces.	**FDA/MHRA:** CLcr 30-60 ml/min: no dose adjustment CLcr < 30 ml/min: total clearance was reduced by 10%, no dose adjustment needed **Langenegger *et al.*** HD: normal dose resulted in therapeutic exposure	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**FDA:** Mild and moderate: no dose adjustment Severe: not studied **MHRA:** Mild: no dose adjustment Moderate and severe: not studied	Mild and moderate: no dose adjustment is needed. Severe: not recommended.	Arimidex label[1] SPC Arimidex[9] Langenegger *et al.*[10]
12	**Apalutamide**	Apalutamide is metabolised in the liver. The major metabolite N-desmethyl apalutamide contributes to the clinical effect. Apalutamide and is metabolites are predominantly excreted in urine (65%) and to a lesser extent in feces (24%)	**EMA/FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: not studied	Child-Pugh A/B: No dose adjustment is needed. Child-Pugh C: no need for dose adjustment is expected.	Erleada label[1] SPC Erleada[2]
13	**Arsenic trioxide**	Arsenic trioxide hydrolyses to the active arsenious acid (AS^{III}). Arsenious acid is metabolised to arsenic acid and pentavalent metabolites, primarily in the liver. Arsenic trioxide and its metabolites are excreted in urine (15% unchanged).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment is needed CLcr < 30 ml/min: dose reduction may be warranted HD: not studied **Firkin *et al.*** A 50% dose decrease in two patients with eGFRs of 18-19 ml/min/1·73m^2 and a dose adjustment to 10 mg three times weekly in one patient receiving HD, resulted in whole-blood arsenic levels comparable to normal renal function. **Sweeney *et al.*** CLcr ≤ 30 ml/min: mean AUC_{0-t} of AS^{III} 40% higher compared to patients with normal renal function after multiple doses.	GFR ≥ 30 ml/min: no need for dose adjustment is expected GFR < 30 ml/min: consider 50% of the original dose HD: consider 10 mg three times weekly post-dialysis	**FDA:** Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: AUC_{0-24h} increased by 40% compared to normal hepatic function. **EMA:** Mild and moderate: no accumulation of arsenious acid and arsenic acid was observed following twice weekly infusion. Severe: limited information	Child-Pugh A/B: no need for dose adjustment is needed. Use with caution due to risk of hepatotoxicity Child-Pugh C: consider 50% of the original dose.	Trisenox label[1] SPC Trisenox[2] Firkin *et al.*[11] Sweeney *et al.*[12] Perrault *et al.*[13]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			Perrault *et al.* HD: dialysed (approximately 38% removed). Arsenic trioxide 10 mg three times weekly post-dialysis was safe and effective.				
14	**Asciminib**	Asciminib is metabolised by CYP3A4, UGT2B7 and UGT2B17. Asciminib is mainly excreted in feces (80%, 56% unchanged) and to a lesser extent in urine (11%).	**EMA:** CLcr ≥ 15 ml/min: no dose adjustment HD: not studied **FDA:** eGFR ≥ 15 ml/min/1·73m^2: no dose adjustment HD: not studied **Hoch *et al.*** Higher exposure in patients with severe renal impairment compared with healthy controls (49-56% higher AUC). The increase in AUC was below the threshold for clinical relevance	GFR ≥ 15 ml/min: no dose adjustment is needed GFR < 15 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Hepatic impairment: no dose adjustment **FDA:** Mild to severe hepatic impairment: no dose adjustment **Hoch *et al.*** Higher exposure of unbound asciminib in patients with mild (14-15%) and severe (44-51%) hepatic impairment compared with healthy subjects. The increase in AUC was below the threshold for clinical relevance.	Hepatic impairment: no dose adjustment is needed	Scemblix label[1] SPC Scemblix[2] Hoch *et al.*[14]
15	**Asparaginase**	Asparaginase is thought to be degraded within the reticulo- histiocytic system and by serum proteases. No renal clearance.	**EMA:** Renal impairment: no dose adjustment HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA:** Mild and moderate: no dose adjustment Severe: contraindicated	Mild and moderate: no dose adjustment is needed Severe: not recommended due to hepatotoxicity	SPC Spectrila [2]
16	**Atezolizumab**	Atezolizumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: not studied HD: not studied	eGFR ≥ 30 ml/min: no dose adjustment is needed eGFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Tecentriq label [1] SPC Tecentriq[2]
17	**Avapritinib**	Avapritinib is primarily metabolised by CYP3A4 and to a lesser extent by CYP2C9. Avapritinib is mainly excreted in feces (70%; 11% unchanged) and minorly in urine (18%; 0·23% unchanged)	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Mild and moderate: no dose adjustment Severe and Child-Pugh C: not studied **FDA:** Mild and moderate: no dose adjustment	Mild and moderate: no dose adjustment is needed Severe: not recommended	Ayvakit label[1] SPC Ayvakyt[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					Severe: not studied		
18	**Avelumab**	Avelumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied **FDA:** CLcr ≥ 15 ml/min: no dose adjustment	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Bavencio label[1] SPC Bavencio[2]
19	**Axitinib**	Axitinib is metabolised in the liver Axitinib and its metabolites are excreted in feces (60%) and to a lesser extent in urine (23%).	**EMA/FDA:** CLcr ≥ 15 ml/min: no dose adjustment CLcr < 15 ml/min: caution when used **Thiery-Vuillemin *et al.*** HD: axitinib is not dialysed	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A: no dose adjustment Child-Pugh B: approximately 50% of the original dose Child-Pugh C: not studied **Tortorici *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 78·34%(90% CI 39·92-153 ·75) Child-Pugh B: $AUC_{0\text{-}inf}$ 195 ·25% (90% CI 99·49-383 ·18)	Child-Pugh A: no dose adjustment is needed Child-Pugh B: 50% of the original dose Child-Pugh C: not recommended	Inlyta label[1] SPC Inlyta[2] Thiery-Vuillemin *et al.*[15] Tortorici *et al.*[16]
20	**Azacitidine**	Azacitidine is hydrolysed and deanimated by cytidine deanimase. Azacitidine and its metabolites are predominantly excreted in urine (50-85%) with less than 1% excreted in feces.	**EMA/FDA:** Renal impairment: no initial dose adjustment is needed **Laille *et al.*** CLcr < 30 ml/min/1·73m^2: $AUC_{0\text{-}inf}$: 141·2% (90% CI 92·2-216 ·2%) **Ham *et al.*** HD: no initial dose adjustment is needed	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA/FDA:** Hepatic impairment: not studied Contraindicated: albumin <30 g/L, advanced malignant hepatic tumours	Mild or moderate: no need for dose adjustment is expected If albumin <30 g/L/or advanced malignant hepatic tumours: not recommended	Vidaza label[1] SPC Vidaza[2] Laille *et al.*[17] Ham *et al*.[18]
21	**Belantamab mafodotin**	Belantamab mafodotin is expected to undergo catabolism to small peptides, amino acids and unconjugated cys-mcMMAF. Cys-mcMMAF has limited metabolic clearance. In animal studies, belantamab mafodotin was excreted in feces (87%) and minorly in urine (13%, no metabolites were found).	**EMA/FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment is needed eGFR < 30 ml/min/1·73m^2: not studied HD: not studied	eGFR ≥ 30 ml/min: no dose adjustment is needed. eGFR < 30 ml/min: No need for dose adjustment is expected HD: No need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment needed Moderate and severe: no data available	Mild: no dose adjustment is needed. Moderate and severe: No data available and therefore not recommended yet.	Blenrep label[1] SPC Blenrep[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
22	**Belinostat**	Belinostat is metabolised in the liver. Belinostat and its metabolites are predominantly excreted in urine (84·8%, 1·7% unchanged) and to a lesser extent in feces (9 ·7%).	**FDA:** CLcr > 39 ml/min: No dose adjustment is needed CLcr ≤ 39 ml/min: not studied HD: not studied	GFR > 39 ml/min: no dose adjustment is needed GFR ≤ 39 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment is needed Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: not recommended	Beleodaq label[1]
23	**Belzutifan**	Belzutifan is primarily metabolised by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A to less active metabolites. Routes of elimination have not been identified. Mass-balance study is ongoing.	**FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment is needed eGFR < 30 ml/min/1·73m^2: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: not recommended HD: not recommended	**FDA:** Mild: no dose adjustment is needed Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: not recommended	Welireg label[1]
24	**Bendamustine**	Bendamustine is cleared by hydrolysis and is metabolised in the liver. Bendamustine and its metabolites are predominantly excreted in urine and to a lesser extent in feces.	**FDA:** CLcr 30-80 ml/min: no dose adjustment is needed CLcr < 30 ml/min: not studied, contraindicated **MHRA:** CLcr > 10 ml/min: no dose adjustment is needed Clcr ≤ 10 ml/min: limited data available HD: no dose adjustment is needed	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**FDA:** Mild: no dose adjustment is needed Moderate and severe: not studied, contraindicated **MHRA:** Mild (bilirubin <20 µmol/L): no dose adjustment is needed Moderate (bilirubin 20 -51 µmol/L): 70% of the original dose Severe (bilirubin > 51 µmol/L): not studied, contraindicated	Mild (bilirubin <20 µmol/L): no dose adjustment is needed Moderate (bilirubin 20 -51 µmol/L): 70% of the original dose Severe (bilirubin > 51 µmol/L): not recommended	Treanda label[1] SPC Levact[9]
25	**Bevacizumab**	Bevacizumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** Not studied in patients with renal impairment. **Ganier-Viougeat *et al.*** HD: 50% of the dose resulted in dose proportional AUC reduction, bevacizumab is not dialysed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Not studied in patients with hepatic impairment	Hepatic impairment: no need for dose adjustment is expected	Avastin label[1] SPC Avastin[2] Garnier-Viougeat *et al.*[19]
26	**Bicalutamide**	The R-enantiomer of bicalutamide has antiandrogenic activity. Bicalutamide is extensively metabolised in the liver. Excretion is both hepatic and renal.	**EMA/FDA:** No dose adjustment is needed for patients with renal impairment **Ito *et al.*** HD: plasma concentration is	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA/FDA:** No dose adjustment is necessary for patients with hepatic impairment. Half-life may be prolonged in patients with severe hepatic	Hepatic impairment: no dose adjustment is needed	Casodex label[1] SPC Casodex[8] Ito *et al.*[20]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			unaffected by haemodialysis.		impairment.		
27	**Binimetinib**	Binimetinib is metabolised in the liver. The active metabolite M3 contributes to the clinical effect. Binimetinib and its metabolites are predominantly excreted in feces (62%, 32% unchanged) and to a lesser extent in urine (31%, 6·5% unchanged)	**FDA:** eGFR ≤ 29 ml/min/1·73m^2: no important changes in binimetinib exposure HD: not studied, unlikely to be dialysed **EMA:** eGFR ≤ 29 ml/min/1·73m^2: no dose adjustment	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: 67% of original dose **EMA:** Child-Pugh A: no dose adjustment Child-Pugh B/C: not recommended, as encorafenib is also not recommended	Mild: no dose adjustment is needed Moderate and severe: 67% of the original dose (30mg BID)	Mektovi label[1] SPC Mektovi[2]
28	**Bleomycin**	Bleomycin is widely distributed to normal tissues and inactivated by bleomycin hydrolases. Bleomycin is excreted in urine (approximately 67% unchanged).	**MHRA:** GFR > 50 ml/min: no dose adjustment GFR 10-50 ml/min: 75% of the original dose GFR < 10 ml/min: 50% of the original dose **Crooke *et al.*** HD: bleomycin is not dialysed	GFR > 50 ml/min: no dose adjustment is needed GFR 10-50 ml/min: 75% of the original dose GFR < 10 ml/min: 50% of the original dose HD: 50% of the original dose may be considered	**MHRA:** Not studied in patients with hepatic impairment	Hepatic impairment: no need for dose adjustment is expected	SPC Bleomycin[9] Crooke *et al.*[21]
29	**Blinatumomab**	Blinatumomab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr ≥ 30 ml/min: values within the range observed in normal renal function. CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Not studied in patients with hepatic impairment **Zhu *et al.*** No association between blinatumomab clearance and baseline ALT or AST levels	Hepatic impairment: no need for dose adjustment is expected	Blincyto label[1] SPC Blincyto[2] Zhu *et al.* 2016[22]
30	**Bortezomib**	Bortezomib is metabolised in the liver. The elimination of bortezomib and its metabolites is unknown, but is believed to be hepatically.	**EMA:** CLcr ≥ 20 ml/min/1·73 m^2: no dose adjustment CLcr < 20 ml/min/1·73 m^2: not studied HD: no dose adjustment, administer after dialysis **FDA:** Renal impairment: no dose adjustment HD: no dose adjustment, administer after dialysis	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed, administer after haemodialysis	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: 54% of the original dose (0·7 mg/m^2) **LoRusso *et al.*** Mild: $AUC_{0\text{-last}}$ 90·2% (90% CI 66·2-122 ·8) Moderate: $AUC_{0\text{-last}}$ 146 ·8% (90% CI 104 ·7-205 ·7) Severe: $AUC_{0\text{-last}}$ 158 ·1%(90% CI 116 ·8-214 ·0)	Mild: no dose adjustment Moderate and severe: 54% of the original dose (0·7 mg/m^2)	Velcade label[1] SPC Velcade[2] LoRusso *et al.*[23] Leal *et al.*[24]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			Leal *et al.* Bortezomib pharmacokinetics are not influenced by CLcr				
31	**Bosutinib**	Bosutinib is metabolised in the liver (CYP3A4). Bosutinib and its metabolites are predominantly excreted in feces (91·3%) with minimal amounts in urine (3·3%)	**EMA/FDA:** CLcr 51-80 ml/min: no dose adjustment is needed CLcr 30-50 ml/min: 300 mg QD (newly diagnosed) 400 mg QD (pretreated) CLcr < 30 ml/min: 200mg QD (newly diagnosed) 300 mg QD (pretreated) HD: not studied **Abbas *et al.*** CLcr 30-50 ml/min: AUC 135·02% (90 % CI 98·53–185·01) CLcr < 30 ml/min: AUC 159·76 % (90 % CI 115·52–220·92)	GFR > 50 ml/min: no dose adjustment is needed GFR < 50 ml/min: 75% of the original dose HD: 75% of the original dose may be considered	**EMA/FDA:** Child-Pugh A, B and C: 200 mg QD **Abbas *et al.*** Child-Pugh A: AUC 225% (90% CI 160-315) Child-Pugh B: AUC 200% (90% CI 143-281) Child-Pugh C: AUC 191% (90% CI 137-268)	Child-Pugh A, B and C: 50% of the original dose (200mg QD)	Bosulif label[1] SPC Bosulif[2] Abbas *et al.*[25] Abbas *et al.* [26]
32	**Brentuximab vedotin**	The anti-CD30 antibody is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance. Only a small fraction of Monomethyl auristatin E (MMAE) is metabolised by CYP3A4/5. Brentuximab vedotin is predominantly excreted unchanged in feces, and to a lesser extent in urine.	**FDA:** CLcr 50-80 ml/min: no dose adjustment CLcr 30-50 ml/min: no dose adjustment CLcr < 30 ml/min: not recommended HD: not studied **EMA:** CLcr < 30 ml/min: approximately 67% (1·2 mg/kg) **Zhao *et al.*** CLcr 51-80 ml/min: MMAE $AUC_{0\text{-}inf}$ 0·85 (90% CI 0·39-1·84) Clcr 30-50ml/min: MMAE $AUC_{0\text{-}inf}$ 1·09 (90% CI 0·49-2·42) CLcr < 30 ml/min: MMAE $AUC_{0\text{-}inf}$ 1·90 (90% CI 0·85-4·21)	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 67% of the original dose HD: 67% of the original dose	**FDA:** Child-Pugh A: 67 or 75% of the original dose (0·9 or 1·2 mg/kg) Child-Pugh B and C: not recommended **EMA**: Child-Pugh A/B/C: 67% of the original dose (1·2mg/kg) **Zhao *et al.*** Child-Pugh B: MMAE $AUC_{0\text{-}inf}$: 2·21 (90% CI 1·11-4·44)	Child-Pugh A: 67% of the original dose Child-Pugh B and C: not recommended	Adcetris label[1] SPC Adcentris[2] Zhao *et al.*[27]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
33	**Brigatinib**	Brigatinib is metabolised in the liver. Brigatinib and its metabolites are excreted in feces (65%, 41% unchanged) and to a lesser extent in urine (25%, 86% unchanged).	**FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr 15-29 ml/min or HD: reduce the dose by approximately 50% **EMA:** eGFR ≥ 30 ml/min: no dose adjustment eGFR < 30 ml/min: reduced starting dose of 60 mg QD for the first 7 days, then 90 mg QD **Gupta *et al.*** Renal clearance of patients with severe renal impairment was ~20% of that observed in volunteers with normal renal function. Reduce dose with 50% in these patients.	GFR 30-90 ml/min: no dose adjustment is needed GFR < 30 ml/min: 50% of the original dose may be considered HD: 50% of the original dose may be considered	**FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: reduce the QD dose by approx. 40% **EMA:** Mild and moderate: no dose adjustment Severe: reduced starting dose of 60 mg QD for the first 7 days, then 120 mg QD	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: approximately 60% of the original dose may be considered	Alunbrig label[1] SPC Alunbrig[2] Gupta *et al.*[28]
34	**Busulfan**	Busulfan is mainly metabolised in the liver. Approximately 30% (1-2% unchanged) of busulfan is excreted in urine with negligible amounts in feces.	**EMA/FDA:** Not studied in patients with renal impairment **Masauzi *et al.*** Busulfan clearance comparable to normal patients on non-HD day, accelerated clearance on HD day.	Renal impairment: no dose adjustment is needed, dosing is based on busulfan plasma levels HD: no initial dose adjustment is needed, dose according to busulfan plasma levels	**EMA/FDA:** Not studied in patients with hepatic impairment	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended	Busulfex label[1] SPC Busulfan Fresenius Kabi[2] Masauzi *et al.*[29]
35	**Cabazitaxel**	Cabazitaxel is extensively metabolised in the liver. Metabolites are predominantly hepatically excreted (76%) and to a lesser extent renally (3·7%)	**EMA/FDA:** CLcr 15-80 ml/min: no dose adjustment CLcr < 15 ml/min: not studied HD: not studied **Azaro *et al.*** eGFR 30-49 ml/min/1·73m2 and eGFR < 30 ml/min/1·73m2: no change in AUC compared to normal renal function.	GFR ≥ 15 ml/min: no dose adjustment is needed GFR < 15 ml/min or HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: 20 mg/m^2 Moderate: 15 mg/m^2 Severe: not recommended **Sarantopoulos *et al.*** Minimal impact of hepatic impairment on cabazitaxel PK parameters. Recommended dosages based on safety data are 20 and 15mg/m^2 for patients with mild and moderate hepatic	Mild: 20 mg/m^2 Moderate: 15 mg/m^2 Severe: not recommended	Jevtana label[1] SPC Jevtana[2] Azaro *et al.*[30] Sarantopoulos *et al.*[31]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					impairment respectively		
36	**Cabozantinib**	Cabozantinib is metabolised in the liver by CYP3A4 and is predominantly excreted in feces (54%, 43% unchanged) and to a lesser extent in urine 27% (only metabolites).	**EMA/FDA:** CLcr 30-80 ml/min: no dose adjustment CLcr < 30 ml/min: not studied. HD: not studied **Nguyen *et al.*** eGFR ≥ 60 ml/min/1·73m^2: $AUC_{0\text{-}inf}$ 130 ·1% (90% CI 98·9-171·3) eGFR 30-59 ml/min/1 ·73m^2: $AUC_{0\text{-}inf}$ 105·6% (90% CI 79·6-140 ·1)	GFR 30-80 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate or Child-Pugh B: 66% of the original dose (40 mg QD) Severe: not studied **EMA:** Mild: no dose adjustment Moderate or Child-Pugh B: insufficient data, not recommended Severe: not studied and therefore not recommended **Nguyen *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 181·2% (90% CI 121·4-270 ·3) Child-Pugh B: $AUC_{0\text{-}inf}$ 162·7% (90% CI 107·4-246 ·7)	Child-Pugh A/B or mild and moderate: consider a starting dose 66% of the original dose, increase if tolerated Child-Pugh C or severe: not recommended	SPC/label Cabometyx[1,2] SPC/label Cometriq[1,2] Nguyen *et al.*[32]
37	**Capecitabine**	Capecitabine (prodrug) is enzymatically converted to 5- fluorouracil (5-FU). 5-FU is converted intracellularly to inactive metabolites by dihydropyrimidine dehydrogenase (DPD). Capecitabine and its metabolites are predominantly excreted renally (95·5%) and to a lesser extent hepatically (2·6%).	**EMA/FDA:** CLcr: 51-80 ml/min: no dose adjustment CLcr 30-50 ml/min: 75% of the original dose CLcr < 30 ml/min: not recommended HD: not studied **Poole *et al.*** No effect of renal impairment on the systemic exposure of capecitabine or 5-FU. Based on safety data: CLcr 30-50 ml/min 75% of original dose CLcr < 30 ml/min: not recommended.	GFR 51-80 ml/min: no dose adjustment is needed GFR 30-50 ml/min: 75% of the original dose GFR < 30 ml/min: not recommended HD: not recommended	**EMA/FDA:** Mild and moderate due to liver metastases: AUC and C_{max} of capecitabine increased by 60%, AUC of 5-FU was unaffected. severe: not studied **Joerger *et al.*** Normal – severe: no dose adjustment is needed, although hepatic impairment was associated with low clearance of capecitabine. **Twelves *et al.*** No statistically significant increase in capecitabine or 5-FU $AUC_{0\text{-}inf}$ in patients with mild – moderate hepatic impairment due to liver metastases (WHO based grading system).	Hepatic impairment: no dose adjustment is needed	Xeloda label[1] SPC Xeloda[2] Poole *et al.*[33] Joerger *et al.*[34] Twelves *et al.*[35]
38	**Capmatinib**	Capmatinib is primarily metabolised by CYP3A4 and aldehyde oxidase.	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need	**EMA/FDA:** Child-Pugh A to C and mild to severe: no dose adjustment	Hepatic impairment: no dose adjustment is needed	Tabrecta label[1] SPC Tabrecta[2] Chen *et al.*[36]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		Capmatinib is mainly excreted in feces (78%, 42% unchanged) and to a lesser extent in urine (22%, unchanged negligible).	CLcr < 30 ml/min: no data available **FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	for dose adjustment is expected HD: no need for dose adjustment is expected	**Chen *et al.*** Mild, moderate and Child-Pugh A-C: no dose adjustment Mild: $AUC_{0\text{-}inf}$ 0·767 (90% CI 0·532-1·11) Moderate: $AUC_{0\text{-}inf}$ 0·914 (90% CI 0·652-1·28) Severe: $AUC_{0\text{-}inf}$ 1·24 (90% CI 0·858-1·78)		
39	**Carboplatin**	Carboplatin is not metabolised. It is highly protein-bound (87%) and is primarily excreted in urine	**MHRA**: Dose according to Calverts formula: dose [mg] = target AUC * (GFR +25) **Watanabe *et al.*** HD: carboplatin dose was calculated with GFR equals 0 according to Calverts formula for a target AUC of 5 µg*min/ml. HD was performed 16-hours after start and resulted in free platinum AUC of 4·43 µg* min/ml.	Renal impairment: dose calculation based on renal function according to Calverts formula HD: dose according to Calvert formula with GFR equals 0. Perform HD between 12 and 24 hours after administration.	**MHRA**: Not studied in patients with hepatic impairment	Hepatic impairment: No need for dose adjustment is expected	SPC Carboplatin[9] Calvert *et al.*[37] Watanabe *et al.*[38]
40	**Carfilzomib**	Carfilzomib is rapidly metabolised into inactive metabolites by peptidase cleavage and epoxide hydrolysis. Carfilzomib is mainly cleared extrahepatically, approximately 25% is excreted in urine as metabolites.	**EMA/FDA:** Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed, dose after dialysis **Badros *et al.*** No difference in carfilzomib $AUC_{0\text{-}inf}$ and CL in patients with renal impairment (CLcr 15-80 ml/min) or HD. **Quach *et al.*** HD: $AUC_{0\text{-}inf}$ 138·1% (90% CI 102·8-185·5)	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA/FDA:** Mild and moderate: 75% of the original dose Severe: not studied **Brown *et al.*** 27 mg/m^2 Mild: $AUC_{0\text{-}inf}$ 151·84% (90% CI 113·59-202·96) Moderate: $AUC_{0\text{-}inf}$ 143·53% (90% CI 103·28-199·45) 56 mg/m^2 Mild: $AUC_{0\text{-}inf}$ 181·90% (90% CI 96·4-343·24) Moderate: $AUC_{0\text{-}inf}$ 152·59% (90% CI 74·87-310·96)	Mild and moderate: 75% of the original dose. Severe: not recommended	Kyprolis label[1] SPC Kyprolis[2] Badros *et al.*[39] Quach *et al.*[40] Brown *et al.*[41]
41	**Carmustine**	Carmustine is metabolised in the liver. Carmustine and its metabolites are mainly excreted in urine (60-70%) and approximately 10% is excreted as respiratory CO_2.	**FDA:** Do not administer to patients with compromised renal function **EMA:**	GFR 46-60 ml/min: 80% of the original dose GFR 31-45 ml/min: 75% of the original dose GFR < 30 ml/min: not recommended HD: not	**EMA/FDA:** Hepatic impairment: no advise given	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	Bicnu label[1] SPC Carmustine Obvius[2] Kintzel *et al.*[42]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			Reduce dose if GFR is reduced, CLcr < 10 ml/min: contra-indicated **Kintzel *et al.*** CLcr 60 ml/min: 80% CLcr 45 ml/min: 75% CLcr < 30 ml/min: not recommended HD: not studied	recommended			
42	**Cemiplimab**	Cemiplimab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no dose adjustment	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Libtayo label[1] SPC Libtayo[2]
43	**Ceritinib**	Ceritinib is metabolised in the liver. Excretion of ceritinib and its metabolites is predominantly in feces (92%, 68% unchanged) with minimal excretion in urine (1·3%)	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A: no dose adjustment (18% increase in $AUC_{0\text{-}inf}$) Child-Pugh B: no dose adjustment (2% increase in $AUC_{0\text{-}inf}$) Child-Pugh C: 67% of the original dose (66% increase in $AUC_{0\text{-}inf}$)	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 67% of original dose	Zykadia label[1] SPC Zykadia[2]
44	**Cetuximab**	Cetuximab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** Not studied in patients with renal impairment **Inauen *et al.*** HD: not dialysed, no dose adjustment needed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Not studied in patients with hepatic impairment	Hepatic impairment: no need for dose adjustment is expected	Erbitux label[1] SPC Eribtux[2] Inauen *et al.*[43]
45	**Chlorambucil**	Chlorambucil is extensively metabolised in the liver, forming the active metabolite phenylacetic acid mustard (PAAM). Excretion of chlorambucil and PAAM in urine is <1%.	**EMA/FDA:** Renal impairment: no dose adjustment is needed HD: not dialysable, no dose adjustment needed (FDA)	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Not studied in patients with hepatic impairment; consider dose reduction in severe hepatic impairment.	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	Leukeran label[1] SPC Leukeran[2]
46	**Chlormethine**	Chlormethine is rapidly metabolised after administration. Its metabolites are mainly excreted in urine.	**FDA:** Renal impairment/HD: no advise given	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Hepatic impairment: no advise given	Mild: no need for dose adjustment is expected Moderate and severe: not recommended	Mustargen label[1]
47	**Cisplatin**	Cisplatin is not metabolised. It is highly	**FDA:** CLcr < 60 ml/min:	Curative GFR 50-59 ml/min: 75% of	**FDA/MHRA:** No advise given	Hepatic impairment: no need for dose	Cisplatin label[1] SPC Cisplatin[9]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		protein bound (90%) and is excreted predominantly in urine and to a minimal extent in feces.	contraindicated **MHRA:** Dose should be reduced adequately **Watanabe *et al.*** HD: Dialysed. Dose escalation from 50% to full dose (80 mg/m^2) was tolerated in patients receiving HD started 10 minutes after completion of cisplatin administration. Platinum PK parameters were comparable to patients with normal renal function. After multiple administration a tendency for decreased total platinum clearance and prolonged hematological toxicity was observed. **Kintzel *et al.*** GFR 60 ml/min: 75% of the original dose GFR 45 ml/min: 50% of the original dose GFR 30 ml/min: not recommended	the original dose GFR 40-49 ml/min: 50% of the original dose GFR < 40 ml/min: not recommended HD: 50% of the original dose may be considered Palliative GFR 50-59 ml/min: 75% of the original dose GFR < 50 ml/min: not recommended HD: not recommended, consider carboplatin		adjustment is expected	Watanabe *et al.*[44] Kintzel *et al.*[42]
48	**Cladribine**	The prodrug cladribine is metabolised intracellularly to its active metabolite. Cladribine is mainly excreted in urine (15-18% unchanged).	**EMA:** CLcr ≤ 50 ml/min: not studied, contra-indicated **Crews *et al.*** Half-life increased approximately 2-fold in a child on CVVH/HD	GFR ≤ 50 ml/min: not recommended HD: not recommended	**EMA:** Mild: not studied, no dose adjustment Moderate and severe (Child-Pugh B or C): not recommended	Mild: no need for dose adjustment is expected Moderate and severe or Child-Pugh B/C: not recommended	SPC Litak[2] Crews *et al.*[45]
49	**Clofarabine**	The prodrug clofarabine is metabolised intercellulary to its active metabolite. Clofarabine is mainly excreted in urine (60% unchanged).	**EMA/FDA:** CLcr 30-59 ml/min: 50% of the original dose CLcr <30 ml/min: not studied HD: not studied **Benitez *et al.*** HD: clofarabine was not effectively dialysed during	GFR 30-59 ml/min: 50% of the dose GFR <30 ml/min: not recommended HD: not recommended	**FDA:** Not studied in patients with hepatic impairment **EMA:** No experience in patients with hepatic impairment (serum bilirubin > 1·5 x ULN plus AST and ALT > 5 x ULN)	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	Cloclar label[1] SPC Evoltra[2] Benitez *et al.*[46]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			intermittent HD, $T_{1/2}$ interdialytic and on haemodialysis was approximately 2·5-3 times higher than in patients without renal impairment.		Severe: contraindicated		
50	**Cobimetinib**	Cobimetinib is metabolised in the liver. Cobimetinib is mainly excreted in feces (76%, 6·6 unchanged) and to a lesser extend in urine (17·8%, 1·6% unchanged).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied **Cheeti *et al.*** No effect of mild and moderate hepatic impairment on the total cobimatinib exposure (C_{max} and AUC) compared to patients with a normal hepatic function.	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A, B and C: no dose adjustment	Hepatic impairment: no dose adjustment is needed	Cotellic label[1] Cotellic SPC[2] Cheeti *et al*.[47]
51	**Copanlisib**	Copanlisib is metabolised by CYP3A (>90%) and CYP1A1 (<10%). Copanlisib is mainly excreted in feces (64%, 30% unchanged) and to a lesser extent in urine (22%, 15% unchanged).	**FDA:** CLcr ≥ 30 ml/min: no clinically significant effect on PK of copanlisib CLcr < 30 ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: not recommended HD: not recommended	**FDA:** Child-Pugh A: no dose adjustment Child-Pugh B: 45 mg Child-Pugh C: 30 mg	Child-Pugh A: no dose adjustment is needed. Child-Pugh B: 75% of the original dose. Child-Pugh C: 50% of the original dose	Aliqopa label[1]
52	**Crizotinib**	Crizotinib is metabolised in the liver. Crizotinib and its metabolites are mainly excreted in feces (63%, 53% unchanged), and to a lesser extent in urine (22%, 1·3% unchanged).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: 250 mg QD **Tan *et al.*** CLcr ≥ 30 ml/min : no relevant change in steady-state PK CLcr < 30 ml/min: $AUC_{0\text{-}inf}$: 179·5 (90% CI 126·8-254·0) (single-dose)	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 50% of the original dose (250 mg QD) HD: a need for dose adjustment to 50% of the original dose is expected (250 mg QD)	**FDA:** Moderate: 200 mg BID Severe: 250 mg QD **EMA:** Mild: no dose adjustment Moderate: 200 mg BID Severe: 250 mg QD **El-Khoueiry *et al.*** Geometric mean compared to normal liver function (250 mg BID): Mild (250 mg BID) : $AUC_{0\text{-}24h}$ 91·12% (90% CI 56·56-146·79) Moderate (200 mg BID): $AUC_{0\text{-}24h}$ 114·08 % (90% CI 73·57-176·89) Severe (250 mg QD): $AUC_{0\text{-}24h}$ 64·67 (90%CI 39·50-105·89)	Mild: no dose adjustment is needed Moderate: 80% of starting dose BID (200 mg BID) Severe: 50% of starting dose QC (250 mg QD), increase if tolerated	Xalkori label[1] SPC Xalkori[2] Tan *et al*.[48] El-Khoueiry *et al*.[49]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
53	**Cyclophosphamide**	Cyclophosphamide (prodrug) is metabolised in the liver in its active metabolites. Liver metabolism also forms the cytotoxic and urotoxic metabolite acrolein. Cyclophosphamide and its metabolites are predominantly excreted in urine (10-20% unchanged) and minimally in feces.	**FDA:** CLcr 10-24 ml/min: monitor closely for toxicity HD: dialysed **MHRA:** GFR < 10 ml/min: 50% of the orginal dose HD: dialysed **Wang *et al.*** HD: dialysed, mean of 37% of administered cyclophosphamide was removed during 4-hour dialysis. **Haubitz *et al.*** CLcr 25-50 ml/min: 42% increase in $AUC_{0\text{-}inf}$ CLcr 10-24 ml/min: 77% increase in $AUC_{0\text{-}inf}$ CLcr < 10 ml/min and a 3-hour HD sessions seven hours after administration: 23% increase in $AUC_{0\text{-}inf}$ **Juma *et al.*** Significantly higher AUC of plasma alkylating activity in group of patients with CLcr 0-51ml/min compared to patients with normal renal function (47·77±19·93 nmol/mL*h vs. 25·15± 8·67 nmol/ml*h)	GFR ≥ 30 ml/min: no dose adjustment is needed GFR 10-29 ml/min: consider 75% of the original dose GFR < 10 ml/min: not recommended, if unavoidable consider 50% of the original dose HD: not recommended, if unavoidable consider 50% of the original dose	**FDA:** Potentially reduced efficacy in patients with hepatic impairment **MHRA:** 3·1-5mg/dL: 75% of the original dose **Juma *et al.*** Significantly prolonged Cyclophosphamide half-life in patients with severe liver failure (all cirrhosis due to hepatitis) compared to normal controls. Fewer adverse events in the liver failure group.	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy	Cyclophosphamide injection Baxter – label[1] SPC Cyclophosphamide injection 1 g[9] Wang *et al*.[50] Haubitz *et al.*[51] Juma *et al*.[52] Juma *et al.*[53]
54	**Cytarabine (high-dose ≥ 1 g/m²)** for low-dose no dose adjustments are needed	Cytarabine is converted intracellulary to its active metabolite aracytidine-5'-triphosphate. Cytarabine is further metabolised, primarily in the liver, among others to uracil arabinoside (Ara-U), which can cause neurotoxicity. Cytarabine and its metabolites, are predominantly excreted in	**MHRA:** Renal impairment: use with caution and at reduced dose. HD: dialysed **Kintzel *et al.*** CLcr 60 ml/min: 60% of the original dose CLcr 45 ml/min: 50% of the original dose CLcr 30 ml/min:	GFR ≥ 60 ml/min: no dose adjustment is needed GFR 31-59 ml/min: 50% of the original dose GFR < 30 ml/min: not recommended HD: 50% of the original dose, start HD 4-5 h after administration	**MHRA:** Hepatic impairment: use with caution and at reduced dose **Barker *et al.*** 1 g/m² every other day for three days was tolerated in a patient with bilirubin > 15 mg/dL.	Mild and moderate: no need for dose adjustment is expected Severe: consider 25-50% of the original dose and increase if tolerated	Cytarabine 100 mg/ml, Pfizer Ltd.[9] Kintzel *et al*.[42] Smith *et al*.[54] Radeski *et al*.[55] Barker *et al.*[56]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		urine (90% as metabolites, 5·8% unchanged).	not recommended **Radeski *et al.*** HD: no dose adjustment, HD initiated 6 h after administration of 1 g/m2 resulted in 63% Ara-U removal.				
55	**Dabrafenib**	Dabrafenib is primarily metabolised in the liver to hydroxy-dabrafenib and desmethyl-dabrafenib, which both contribute to the clinical effect. Dabrafenib and its metabolites are predominantly excreted in feces (71%) and to a lesser extent in urine (23%).	**EMA/FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: not studied **Park *et al.*** HD: not dialysed, plasma concentrations comparable to patients with normal renal function	GFR ≥30 ml/min: no dose adjustment is needed GFR< 30 ml/min or HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: 50% of the original dose may be considered	Tafinlar label[1] SPC Tafinlar[2] Park *et al.*[57]
56	**Dacarbazine**	Dacarbazine (prodrug) is metabolised in the liver to its reactive metabolites. These metabolites are also inactivated by the liver. Approximately 20- 50% of dacarbazine is excreted unchanged in urine by tubular secretion.	**MHRA:** Mild and moderate without hepatic impairment: no dose adjustment Severe: no advice In patients with combined renal and hepatic impairment elimination is prolonged HD: not studied	GFR ≥ 30 ml/min without hepatic impairment: no dose adjustment is needed GFR < 30 ml/min: 70% of the original dose may be considered HD: 70% of the original dose may be considered	**MHRA:** Mild and moderate without renal impairment: no dose adjustment Severe: no advice in patients with combined renal and hepatic impairment elimination is prolonged	Mild and moderate without renal impairment: no dose adjustment is needed Severe: not recommended	SPC Dacarbazine[9]
57	**Dacomitinib**	Dacomitinib is primary metabolised by oxidation and glutathione conjugation. Dacomitinib is mainly excreted in feces (20% as dacomitinib) and minorly 3% in urine (<1% as dacomitinib)	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A-C: no dose adjustment needed **EMA:** Mild and moderate or Child-Pugh A/B: no dose adjustment needed Severe or Child-Pugh C: no PK changes, recommended starting dose 30 mg QD (33% dose reduction) based on safety and tolerability	Mild and moderate: no dose adjustment is needed Severe: 66% of the original dose, increase if tolerated	Vizimpro label[1] SPC Vizimpro[2]
58	**Dactinomycin**	Dactinomycin is minimally metabolised. Approximately 30% of the dose is excreted in urine and feces.	**FDA/MHRA:** Not studied in patients with renal impairment HD: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA/MHRA:** Not studied in patients with hepatic impairment	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	Cosmegen label[1] SPC Cosmegen[9]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
59	**Daratumumab**	Daratumumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**FDA:** CLcr: ≥ 15 ml/min: no dose adjustment is needed **EMA**: Renal impairment: no dose adjustment needed	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: no dose adjustment Severe: not studied **EMA**: Hepatic impairment: no dose adjustment needed	Hepatic impairment: no dose adjustment is needed	Darzalex label[1] SPC Darzalex[2]
60	**Darolutamide**	Darolutamide is metabolised primarily by oxidative metabolism BY CYP3A4 and glucuronidation by UGT1A9 and UGT1A1. Darolutamide is mainly excreted in urine (63·4%; 7% unchanged) and in feces (32·4%; 30·7% unchanged).	**EMA/FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR 15-29 ml/min/1·73m^2: 50% dose reduction eGFR < 15 ml/min/1·73m^2: no data available HD: no data available **Zurth *et al.*** Severe: compared to healthy subjects, C_{max} increased 1·6-fold and AUC_{0-48} increased 2·5-fold.	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 50% of the original dose HD: 50% of the original dose	**FDA:** Mild: no dose adjustment Moderate or Child-Pugh B: 50% dose reduction Severe or Child-Pugh C: no data available **EMA:** Mild: no dose adjustment Moderate,severe and Child-Pugh B/C: 50% dose reduction **Zurth *et al.*** Child-Pugh B: compared to healthy subjects, C_{max} increased 1·5-fold and AUC_{0-48} increased 1·9-fold.	Child-Pugh A or mild: no dose adjustment is needed Child-Pugh B/C or moderate/severe: 50% of the original dose	Nebuqa label[1] SPC Nebuqa[2] Zurth *et al.* [58]
61	**Dasatinib**	Dasatinib is metabolised in the liver. Dasatinib and its metabolites are predominantly excreted in feces (85%, 19% unchanged) with minimal excretion in urine (4%, 0·1% unchanged).	**EMA/FDA:** CLcr had no clinically relevant effect on the pharmacokinetics HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** No initial dose adjustment is needed, although caution is recommended Child-Pugh-A: not studied Child-Pugh B: 8% decrease in mean AUC Child-Pugh C: 28% decrease in mean AUC	Hepatic impairment: no dose adjustment is needed, although caution is recommended	Sprycel label[1] SPC Sprycel[2]
62	**Daunorubicin**	Daunorubicin is metabolised in the liver. The metabolite daunorubicinol contributes to the clinical effect. Daunorubicin and its metabolites are excreted in both urine (25%) and feces (40%)	**MHRA:** Serum creatinine 105-265 µmol/L: 75% serum creatinine > 265 µmol/L: 50% **Krashin *et al.*** HD: 50% of the dose (30 mg/m^2 resulted in a comparable AUC of that in patients with 45mg/m^2 without renal impairment.	GFR 30-50 ml/min: 75% of the original dose GFR < 30 ml/min: 50% of the original dose HD: 50% of the original dose	**MHRA:** Serum bilirubin 20-50 µmol/L: 75% of the original dose Serum bilirubin > 50 µmol/L: 50% of the original dose	Bilirubin 20-50 µmol/L: 75% of the original dose Bilirubin > 50 µmol/L: 50% of the original dose	SPC Daunorubicin[9] Krashin *et al.*[59]
63	**Decitabine**	Decitabine is converted intracellularly to its active	**EMA/FDA:** Renal impairment: not	Renal impairment: no need for dose adjustment at	**EMA/FDA:** Hepatic impairment: not	Hepatic impairment: no need for dose adjustment	Dacogen label[1] SPC Dacogen[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		metabolite. Decitabine is metabolised by cytidine deaminase in, among others, the liver and kidneys. Decitabine and its metabolites are excreted in urine (90%, 4% unchanged).	studied. Exposure not likely to be affected in patients with impaired renal function (EMA). **Levine *et al.*** Retrospective safety data: higher incidence of grade ≥ 3 cardiac and respiratory toxicities in group with CLcr < 60ml/min compared to CLcr ≥ 60ml/min.	start is expected, close monitoring for toxicity is recommended HD: not recommended	studied	is expected	Levine *et al.*[60]
64	**Decitabine/ cedazuridine**	Decitabine is primarily metabolised by cytidine deaminase and physicochemical degradation. Cedazuridine is primarily metabolised by physicochemical degradation. Cedazuridine is mainly excreted in feces (51%, 27% unchanged) and urine (46%, 21% unchanged).	**FDA:** CLcr ≥ 60 ml/min: no dose adjustment CLcr 30-59 ml/min: no dose adjustment, monitor patients CLcr < 30 ml/min: no data available	GFR ≥ 60 ml/min: no dose adjustment is needed GFR 30-59 ml/min: no dose adjustment is needed, consider monitoring GFR < 30 ml/min: not recommended HD: not recommended	**FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: not recommended	Inqovi label[1]
65	**Dinutuximab (-beta)**	Dinutuximab(-beta) is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA: dinutuxumab-beta** **FDA: dinutuxumab** eGFR < 70 ml/min/1·73m^2: not studied HD: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA: dinutuxumab-beta** **FDA: dinutuxumab** Not studied in patients with hepatic impairment	Hepatic impairment: no need for dose adjustment is expected.	Unituxin label[1] SPC Qarziba[2]
66	**Docetaxel**	Docetaxel is primarily metabolised by CYP-mediated oxidative metabolism. Docetaxel is mainly excreted in feces (75%) and to a lesser extent with urine (6%), mostly as metabolites.	**EMA/FDA:** Renal impairment: not studied **Dimopoulos *et al.*** Full dose was tolerated in 11 patients with CLcr < 10-39 ml/min (median 28 ml/min). **Hochegger *et al.*** HD: not dialysed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** AST and/or ALT > 1·5 x ULN with AP > 2·5 x ULN: reduce to 75 mg/m^2 ALT and AST > 3·5 x ULN with AP > 6 x ULN and/or serum bilirubin > ULN: only use on strict indication **FDA:** Bilirubin > ULN or AST and/or ALT > 1·5x ULN with AP >2·5x ULN: avoid use	AST and/or ALT > 1·5-5 x ULN concomitant with AP > 2·5 – 5 x ULN and normal bilirubin: consider 75% of the original dose AST or ALT > 5-10 x ULN concomitant with AP < 6 x ULN and/or bilirubin ≤ 1-1·5 x ULN: consider 50% of the original dose Bilirubin > 1·5 x ULN or AST/ALT > 10 x ULN or AP	Taxotere label[1] SPC taxotere[2] Dimopoulos *et al.*[61] Hochegger *et al.* [62] Bruno *et al*.[63] Syn *et al.*[64] Minami *et al.*[65] Eckmann *et al.*[66]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					Bruno *et al.* PopPK: 27% decrease in CL in patients with ALT or AST > 1·5 X ULN and AP > 2·5 X ULN **Syn *et al.*** AP, AST and/or AST ≤ 5 x ULN and bilirubin < 1 x ULN: 75% of the original dose Any AP, and AST or ALT ≤ 5-10 x ULN and/or bilirubin ≤ 1-1·5x ULN: 50% of the original dose resulted in comparable $AUC_{0\text{-}inf}$. **Minami *et al.*** popPK: AP > 2·5 x ULN and AST/ALT > 2·5 - 5·0 x ULN 22% decrease in CL, suggesting a 20% dose reduction AP > 2·5 x ULN and AST/ALT >5·0 - 20·0 x ULN 38% decrease in CL, suggesting a 40% dose reduction. **Eckmann *et al.*** A dose of 25 mg/m^2(25% of the original dose) in patients with bilirubin 1·5-3 x ULN and ALT/AST 2·5 – 5 x ULN and AP ≥ 2·5 X ULN due to liver metastases resulted in significantly lower AUC compared to patients with normal hepatic function. (1·7 mg/L/h compared to 4·81 mg/L/h)	> 6 x ULN: not recommended	
67	**Dostarlimab**	Dostarlimab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: limited data available HD: limited data available **FDA:** Renal impairment: no clinically significant effect on PK of dostarlimab	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA:** Mild and moderate: no dose adjustment Severe : limited data available **FDA:** Hepatic impairment: no clinically significant effect on PK of dostarlimab	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Jemperli label[1] SPC Jemperli[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
68	**Doxorubicin**	Doxorubicin is metabolised in the liver. Doxorubicinol is the main active metabolite. Doxorubicin and its metabolites are mainly excreted biliary in feces (40%-50%) and to a lesser extent in urine (5-12%).	**FDA:** Renal impairment: no advice given **MHRA** eGFR < 10 ml/min: 75% of the dose **Yoshida *et al.*** HD: AUC of doxorubicin and doxorubicinol increased 1·5 and 3-fold respectively in HD-patients.	GFR > 10 ml/min: no dose adjustment is needed GFR < 10 ml/min: no need for dose adjustment is expected HD: 75% of the original dose may be considered	**FDA/ MHRA:** Serum bilirubin 20-50 µmol/L: 50% of the original dose Serum bilirubin 50 µmol/L – 85·5 µmol/ : 25% of the original dose Serum bilirubin > 85·5 µmol/: contraindicated (FDA) Child-Pugh C: contraindicated	Bilirubin 20-50 µmol/L: 50% of the original dose Bilirubin 51 – 86 µmol/ : 25% of the original dose Bilirubin > 86 µmol/L or Child-Pugh C: not recommended	Doxorubicin label[1] SPC Doxorubicin[9] Yoshinda *et al.*[67]
69	**Liposomal doxorubicin (Myocet®)**	Doxorubicin is metabolised in the liver. Doxorubicinol is the main active metabolite. Doxorubicin and its metabolites are mainly excreted biliary in feces (40%-50%) and to a lesser extent in urine (5-12%). With the liposomal formulation total doxorubicin plasma levels are higher compared to conventional doxorubicin, but peak plasma levels of free doxorubicin are lower.	**EMA:** No dose adjustment is needed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Bilirubin < ULN and normal AST: no dose adjustment Bilirubin < ULN and raised AST: consider a 25% dose reduction Bilirubin > ULN but < 50 µmol/l: 50% dose reduction Bilirubin >50 µmol/l: avoid if possible, otherwise 75% dose reduction	AST > ULN: 75% of the original dose Bilirubin 20-50 µmol/L: 50% of the original dose Bilirubin 51 – 86 µmol/L : 25% of the original dose Bilirubin > 86 µmol/L or Child-Pugh C: not recommended	SPC Myocet liposomal[2]
70	**Pegylated liposomal doxorubicin (Doxil, Caelyx®)**	Doxorubicin is metabolised in the liver. Doxorubicinol is the main active metabolite. Doxorubicin and its metabolites are mainly excreted biliary in feces (40%-50%) and to a lesser extent in urine (5-12%). With the pegylated liposomal formulation total doxorubicin plasma levels and AUC are higher compared to conventional doxorubicin.	**FDA:** No information **EMA:** CLcr ≥ 30 ml/min: doxorubicine clearance is not influenced by renal function CLcr < 30 ml/min: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Bilirubin ≥ 1·2 mg/dL: a dose reduction is needed **EMA:** Bilirubin ≥ 1·2-3·0 mg/dl: 75% of the original dose Bilirubin > 3·0 mg/dl: 50% of the original dose	Bilirubin >20 – 50 µmol/L: 75% of the original dose Bilirubin 51-86 µmol/L: 50% of the original dose Bilirubin > 86 µmol/L: not recommended	Doxil label[1] SPC Caelyx[2]
71	**Durvalumab**	Durvalumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr: ≥ 30 ml/min: no dose adjustment is needed CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment is needed Moderate and severe: not studied	Mild: No dose adjustment is needed Moderate and severe: no	Imfinzi label[1] SPC Imfinzi[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			HD: not studied	HD: no need for dose adjustment is expected		need for dose adjustment is expected	
72	**Duvelisib**	Duvelisib is primarily metabolised by CYP3A4. Its major metabolite, IPI-656, is pharmacologically inactive. Duvelisib is mainly excreted in feces (79%, 11% unchanged) and 14% is excreted in urine (1% unchanged).	**EMA:** CLcr 23-80 ml/min: no dose adjustment CLcr < 23 ml/min and HD: no data available **FDA:** CLcr 23-80 ml/min: no clinically significant effect on exposure of duvelisib	GFR 23-80 ml/min: no dose adjustment is needed GFR < 23 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child Pugh Class A, B and C: no dose adjustment	Hepatic impairment: no dose adjustment is needed	Copiktra label[1] SPC Copiktra[2]
73	**Elotuzumab**	Elotuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** Renal impairment/HD: no dose adjustment needed **Berdeja *et al.*** No statistically significant $AUC_{0\text{-}inf}$ differences between patients with CLcr ≥ 90 ml/min and patients with CLcr < 30 ml/min or ESRD with HD. Not dialysed	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA/FDA:** Mild: no dose adjustment is needed. Moderate and severe: not studied.	Mild: No dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Empliciti label[1] SPC Empliciti[2] Berdeja *et al.*[68]
74	**Enasidenib**	Enasidenib is metabolised in the liver. The metabolite AGI-16903 contributes to the clinical effect. Enasidenib is mainly excreted in feces (89%, 34% unchanged) and to a lesser extent in urine (11%, 0·4% unchanged).	**FDA:** CLcr ≥ 30 ml/min: no clinically meaningful effect on PK CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild (TB ≤ ULN & AST > ULN or TB 1-1·5x ULN & any AST): no clinically meaningful effect on PK Moderate and severe: not studied	Mild: No dose adjustment is needed Moderate: 50% of the original dose may be considered Severe: not recommended	Idhifa label[1]
75	**Encorafenib**	Encorafenib is metabolised in the liver. Encorafenib and its metabolites are excreted in feces (47%, 5% unchanged) and urine (47%, 2% unchanged).	**EMA/FDA:** CLcr 30-90 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min without hepatic impairment: no need for dose adjustment is expected HD without hepatic impairment: no need for dose adjustment is expected	**FDA:** Child-Pugh A: no dose adjustment Child-Pugh B and C: not studied **EMA:** Child-Pugh A: 67% of original dose (300 mg QD) Child-Pugh B/C: no dose recommendation	Child-Pugh A: 67% of original dose (300 mg QD) Child-Pugh B/C: not recommended	Braftovi label[1] SPC Braftovi[2]
76	**Enfortumab vedotin**	The monoclonal antibody portion is expected to undergo proteolysis by	**EMA:** CLcr ≥ 15 ml/min: no dose adjustment	GFR ≥ 15 ml/min: no dose adjustment is needed GFR < 15 ml/min: no need for	**EMA:** Mild: no dose adjustment Moderate and severe: no data	Mild: no dose adjustment is needed Child-Pugh B/C or	Padcev label[1] SPC Padcev[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		ubiquitous proteolytic enzymes to small peptides and individual amino acids. Only a small fraction of MMAE released from enfortumab is metabolised, mainly by CYP3A4. MMAE is excreted mainly in feces and to a lesser extent in urine.	CLcr < 15 ml/min and HD: no data available **FDA:** Renal impairment: no dose adjustment	dose adjustment is expected HD: no need for dose adjustment is expected	available **FDA:** Mild: no dose adjustment Child-Pugh B and C or moderate and severe: avoid use	moderate/severe: not recommended	
77	**Entrectinib**	Entrectinib is primarily metabolised by CYP3A4 (~76%) into the equipotent metabolite M5. Entrectinib and M5 are mainly excreted in feces (83%; 36% unchanged and 22% as M5), with minimal excretion in urine (3%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: not recommended	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: consider starting with a 50% lower dose and increase the dose if tolerated.	Rozlytrek label[1] SPC Rozlytrek[2]
78	**Enzalutamide**	Enzalutamide is metabolised in the liver. The N-desmethyl metabolite contributes to the clinical effect. Enzalutamide and its metabolites are mainly excreted in urine (71%) and to a lesser extent in feces (14%), mostly as inactive metabolites.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied, unlikely to be dialysable	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A, B and C: no dose adjustment **Krauwinkel *et al.*** Sum of active moieties: Child-Pugh A: $AUC_{0\text{-}inf}$ 113% (90% CI 89-143) Child-Pugh B: $AUC_{0\text{-}inf}$ 118% (90% CI 96-145) Child-Pugh C: $AUC_{0\text{-}inf}$ 104% (90% CI 86-124)	Hepatic impairment: no dose adjustment is needed	Xtandi label[1] SPC Xtandi[2] Krauwinkel *et al.* [69]
79	**Epirubicin**	Epirubicin is extensively and rapidly metabolised in the liver. Epirubicinol is the main active metabolite. Epirubicin and its metabolites are mainly excreted in feces (34%) and to a lesser extent in urine (27%).	**FDA/MHRA:** Serum creatinine < 5 mg/dL: no clinically relevant effect on PK, no dose adjustment Serum creatinine > 5 mg/dL: not studied, consider dose reduction HD: not studied (FDA) not dialysed (MHRA) **Gori *et al.*** HD: 30 mg/m^2 weekly was tolerated	GFR ≥ 10 ml/min: no dose adjustment is needed GFR < 10 ml/min: no need for dose adjustment is expected. HD: no need for dose adjustment is expected, consider weekly schedule	**FDA:** Bilirubin 1·2-3 mg/dL or AST 2-4 ULN: 50% of the original dose Bilirubin > 3 mg/dL or AST > 4x ULN: 25% of the original dose **MHRA:** Elevated bilirubin/AST: lower doses are recommended Severe: contraindicated **Twelves *et al.*** 25 mg/m^2 once weekly was tolerated in breast cancer patients with liver	Bilirubin 21-51 µmol/L or AST 2-4 x ULN: consider 50% of the original dose Bilirubin > 51 µmol/L or AST > 4x ULN: consider 25% of the original dose Bilirubin > 86 µmol/L or Child-Pugh C: not recommended	Ellence label[1] SPC Epirubicin[9] Gori *et al.*[70] Dobbs *et al.*[71] Twelves *et al.*[72]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					metastases and AST > 2 x ULN or bilirubin > ULN **Dobbs *et al.*** Proposed dosing scheme ranging from 20-90 mg/m^2 based on AST levels and target AUC.		
80	**Erdafitinib**	Erdafitinib is primarily metabolised by CYP2C9 and CYP3A4. Erdafitinib is mainly excreted in feces (69%, 19% unchanged) and 19% is excreted in urine (13% unchanged	**FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: no data available HD: no data available	eGFR ≥ 30 ml/min: no dose adjustment is needed eGFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: limited data available	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: not recommended	Balversa label[1]
81	**Eribulin**	Eribulin is minimally metabolised. Eribulin is predominantly excreted in feces (82%) and to a lesser extent in urine (9%), mostly unchanged.	**FDA:** CLcr 15- 49 ml/min: 1·1 mg/m^2 **EMA**: CLcr < 50 ml/min: dose reduction may be needed **Tan *et al.*** CLcr 15-29 ml/min and 30-50 ml/min: $AUC_{0\text{-}inf}$ 1·49 (90% CI 0·9-2·45) HD: not studied	GFR > 50 ml/min: no dose adjustment is needed GFR < 50 ml/min: 80% of the original dose HD: 80% of the original dose may be considered	**FDA:** Child-Pugh A: 1·1 mg/m2 Child-Pugh B: 0·7 mg/m2 Child-Pugh C: not studied **EMA:** Hepatic impairment due to liver metastases: Child-Pugh A: 0·97 mg/m2 Child-Pugh B: 0·62 mg/m2 Child-Pugh C: not studied **Devriese *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 1·75 (90% CI 1·15-2·66) Child-Pugh B: $AUC_{0\text{-}inf}$ 2·48 (90% CI 1·57-3·92)	Child-Pugh A: 80% of the original dose Child-Pugh B: 50% of the original dose Child-Pugh C: not recommended	Halaven Label[1] SPC Halaven[2] Tan *et al*.[73] Devriese *et al*.[74]
82	**Erlotinib**	Erlotinib is metabolised in the liver. Erlotinib and its metabolites are predominantly excreted as metabolites in feces (>90%) with minimal excretion in urine (9%).	**FDA:** Renal impairment: not studied **EMA:** CLcr ≥ 30 ml/min: not studied, no dose adjustment CLcr < 30 ml/min: not studied, not recommended **Miller *et al.*** Similar clearance in patients with renal impairment (1·6-5	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Increased frequency of monitoring is required in patients with bilirubin > 3 x ULN **EMA**: Severe: not recommended **O'Bryant *et al.*** Child-Pugh B: $AUC_{0\text{-}last}$ 92% (90%CI 69·1-123·2) **Miller *et al.***	Direct bilirubin > 17 µmol/L or AST ≥ 3x ULN: consider a starting dose of 50%, increase if tolerated	Tarceva label[1] Tarceva SPC[2] O'Bryant *et al.*[75] Togashi *et al*[76] Miller *et al*[77]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			mg/dl) and patients with normal renal function **Togashi *et al.*** HD: similar PK, not dialysed.		Reduced clearance in patients with hepatic impairment (AST≥ 3 x ULN and normal direct bilirubin or direct bilirubin 1·0-7·0 mg/dl with any AST). Recommended starting dose of 75mg QD (50% of the original dose).		
83	**Etoposide (intravenous)**	Etoposide is metabolised in the liver, among others to the active catechol metabolite. Etoposide and its metabolites are excreted in urine (56%, 45% unchanged) and in feces (44%).	**FDA/MHRA:** CLcr > 50 ml/min: no dose adjustment CLcr 15-50 ml/min: 75% of the original dose CLcr < 15 ml/min: not studied, consider further dose reduction HD: not dialysed (MHRA) **Watanabe *et al.*** Similar etoposide PK parameters in 5 patients on HD compared to controls. Etoposide has low dialysability, full dose was tolerated.	GFR > 50 ml/min: no dose adjustment is needed GFR 10-50 ml/min: 75% of the original dose, increase if tolerated HD: not dialysed, consider 75% of the original dose	**FDA:** Not reported. Total body clearance correlated with albumin concentration. **MHRA:** Total body clearance of etoposide is not reduced in adult patients with liver dysfunction **Stewart *et al.*** Patients with bilirubin ≥1mg/dL compared to patients with bilirubin <1mg/dl: similar total clearance, increased unbound fraction, decreased unbound clearance.	Bilirubin < 50 µmol/L and normal albumin and normal renal function: no need for dose adjustment is expected Bilirubin ≥ 50 µmol/L or decreased albumin levels: consider 50% of the dose, increase if tolerated	Etophos label[1] SPC Etophos[9] Stewart *et al*.[78] Watanabe *et al*.[44]
84	**Everolimus**	Everolimus is metabolised in the liver. Its metabolites are mainly excreted in feces (80%) and to a lesser extent in urine (5%).	**EMA/FDA:** Renal impairment: no dose adjustment HD: not studied **Thiery-Vuillemin *et al.*** HD: not dialysed	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA: (original dose 10 mg QD)** Child-Pugh A: 7·5 mg QD Child-Pugh B: 5 mg QD Child-Pugh C: 2·5 mg QD **Peveling-Oberhag *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 1·84 (90%CI: 1·36-2·50) Child-Pugh B: $AUC_{0\text{-}inf}$ 3·15 (90%CI: 2.36-4.21) Child-Pugh C: $AUC_{0\text{-}inf}$ 3·64 (90%CI: 2·64-5·00)	Child-Pugh A: 75% of the original dose Child-Pugh B: 50% of the original dose Child-Pugh C: 25% of the original dose	Afinitor label[1] SPC Afinitor[2] Thiery-Vuillemin *et al*.[79] Peveling-Oberhag *et al*.[80] Kovarik *et al*.[81]
85	**Exemestane**	Exemestane is extensively metabolised in the liver. Exemestane and its metabolites are excreted in urine (42%) and feces (42%), mostly as metabolites.	**FDA/MHRA:** Although renal impairment increases exposure to exemestane, no dose adjustment is necessary **Jannuzzo *et al.*** 	Renal impairment: due to large therapeutic index no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA/MHRA:** Child-Pugh A: not studied Child-Pugh B and C: although hepatic impairment increases exposure to exemestane, no dose adjustment is necessary	Hepatic impairment: Due to large therapeutic index no dose adjustment is needed	Aromasin label[1] SPC Aromasin[9] Januzzo *et al*.[82]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			CLcr ≤ 60 ml/min/1·73^2: 2 to 3-fold increase in $AUC_{0\text{-}inf}$ compared with CLcr > 60 ml/min/1·73m^2		**Jannuzzo *et al.*** Child-Pugh B and C: 2-3 fold increase in $AUC_{0\text{-}inf}$ compared with normal hepatic function		
86	**Fedratinib**	Fedratinib is predominantly metabolised by CYP3A4, in vitro. CYP2C19 and FMOs play a minor role in the metabolism. Fedratinib is mainly excreted in feces (77%, 23% unchanged) and to a lesser extent in urine (5%, 3% unchanged).	**EMA:** CLcr 30-59 ml/min: $AUC_{0\text{-}inf}$ 1·5-fold increase compared to subjects with normal renal function; no dose adjustment is needed CLcr 15-29 ml/min: $AUC_{0\text{-}inf}$ 1.9-fold increase compared to subjects with normal renal function; reduce dose to 200 mg **FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr 15-29 ml/min: reduce dose to 200 mg **Ogasawara *et al.*** Fedratinib C_{max} and $AUC_{0\text{-}inf}$ increased by approximately 1·5-fold in subjects with moderate renal impairment (CLcr 30 – 50 ml/min) and by nearly 1.9-fold in those with severe (15 – 29 ml/min) renal impairment compared with healthy subjects with normal renal function. Patients with severe renal impairment (CLcr 15 – 29 ml/min): reduce dose to 200 mg.	GFR ≥ 30 ml/min: no dose adjustment is needed GFR 15-30 ml/min and HD: 50% of the original dose	**EMA/FDA:** Child-Pugh A/B or mild and moderate: no dose adjustment Child-Pugh C and severe: use should be avoided	Child-Pugh A/B or mild/moderate: no dose adjustment is needed Child-Pugh C and severe: not recommended	Inrebic label[1] SPC Inrebic[2] Ogasawara *et al.*[83]
87	**Fludarabine**	Fludarabine is dephosporylated in plasma to the primary metabolite F-ara-A, which is converted intracellularly to its active metabolite. Fludarabine and its metabolites are mainly excreted in urine (40-60%).	**FDA:** CLcr ≥ 80 ml/min: no dose adjustment CLcr 50-79 ml/min: 20 mg/m^2 CLcr 30-49 ml/min: 15 mg/m^2 CLcr < 30 ml/min: do not administer HD: not studied	GFR > 70 ml/min: no dose adjustment is needed GFR 30-70 ml/min: 80% of the original dose GFR < 30 ml/min: not recommended HD: 80% of the original dose. Start dialysis 12h after administration.	**MHRA/FDA:** Not studied	Hepatic impairment: no need for dose adjustment is expected	Fludarabine phosphate Sandoz label[1] SPC Fludara[9] Lichtman *et al.*[84] Kielstein *et al.*[85]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			MHRA: CLcr 30-70 ml/min: reduce up to 50% of the original dose CLcr < 30 ml/min: contraindicated **Lichtman *et al.*** The following dose adjustments resulted in similar F-ara-A exposure (AUC0-24h) levels: CLcr > 70 ml/min/1·73m^2: 25 mg/m^2 CLcr 30-70 ml/min/1·73 m^2: 20 mg/m^2 CLcr < 30 ml/min/1·73m^2: 15 mg/m^2 **Kielstein *et al.*** HD: average dialysis clearance was 25% of clearance in patients with normal renal function (dialysis 12h after administration of 40mg/m^2).				
88	**Fluorouracil**	Fluorouracil (FU) is converted intracellularly mainly by DPD to inactive metabolites. A small part of FU is excreted unchanged in urine (15%). The remainder is metabolised in the liver. Metabolites are mainly excreted in urine.	**FDA:** No advice given **MHRA:** Renal impairment: dose should be reduced by 33-50%. **Fleming *et al.*** full dose (2600 mg/m^2) was tolerated in patients with creatinine 1·6-2·6 mg/dL. No correlation between creatinine level and 5-FU clearance. **Rengelshausen *et al.*** HD: not dialysed. PK of 5-FU comparable to patients with	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** No advice given **MHRA:** Hepatic impairment: dose should be reduced by 33-50%. **Fleming *et al.*** Full dose (2600 mg/m^2 over 24h) was tolerated in patients with bilirubin 1·5-5 mg/dL or > 5 mg/dL. No correlation between bilirubin level and 5-FU clearance.	Mild and moderate (without renal impairment): no need for dose adjustment is expected Severe: not recommended	Fluorouracil, injection USP[1] Fluorouracil 25 mg/ml injection Hospira Uk Ltd[9] Rengelshausen *et al*.[86] Fleming *et al*.[87]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			normal renal function. Higher levels of the potentially toxic metabolite fluoro-beta-alanine were observed.				
89	**Flutamide**	Flutamide is metabolised in the liver. The metabolite 2-hydroxyflutamide contributes to the clinical effect. Flutamide and its metabolites are excreted in urine (45%) and to a lesser extent in feces (2%).	**MHRA:** Renal impairment: not studied, use with caution HD: not studied **Anjum *et al.*** No difference in flutamide and hydroxyflutamide AUC between groups with varying degrees of renal function (range: HD/CLcr < 5ml/min – CLcr > 80 ml/min). HD: not dialysed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**MHRA:** Transaminase 2-3 x ULN: not recommended	Treatment in patients with hepatic impairment is not recommended due to liver toxicity	Flutamide 250 mg tablets[9] Anjum *et al*.[88]
90	**Fulvestrant**	Fulvestrant is metabolised in the liver. Fulvestrant and its metabolites are mainly excreted in feces (90%) with minimal renal excretion (<1%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment (EMA), no advice given (FDA) CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A: no dose adjustment Child-Pugh B: 250 mg Child-Pugh C: not studied **EMA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: not studied, contraindicated	Child-Pugh A: no dose adjustment Child-Pugh B: 50% of the original dose (250mg) Child-Pugh C: not recommended due to risk of hepatotoxicity	Faslodex label[1] SPC Faslodex[2]
91	**Futibatinib**	Futibatinib is extensively metabolised in the liver and is mainly excreted in feces (91%, negligible unchanged), and to a lesser extent in urine (9%, negligible unchanged).	**FDA:** CLcr ≥ 30 ml/min: no clinically meaningful differences in futibatinib PK CLcr 15-29 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no clinically meaningful differences in futibatinib PK Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: not recommended	Lytgobi label[1]
92	**Gefitinib**	Gefitinib is metabolised in the liver. Gefitinib and its metabolites are predominantly excreted in feces (86%) with minimal excretion in urine (< 4%).	**EMA/FDA:** CLcr > 20 ml/min: no clinically relevant effect on PK. No dose adjustment (EMA) **Shinagawa *et al*.** Not dialysed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Hepatic impairment due to liver metastases: PK not altered Child Pugh A, B or C due to cirrhosis: increased plasma exposure (40, 263 and 166% respectively).	Hepatic impairment due to metastasis and Child Pugh A: no dose adjustment is needed. Child-Pugh B and C: 50% of the original dose	Iressa label[1] SPC Iressa[2] Shinagawa *et al.*[89] Horak *et al.*[90]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					Horak *et al.* Child-Pugh A: $AUC_{0\text{-}inf}$: 1·40 Child-Pugh B: $AUC_{0\text{-}inf}$: 3·63 Child-Pugh C: $AUC_{0\text{-}inf}$: 2·66 Hepatic impairment due to liver metastases: no significant difference in PK parameters		
93	**Gemcitabine**	Gemcitabine is converted intracellularly to active metabolites. Gemcitabine is also metabolised by cytidine deaminase in the liver, kidney, blood and other tissues. Gemcitabine and its metabolites are predominantly excreted in urine (92-98%, 10% unchanged).	**MHRA/FDA:** Renal impairment: not studied. GFR 30-80 ml/min: no significant effect on PK (MHRA) **Venook *et al.*** No statistically significant difference in gemcitabine PK in patients with renal impairment, however tolerance might be decreased. **Kiani *et al.*** HD: no apparent gemcitabine PK differences in patient on HD receiving standard dose compared to reported data. Tenfold AUC increase of non-toxic metabolite 2',2'-difluorodeoxyuridine, which can be effectively dialysed. Start HD 6-12 h after administration.	GFR ≥ 30ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected. Start HD 6-12 h after administration.	**MHRA/FDA:** Not studied **Venook *et al.*** No statistically significant differences in gemcitabine PK in patients with TB ≤ 1·6mg/dL and AST ≤ 2xULN or bilirubin 1·6 - 7·0 mg/dl. However increased risk for hepatotoxicity in patients with elevated bilirubin. **Joerger *et al.*** Hepatic impairment (cohorts wild mild/moderate/severe) associated with lower clearance, not with DLT. **Teusink *et al.*** Retrospective safety data: full dose can be given safely in patients with severe hepatic impairment (TB ≥ 4·5 mg/dL)	TB < 27 µmol/L: no dose adjustment is needed TB ≥ 27 µmol/L: either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring	Gemzar label[1] SPC Gemzar[9] Venook *et al*[91] Kiani *et al*.[92] Joerger *et al*.[34] Teusink *et al*.[93]
94	**Gemtuzumab ozogamicin**	Gemtuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance. The metabolic pathway of gemtuzumab ozogamicin is anticipated to be the release of N-acetyl-gamma-calicheamicin dimethylhydrazide by hydrolytic cleavage, which is further metabolised via non-enzymatic reduction.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30ml/min: no need for dose adjustment is expected. HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: not studied **EMA:** Bilirubin ≤ 2 × ULN and AST/ ALT ≤ 2·5 × ULN: no dose adjustment Bilirubin > 2× ULN and AST/ ALT > 2·5 × ULN: postpone until recovery	Mild: no dose adjustment is needed Moderate/ severe: no need for dose adjustment is expected	Mylotarg label[1] SPC Mylotarg[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
95	**Gilteritinib**	Gilteritinib is primarily metabolised by CYP3A4. Gilteritinib is mainly excreted in feces (64·5%) and to a lesser extent in urine (16·4%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B or mild and moderate: no dose adjustment Child-Pugh C and severe: no data available	Child-Pugh A/B or mild/moderate: no dose adjustment is needed Child-Pugh C and severe: not recommended	Xospata label[1] SPC Xospata[2]
96	**Glasdegib**	Glasdegib is *in vitro* primarily metabolised by CYP3A4. CYP2C8 and UGT1A9 play a minor role in the metabolism of glasdegib. Glasdegib is mainly excreted in urine (48·9%, 17·2% unchanged) and in feces (41·7%, 19·5% unchanged).	**EMA/FDA:** Renal impairment: no dose adjustment is needed HD: no data available	GFR ≥ 60 ml/min: no dose adjustment is needed GFR < 60 ml/min: no dose adjustment is needed. HD: not recommended	**EMA/FDA:** Mild, moderate or severe: no dose adjustment	Hepatic impairment: no dose adjustment is needed	Daurismo label[1] SPC Daurismo[2]
97	**Hydroxycarbamide (Hydroxyurea)**	Hydroxycarbamide is for up to 60% metabolised in the liver. Hydroxycarbamide and its metabolites are excreted in urine (up to 80%).	**FDA:** CLcr < 60 ml/min: 50% of the original dose HD: 50% of the original dose following dialysis **EMA:** CLcr > 60 ml/min: no dose adjustment CLcr 30-60 ml/min: 50% of the original dose CLcr < 30 ml/min: not recommended **Yan *et al.*** CLcr ≥ 60 ml/min: $AUC_{0\text{-}inf}$ 188% CLcr 30-59 ml/min:$AUC_{0\text{-}inf}$ 170% CLcr 15-29 ml/min:$AUC_{0\text{-}inf}$ 162% CLcr < 15 ml/min: $AUC_{0\text{-}inf}$ 180% HD: $AUC_{0\text{-}inf}$ 152%	GFR ≥ 60 ml/min: no dose adjustment is needed GFR < 60 ml/min: 50% of the original dose HD: 50% of the original dose following HD	**FDA/ MHRA:** Not studied	No need for dose adjustment is expected Monitor for haematological toxicity	Siklos label[1] SPC Hydrea[2] Yan *et al*.[94]
98	**Ibrutinib**	Ibrutinib is metabolised in the liver. The metabolite PCI-45227 contributes to the clinical effect. Ibrutinib and its metabolites are predominantly excreted in feces (80%, 1% unchanged)	**FDA:** CLcr > 25 ml/min: no dose adjustment CLcr ≤ 25 ml/min: not studied HD: not studied	Renal impairment: no dose adjustment is needed. HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A: 280 mg (EMA) 140 mg (FDA) Child-Pugh B: 140 mg (EMA) 70 mg (FDA) Child-Pugh C: avoid	Child-Pugh A: 50% of the dose Child-Pugh B: 12·5% of the dose. Child-Pugh C: not recommended	Imbruvica label[1] SPC Imbruvica[2] Filanovsky *et al*.[95] de Jong *et al*.[96]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		and with minimally in urine (<10%).	**EMA:** CLcr > 30 ml/min: no dose adjustment CLcr ≤ 30 ml/min: administer only if benefits outweigh the risks; closely monitor patient **Filanovsky *et al.*** Full dose (560 mg) was tolerated in a patient with CLcr 13 ml/min.		**De Jong *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 265·20% (90% CI 138·34-508·41) Child-Pugh B: $AUC_{0\text{-}inf}$ 795·84%(90% CI 456·87-1386·31) Child-Pugh C: $AUC_{0\text{-}inf}$ 956·46%(90% CI 529·69-1691·15)		
99	**Idarubicin**	Idarubicin is extensively metabolised in the liver. Idarubicinol is the main active metabolite. Idarubicin and its metabolites are excreted in feces and urine, mostly as idarubicinol.	**FDA** Creatinin > ULN: consider dose reduction HD: not studied, unlikely to be dialysed **MHRA** Severe (creatinine > 2mg/dL): contraindicated **Tsuchiya *et al.*** HD: 67% of the original dose was tolerated and effective	GFR ≥ 30 ml /min: no need for dose adjustment is expected GFR < 30 ml/min: consider 67% of the original dose HD: consider 67% of the original dose	**FDA :** Bilirubin > ULN: consider dose reduction Bilirubin > 5 mg/dL: not recommended Patients with bilirubin 2·6-5 mg/dL received 50% of the original dose **MHRA:** Bilirubin ≥1·2-2 mg/dL: 50% of the original dose Severe (bilirubin > 2 mg/dL): contraindicated	Bilirubin 45 - 86 µmol/L: 50% of the original dose Bilirubin > 86 µmol/L: not recommended	Idamycin PSF label[1] SPC Zavedos[9] Tsuchiya *et al*.[97]
100	**Idelalisib**	Idelalisib is metabolised in the liver. Idelalisib and its metabolites are mainly excreted in feces (78%, 12% unchanged) and to a lesser extent in urine (15%, 23% unchanged).	**EMA/FDA:** CLcr ≥ 15 ml/min: no dose adjustment is needed HD: not studied **Jin *et al.*** CLcr 15-29 ml/min: $AUC_{0\text{-}inf}$ 127% (90% CI 92-176)	Renal impairment: No dose adjustment is needed HD: no need for dose adjustment is expected	**FDA** ALT or AST or bilirubin > ULN: no dose adjustment AST or ALT > 2·5 x ULN or bilirubin > 1·5 x ULN: limited information **EMA:** Child-Pugh A/B: no dose adjustment, intensified monitoring Child-Pugh C: limited information **Jin *et al.*** Child-Pugh B: $AUC_{0\text{-}inf}$ 158% (90% CI 125-199%) Child-Pugh C: $AUC_{0\text{-}inf}$ 159% (90%CI 121-208%)	Child-Pugh A or B: no dose adjustment is needed Child-Pugh C: start with 50% of the original dose (150 mg QD), increase if tolerated	Zydelig label[1] SPC Zydelig[2] Jin *et al*.[98] Jin *et al*.[99]
101	**Ifosfamide**	Ifosfamide (prodrug) is metabolised in the liver to its active metabolites, one of which is the cytotoxic and	**FDA:** Not studied, monitor for toxicity and consider dose reduction.	GFR ≥ 50 ml/min: no dose adjustment is needed GFR < 50 ml/min or HD: not recommended	**FDA:** Not studied, give cautiously **MHRA**	Mild and moderate: no need for dose adjustment is expected. *	Ifex label[1] SPC Ifosfamide injection 1 g[9] Carlson *et al*. [100]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		urotoxic acrolein.	HD: dialysed		Hepatic impairment: contraindicated	Severe: not recommended, due to risk of reduced efficacy* *due to limited information extrapolated from cyclophosphamide	
102	**Imatinib**	Imatinib is metabolised in the liver. The active metabolite CGP74588 contributes to the clinical effect. Imatinib and its metabolites are predominantly excreted in feces (68%, 20% unchanged) and to a lesser extent in urine (13%, 5% unchanged).	**FDA:** CLcr ≥ 60 ml/min: no dose adjustment CLcr 40-59 ml/min: no dose adjustment, max 600 mg CLcr 20-39 ml/min: 50% of the dose, max 400 mg CLcr < 20 ml/min: 100 mg **EMA:** Renal impairment or HD: minimum of 400 mg/day as starting dose **Gibbons *et al.*** CLcr 40-59 ml/min and CLcr 20-39 ml/min: significantly greater $AUC_{0\text{-}inf}$ compared to normal renal function, no increase in toxicity. No requirement for initial dose adjustment in these patients. **Pappas *et al.*** HD: no change in imatinib and CGP74588 PK compared to normal renal function.	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**FDA:** Mild and moderate: no dose adjustment Severe: 75% of the original dose **EMA:** Hepatic impairment: minimum of 400 mg/day as starting dose **Ramanathan *et al.*** Mild and moderate: no change in AUC severe: approximately a1·5 increase of AUC for imatinib and CGP74588,	Hepatic impairment: no dose adjustment is needed	Gleevec label[1] Glivec SPC[2] Gibbons *et al*.[101] Pappas *et al*.[102] Ramanathan *et al*.[103]
103	**Infigratinib**	Infigratinib is primarily metabolised by CYP3A4 (~94%). Infigratinib is mainly excreted in feces (77%, 3·4% unchanged) and to a lesser extent in urine (7·2%, 1·9% unchanged).	**FDA:** CLcr ≥ 30 ml/min: reduce dose to 100 mg QD for 21 days, followed by 7 days off therapy (28-day cycles) CLcr < 30 ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: 80% of the original dose (100 mg QD) for 21 days, followed by 7 days off therapy (28-day cycles) GFR < 30 ml/min: not recommended HD: not recommended	**FDA:** Mild: 100 mg QD for 21 days, followed by 7 days off therapy (28-day cycles) Moderate: 75 mg QD for 21 days, followed by 7 days off therapy (28-day cycles) Severe: no data available	Mild: 80% of the original dose (100 mg QD) for 21 days, followed by 7 days off therapy (28-day cycles) Moderate: 60% of the original dose (75 mg QD) for 21 days, followed by 7 days off therapy (28-day cycles) Severe: not recommended	Truseltiq label[1]
104	**Inotuzumab ozogamicin**	Inotuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr ≥ 15 ml/min: no change in clearance HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Hepatic impairment: no need for dose adjustment is expected	Besponsa label[1] SPC Besponsa[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		N-acetyl- gamma-calicheamicin dimethylhydrazide is metabolised via non-enzymatic reduction.		adjustment is expected	Serious ongoing hepatic liver disease (e.g. cirrhosis): contraindicated		
105	**Ipilimumab**	Ipilimumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no dose adjustment (FDA) not studied (EMA)	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Hepatic impairment: no need for dose adjustment is expected	Yervoy label[1] SPC Yervoy[2]
106	**Irinotecan**	Irinotecan (prodrug) is converted in the liver to its active metabolite SN-38. SN-38 is glucuronidated to the inactive glucuronide metabolite SN-38G. Irinotecan and its metabolites are excreted in urine (11-20% unchanged) and in feces.	**FDA:** Renal impairment: not studied, use with caution HD: not recommended **MHRA:** Not recommended in renal impairment. **Czock *et al*., Stemmler *et al*. (weekly)** HD: minimally dialysed, low clearance of SN-38. Dose escalation from 50 mg/m² to 80 mg/m² was tolerated. **Fujita *et al*. (weekly/2-weekly)** HD: SN-38 is partly dialysed (27-50% depending on the dialysis membrane). Elimination of SN-38 is significantly delayed in patients with renal failure. **Venook *et al*. (3-weekly)** No significant difference in irinotecan or its metabolites PK parameters for patients with CLcr 21-60 ml/min compared to patients with prior pelvic radiotherapy and	GFR ≥ 10 ml/min: no need for dose adjustment is expected GRF < 10 ml/min: start with 50-66% of the original dose, increase if tolerated HD: start with 50-66% of the original dose, increase if tolerated	**FDA:** Use with caution, not studied in patients with bilirubin > 2 mg/dl or transaminase > 3 x ULN (or transaminase > 5 x ULN in case of liver metastases). **MHRA (3-weekly):** Bilirubin < 1·5 x ULN: no dose adjustment Bilirubin 1·5 -3 x ULN: 200 mg/m². Bilirubin > 3 x ULN: contraindicated **Raymond *et al*. (3-weekly)** Reduced irinotecan clearance in hepatic impairment. Hyperbilirubinemia is associated with exponential decrease in clearance and increase in dose normalized AUC. Dose advice: bilirubin < 1·5 x ULN: 350 mg/m², bilirubin ≥ 1·5 to 3 x ULN: 200 mg/m². **Schaaf *et al*. (weekly)** Bilirubin 1·5-3·0 x ULN and ALT/AST ≤ 5·0 x ULN or bilirubin ≤ 1·5 x ULN and ALT/AST 5·1-20·0 x ULN: 60 mg/m². Bilirubin 3·1-5·0 x ULN and ALT/AST ≤ 5·0 x ULN 50	**3-weekly** Bilirubin ≥1·5 to 3 x ULN: 200 mg/m² Bilirubin > 3 x ULN: not recommended **Weekly** Bilirubin 1·5-3.0 x ULN and ALT/AST ≤5·0 x ULN or bilirubin ≤1·5 x ULN and ALT/AST 5·1-20·0 x ULN: 60 mg/m² Bilirubin 3·1-5·0 x ULN and ALT/AST ≤ 5·0 x ULN: 50 mg/m² Bilirubin 1·5-3·0 x ULN and ALT/AST 5·1-20·0 x ULN: 40mg/m²	Camptosar label[1] SPC Campto[9] Czock *et al*.[104] Stemmler *et al*.[105] Fujita *et al*.[106] Raymond *et al*.[107] Schaaf *et al*.[108] Venook *et al*.[109]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			creatinine < 1·5mg/dL.		mg/m^2; bilirubin 1·5-3·0 x ULN and ALT/AST 5·1-20·0 x ULN: 40 mg/m^2. Similar SN-38 exposure and observed toxicities with these dose reductions compared to patients with normal liver function (despite lower irinotecan $AUC_{0\text{-}24h}$).		
107	**Isatuximab**	Isatuximab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no dose adjustment	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied	Hepatic impairment: no dose adjustment is needed	Sarclisa label[1] SPC Sarclisa[2]
108	**Ivosidenib**	Only a limited part of ivosidenib is metabolised in the by CYP3A4. Ivosidenib is mainly excreted in feces (77%, 67% unchanged), and to a lesser extent in urine (17%, 10% unchanged).	**FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: no data available HD: no data available	eGFR ≥ 30 ml/min: no dose adjustment is needed eGFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: no data available **Fan *et al.*** Child-Pugh A/B: a single dose of 500 mg ivosidenib was well tolerated. No increased risk compared to matched participants with normal hepatic function.	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: not recommended	Tibsovo label[1] Fan *et al.*[110]
109	**Ixabepilone**	Ixabepilone is extensively metabolised in the liver. Ixabepilone and its metabolites are predominantly excreted in feces (65%) and to a lesser extent in urine (21%), mostly as inactive metabolites.	**FDA:** CLcr > 30 ml/min: no meaningful effect on PK CLcr ≤ 30 ml/min: not studied	GFR > 30 ml/min: no dose adjustment is needed GFR ≤ 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Monotherapy AST and ALT ≤ 2·5 x ULN and bilirubin ≤ ULN: 40 mg/m^2 AST and ALT ≤ 10 x ULN and bilirubin ≤ 1·5 x ULN: 32 mg/m^2 AST and ALT ≤10 x ULN and bilirubin > 1·5 x ULN - ≤ 3 x ULN: 20 mg/m^2, max 30 mg/m^2 AST or ALT > 10 x ULN or bilirubin > 3 x ULN: not recommended Combined with capecitabine AST or ALT ≤ 2·5 x ULN and bilirubin ≤ 1 x ULN: No dose adjustment is needed AST or ALT > 2·5 x ULN or bilirubin > 1 x ULN:	Hepatic impairment: Adjust the dose according to FDA recommendations	Ixempra label[1]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					contraindicated		
110	**Ixazomib**	Ixazomib is metabolised in the liver. Ixazomib and its metabolites are predominantly excreted in feces (62%) and to a lesser extent in urine (22%, <3·5% unchanged).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: 3 mg QD HD: 3 mg QD, not dialysed **Gupta *et al.*** CLcr < 30 ml/min or HD: $AUC_{0\text{-}last}$: 1·39 (90% 1·04-1·86), not dialysed.	GFR > 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 75% of the original dose HD: 75% of the original dose	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: 3 mg QD **Gupta *et al.*** Moderate (2·3 mg): dose-normalized $AUC_{0\text{-}last}$ 1·27 (90% CI 1.27-2.11) Severe (1·5 mg): dose-normalized $AUC_{0\text{-}last}$ 1.13 (90% CI 0.69-1.84)	Mild: no dose adjustment is needed Moderate and severe: 75% of the original dose	Ninlaro label[1] SPC Ninlaro[2] Gupta *et al.*[111] Gupta *et al.*[112]
111	**Lapatinib**	Lapatinib is metabolised in the liver. Lapatinib is predominantly excreted in feces (27% unchanged). Less than 2% is eliminated in urine.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: unlikely to be dialysed **Pai *et al.*:** Following a 250 mg QD dose in end-stage renal disease patients on maintenance HD, PK parameters were comparable with those in healthy subjects. Renal impairment and HD seemed not to affect lapatinib pharmacokinetics.	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A: not studied, no dose adjustment Child-Pugh B: 14% increase in AUC, no dose adjustment Child-Pugh C: 63% increase in AUC: 750 mg QD (HER2-positive metastatic breast cancer) or 1000 mg QD (hormone receptor and HER2-positive breast cancer) **EMA:** Child-Pugh A: not studied Child-Pugh B: 56% increase in AUC Child-Pugh C: 85% increase in AUC	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 750mg QD (HER2 positive metastatic breast cancer) or 1000 mg QD (hormone receptor and HER2-positive breast cancer)	Tykerb label[1] SPC Tyverb[2] Pai *et al.*[113]
112	**Larotrectinib**	Larotrectinib is predominantly metabolised by CYP3A4. Larotrectinib and its metabolites are mainly excreted in feces (58%, 5% unchanged) and urine (39%, 20% unchanged).	**EMA/FDA:** Renal impairment: no dose adjustment HD: 1·5-fold increase in $AUC_{0\text{-}inf}$; no dose adjustment recommended	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment is needed Moderate and severe: 50% dose reduction Child-Pugh A: 1·3-fold increase in $AUC_{0\text{-}inf}$ Child-Pugh B: 2-fold increase in $AUC_{0\text{-}inf}$ Child-Pugh-C: 3·2-fold increase in $AUC_{0\text{-}inf}$	Child-Pugh A: no dose adjustment is needed Child-Pugh B/C: 50% of original dose	Vitrakvi label[1] SPC Vitrakvi[2]
113	**Lenalidomide**	Lenalidomide is not metabolised by CYP enzymes in humans. Lenalidomide is mainly excreted in urine (90%, 82% unchanged) and	**EMA/FDA:** Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and	GFR ≥ 50 ml/min: no dose adjustment is needed GFR < 50 ml/min dose reductions per indication according to drug label	**EMA/FDA** Lenalidomide has not formally been studied in patients with hepatic impairment	Hepatic impairment: no need for dose adjustment is expected	Revlimid label[1] SPC Revlimid[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		minorly in feces (4%).	monitoring of renal function is advised in patients with renal impairment.	HD: dose reductions per indication according to the drug label			
114	**Lenvatinib**	Lenvatinib is metabolised in the liver. Lenvatinib and its metabolites are mainly excreted in feces (64%) and to a lesser extent in urine (24%), with approximately 2% as intactLenvatinib.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: Renal cell carcinoma (RCC): 10 mg QD; differentiated thyroid carcinoma (DTC): 14 mg QD; endometrial carcinoma (EC): 10 mg QD; hepatocellular carcinoma (HCC): not studied (EMA) HD: not studied (FDA), not recommended (EMA)	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 50 % of the original dose (RCC and EC 10 mg QD, DTC: 14 mg QD) HD: 50% of the original dose may be considered	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: RCC and EC 10 mg QD, DTC 14 mg QD, HCC not recommended (EMA) **Shumaker *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 1·2 (90% CI 0·8-1·8) Child-Pugh B: $AUC_{0\text{-}inf}$ 1·1 (90% CI 0·7-1·6) Child-Pugh C: $AUC_{0\text{-}inf}$ 1·8 (90% CI 1·2-2·7)	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 50% of the original dose (RCC and EC 10 mg QD, DTC 14 mg QD)	Lenvima label[1] SPC Lenvima[2] SPC Kisplyx[2] Shumaker *et al.*[114]
115	**Letrozole**	Letrozole is metabolised in the liver. Letrozole and its metabolites are mainly excreted in urine (90%, 6% unchanged).	**FDA/MHRA:** CLcr ≥ 10 ml/min: no dose adjustment HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C/cirrhosis: 50% (2·5 mg every other day) **MHRA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: 95% increase in AUC, administer with caution	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 50% of the original dose (2·5mg every other day)	Femara label[1] SPC Femara[9]
116	**Lomustine**	Lomustine is rapidly metabolised to its active metabolites. Its metabolites are mainly excreted in urine.	**FDA:** Renal impairment: not studied HD: not studied **MHRA:** CLcr < 30 ml/min: contraindicated **Kintzel *et al.*** CLcr 60 ml/min: 75% of the original dose CLcr 45 ml/min: 70% of the original dose CLcr 30 ml/min: not recommended	GFR > 50 ml/min: no dose adjustment is needed GFR 30-50 ml/min: 75% of the original dose GFR < 30 ml/min: not recommended HD: not recommended	**FDA/ MHRA:** Hepatic impairment: not studied	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	Gleostine label[1] SPC lomustine medac[9] Kintzel *et al.* [42]
117	**Loncastuximab tesirine**	The monoclonal antibody portion (loncastuximab) is	**FDA:** CLcr ≥ 30 ml/min: no clinically	GFR ≥ 30 ml/min: no dose adjustment is needed	**FDA:** Mild: no dose adjustment	Mild: no dose adjustment is needed	Zynlonta label[1]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		expected to undergo proteolytic degradation to smaller peptides. No renal or hepatic elimination. Tesirine (SG3199) is metabolised by CYP3A4/5. Tesirine is expected to be minimally renally excreted.	significant differences in PK CLcr 15-29 ml/min: not studied HD: not studied	GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	Moderate and severe: not studied	Moderate and severe: not recommended	
118	**Lorlatinib**	Lorlatinib is *in vitro* primarily metabolised by CYP3A4 and UGT1A4, with minor contribution of CYP2C8, CYP2C19, CYP3A5 and UGT1A3. The major metabolite is inactive. Unchanged lorlatinib was the major component in plasma (44%). 47·7% (<1% unchanged) was recovered in urine and 40·9% (9·1% unchanged) is recovered in feces.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min and HD: not studied and therefore not recommended	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no dose adjustment expected though monitor for toxicity due to potentially increased exposure HD: not recommended	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not studied and therefore not recommended	Mild: no dose adjustment is needed Moderate: no dose adjustment expected though monitor for toxicity due to potentially increased exposure Severe: not recommended	Lorviqua label[1] SPC Lorviqua[2]
119	**Lurbinectedin**	Lurbinectedin is metabolised by CYP3A4, *in vitro*. Lurbinectedin is mainly excreted in feces (89%, < 0·2 unchanged) and to a lesser extent in urine (6%, 1% unchanged).	**FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: not recommended	Zepzelca label[1]
120	**Margetuximab**	Margetuximab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Margenza label[1]
121	**Melphalan**	Melphalan is hydrolyzed in plasma to inactive metabolites. Approximately 10% is excreted in urine unchanged.	**FDA/MHRA** Oral: no dose advice given HD: not dialysed **FDA:** (IV) Consider 50% of the dose if Blood Urea Nitrogen ≥ 30mg/dL for palliative treatment	**Conditioning treatment** Renal impairment/HD: no need for dose adjustment is expected **Palliative treatment** GFR 30-50 ml/min: consider 50% of the dose GFR < 30 ml/min or HD: not recommended	**FDA/MHRA:** Hepatic impairment: not studied	Hepatic impairment: no need for dose adjustment is expected	Evomela/Alkeran label[1] SPC Alkeran/Melphlan hydrochloride [9] Kergueris *et al.*[115]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			MHRA: (IV) CLcr 30-50 ml/min: 50% of the original dose CLcr < 30 ml/min: high-dose melphalan contraindicated ***Kergueris et al.*** PK parameters correlated with creatinine clearance. Renal impairment did not result in a large decrease in CL compared to inter-individual variation in CL				
122	**Melphalan flufenamide**	Melphalan flufenamide is rapidly distributed to peripheral tissue with no late redistribution back to plasma. Melphalan flufenamide is metabolised in tissue to desethyl-melphalan flufenamide and melphalan. Renal and hepatic excretion of unchanged melphalan flufenamide is negligible	**EMA:** eGFR > 45 ml/min/1·73m^2: no dose adjustment eGFR 30-45 ml/min/1·73m^2: dose adjustment to 30 mg (75% of original dose) eGFR < 30 ml/min/1·73m^2: no data available **FDA** CLcr 45-89 ml/min: no dose adjustment CLcr 15-44 ml/min: no data available	eGFR > 45 ml/min 1·73m^2: no dose adjustment is needed eGFR 30-45 ml/min: 75% of the original dose eGFR < 30 ml/min: not recommended HD: not recommended	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Pepaxti label[1] SPC Pepaxti[2]
123	**Mercaptopurine**	Mercaptopurine (prodrug) is metabolised in the liver to form among others, active 6- thioguanine nucleotides. The main elimination route of 6- mercaptopurine is by metabolism. Xanthine oxidase converts 6-mercaptopurine into the inactive metabolite 6-thiouric acid, which is excreted in urine. About 46% of het dose is excreted in urine (approximately 7% unchanged)	**EMA/FDA:** Not studied, consider dose reduction, starting at the low end of dosing range, or increasing the dosing interval to 36-48 hours. HD: no clearance expected	GFR ≥ 30 ml/min: no need for dose adjustment is expected GFR < 30 ml/min: increase dosing interval to 48 hours HD: not recommended	**EMA/FDA**: Not studied, consider dose reduction, starting at the low end of dosing range.	Mild : no need for dose adjustment is expected Moderate: consider starting with a lower dose or increase dosing interval. Severe: not recommended	Purinethol/Purixan label[1] SPC Xaluprine[2]
124	**Methotrexate**	Methotrexate is partly metabolised in the liver. Methotrexate and its metabolites are mainly excreted in urine by	**FDA** Reduced clearance in renal impairment. No dose advice given.	GFR ≥ 50 ml/min: no dose adjustment is needed GFR 20-50 ml/min: 50% of the original dose GFR < 20 ml/min not	**FDA** No advice given **MHRA:** Bilirubin > 5 mg/dL:	Hepatic impairment: no need for dose adjustment is expected Bilirubin > 86	Methotrexate injection USP label[1] Methotrexate concentration for solution for infusion[9]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		glomerular filtration and active tubular secretion (80-90% unchanged). Excretion in feces is minimal (10% or less).	**MHRA:** CLcr > 50 ml/min: no dose adjustment CLcr 20-50 ml/min: 50% of the dose CLcr < 20 ml/min: not recommended Conventional HD and peritoneal dialysis: not dialysed **Wall *et al.*** HD: approximately 63% of infused methotrexate removed by 6 hours of high-flux dialysis initiated 1 hour after administration	recommended. If unavoidable consider HD HD: not recommended, if unavoidable 50% of the original dose, can be dialysed with daily high flux dialysis.	contraindicated	µmol/L: avoid use	Wall *et al.* [116]
125	**Midostaurin**	Midostaurin is metabolised in the liver. The metabolites CGP62221 and CGP52421 contribute to the clinical effect. Midostaurin and its metabolites are predominantly excreted in feces (78-95%, mostly as metabolites) and to a minimal extent in urine (5%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no clinically meaningful effect on PK, no dose adjustment CLcr < 30 ml/min: not studied **Tollkuci *et al.*** HD: full dose was tolerated and effective	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: no clinically meaningful effect on PK Severe: not studied **EMA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: not studied	Mild and moderate: no dose adjustment is needed Severe: not recommended	Rydapt Label[1] SPC Rydapt[2] Tollkuci *et al.*[117]
126	**Mirvetuximab soravtansine-gynx**	The monoclonal antibody portion of mirvetuximab soravtansine-gynx is expected to be metabolised into small peptides by catabolic pathways. Unconjugated DM4 (the small molecule) and S-methyl-DM4 undergo metabolism by CYP3A4. S-methyl DM4 and DM4-sulfo-SPDB-lysine were detected in urine within 24 hours of infusion as the main metabolites.	**FDA:** CLcr ≥ 30 ml/min: no dose adjustment is recommended CLcr < 30 ml/min: not studied.	GFR ≥ 30 ml/min: no dose adjustment is needed. GFR < 30 ml/min: not recommended.	**FDA**: Mild (TB ≤ULN and AST > ULN or TB > 1 to 1·5 times ULN and any AST): no dose adjustment needed. Moderate or severe (TB > 1·5 ULN): avoid use.	Mild: no need for dose adjustment. Moderate and severe: not recommended.	Mirvetuximab soravtansine-gynx label[1]
127	**Mitomycin**	Mitomcyin is metabolised and inactivated in the liver but also in other tissues. Excretion is mainly in feces	**MHRA:** Renal impairment: not studied	GFR ≥ 30 ml/min: no need for dose adjustment is expected GFR < 30 ml/min: not	**MHRA:** Hepatic impairment: not studied	Mild and moderate: no need for dose adjustment is expected Severe: consider 50% of	Jelcyto label[1] Mitomycin-C Kyowa SPC[9]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		and to a lesser extent in urine (approximately 10% unchanged)	**FDA:** GFR < 30 ml/min: no data available, avoid use	recommended HD: not recommended due to nephrotoxicity		the original dose	
128	**Mitotane**	Mitotane is metabolised in the liver to a water soluble metabolite. Its metabolites are slowly excreted in urine (10%) and a variable amount (1-17%) in feces.	**FDA:** Renal impairment: no advice given **EMA:** CLcr ≥ 30 ml/min: exercise caution, monitor mitotane plasma levels CLcr < 30 ml/min: not recommended	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Hepatic impairment: not studied, use with caution Monitor mitotane plasma levels (EMA) Severe: not recommended (EMA)	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended	Lysodren label[1] SPC Lysodren[2]
129	**Mitoxantrone**	Mitoxantrone is metabolised in the liver. Mitoxantrone and its metabolites are slowly excreted in feces (18%) and urine (10%, of which 65% unchanged).	**MHRA:** Renal impairment: not studied, use with caution HD: not studied **Boros *et al.*** HD: not dialysed	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**MHRA:** Hepatic impairment: not studied, use with caution **Savaraj *et al.*** Total clearance in patients with liver dysfunction or ascites was less than 50% of that observed in patients without liver dysfunction or ascites.	Mild and moderate: no need for dose adjustment is expected Severe: consider 50% of the original dose	SPC Mitoxantrone 2 mg/ml concentrate for solution for infusion (Accord Healthcare Limited)[9] Boros *et al.*[118] Savaraj *et al.*[119]
130	**Mobocertinib**	Mobocertinib is metabolised in the liver by CYP3A to equipotent metabolites. Mobocertinib is mainly excreted in feces (76%, 6% unchanged), and to a lesser extent in urine (4%, 1% unchanged)	**FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: not studied	eGFR ≥ 30 ml/min: no dose adjustment is needed eGFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: no dose adjustment Severe: not studied	Mild and moderate: no dose adjustment is needed Severe: not recommended	Exkivity label[1]
131	**Mogamulizumab**	Mogamulizumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** Renal impairment: no clinically significant PK changes **Yoshihara *et al.*** HD: not dialysed, no dose adjustment is needed	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA/FDA:** Mild and moderate: no clinically significant changes in PK Severe: not studied	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Potelegeo label[1] SPC Poteligeo[2] Yoshihara *et al*.[120]
132	**Mosunetuzumab**	Mosenutuzumab is expected to be catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/ FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected	**EMA/ FDA:** Mild: no dose adjustment Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Lunsumio label[1] SPC Lunsumio[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
				HD: no need for dose adjustment is expected			
133	**Necitumumab**	Necitumumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**FDA:** CLcr: ≥ 11 ml/min: No influence on exposure	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: no influence on exposure Severe: not studied	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Label Portrazza[1]
134	**Nelarabine**	Nelarabine (prodrug) is metabolised by adenosine deanimase to its metabolite (ara-G), which is intracellularly phosphorylated to the active metabolite (ara-GTP) Nelarabine (5-10%) and ara-G (20-30%) are partially eliminated in urine.	**EMA/FDA:** CLcr ≥ 50 ml/min: no dose adjustment CLcr < 50 ml/min: not studied HD: not studied	Renal impairment: no need for dose adjustment is expected. HD: no need for dose adjustment is expected	**EMA/FDA:** Hepatic impairment: not studied	Hepatic impairment: no need for dose adjustment is expected	Arranon label[1] Atriance SPC[2]
135	**Neratinib**	Neratinib is metabolised in the liver. The metabolites M3, M6, M7 and M11 contribute to the clinical effect. Neratinib and its metabolites are predominantly excreted in feces (97·1%) with minimal excretion in urine (1·1%).	**FDA:** Renal impairment: no clinically significant effect on PK HD: not studied **EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min or HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: 2·8-fold increase of AUC 80 mg QD (33% of the original dose) (FDA), not recommended (EMA).	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 33% of the original dose	Nerlynx label[1] SPC Nerlynx[2]
136	**Nilotinib**	Nilotinib is metabolised in the liver. Nilotinib and its metabolites are predominantly excreted in feces (93-94%, 69% unchanged).	**EMA/FDA:** Renal impairment: not studied **Onaka *et al.*** HD: not dialysed, dose adjustment AUC similar to previously reported in patients with normal renal function	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA**: Newly diagnosed Ph+ Chronic Myelogenous Leukemia (CML) Child-Pugh A-C: start at 200 mg BID, max 300 mg BID Resistant or chronic phase Ph+ CML Child-Pugh A-B: start at 300 mg BID, max 400 mg BID Child-Pugh C: start at200 mg BID, max 400 mg BID **EMA:** No dose adjustment is needed	Hepatic impairment: no dose adjustment is needed	Tasigna label[1] Tasigna SPC[2] Onaka *et al.*[121] Yin *et al.*[122]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					Yin *et al.* Child-Pugh A: $AUC_{0\text{-}inf}$: 1·35 (90% CI 0·91-2·02) Child-Pugh B: $AUC_{0\text{-}inf}$: 1·35 (90% CI 0·89-2·07) Child-Pugh C: $AUC_{0\text{-}inf}$: 1·19 (90% CI 0·80-1·78)		
137	**Nilutamide**	Nilutamide is extensively metabolised in the liver, less than 2% is excreted unchanged. Two metabolites contribute to the clinical effect. The metabolites of nilutamide are slowly excreted in urine (62%) with minimal fecal elimination	**FDA:** Renal impairment: not studied HD: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Hepatic impairment: not studied Severe: contraindicated	Mild and moderate: no need for dose adjustment is expected Severe: not recommended due to risk of hepatotoxicity	Nilandron label[1]
138	**Nintedanib**	Nintedanib is metabolised in the liver, mainly to inactive metabolites. Nintedanib and its metabolites are predominantly excreted in feces/bile (93·4%) with minimal renal excretion (<1%).	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected.	**EMA:** Child-Pugh A: no dose adjustment Child-Pugh B and C: not recommended ***Marzin et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$: 215·4% (90% CI 121-384%) Child-Pugh B : $AUC_{0\text{-}inf}$: 867·1% (90% CI 573-1312%) ***Okusaka et al.*** Slightly higher exposure (37% increase) in patients with Child-Pugh score 7 compared to patients with score 5-6. MTD 200 mg BID for both groups.	Child-Pugh A: consider 50% of the original dose Child-Pugh B and C: not recommended	SPC Vargatef [2] Marzin *et al.*[123] Okusaka *et al.*[124]
139	**Niraparib**	Niraparib is metabolised via amide hydrolysis by carboxylesterases forming the inactive metabolite M1. Niraparib is eliminated by hepatobiliary (38·8%) and renal routes (47·5%). In urine niraparib was mainly recovered as metabolites, in the feces primarily as unchanged niraparib	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate: 200 mg QDSevere: not studied **EMA:** Mild: no dose adjustment Moderate: recommended starting dose 200 mg QD (33% dose reduction) Severe: no data available **Akce *et al.*** Moderate: $AUC_{0\text{-}inf}$: 1·5639 (90% CI 1·0618-2·3034)	Mild: no dose adjustment is needed Moderate and severe: 66% of the original dose	Zejula label[1] SPC Zejula[2] Akce *et al.*[125]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
140	**Nivolumab**	Nivolumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** GFR ≥ 30 ml/min: no dose adjustment GFR < 30 ml/min: no dose adjustment (FDA), not studied (EMA)	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate: no dose adjustment (FDA), not studied (EMA) Severe: not studied	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Opdivo label [1] SPC Opdivo[2]
141	**Nivolumab/ relatlimab**	Nivolumab and relatlimab are catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: limited data available **FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild and moderate: no dose adjustment Severe: limited data available	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Opdualag label[1] SPC Opdivo[2]
142	**Obinutuzumab**	Obinutuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**FDA:** No effect of baseline CLcr on PK. **EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30ml/min: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Not studied in patients with hepatic impairment	Hepatic impairment: no need for dose adjustment is expected	Label Gazyva[1] SPC Gazyvaro[2]
143	**Ofatumumab**	Ofatumumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Hepatic impairment: not studied	Hepatic impairment: no need for dose adjustment is expected	Label Arzerra[1] SPC Arzerra[2]
144	**Olaparib**	Olaparib is extensively metabolised in the liver. Olaparib and its metabolites are excreted both in urine (approximately 44%) and feces (approximately 42%), mostly as metabolites.	**EMA/FDA:** CLcr 51-80 ml/min: no dose adjustment CLcr 31-50 ml/min: 200 mg BID CLcr < 30 ml/min: not studied, not recommended (EMA) HD: not studied **Pilla Reddy *et al.*** CLcr < 30 ml/min: PBPK predicted AUC ratio 2·21 (90% CI 2·19–2·22) **Rolfo *et al.***	GFR > 50 ml/min: no dose adjustment GFR 30-50 ml/min: approximately 70 % of the original dose (200mg BID) GFR < 30 ml/min: consider 50% of the dose HD: consider 50% of the original dose	**EMA/FDA:** Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: not studied, not recommended (EMA) **Pilla Reddy *et al.*** Child-Pugh C: PBPK predicted AUC ratio between 1·06 (90% CI 1·03 - 1·08) and 3·88 (3·74 - 4·02) **Rolfo *et al.*** Based on a PK assessment, no safety signals were detected in patients with mild/moderate	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: consider 50% of the original dose	Lynparza label[1] SPC Lynparza[2] Pilla Reddy *et al.*[126] Baum *et al.*[127] Rolfo *et al.*[128] Rolfo *et al*.[129]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			CLcr 60-89 ml/min: AUC ratio 1·24 (90% CI 1·06-1·47) CLcr 30-59 ml/min: AUC ratio 1·44 (90% CI 1·10-1·89) **Baum *et al.*** A dose of 200 mg BID was well tolerated by one patient with HD.		hepatic impairment.		
145	**Olaratumab**	Olaratumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**FDA:** CLcr ≥ 30 ml/min: no clinically important effect on PK CLcr < 30 ml/min: not studied HD: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: no clinically important effect on PK Severe: not studied	Mild and moderate: no need for dose adjustment is expected Severe: no need for dose adjustment is expected	Label Lartruvo[1]
146	**Olutasidenib**	Olutasidenib is primarily (90%) metabolised by cytochrome P450(CYP)3A4, with minor contributions from CYP2C8, CYP2C9, CYP1A2, and CYP2C19. Approximately 75% of olutasidenib was recovered in feces (35% unchanged) and 17% in the urine (1% unchanged).	**FDA**: CLcr ≥ 30 ml/min: no dosage modification is recommended. CLcr < 30 ml/min or HD: not studied.	GFR ≥ 30 ml/min: no dose adjustment is needed. GFR <30 ml/min or HD: no need for dose adjustment is expected.	**FDA**: Mild and moderate: no dose modification is recommended. Severe: not studied.	Mild and moderate: no need for dose adjustment. Severe: not recommended.	Olutasidenib label[1]
147	**Omacetaxine mepesuccinate**	Omacetaxine mepesuccinate is primarily metabolised by plasma-esterases with little hepatic metabolism. Omacetaxine and its metabolites are excreted in feces (44%) and urine (37%).	**FDA:** Renal impairment: not studied HD: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Hepatic impairment: not studied	Hepatic impairment: no need for dose adjustment is expected	Synribo label[1]
148	**Osimertinib**	Osimertinib is metabolised in the liver. Two metabolites (AZ7550 and AZ5104) contribute to the pharmacological effect. Osimertinib is primarily excreted in feces (68%, 1·2% unchanged) and to a lesser extent in urine (14%, 0·8% unchanged), mostly as metabolites.	**EMA/FDA:** CLcr ≥ 15 ml/min: no dose adjustment CLcr < 15 ml/min: not studied HD: not studied **Tamura *et al.*** HD: not dialysed, full dose was tolerated. **Vishwanathan *et al.*** No dose adjustment is required for patients with	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild or moderate or Child-Pugh A/B: no dose adjustment Severe or Child-Pugh C: not studied	Mild and moderate or Child-Pugh A/B: no dose adjustment Severe or Child-Pugh C: 50% of the original dose may be considered	Tagrisso label[1] SPC Tagrisso[2] Tamura *et al.*[130] Vishwanathan *et al.*[131]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			CrCL < 30 ml/min				
149	**Oxaliplatin**	Oxaliplatin is not metabolised. It is highly protein bound (>90%). Oxaliplatin is mainly excreted in urine (54%) and minimally in feces (<3%).	**FDA/MHRA** CLcr 30-80 ml/min: no dose adjustment CLcr < 30 ml/min: 65 mg/m^2 (FDA), contraindicated (MHRA) **Gori *et al.*, Watayo *et al.*** HD: administration of 50% of the original dose with HD directly or 1·5 hours after administration resulted in AUC comparable to normal renal function. **Takimoto *et al.*** Decreased CLcr correlated strongly with decrease in clearance of plasma ultrafiltrable platinum (r^2 = 0·765), no corresponding increase in toxicity was observed in patients with normal, mild (CLcr 40-59 ml/min) and moderate (CLcr 20-39 ml/min) renal function.	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: consider 50% of the original dose HD: consider 50% of the original dose, HD within 1·5 hour after administration.	**FDA/MHRA:** Hepatic impairment: not studied **Synold *et al.*** Mild, moderate, severe and liver transplantation: full dose (130 mg/m^2) was tolerated, platinum clearance was not correlated with any liver function variable (bilirubin, AST or AP).	Hepatic impairment: No dose adjustment is needed	Eloxatin label[1] SPC Eloxatin[9] Gori *et al*.[132] Watayo *et al*.[133] Takimoto *et al.*[134] Synold *et al*.[135]
150	**Nab-paclitaxel**	Nab-paclitaxel is a nanoparticle albumin-bound form of paclitaxel. Paclitaxel is metabolised in the liver. Paclitaxel and its metabolites are mainly excreted in feces (approximately 20%) and minimally in urine (4%, < 1% unchanged).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment required CLcr < 30 ml/min: insufficient data, no advise given	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected.	**FDA:** Mild: no dose adjustment required Moderate and severe: metastatic breast carcinoma (MBC) 77% of original dose (200mg/m^2), non-small cell lung cancer (NSCLC) 80% of original dose (80mg/m^2), pancreatic adenocarcinoma not recommended Bilirubin > 5 x ULN or AST > 10 x ULN: not recommended **EMA:** Mild: No dose adjustment required Moderate and severe: 80% of original	Mild: no dose adjustment is needed Moderate and severe: MBC or NSCLC: approximately 80% of original dose, pancreatic adenocarcinoma: contraindicated Bilirubin > 5 x ULN or AST > 10 x ULN: contraindicated	Abraxane label [1] SPC Abraxane[2] Biakhov *et al*.[136]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					dose (MBC 200mg/m^2, NSCLC 80 mg/m^2), pancreatic adenocarcinoma insufficient data, not recommended Bilirubin > 5 x ULN or AST > 10 x ULN: insufficient data, not recommended **Biakhov *et al.*** The recommended modification schema of solvent-based paclitaxel was tested for nab-paclitaxel and resulted in an acceptable safety and pharmacokinetic profile (bilirubin ≤ 1·25 x ULN: 100%of the dose; bilirubin 1·26-2 x ULN: 80% of the dose; bilirubin 2·01-5 x ULN: 50% of the dose).		
151	**Paclitaxel**	Paclitaxel is metabolised in the liver by CYP2C8 and CYP3A4. Paclitaxel and its metabolites are predominantly excreted in feces (71%) and to a lesser extent in urine (14%).	**FDA:** No advise given **MHRA:** Renal impairment: not studied, no dose advise given HD: pharmacokinetic properties in one patient undergoing HD in range with non-dialysis patients **Tomita *et al*.** Paclitaxel is not dialysed. AUC and C_{max} were comparable to values reported in patients with normal renal function. **Gelderblom *et al*.** 1·5-2-fold higher paclitaxel AUC value in a patient with CLcr 20 ml/min compared to values reported in patients with normal renal function. However, no major hematological toxicity was observed.	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** **24-hour infusion:** Transaminase < 2 x ULN and bilirubin ≤ 1·5 mg/dL: no dose reduction (135 mg/m^2) Transaminase 2-<10 x ULN and bilirubin ≤ 1·5 mg/dL: 74% of original dose (100mg/m^2) Transaminase < 10 x ULN and bilirubin 1·6-7·5 mg/dL: 37% of original dose (50 mg/m^2) Transaminase ≥ 10 x ULN or bilirubin > 7·5 mg/dL: not recommended **3-hour infusion:** Transaminase < 10 x ULN and bilirubin ≤ 1·25 x ULN: no dose reduction (175 mg/m^2) Transaminase < 10 x ULN and bilirubin 1·26-2 x ULN: 77% of original dose (135mg/m^2) Transaminase < 10 x ULN and bilirubin 2·01-5xULN: 51% of orginal dose (90mg/m^2) Transaminase ≥	**24-hour infusion:** Transaminases < 2 x ULN and bilirubin ≤ 26 µmol/l: no dose adjustment is needed (135mg/m^2) Transaminases 2-10 x ULN and bilirubin ≤ 26 µmol/l: 74% of original dose (100mg/m^2) Transaminases < 10 x ULN and bilirubin 27-128 µmol/l: 37% of orginal dose (50mg/m^2) Transaminases ≥ 10 x ULN or bilirubin > 128 µmol/l: contraindicated **1 to 3-hour infusion (regardless of interval)**: Transaminases < 10xULN and bilirubin ≤ 1.25xULN: no dose reduction.	Taxol label[1] Paclitaxel SPC[9] Briasoulis *et al.*[137] Tomita *et al.*[138] Gelderblom *et al.* [139] Joerger *et al.*[140]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					10 x ULN or bilirubin > 5 x ULN: not recommended **MHRA:** Mild and moderate: not studied, no dose advise given Severe: contraindicated **Briasoulis *et al.*** 70mg/m^2 as 1 hour infusion every 2 weeks safe in 9 patients with severe hepatic dysfunction (transaminase > 10xULN or bilirubin > 5xULN), despite altered pharmacokinetics. **Joerger *et al.*** TB concentrations were a significant predictor of paclitaxel elimination capacity (P=0·002). Patients with ALT/AST < 10 x ULN and bilirubin 2·1-3·5 x ULN initially treated with 135mg/m^2 or ALT/AST < 10 x ULN and bilirubin 3·6-10 x ULN initially treated with 110mg/m^2 (3-hour infusions) had significantly lower AUC and higher incidence of hematological toxicity compared to patient with bilirubin < 2 x ULN initially treated with 175 mg/m^2.	Transaminases < 10xULN and bilirubin 1·26-2xULN: 75% of original dose. Transaminases < 10 x ULN and bilirubin 2·01-5 x ULN: 50% of original dose. Transaminases ≥ 10 x ULN or bilirubin > 5 x ULN: contraindicated.	
152	**Palbociclib**	Palbociclib is metabolised in the liver. Palbociclib and its metabolites are mainly excreted in feces (74·1%) and to a lesser extent in urine (17·5%), mostly as metabolites.	**EMA/FDA:** CLcr ≥ 15 ml/min: no dose adjustment HD: not studied **Yu *et al.*** No dose adjustment is required in patients with a CLcr > 30 ml/min	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: 75 mg QD for 21 days	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 60% of the original dose	Ibrance label[1] SPC Ibrance[2] Yu *et al.*[141]
153	**Panitumumab**	Panitumumab is catabolised by proteolytic	**EMA/FDA:** CLcr: ≥ 30 ml/min: no	Renal impairment: no need for dose adjustment is	**EMA/FDA:** Mild and moderate: no	Mild and moderate: no dose adjustment is	Vectibix label[1] SPC Vectibix[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		degradation to smaller peptides. No renal or hepatic clearance.	clinically important effect on PK CLcr < 30 ml/min: not studied	expected HD: no need for dose adjustment is expected	clinically important effect on PK Severe: not studied **Krens *et al.*** Child-Pugh B: no clinically significant deviations in AUC and CL.	needed Severe: no need for dose adjustment is expected	Krens *et al.* [142]
154	**Panobinostat**	Panobinostat is extensively metabolised in the liver. Panobinostat and its metabolites are excreted in both feces (44- 77%) and urine (29-51%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment is needed CLcr < 30 ml/min or HD: not studied **Sharma *et al*.** Panobinostat $AUC_{0\text{-}inf}$ geometric mean ratios compared to CLcr> 80ml/min: CLcr 50-79 ml/min: 0·67 (90% CI 0·39-1·17) CLcr 30-49 ml/min: 1·05 (90% CI 0·58-1·91) CLcr < 30 ml/min: 0·63 (0·33-1·20) **Sekiguchi *et al.*** HD: dialysable. Elimination of panobinostat by HD 14·1-36·3%.	Renal impairment: no need for dose adjustment is expected. HD: no need for dose adjustment is expected.	**EMA/FDA:** Mild: 75% of original dose (15mg) Moderate: 50% of original dose (10mg) Severe: avoid use **Slingerland *et al.*** Panobinostat exposure ($AUC_{0\text{-}inf}$) increased by 43% in patients with mild hepatic impairment and by 105% in moderate hepatic impairment	Mild: 75% of original dose Moderate: 50% of original dose Severe: not recommended	Farydak label[1] SPC Farydak[2] Sharma *et al.*[143] Slingerland *et al.*[144] Sekiguchi *et al.*[145]
155	**Pazopanib**	Pazopanib is metabolised in the liver. Pazopanib and its metabolites are predominantly excreted in feces. Renal elimination is less than 4%.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied, unlikely to be dialysed	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate: 25% of the dose (200 mg QD) as MTD Severe: not recommended ***Shibata et al.*** Mild: (MTD 800 mg QD): $AUC_{0\text{-}24h}$ 87% Moderate (MTD 200 mg QD): $AUC_{0\text{-}24h}$ 29% Severe (MTD 200 mg QD): $AUC_{0\text{-}24h}$ 15%	Mild: no dose adjustment is needed Moderate: select alternative therapy if possible. If not possible start with 25% of the original dose, titrate up to a C_{trough} > 20 mg/L Severe: not recommended	Votrient label[1] SPC Votrient[2] Shibata *et al.* [146]
156	**Pegaspargase**	Pegylated L-asparaginase is degraded by proteolytic degradation. No renal or hepatic clearance.	**FDA:** No advise given **EMA:**	Renal impairment: no dose adjustment is needed HD: no need for dose	**FDA:** No advise given **EMA:**	Hepatic impairment: no dose adjustment is needed	Oncaspar label[1] SPC Oncaspar[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			Renal impairment: no dose adjustment is needed	adjustment is expected	No dose adjustment is needed		
157	**Pembrolizumab**	Pembrolizumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** eGFR: ≥ 15 ml/min/1·73m^2: no clinically important effect on clearance HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no clinically important effect on clearance (FDA), no dose adjustment (EMA) Moderate and severe: not studied	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Keytruda label[1] SPC Keytruda[2]
158	**Pemetrexed**	Pemetrexed undergoes intracellular polyglutamation and is primarily excreted unchanged in urine (70-90%). Hepatic metabolism is minimal.	**EMA/FDA:** CLcr ≥ 45 ml/min: no dose adjustment CLcr < 45 ml/min: no dose recommendations (FDA), not recommended (EMA) **Hill *et al.*** CLcr 30-45 ml/min: 80% of dose was tolerated without grade ≥3 hematological toxicity **Mita *et al.*** Increased drug exposures in patients with renal impairment, GFR ≥ 40 ml/min: no dose adjustment needed **Brandes *et al.*** HD: not dialysed **De Rouw *et al.*** Pemetrexed clearance was increased 30-fold (from 1.00 L/h to 3.01 L/h) during high-flux HD **Boosman *et al.*** eGFR < 45 ml/min: 51·0-92·6% probability of severe neutropenia under standard dose of 500 mg/m^2 eGFR 20 ml/min: at a dose of 20mg a 13-fold lower AUC was observed in these patients compared to patients with a renal function of 90 ml/min.	CLcr ≥ 45 ml/min: no dose adjustment is needed. CLcr < 45 ml/min and HD: not recommended	**EMA/FDA:** Not studied in patients with hepatic impairment	Mild and moderate: no need for dose adjustment is expected Severe: not recommended, based on the risk of pemetrexed induced liver dysfunction	Alimta label [1] SPC Alimta[2] Mita *et al.*[147] Brandes *et al.*[148] Hill *et al.*[149] Boosman *et al.*[150] De Rouw et al.[151]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
159	**Pemigatinib**	Pemigatinib is in vitro mainly metabolised by CYP3A4. The major drug-related moiety in plasma is unchanged pemigatinib. Pemigatinib is mainly excreted in feces (82·4%, 1·4% unchanged), and to a lesser extent in urine (12·6%, 1·0% unchanged).	**EMA:** GFR ≥ 30 ml/min: no dose adjustment GFR < 30 ml/min: reduce dose of patients on 13·5 mg QD to 9 mg QD; reduce dose of patients on 9 mg QD to 4·5 mg QD HD: no dose adjustment **FDA:** GFR ≥ 30 ml/min: no dose adjustment GFR < 30 ml/min: no data available HD: no data available **Ji *et al.*** Severe: clinically significant increase in AUC (59%) compared with healthy subjects ESRD on HD: AUC not significantly different from healthy subjects	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: reduce dose from 13·5 mg QD to 9 mg QD and from 9 mg QD to 4·5 mg QD HD: no dose adjustment is needed	**EMA:** Child-Pugh A/B or mild and moderate: no dose adjustment Child-Pugh C or severe: reduce dose of patients on 13·5 mg QD to 9 mg QD; reduce dose of patients on 9 mg QD to 4.5 mg QD **FDA:** Hepatic impairment: no dose adjustment **Ji *et al.*** Mild and moderate: no dose adjustment Severe: clinically significant increase in AUC (74%) compared with healthy subjects, indicating a need for dose reduction. Pemigatinib was well tolerated as a single 9 mg dose in patients with severe hepatic impairment.	Child-Pugh A/B or mild/moderate: no dose adjustment is needed Child-Pugh C or severe: reduce dose from 13.5 mg QD to 9 mg QD and from 9 mg QD to 4.5 mg QD	Pemazyre label[1] SPC Pemazyre[2] Ji *et al.*[152]
160	**Pentostatin**	Only a small amount of pentostatin is metabolised. Pentostatin is predominantly excreted unchanged in urine (90%).	**MHRA:** Ambiguous advice: CLcr < 60 ml/min: contraindicated. However a study with 13 renally impaired patients suggest the following dose adjustments: CLcr 40-59 ml/min: 75% of original dose (3 mg/m^2) CLcr 35-39 ml/min: 50% of original dose (2 mg/m^2) **Lathia *et al.*** Pentostatin $AUC_{0\text{-}inf}$ was comparable when treated with 4 mg/m^2 in patients with CLcr > 60 ml/min, 3 mg/m^2 in patients with CLcr 41-60 ml/min and 2 mg/m^2 in one patient with CLcr 35- 40	GFR 40-59 ml/min: 75% of original dose GFR 35-39 ml/min: 50% of original dose GFR < 35 ml/min: not recommended HD: not recommended. If unavoidable consider 50% of the original dose, start HD 1-2 h after administration	**MHRA:** Limited experience, treat with caution	Hepatic impairment: No need for dose adjustments is expected	SPC Nipent[9] Lathia *et al.*[153]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			mg/m^2.				
161	**Pertuzumab**	Pertuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr ≥ 30 ml/min: No dose adjustment is needed CLcr < 30 ml/min: not studied	Renal impairment: no dose adjustment is needed HD: no need of dose adjustment is expected	**EMA/FDA:** Not studied in patients with hepatic impairment	Hepatic impairment: no need of dose adjustment is expected	Perjeta label[1] SPC Perjeta[2]
162	**Pexidartinib**	Pexidartinib is primarily metabolised by CYP3A4 and UGT1A4 to inactive metabolites. Pexidartinib is mainly excreted in feces (65%, 44% unchanged) and to a lesser extent in urine (27%, not unchanged).	**FDA:** CLcr ≥ 15 ml/min: increased exposure by 30%, adjust dose to 200 mg in the morning and 400 mg in the evening	GFR ≤ 90 ml/min: 75% of original dose (200 mg orally in the morning, 400 mg orally in the evening) HD: not recommended	**FDA:** Mild: no dose adjustment Moderate: 50% of the original dose Severe: no data available	Mild: no dose adjustment is needed Moderate: 50% of the original dose Severe: not recommended	Turalio label[1]
163	**Pixantrone**	Only a small amount of pixantrone is metabolised. Pixantrone is mainly excreted unchanged in bile with minimal excretion in urine (<10%).	**EMA:** Use with caution in patients with renal impairment	Renal impairment or HD: no need for dose adjustment is expected	**EMA:** Mild and moderate: use with caution Severe: not recommended	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	SPC Pixuvri[2]
164	**Polatuzumab vedotin**	Polatuzumab vedotin is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. MMAE is a substrate for CYP3A4. MMAE is mainly excreted in feces and minorly in urine.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not recommended	Mild: no dose adjustment is needed Moderate and severe: not recommended	Polivy label[1] SPC Polivy[2]
165	**Ponatinib**	Ponatinib is metabolised in the liver. Ponatinib and its metabolites are predominantly excreted in feces (87%) and to a minimal extent in urine (5%).	**FDA:** Renal impairment: not studied **EMA:** CLcr ≥ 50 ml/min: no dose adjustment needed CLcr < 50 ml/min/ESRD: caution is recommended	GFR ≥ 50 ml/min: no dose adjustment is needed GFR <50 ml/min or HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A/B/C: 67% of original dose (30mg QD) **EMA:** No dose reduction needed for hepatic impairment **Narasimhan *et al.*** No major differences in ponatinib exposure were observed for Child-Pugh A ($AUC_{0\text{-}inf}$ 122·8%) Child-Pugh B ($AUC_{0\text{-}inf}$ 90·6%) or Child- Pugh	Child-Pugh A to C: No need for dose adjustment is expected	FDA label Iclusig[1] SPC Iclusig[2] Narasimhan *et al.*[154]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					C ($AUC_{0\text{-}inf}$ 79·4%) respectively.		
166	**Pomalidomide**	Pomalidomide is metabolised by hydrolysis or hydroxylation with subsequent glucuronidation. Hydroxylation is predominantly via CYP1A2 and CYP3A4. Pomalidomide is mainly excreted in urine (73%, 2% unchanged) and to a lesser extent in feces (15%, 8% unchanged).	**EMA:** Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed. Take dose following haemodialysis **FDA:** CLcr ≥ 30 ml/min: no dose adjustment is needed CLcr < 30 ml/min: reduce dose to 3 mg (25% dose reduction) HD: reduce dose to 3mg (25% dose reduction). Take dose following haemodialysis	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 75% of the original dose HD: 75% of the original dose. Take dose following haemodialysis	**EMA:** Child-Pugh A to C: no starting dose adjustment is needed. Monitor closely for adverse events, dose reduction should be used as needed **FDA:** Child-Pugh A/B: reduce dose to 3 mg (25% dose reduction) Child-Pugh C: reduce dose to 2 mg (50% dose reduction) **Li *et al.*** GMR (%) of pomalidomide AUC was 151·2% (mild), 157·5% (moderate) and 171·5% (severe) vs. healthy subjects. Mild and moderate: reduce dose to 3 mg (25% dose reduction) Severe: reduce dose to 2 mg (50% dose reduction)	Child-Pugh A/B: 75% of the original dose Child-Pugh C: 50% of the original dose	Pomalyst label[1] SPC Imnovid[2] Li *et al.*[155]
167	**Pralatrexate**	Pralatrexate is minimally metabolised. Pralatrexate is mainly excreted unchanged in urine (39%) and to a lesser extent in feces (34%: unchanged and metabolites). On average, 10% of a total dose is exhaled.	**FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose reduction needed eGFR 15-29 ml/min/1·73m^2: 50% of the original dose (15 mg/m^2) eGFR < 15 ml/min/1·73m^2 or HD: (relatively) contraindicated **Kelly *et al.*** Comparable $AUC_{0\text{-}inf}$ between cohorts with eGFR ≥ 90 ml/min, eGFR 60-89 ml/min, eGFR 30-59 ml/min treated with 30 mg/m^2 and a cohort with eGFR 15-29 ml/min treated with 15 mg/m^2	GFR ≥ 30 ml/min: no dose adjustment is needed GFR 15-29 ml/min: 50% of the original dose (15 mg/m^2) GFR < 15 ml/min: not recommended HD: not recommended	**FDA:** Not studied (excluded patients with bilirubin ≥ 1·5 mg/dl and AST/ALT ≥2·5 x ULN)	Hepatic impairment: No need for dose adjustments is expected.	Folotyn label[1] Kelly *et al*.[156]
168	**Pralsetinib**	Pralsetinib is primarily metabolised by CYP3A4 and UGT1A4. CYP2D6 and CYP1A2 play a minor role in	**EMA/FDA:** Renal impairment: no dose adjustment	Renal impairment: no dose adjustment is needed HD: no need for dose	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: not recommended	Mild: no dose adjustment is needed Moderate and severe: not	Gavreto label[1] SPC Gavreto[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		the metabolism. Pralsetinib is mainly excreted in feces (72·5%, 66% unchanged) and in urine (6·1%, 4·8% unchanged).		adjustment is expected		recommended	
169	**Procarbazine**	Procarbazine (prodrug) is rapidly metabolised after administration, primarily in the liver and kidneys, into reactive metabolites. Procarbazine and its metabolites are predominantly excreted in urine (70%, 5% unchanged). Some of procarbazine metabolites are excreted via the lungs.	**MHRA:** CLcr < 10 ml/min: contraindicated	GFR ≥ 10 ml/min: no dose adjustment is needed GFR < 10 ml/min: not recommended HD: not recommended	**MHRA:** Severe hepatic impairment: contraindicated	Hepatic impairment: No need for dose adjustments is expected	SPC Procarbazine[9]
170	**Raltitrexed**	Raltitrexed undergoes intracellular polyglutamation and is primarily excreted unchanged in urine (40-50%) and to a lesser extent in feces (15%).	**MHRA:** CLcr > 65 ml/min: no dose adjustment CLcr 55-65 ml/min: 75%, 4 weeks interval CLcr 25-54 ml/min: 50%,4 weeks interval CLcr < 25 ml/min: contraindicated **Judson *et al.*** CLcr 25-65 ml/min: $AUC_{0\text{-}inf}$: 1·97 (95% CI 1·36-2·84), compared to CLcr >65 ml/min	GFR > 65 ml/min: no dose adjustment GFR 55-65 ml/min: 75% of the original, 4 weeks interval GFR 25-54 ml/min: 50% of the original dose, 4 weeks interval GFR < 25 ml/min: not recommended HD: not recommended	**MHRA:** Mild and moderate: no dose adjustment Severe: not studied	Mild and moderate: no dose adjustment is needed Severe: not recommended, based on the risk of raltitrexed induced liver dysfunction	SPC Tomudex[9] Judson *et al.*[157]
171	**Ramucirumab**	Ramucirumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA** CLcr ≥ 15 ml/min: no dose adjustment	Renal impairment: no need for dose adjustment HD: no need for dose adjustment is expected	**EMA/FDA:** Mild and moderate: no dose adjustment needed Severe: not studied Child-Pugh B and C cirrhosis: clinical deterioration is reported (FDA)	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected Child-Pugh B and C cirrhosis: not recommended	Cyramza label[1] SPC Cyramza[2]
172	**Regorafenib**	Regorafenib is metabolised in the liver. The M-2 and M-5 metabolite contribute to the clinical effect. Regorafenib and its metabolites are	**EMA/FDA:** Renal impairment: no dose adjustment recommended HD: not studied	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: no dose adjustment recommended, close monitoring Severe: not studied, not	Mild, moderate or Child-Pugh A: no dose adjustment is needed Child-Pugh B: no need for dose adjustment is expected	Stivarga label[1] SPC Stivarga[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		predominantly excreted in feces (71%, 47% unchanged) and to a lesser extent in urine (19%).			recommended **EMA:** Child-Pugh A: no dose adjustment is needed Child-Pugh B: limited data indicate similar exposure Child-Pugh C: not studied	Child-Pugh C: not recommended	
173	**Ribociclib**	Ribociclib is metabolised in the liver. Ribociclib and its metabolites are primarily excreted in feces (69%) and to a lesser extent in urine (23%), predominantly as metabolites.	**EMA/FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR 15-30 ml/min/1·73m^2: 33% of the original starting dose (200 mg QD)	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: 33% of the original starting dose (200 mg QD) HD: not recommended	**EMA/FDA:** Child-Pugh A: no dose adjustment needed Child-Pugh B: 1·32-fold increase in $AUC_{0\text{-}inf}$; 400 mg QD Child-Pugh C: 1·29-fold increase in $AUC_{0\text{-}inf}$; 400 mg QD	Child-Pugh A: no dose adjustment is needed Child-Pugh B: 67% of the original dose Child-Pugh C: 67% of the original dose	Kisqali label[1] SPC Kisqali[2]
174	**Ripretinib**	Ripretinib is primarily metabolised by CYP3A4 into the active metabolite DP-5439. Ripretinib is mainly excreted in feces (34% as ripretinib; 6% as DP-5439). Excretion by urine was < 1%.	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no dosing recommendation can be made **FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: not studied **EMA:** Child-Pugh A or mild: no dose adjustment Child-Pugh B and C or moderate and severe: not studied	Child-Pugh A or mild: no dose adjustment is needed Child-Pugh B/C or moderate/severe: not recommended	Qinlock label[1] SPC Qinlock[2]
175	**Rituximab**	Rituximab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** Renal impairment: not studied **Jillella *et al.*** HD: not dialysed, comparable plasma levels	Renal impairment: no need for dose adjustment is expected HD: no dose adjustment is needed	**EMA/FDA:** Hepatic impairment: not studied	Hepatic impairment: no need for dose adjustment is expected	Rituxan label[1] SPC MabThera[2] Jillella *et al.*[158]
176	**Romidepsin**	Romidepsin is extensively metabolised in the liver. Romidepsin's route of excretion is unknown.	**FDA:** CLcr ≥ 15 ml/min: pharmacokinetics not affected. CLcr < 15 ml/min or HD: not studied	Renal impairment or HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate: 7 mg/m^2 (50% of original dose) Severe: 5 mg/m^2 (~33% of original dose)	Mild: no need for dose adjustment is expected Moderate: consider 50% of starting dose (7 mg/m2) Severe: consider ~33% of starting dose (5 mg/m2)	Istodax label[1]
177	**Rucaparib**	Rucaparib is *in vitro* primarily metabolised by CYP2D6 and to a lesser extent by CYP1A2 and	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min and HD : not	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected	**EMA/FDA:** Mild: no dose adjustment Moderate: no dose adjustment but careful	Mild and moderate: no dose adjustment is needed Severe: not	Rubraca label[1] SPC Rubraca[2] Grechko *et al.*[159]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		CYP3A4. Unchanged rucaparib accounts for the largest fraction on plasma (64%), the most abundant metabolite M324 counts for 19%. Rucaparib is mainly excreted in feces (72%) with minor excretion in urine (17%).	studied and therefore not recommended	HD: no need for dose adjustment is expected	monitoring for hepatic function and adverse reactions Severe: not studied and therefore not recommended **Grechko *et al.*** Moderate: slightly higher $AUC_{0\text{-}INF}$ compared to normal hepatic function (GMR 1·446, 90% CI 0·668-3·131)	recommended	
178	**Ruxolitinib (for myelofibrosis)**	Ruxolitinib is metabolised in the liver. Two metabolites of ruxolitinib are active and contribute for approximately 18% to the clinical effect. Ruxolitinib and its metabolites are mainly excreted in urine (74%) and to a lesser extent in feces (22%), mostly as metabolites.	**FDA:** CLcr 15-59 ml/min and platelet count > 150x10^9/L: no dose adjustment CLcr 15-59 ml/min and platelet count 100-150x10^9/L: 10 mg BID CLcr 15-59 ml/min and platelet count 50 – 99x10^9/L: 5 mg QD CLcr 15-59 ml/min and platelet count < 50 x 10^9/L: avoid HD with platelet count 100-200x10^9/L: 15 mg after dialysis, on dialysis days HD with platelet count >200x 10^9/L: 20 mg after dialysis, on dialysis days **EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: approximately 50% of the dose based on platelet count HD with platelet count 100-200x10^9/L: 15 mg QD after dialysis HD with platelet count >200x 10^9/L: 20 mg QD or 10 mg BID after dialysis **Chen *et al.*** eGFR 50-80 ml/min/1·73m^2: $AUC_{0\text{-}inf}$ 1·10 (90% CI 0·90-	Renal impairment: Adjust the dose according to FDA recommendations	**FDA:** Child-Pugh A-C and platelet count: > 150 x10^9/L: no dose adjustment 100-150 x10^9/L: 10 mg BID 50-100 x10^9/L: 5 mg QD < 50 x 10^9/L: avoid **EMA:** Child-Pugh A-C: approximately 50% of the original daily dose based on platelet count, divided in two doses **Chen *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 1·87(90% CI 1·29-2·71) Child-Pugh B: $AUC_{0\text{-}inf}$ 1·28 (90% CI 0·88-1·85) Child-Pugh C: $AUC_{0\text{-}inf}$ 1·65(90% CI 1·14-2·40)	Child-Pugh A to C: Adjust the dose according to FDA recommendations	Jakafi label[1] SPC Jakavi[2] Chen *et al*.[160]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			1·36) eGFR 30-49 ml/min/1·73m^2 :$AUC_{0\text{-}inf}$ 1·22 (90% CI 0·99-1·50) eGFR < 30 ml/min/1·73m^2: $AUC_{0\text{-}inf}$ 1·03 (90% CI 0·84-1·27) HD: $AUC_{0\text{-}inf}$ 0·93 (90% CI 0·72-1·19)				
179	**Sacituzumab govitecan**	The monoclonal antibody portion is expected to undergo proteolysis by ubiquitous proteolytic enzymes to small peptides and individual amino acids. SN-38, the small molecule moiety, is metabolised via UGT1A.	**EMA:** CLcr ≥ 60 ml/min: no dose adjustment CLcr < 60 ml/min: no data available **FDA:** Renal impairment: no data available	GFR ≥ 60 ml/min: no dose adjustment is needed GFR < 60 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild: similar exposure to patients with normal hepatic function, no dose adjustment Moderate and severe: no data available, not recommended	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Trodelvy label[1] SPC Trodelvy[2]
180	**Selinexor**	Selinexor is metabolised by CYP3A4, multiple UGTs and glutathione S-transferases. Hepatic clearance is presumably the main route of elimination.	**EMA:** CLcr ≥ 15 ml/min: no dose adjustment is needed CLcr < 15 ml/min: no data available **FDA:** CLcr ≥ 15 ml/min: no dose adjustment CLcr < 15 ml/min: no data available HD: no data available	GFR ≥ 15 ml/min: no dose adjustment is needed GFR < 15 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Mild: no dose adjustment Moderate and severe: No data available **FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: not recommended	Xpovio label[1] SPC Nexpovio[2] Bader *et al.*[161]
181	**Selpercatinib**	Selpercatinib is mainly metabolised by CYP3A4. Tucatinib is mainly excreted in feces (69%, 14% unchanged) and to a lesser extent in urine (24%, 11·5% unchanged).	**EMA:** eGFR ≥ 15 ml/min: no dose adjustment ESRD/HD: no data available **FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	GFR ≥ 15 ml/min: no dose adjustment is needed GFR < 15 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: $AUC_{0\text{-}inf}$: increased by 77% compared to normal hepatic function. Dose modification is recommended **FDA:** Mild and moderate ($AUC_{0\text{-}inf}$ increased with 7% and 32%): no dose adjustment Severe ($AUC_{0\text{-}in}$ increased with 77%): reduce the dosage of selpercatinib to 80 mg BID	Child-Pugh A/B or mild/moderate: no dose adjustment is needed Child-Pugh C or severe: 50% of starting dose.	Retevmo label[1] SPC Retesvmo[2]
182	**Sonidegib**	Sonidegib is metabolised in	**FDA**	Renal impairment: no need	**FDA**	Hepatic impairment: no	Odomzo label[1]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		the liver. Sonidegib and its metabolites are predominantly excreted in feces (93·4%, 88·7%unchanged) and to a lesser extent in urine (1·95%).	CLcr ≥ 30 ml/min: no effect on steady-state exposure **EMA** CLcr ≥ 30 ml/min: dose adjustment probably not required. CLcr < 30 ml/min: not studied	for dose adjustment is expected HD: no need for dose adjustment is expected.	Child-Pugh A/B/C: no effect on steady-state exposure **EMA** No dose adjustment needed **Horsmans *et al.*** Child-Pugh A: $AUC_{0\text{-}inf}$ 0·599 (90% CI 0·335-1·07) Child-Pugh B: $AUC_{0\text{-}inf}$ 0·776 (90% CI 0·391-1·54) Child-Pugh C: $AUC_{0\text{-}inf}$ 0·916 (90% CI 0·462-1·82)	dose adjustment is needed	SPC Odomzo[2] Horsmans *et al.*[162]
183	**Sorafenib**	Sorafenib is metabolised in the liver. The active metabolite sorafenib N-oxide contributes to the clinical effect. Sorafenib and its metabolites are predominantly excreted in feces (77%, 51% unchanged) and to a lesser extent in urine (19%). No unchanged sorafenib is found in urine.	**EMA/FDA:** Renal impairment: no dose adjustment is needed HD: not studied **Miller *et al.*** No relationship between sorafenib AUC and varying degrees of renal impairment or HD was observed. Dose reduction to 200 mg BID and 200 mg QD for CLcr 20-39 ml/min and HD, respectively were given due to less tolerability. **Kennoki *et al.*** Not dialysed. An increased incidence of adverse events was observed in patients with haemodialysis, however AUC0-10 was lower than reported values in patients with normal renal function.	GFR > 40 ml/min: no dose adjustment is needed GFR 20-39 ml/min: 200 mg BID, dose- escalation based on tolerability GFR < 20 ml/min or HD: 200 mg QD, dose-escalation based on tolerability	**EMA/FDA:** Child-Pugh A/B: no dose adjustment needed Child-Pugh C: not studied **Miller *et al.*** No significant relationship between sorafenib AUC and varying degrees of hepatic impairment (mild, moderate, severe, very severe). Dose reduction recommended in moderate-severe hepatic dysfunction due to less tolerability.	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: starting dose of 200mg QD, dose-escalation based on tolerability	FDA label Nexovar[1] SPC Nexavar[2] Miller *et al*.[163] Kennoki *et al.*[164]
184	**Sotorasib**	Sotorasib is primarily metabolised by non-enyzmatic conjugation and oxidation to inactive metabolites by CYP2C8, CYP3A4 and CYP3A5. Sotorasib is mainly excreted in feces (74%) and to a lesser extent in urine (6%, 1% unchanged).	**EMA:** CLcr ≥ 60 ml/min: no dose adjustment CLcr < 60 ml/min: no data available **FDA:** eGFR ≥ 30 ml/min/1·73m^2: no clinically meaningful differences	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Mild: no dose adjustment Moderate and severe: not recommended **FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: not recommended	Lumakras label[1] SPC Lumykras[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			eGFR < 30 ml/min/1·73m^2: no data available				
185	**Streptozocin**	Streptozocin is cleared rapidly from the plasma, its metabolites have markedly longer half-life's. In vitro data suggests no involvement of CYP enzymes in streptozocin degradation. Streptozocin and its metabolites are predominantly excreted in urine (30% of the dose as nitrosurea containing metabolites, 10-20% as parent compound) and to a minimal extent in feces (<1%).	**MHRA:** GFR 45-60 ml/min: 50% of original dose GFR 31-44 ml/min: evaluation risk/benefits GFR ≤ 30 ml/min: contraindicated	GFR 46-60 ml/min: 50% of original dose GFR 31-45 ml/min: not recommended, if unavoidable consider 25% of the original dose. GFR ≤ 30 ml/min or HD: not recommended	**MHRA:** Consider dose reduction	Hepatic impairment: no need for dose adjustment is expected	Zanosar SPC[9]
186	**Sunitinib**	Sunitinib is metabolised in the liver. The active metabolite N-desmethylsunitinib contributes to the clinical effect. Sunitinib and its metabolites are predominantly excreted in feces (61%) and to a lesser extent in urine (16%).	**FDA:** Renal impairment: no dose adjustment needed HD: no initial dose adjustment needed, consider dose increase up to 2-fold based on tolerability and safety due to 47% lower sunitinib exposure in patients on HD **EMA:** Renal impairment/HD: no dose adjustment needed **Khosravan *et al.*** Sunitinib geometric mean ratio: CLcr < 30 ml/min: 86% (90% CI: 61-120%) HD: 53% (90% CI: 37-74%) **Izzedine *et al.*** Sunitinib PK in two dialysed patients were comparable to patients with normal renal function. Sunitinib is not dialysed.	Renal impairment: no dose adjustment is needed HD: no initial dose adjustment is needed, increase dose based on sunitinib + active metabolite C_{trough} levels	**FDA:** Child-Pugh A/B: no dose adjustment needed Child-Pugh C: not studied **EMA** Child-Pugh A/B: no dose adjustment needed Child-Pugh C: not recommended **Bello *et al*** Child-Pugh A: $AUC_{0\text{-}inf}$ 1·03 (90%CI: 0·80-1·33) Child-Pugh B: $AUC_{0\text{-}inf}$ 1·03 (90% CI: 0·80-1·32)	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: consider 75% of the original dose, increase if tolerated	Sutent label[1] SPC Sutent[2] Khosravan *et al.*[165] Izzedine *et al.*[166] Bello *et al*.[167]
187	**Tafasitamab**	Tafasitamab is catabolised by proteolytic degradation to smaller peptides. No renal or	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need	**EMA/FDA:** Mild: no dose adjustment Moderate and severe: no	Mild: no dose adjustment is needed	Monjuvi label[1] SPC Minjuvi[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		hepatic clearance.	CLcr < 30 ml/min: no data available	for dose adjustment is expected HD: no need for dose adjustment is expected	data available	Moderate and severe: no need for dose adjustment is expected	
188	**Tamoxifen**	Tamoxifen is extensively metabolised in the liver to several active metabolites which significantly contribute to the therapeutic effect, with N-desmethyl tamoxifen as major metabolite. Tamoxifen and its metabolites are predominantly excreted in feces.	**FDA/MHRA:** no advise given **Langenegger *et al.*** In HD patients: tamoxifen and N-desmethyl tamoxifen plasma levels were lower than expected, but within therapeutic range	Renal impairment or HD: no need for dose adjustment is expected	**FDA/MHRA:** not studied **Floren *et al.*** Tamoxifen dose was adjusted based on tamoxifen and N-desmethyltamoxifen levels in a patient with acute hepatic decompensation (TB 340 µmol/L, AST 99 UI/L, INR 3·0) after transjugular intrahepatic portosystemic shunt placement.	Mild/ moderate: no dose adjustment is needed Severe: not recommended	Nolvadex label[1] SPC Nolvadex[9] Langenegger *et al.*[10] Floren *et al.*[168]
189	**Tagraxofusp**	Tagraxofusp is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA:** No data available **FDA:** eGFR ≥ 30 ml/min/1·73m^2: no dose adjustment eGFR < 30 ml/min/1·73m^2: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min/: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** No data available **FDA:** Mild and moderate: no dose adjustment Severe: no data available	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected	Elzonris label[1] SPC Elzonris[2]
190	**Talazoparib**	Talazoparib undergoes minimal hepatic metabolism. Renal elimination through passive diffusion and active secretion is the primary route of excretion (69%, 55% unchanged) with 20% (14% unchanged) recovered in feces.	**FDA:** CLcr ≥ 60 ml/min: no dose adjustment CLcr 30-59 ml/min: 25% dose reduction CLcr < 30 ml/min: not studied HD: not studied **EMA:** CLcr ≥ 60 ml/min: no dose adjustment CLcr 30-59 ml/min: 25% dose reduction CLcr 15-29 ml/min: 50% dose reduction CLcr < 15 ml/min: not studied HD: not studied **Yu *et al.*** CLcr ≥ 60 ml/min: Cl/F -15.2% CLcr 30-59 ml/min:	GFR ≥ 60 ml/min: no dose adjustment (1 mg) GFR 30-59 ml/min: 25% reduction of original dose GFR 15-29 ml/min: 50% dose reduction (0·5 mg) GFR < 15 ml/min: 50% of the original dose may be considered HD: 50% of the original dose may be considered.	**FDA:** Mild: no dose adjustment Moderate and severe: not studied **EMA:** Mild: no dose adjustment Moderate and severe: not studied, only use when the benefit outweighs the potential risk, and the patient should be carefully monitored for hepatic function and adverse events	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Talzenna label[1] SPC Talzenna[2] Yu *et al.*[169]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			Cl/F -38.2% CLcr < 30 ml/min: insufficient data				
191	**Tazemetostat**	Tazemetostat is metabolised by CYP3A to inactive metabolites. Tazemetostat is mainly excreted in feces (79%), and to a lesser extent in urine (15%)	**FDA:** Renal impairment: no dose adjustment	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: not recommended	Tazverik label[1]
192	**Tebentafusp**	Tebentafusp is expected to be catabolised by proteolytic degradation to smaller peptides. Although the metabolic pathway of tebentafusp has not been characterized, no renal or hepatic clearance is expected.	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available **FDA:** CLcr ≥ 30 ml/min: no clinically significant differences in tebentafusp PK CLcr < 30 ml/min: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** No dose adjustment on ALT/AST levels **FDA:** Mild: no dose adjustment is needed Moderate and severe: no data available	Mild: no dose adjustment is needed Moderate and severe: no need for dose adjustment is expected	Kimmtrak label[1] SPC Kimmtrak[2]
193	**Tegafur/gimeracil/oteracil**	Tegafur is a prodrug, which is converted in the liver to the active metabolite 5-FU. 5-FU is converted intracellularly to inactive metabolites by DPD. Tegafur and its metabolites are excreted in urine (83-91%, of which 3·8-4·2% unchanged).	**EMA** CLcr 51-80 ml/min: no dose adjustment CLcr 30-50 ml/min: 80% of original dose (20 mg/m^2 BID) CLcr: < 30 ml/min: not recommended due to increased adverse events HD: not studied **Booka *et al.*** Moderate correlation between 5-FU $AUC_{0\text{-}24h}$ and CLcr in 16 patients with varying degrees of renal impairment. **Tomiyama *et al*.** Comparable 5-FU $AUC_{0\text{-}24h}$ in a patient undergoing HD receiving 40mg and reported 5-FU $AUC_{0\text{-}24h}$ in patients receiving 100mg.	GFR > 50 ml/min: no dose adjustment is needed GFR 30-50 ml/min: 80% of original dose (20mg/m^2 BID GFR < 30 ml/min or HD: 40% of the original dose (20 mg/m^2 QD)	**EMA:** No dose adjustment recommended **Yoon *et al.*** Mild: 80mg/m^2/day Moderate: 70 mg/m^2/day Severe: 50 mg/m^2/day	Hepatic impairment: no dose adjustment is needed	Teysuno SPC[2] Booka *et al.*[170] Tomiyama *et al*.[171]
194	**Temozolomide**	Temozolomide is spontaneously hydrolyzed,	**FDA:**	GFR ≥ 36 ml/min: no dose adjustment is needed	**FDA:**	Child-Pugh A/B: no dose adjustment is needed	Temodar label[1] SPC Temodal[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		primarily to the active 3-methyl(triazen-1-yl)imidazole-4-carboxamide (MTIC). Temozolomide and its metabolites are predominantly excreted in urine (37·7%, 5-10% unchanged) and minimally in feces (0·8%).	CLcr ≥ 36 ml/min: no dose adjustment needed CLcr < 36 ml/min: no dose advice given, exercise caution HD: not studied **EMA:** Renal impairment: dose reductions probably not necessary. Exercise caution.	GFR < 36 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment expected	Child-Pugh A/B: no dose adjustment needed Child-Pugh C: no dose advise given, exercise caution **EMA:** Mild and moderate: no dose adjustment needed Severe: dose reductions probably not necessary	Child-Pugh C: no need for dose adjustment is expected	
195	**Temsirolimus**	Temsirolimus is mainly metabolised in the liver. The principle metabolite is sirolimus, which is equally potent as temsirolimus. Temsirolimus and its metabolites are predominantly excreted in feces (78%) and to a lesser extent in urine (4·6%).	**EMA/FDA:** Renal impairment: no dose adjustment recommended HD: not studied **Lunardi *et al.*** (Tem)sirolimus pharmacokinetics not significantly altered by haemodialysis compared to controls with normal renal function	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA:** Bilirubin 1-1·5 x ULN or AST > ULN but bilirubin ≤ ULN): 60% of original dose (15mg/week) Bilirubin > 1·5xULN: contraindicated **EMA:** Renal cell carcinoma (RCC), if platelet count ≥ 100 x 10^9/l: Mild and moderate or Child-Pugh A/B: no dose adjustment is needed Severe or Child-Pugh C: 40% of original dose (10 mg/week) Mantel cell lymphoma (MCL): Mild: no dose adjustment recommended Moderate and severe: contraindicated	RCC Mild or moderate: no dose adjustment is needed Severe: 40% of the original dose MCL Mild: no dose adjustment Moderate and severe: not recommended	Torisel label[1] SPC Torisel[2] Lunardi *et al.*[172]
196	**Teniposide**	Teniposide is metabolised in the liver. Teniposide and its metabolites are predominantly excreted in urine (44%, of which 4-12% as unchanged parent compound) and to a lesser extent in feces (0-10%).	**FDA:** Insufficient data, dose adjustment may be necessary.	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Insufficient data, dose adjustment may be necessary	Mild and moderate: no need for dose adjustment is expected Severe: not recommended	Vumon label[1]
197	**Tepotinib**	Tepotinib is metabolised in the liver by CYP3A4 and CYP2C8. Tepotinib is mainly	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for	**EMA:** Child-Pugh A/B or mild and moderate: no dose adjustment	Child-Pugh A/B or mild/moderate: no dose adjustment is needed	Tepmetko label[1] SPC Tepmetko[2]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		excreted in feces (~78%, 45% unchanged), and to a lesser extent in urine (13·6%, 7% unchanged).	Clcr < 30 ml/min: no data available, not recommended **FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	dose adjustment is expected HD: no need for dose adjustment is expected	Child-Pugh C and severe: no data available **FDA:** Child-Pugh A/B or mild and moderat: no dose adjustment Child-Pugh C and severe: no data available	Child-Pugh C and severe: not recommended	
198	**Thalidomide**	Thalidomide is primarily metabolised by non-enzymatic hydrolysis. There is minimal CYP catalyzed hepatic metabolism. Thalidomide is mainly excreted in urine (>90%), and to a lesser extent in feces.	**EMA:** Studies in healthy subjects suggest that thalidomide PK is not influenced to any significant extent by impaired renal function. Severe: no dose adjustment, carefully monitor for any adverse events. **FDA:** Renal impairment: not expected to influence drug exposure **Eriksson *et al.*:** No need to increase the dose due to haemodialysis, although clearance is doubled during dialysis.	Renal impairment: no dose adjustment is needed HD: no dose adjustment is needed	**EMA:** Studies in healthy subjects suggest that thalidomide PK is not influenced to any significant extent by impaired hepatic function. Severe: no dose adjustment, carefully monitor for any adverse events. **FDA:** No data available	Mild and moderate: no dose adjustment is needed Severe: no dose adjustment is needed	Thalidomide label[1] SPC Thalidomide BMS[2] Eriksson *et al.*[173]
199	**Thiotepa**	Thiotepa is extensively and rapidly metabolised in the liver. One of the major active metabolites is triethylene phosphoramide (TEPA). Several known metabolites are all excreted in the urine. Urinary excretion of the parent compound accounts for < 2% of the given dose, TEPA for ≤ 11% of the given dose.	**FDA:** CLcr 15-59 ml/min: more extensive monitoring indicated. **EMA:** CLcr ≥ 30 ml/min: not studied. No need for dose adjustment **Ekhart *et al*:** Increased exposure (AUC) to thiotepa (+43%) and TEPA (+157%) in a patient with CLcr 38ml/min compared to AUC of reference population.	GFR ≥ 30 ml/min: no need for dose adjustment is expected GFR < 30 ml/min: consider 70% of the original dose, increase if tolerated HD: consider 70% of the original dose, increase if tolerated	**FDA:** Mild: similar clearance compared to normal liver function. Moderate: 1·6-1·8 fold increase of thiotepa AUC. More extensive monitoring indicated. Severe: unknown. More extensive monitoring indicated. **EMA:** Dose modification not recommended for transient alterations of hepatic parameters. Exercise caution in patients with pre-existing hepatic impairment,	Mild: no dose adjustment is needed Moderate: intensify monitoring Severe: not recommended	Tepadina label[1] Tepadina SPC[2] Ekhart *et al.*[174]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					especially severe		
200	**Tioguanine**	Tioguanine (prodrug) is extensively metabolised into several active and inactive metabolised in the liver and other tissues. Tioguanine and its metabolites are mainly excreted in urine, mostly as metabolites.	**FDA:** No advise given **MHRA:** Consider dose adjustment	Renal impairment or HD: no need for dose adjustment is expected	**FDA:** No advise given **MHRA:** Consider dose adjustment	Hepatic impairment: no need for dose adjustment is expected	Tabloid label[1] SPC Tioguanine[9]
201	**Tisotumab vedotin**	The monoclonal antibody portion (tisotumab) is expected to undergo proteolytic degradation to smaller peptides. No renal or hepatic elimination. Vedotin (MMAE) is primarily metabolised by CYP3A4. It is expected that vedotin is mainly excreted in feces and to a lesser extent in urine.	**FDA:** CLcr ≥ 30 ml/min: no clinically significant difference in exposure CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: not studied, avoid use	Mild: no dose adjustment is needed Moderate and severe not recommended	Tivdak label[1]
202	**Tivozanib**	Only a small part of tivozanib is metabolised in the liver by CYP3A4 and CYP1A1. Tivozanib is mainly excreted in feces (79%, 26% unchanged), and to a lesser extent in urine (12%, not unchanged).	**EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min or HD: no dose recommendation given **FDA:** CLcr ≥ 15 ml/min: no dose adjustment CLcr < 15 ml/min or HD: no data available	GFR ≥ 15 ml/min: no dose adjustment is needed GFR < 15 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Child-Pugh A or mild: No dose adjustment Child-Pugh B or moderate: AUC_{tau} 62% increase. Reduce dose to 0·89 mg QD Child-Pugh C or severe: no data available **EMA:** Mild: No dose adjustment Moderate: significant increase (2·6-fold) in $AUC_{0\text{-}inf}$. Reduce dose to one capsule (1·34 mg) every other day Severe: significant increase (4·0-fold) in $AUC_{0\text{-}inf}$. Do not use tivozanib	Child-Pugh A or mild: no dose adjustment is needed Child-Pugh B or moderate: 50% of the original dose by increasing the dose interval to use every other day Child-Pugh C or severe: not recommended	Fotivda label[1] SPC Fotivda[2]
203	**Topotecan**	Topotecan undergoes pH dependent hydrolysis to a pharmacologically active lactone form. Topotecan is to a lesser extent eliminated (<10%) by metabolisation to a N- demethylated metabolite. Topotecan and its	Intravenous: **EMA/FDA**: CLcr ≥ 40 ml/min: no dose adjustment needed CLcr 20-39 ml/min: 50% of original dose (0·75mg/m^2) CLcr < 20 ml/min: not studied, not recommended **O'Reilly *et al*.**	(Oral and intravenous) GFR ≥ 40 ml/min: no dose adjustment is needed GFR 20-39 ml/min: 50% of original dose GFR < 20 ml/min: not recommended, if unavoidable consider 25% of the original dose	Intravenous: **FDA:** no differences in pharmacokinetics in patients with hepatic impairment. **EMA:** Bilirubin 1·5-10 mg/dl: insufficient data to make	(Oral and intravenous) Bilirubin ≤171 µmol/l: no need for dose adjustment is expected Bilirubin >171 µmol/l: not recommended	Hycamtin label[1] SPC Hycamtin[2] O'Reilly *et al*.[175] Devriese *et al*.[176] O'Reilly *et al*.[177] Herrington *et al*. [178]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		metabolites are predominantly excreted in urine (54%) and to a lesser extent in feces (20%).	Significantly reduced clearance of topotecan in patients with mild and moderate renal impairment: CLcr ≥ 60 ml/min: 0·4±0·18 L/min/m^2 CLcr 40-59 ml/min: 0·27±0·11 L/min/m^2 CLcr 20-39 ml/min: 0·14±0·05 L/min/m^2 **Herrington *et al*.** Case report, almost fourfold increase of topotecan clearance on dialysis compared to off dialysis Oral: **FDA:** CLcr > 50 ml/min: no dose adjustment CLcr 30-49 ml/min: 65% of original dose (1·5 mg/m^2) CLcr < 30 ml/min: 26% of original dose (0·6 mg/m^2) **EMA:** CLcr > 50 ml/min: no dose adjustment CLcr 30-49 ml/min: 83% of original dose (1·9 mg/m2) CLcr < 30 ml/min: limited data **Devriese *et al.*** CLcr 50-79 ml/min: $AUC_{0\text{-}inf}$: 1·61 (90% CI 1·14-2·28) CLcr 30-49 ml/min: $AUC_{0\text{-}inf}$ 2·48 (90% CI 1·72-3·56) CLcr < 30 ml/min: $AUC_{0\text{-}inf}$ 3·98 (2·64-6·01)	HD: not recommended, if unavoidable consider 25% of the original dose	dose recommendations Bilirubin >10 mg/dl: not recommended **O'Reilly *et al.*** No statistically significant pharmacokinetic differences of total topotecan or topotecan lactone between patients with normal hepatic function (bilirubin ≤1·2 mg/dl) and hepatic impairment (bilirubin >1·2 mg/dl). Oral: **FDA:** No differences in pharmacokinetics in patients with hepatic impairment. **EMA:** Mild and moderate (bilirubin 1·5-10 mg/dl): insufficient data to make recommendations Severe: not recommended		
204	**Toremifene**	Toremifene is extensively metabolised in the liver. The active metabolite N-demethyltoremifene contributes to the clinical	**FDA:** No dose advise given, no change in PK patients with impaired renal function	Renal impairment: no dose adjustment is needed HD: no need for dose adjustments is expected	**FDA**: No dose advise given, although stated mean elimination half-life of toremifene increased less	Mild and moderate : no need for dose adjustment is expected due to large therapeutic index Severe: consider starting	Fareston label[1] SPC Fareston[2] Anttila *et al*. [179]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		effect. Toremifene and its metabolites are predominantly excreted in feces and to a lesser extent in urine (approximately 10%).	**EMA:** Renal impairment: no dose adjustment is needed **Antilla *et al.*** No difference in PK in patients with renal impairment		than twofold in patients with hepatic impairment. **EMA**: Use with caution in patients with hepatic impairment **Antilla *et al.*** AUC was significantly increased in patients with hepatic impairment (bilirubin 1·5-2 x ULN) compared to normal hepatic function (28·4± 12·3 vs. 44·5± 28·9 µg·hr/ml)	with 50% of the original dose, increase if tolerated	
205	**Trabectedin**	Trabectedin is extensively metabolised in the liver. Trabectedin and its metabolites are predominantly excreted in feces (58%) and to a lesser extent in urine (5·8%), mostly as metabolites.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 or HD: not studied/contraindicated **Thariat *et al.*** $AUC_{0\text{-}inf}$ of normal dose trabectedin in patient on haemodialysis was 2-fold that of the control population, although within 95%CI.	GFR ≥ 30ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: No need for dose adjustment is expected	**FDA:** Moderate (bilirubin 1·5-3 x ULN and AST and ALT <8 x ULN): 60% of original dose (0·9 mg/m2) Severe: contraindicated **EMA:** Bilirubin >ULN: contraindicated **Calvo *et al.*** Hepatic impairment (bilirubin 1·5 – 3 x ULN, AST and ALT ≤ 8 x ULN): dose normalized $AUC_{0\text{-}last}$ 1·97 (90% CI 1·20-3·22)	Mild: no need for dose adjustment is expected Moderate: 60% of original dose (0·9 mg/m^2) Severe: not recommended	Yondelis[1] SPC Yondelis[2] Thariat *et al*[180] Calvo *et al*. [181]
206	**Trametinib**	Trametinib is metabolised in the liver. Trametinib and its metabolites are predominantly excreted in feces (>80%) and to a lesser extent in urine (≤19%), mostly as metabolites.	**EMA/FDA** GFR ≥ 30 ml/min/1·73m^2: no dose adjustment is needed GFR < 30 ml/min/1·73m^2 or HD: not studied **Park *et al***. Comparable C_{max} in a dialysed patient receiving a reduced dose (1mg QD) of trametinib compared to previously reported concentrations at that dose.	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild: no dose adjustment Moderate and severe: not studied **EMA**: Mild: no dose adjustment Moderate and severe: limited impact of moderate to severe hepatic impairment on trametinib exposure	Mild and moderate: no dose adjustment is needed Severe: consider 50% of the original dose	Mikinist label[1] SPC Mekinist[2] Park *et al*[57]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
207	**Trastuzumab deruxtecan**	Trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release deruxtecan (DXd). In vitro, DXd is mainly metabolised by CYP3A4.	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available HD: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA:** Mild: no dose adjustment Moderate and severe: no data available, monitor closely when administered **FDA:** Mild: no dose adjustment Moderate: monitor closely when administered Severe: no data available	Mild: no dose adjustment is needed Moderate: no need for dose adjustment is expected, close monitoring for toxicity is recommended Severe: not recommended	Enhertu label[1] SPC Enhertu[2]
208	**Trastuzumab emtansine**	Trastuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic elimination. DM1 is mainly metabolised in the liver. DM1 and DM1-containing catabolites are mainly excreted in bile with minimal elimination in urine.	**EMA/FDA:** CLcr: ≥ 30 ml/min: No dose adjustment is needed CLcr < 30 ml/min: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A: no dose adjustment Child-Pugh B: no dose adjustment Child-Pugh C: not studied	Child-Pugh A/B: no dose adjustment is needed Child Pugh C: not recommended	Label Kadcyla[1] SPC Kadcyla[2]
209	**Trastuzumab**	Trastuzumab is catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance.	**EMA/FDA:** CLcr: ≥ 30 ml/min: no clinically significant differences in PK HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Hepatic impairment: not studied	Hepatic impairment: no need for dose adjustment is expected	Label Herceptin[1] SPC Herceptin[2]
210	**Tremelimumab**	Tremelimumab is thought to be cleared through proteolytic degradation and catabolism. Excretion was not studied, but expected to be cleared as small peptides or aminoacids or incorporated in the endogenous aminoacid pool.	**EMA/FDA**: CLcr ≥ 30 ml/min: no clinically significant effect on the PK of tremelimumab. CrCl < 30 ml/min: not studied.	GFR ≥ 30 ml/min: no dose adjustment is needed. GFR < 30 ml/min: no need for dose adjustment is expected. HD: no need for dose adjustment is expected.	**EMA**: Mild: no clinically significant effect on the PK of tremelimumab. Moderate: not studied. **FDA**: Mild to moderate: no clinically significant effect on the PK of tremelimumab. Severe: not studied.	Mild and moderate: no dose adjustment is needed. Severe: no need for dose adjustment is expected.	Imjudo label[1] SmPC Imjudo[2]
211	**Treosulfan**	Treosulfan (prodrug) is spontaneously converted to an active monoepoxide	**MHRA:** Renal impairment: careful monitoring of blood counts	GFR ≥ 50 ml/min: no need for dose adjustment is expected GFR < 50ml/min: consider the	**MHRA:** no advise given	Hepatic impairment: no need for dose adjustment is expected, however due to limited knowledge about	SPC treosulfan[9]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
		intermediate and finally tot L- diepoxibutane. Treosulfan is renally excreted, with cumulative renal elimination of 5-49% of unchanged treosulfan.		use of busulfan and dose according to busulfan plasma levels HD: not recommended		treosulfan pharmacokinetics careful monitoring is advised.	
212	**Trifluridine/ tipiracil**	Trifluridine and tipiracil are not metabolised by CYP enzymes. Trifluridine is primarily metabolised by TPase and excreted in urine as the inactive metabolite TPY. Trifluridine is excreted in feces (3%). Tipiracil is excreted in feces (50%).	**EMA/FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: reduce dose to 20 mg/m^2 BID HD: no data available **Saif *et al.*** CLcr ≥ 30 ml/min: safe and tolerable at the recommended dose of 35 mg/m^2 BID CLcr < 30 ml/min: safe and tolerable at a reduced dose of 20 mg/m^2 BID	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: reduce dose according to drug label, based on BSA HD: not recommended	**EMA:** Mild: no dose adjustment Moderate: not recommended **FDA:** Mild: no dose adjustment Moderate and severe: no data available **Saif *et al.*** Mild: no dose adjustment Moderate and severe: not recommended, due to grade 3 or 4 increased blood bilirubin	Mild: no dose adjustment is needed Moderate and severe: not recommended	Lonsurf label[1] SPC Lonsurf[2] Saif *et al.*[182] Saif *et al.*[183]
213	**Tucatinib**	Tucatinib is primarily metabolised by CYP2C8 and to a lesser extent by CYP3A4. Tucatinib is mainly excreted in feces (85·8%, 15·9% unchanged) and to a lesser extent in urine (4·1%).	**EMA:** CLcr < 90 ml/min: no dose adjustment **FDA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: no data available	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B or mild and moderate: no dose adjustment Child-Pugh C or severe: 1.6-fold increase $AUC_{0\text{-}inf}$ compared to subjects with normal hepatic function. Reduced starting dose of 200 mg orally BID is recommended.	Child-Pugh A/B or mild/moderate: no dose adjustment is needed Child-Pugh C or severe: 66% of the original dose	Tukysa label[1] SPC Tukysa[2]
214	**Vandetanib**	Vandetanib is partly metabolised in the liver. Vandetanib and its active metabolites are excreted in urine (44%) and feces (25%).	**EMA:** CLcr ≥ 50 ml/min: no dose adjustment CLcr 30-50 ml/min: reduce dose to 200 mg QD (67% of the original dose) CLcr < 30 ml/min: not recommended **FDA:** CLcr ≥ 60 ml/min: no dose adjustment	GFR > 50 ml/min: no dose adjustment is needed GFR 30 - 50 ml/min: 67% of the original dose GFR < 30 ml/min: 50% of the dose may be considered HD: 50% of the dose may be considered	**EMA/FDA:** Child-Pugh A-C did not affect vandetanib exposure. Bilirubin > 1·5 x ULN: not recommended **FDA:** Mild: no dose adjustment Moderate and severe: not recommended **Weil *et al.***	Hepatic impairment: no dose adjustment is needed	Caprelsa label[1] SPC Caprelsa[2] Weil *et al.* [184]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			CLcr 15-59 ml/min: reduce dose to 200 mg QD (67% of the original dose) **Weil *et al.*** CLcr 50-81 ml/min: $AUC_{o\text{-}inf}$ 1·46 (90% CI 1·24-1·72) CLcr 30 -49 ml/min: $AUC_{o\text{-}inf}$ 1·62 (90% CI 1·31-1·99) CLcr <30 ml/min: $AUC_{o\text{-}inf}$ 1·79 (90% CI 1·39-2·31)		Child-Pugh A: $AUC_{o\text{-}inf}$ 1·04 (90% CI 0·86-1·26) Child-Pugh B: $AUC_{o\text{-}inf}$ 0·94 (90% CI 0·78-1·15) Child-Pugh C: $AUC_{o\text{-}inf}$ 0·93 (90% CI 0·76-1·14)		
215	**Vemurafenib**	Vemurafenib is only partly metabolised in the liver. Vemurafenib is predominantly excreted unchanged in feces (94%) and in minimal amounts (<1%) in urine.	**FDA:** CLcr ≥ 60 ml/min: no dose adjustment is needed CLcr 30-59 ml/min: no dose adjustment is needed CLcr < 30 ml/min: not sufficiently studied **EMA:** CLcr > 40 ml/min: no dose adjustment is needed CLcr ≤ 30 ml/min: limited data available.	GFR ≥ 30/ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild and moderate (TB <3 x ULN): no dose adjustment recommended Severe: limited data **EMA:** No need for dose adjustment in patients with hepatic impairment. Close monitoring warranted in moderate and severe hepatic impairment.	Mild and moderate: no dose adjustment is needed Severe: no need for dose adjustment is expected, monitor liver biochemistry twice a week.	Vemurafenib label[1] SPC Zelboraf[2]
216	**Venetoclax**	Venetoclax is primarily metabolised by CYP3A4, *in vitro*. Venetoclax is mainly eliminated in feces (>99·9%, 20·8% unchanged) and to a lesser extent in urine (<0·1%).	**EMA:** CLcr ≥ 15 ml/min: no dose adjustment CLcr < 15 ml/min: no data available **FDA:** CLcr ≥ 30-80 ml/min: no dose adjustment CLcr < 30 ml/min: no data available HD: no data available	GFR ≥ 15 ml/min: no dose adjustment is needed. GFR < 15 ml/min: no need for dose adjustment is expected. Monitor closely due to increased risk of TLS HD: no need for dose adjustment is expected. Monitor closely due to increased risk of TLS	**EMA:** Child-Pugh A/B, and mild and moderate: no dose adjustment Severe: reduce dose with at least 50% **FDA:** Mild and moderate: no dose adjustment Severe: no data available **Salem *et al.*** Mild: $AUC_{0\text{-}inf}$ ratio of central values estimate: 1·261 (90% CI 0·808-1·970) Child-Pugh B: $AUC_{0\text{-}inf}$: 1·396 (90% CI 0·869-2·242) Child-Pugh C: $AUC_{0\text{-}inf}$: 2·700 (90% CI 1·625-4·487) Mild and moderate: no dose adjustment Severe: Reduce dose with at	Child-Pugh A/B and mild/moderate: no dose adjdustment is needed Child-Pugh C and severe: 50% of the original dose	Venclexta label[1] SPC Venclyxto[2] Salem *et al.*[185]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					least 50%		
217	**Vinblastine sulfate**	Vinblastine is extensively metabolised in the liver to the more active desacetylvinblastine. It is excreted slowly in urine and feces.	**MHRA:** Renal impairment: no dose adjustment is needed	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**MHRA:** direct serum bilirubin > 3 mg/dl: 50% dose reduction is recommended.	Bilirubin > 51 µmol/L: 50% of the original dose	SPC vinblastine sulphate[9]
218	**Vincristine sulfate**	Vincristine is metabolised in the liver. Vincristine and its metabolites are mainly excreted in feces (80%) and to a lesser extent in urine (10-20%).	**FDA/MHRA:** Renal impairment: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA/MHRA:** Direct serum bilirubin >3 mg/dl: 50% dose reduction is recommended. **MHRA:** Direct serum bilirubin >3 mg/dl: 50% dose reduction is recommended.	Bilirubin > 51 µmol/l: 50% of original dose	Vincristine sulfate label[1] SPC vincristine sulfate[9]
219	**Vincristine sulfate liposomal**	Liposomal-encapsulated formulation of vincristine sulfate. Vincristine is metabolised in the liver. Vincristine and its metabolites are mainly excreted in feces (80%) and to a lesser extent in urine (10-20%).	**FDA/MHRA:** Renal impairment: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA (liposomal vincirstine)** Child-Pugh A: not studied Child-Pugh B: AUC and C_{max} were comparable to normal hepatic function Child-Pugh C: not studied **Bedikian *et al*:** After adjustment for dose differences, no statistically significant $AUC_{0\text{-}nf}$ differences between patients with hepatic impairment (6 patients with Child-Pugh B and one with Child-Pugh C) and patients with normal liver function were observed (p=0·81).	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: consider a 50% dose reduction	Marqibo label[1] Bedikian *et al*.[186]
220	**Vinflunine**	Vinflunine is metabolised in the liver. The active metabolite 4-O-deacetylvinflunine contributes to the clinical effect. Vinflunine and its metabolites are mainly excreted in feces (67%) and to a lesser extent in urine (33%).	**EMA:** CLcr > 60 ml/min: no dose adjustment CLcr 40-60 ml/min: 87·5% of the original dose (280 mg/m^2) CLcr 20-39 ml/min: 78% of the original dose (250 mg/m^2) **Isambert *et al*.** Geometric mean ratio of clearance: CLcr 40-60 ml/min: 0·88 (90% CI 0·78-0·98)	GFR > 60 ml/min: no dose adjustment is needed GFR 40-60 ml/min: 87·5% of the original dose (280 mg/m^2) GFR 20-39 ml/min: 78% of the original dose (250 mg/m^2) HD: 50% of the original dose (160 mg/m^2)	**EMA:** Child-Pugh A or prothrombin ≥ 60% of the normal value and bilirubin 1·5-3 x ULN and at least one of the following: transaminases > ULN and/or GGT > 5 x ULN: 78% of the original dose (250 mg/m^2) Child-Pugh B or prothrombin ≥ 50% of the normal value and bilirubin > 3 x ULN and transaminases > ULN and GGT >ULN: 62·5% of	Child-Pugh A, mild or moderate: 78% of the original dose Child-Pugh B: 62.5% of the original dose Child-Pugh C or severe: not recommended	SPC Javlor[2] Isambert *et al*.[187] Delord *et al*.[188]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
			CLcr 20-39 ml/min: 0·72 (90% CI 0·65-0·79)		the original dose (200 mg/m^2) Child-Pugh C or prothrombin < 50% of the normal value or bilirubin >5xULN or isolated transaminases >2·5x ULN (≥5 only in case of liver metastases) or GGT >15 x ULN: not studied **Delord *et al.*** No difference in PK parameters (CL +AUC) for mild and moderate impairment*, dose adjustment solely based on safety data. Child-Pugh A/ mild-moderate*: 250 mg/m2 Child-Pugh B/ moderate-severe*: 200 mg/m2 * definition of mild/moderate/severe impairment as stated in the EMA advice above.		
221	**Vinorelbine**	Vinorelbine is metabolised in the liver. Vinorelbine and its metabolites are mainly excreted in feces (46%) and to a lesser extent in urine (18% or less).	**FDA:** No information **MHRA:** Not studied, no dose adjustment is needed	Renal impairment: no dose adjustment is needed HD: no need for dose adjustment is expected	**FDA**: (IV) Serum TB ≤ 2·0 mg/dl: no dose adjustment Serum TB 2·1-3·0 mg/dl: 50% of starting dose Serum TB > 3·0 mg/dl: 25% of starting dose **MHRA: (IV)** Mild and moderate: no dose adjustment Severe: reduced dose of 20mg/m^2 is recommended Oral: Mild: 60 mg/m^2/week Moderate: 50 mg/m^2/week Severe: not recommended	**IV/Oral** Mild and moderate: no dose adjustment is needed Severe: consider 66% of original dose	Navelbine label[1] SPC Navelbine injection[9] SPC Navelbine 80 mg soft capsule[9] Kitzen *et al.*[189]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					Kitzen *et al*. No pharmacokinetic differences between patients with mild and moderate liver dysfunction compared to patients with normal hepatic function.		
222	**Vismodegib**	Vismodegib is metabolised in the liver. Vismodegib is mainly excreted in feces (82%) and to a lesser extent in urine(4·4%).	**EMA/FDA:** CLcr 30-79 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied **Sbrana *et al.*** HD: full dose was tolerated in one case report	GFR 30-79 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Mild to severe: no dose adjustment **Abou-Alfa *et al.*** Mild: $AUC_{0\text{-}24h}$: 1·24 (90% CI 0·9-1·7) Moderate: $AUC_{0\text{-}24h}$: 1·31 (90% CI 0·9-1·8) Severe: $AUC_{0\text{-}24h}$: 0·86 (90% CI 0·5-1·4)	Hepatic impairment: no dose adjustment is needed	Erivedge label[1] SPC Erivedge[2] Abou-Alfa *et al.*[190] Sbrana *et al.*[191]
223	**Vorinostat**	Vorinostat is metabolised in the liver. Excretion is mainly though metabolism with < 1% of unchanged vorinostat excreted in urine.	**FDA:** Renal impairment: not studied, treat with caution HD: not studied	Renal impairment: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**FDA:** Mild and moderate: treat with caution Severe: contraindicated **Ramalingam *et al.*** No PK- differences between patients with mild, moderate and severe hepatic impairment, dose adjustments of 300mg QD, 200mg QD and 100mg QD respectively, are solely based on safety data	Mild: 75% of the original dose Moderate: 50% of the original dose Severe: 25% of the original dose	Zolinza label[1] Ramalingam *et al.*[192]
224	**Zanubrutinib**	Zanubrutinib is primarily metabolised by CYP3A enzymes. Zanubrutinib is mainly excreted in feces (87%, 38% unchanged) and minorly in urine (8%, <1% unchanged).	**FDA:** CLcr ≥ 15 ml/min: no dose adjustment CLcr < 15 ml/min: not studied HD: not studied **EMA:** CLcr ≥ 30 ml/min: no dose adjustment CLcr < 30 ml/min: not studied HD: not studied	GFR ≥ 30 ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected HD: no need for dose adjustment is expected	**EMA/FDA:** Child-Pugh A/B: no dose adjustment Child-Pugh C: . Adjust dose to 80 mg BID. **Ou *et al.*** Child-Pugh A: zanubrutinib total (bound + unbound) $AUC_{0\text{-}inf}$: 1·1 (90% CI 0·8-1·5) Child-Pugh B: zanubrutinib total $AUC_{0\text{-}inf}$: 1·2 (90% CI 0·9-1·6) Child-Pugh C: : zanubrutinib total $AUC_{0\text{-}inf}$: 2·6 (90% CI 1·2-	Child-Pugh A/B: no dose adjustment is needed Child-Pugh C: 25% of the original dose	Brukinsa label[1] SPC Brukinsa[2] Ou *et al.*[193]

			Renal impairment		Hepatic impairment		
	Agent	**PK summary**	**Available evidence**	**Authors' recommendations**	**Available evidence**	**Authors' recommendations**	**References**
					2·1)		

Abbreviations: 5-FU, 5-fluorouracil; ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; $AUC_{0\text{-}inf}$, area under the plasma concentration time profile of the drug of interest from time zero to infinity; $AUC_{0\text{-}last}$, area under the plasma concentration time profile of the drug of interest from time zero to last measured concentration; $AUC_{0\text{-}24h}$, area under the plasma concentration time profile of the drug of interest from time 0 to 24 hours; BID, twice daily; CI, confidence interval; CL, clearance; CLcr, creatinine clearance; C_{max}, maximum concentration; C_{trough}, trough concentration; CVVH, continuous veno-venous hemofiltration; CYP, cytochrome P450; DLT, dose limiting toxicity; DPD, dihydropyrimidine-dehydrogenase; EMA, European Medicines Agency; ESRD, end-stage renal disease; FDA, Food and Drug Administration; FMO, Flavin-containing monooxygenase; (e)GFR, (estimated) glomerular filtrating rate; HD, haemodialysis; HER, human epidermal growth factor receptor 2; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; MMAE, monomethylauristatin E; MMAF, monomethylauristatin F, MTD, maximum tolerated dose; PBPK, physiologically- based pharmacokinetic model; PK, pharmacokinetics; PopPK, population pharmacokinetic model; QD, once daily, SPC, Summary of Product Characteristics; t½, half-life; TB, total bilirubin; TLS, tumor lysis syndrome; UGT, uridine 5'-diphospho-glyceronosyltransferase; ULN, upper limit of normal.

Explanation: AUC changes are presented as geometric means compared to normal renal or hepatic function, unless otherwise stated. Hepatic impairment is categorised according to Child-Pugh score or the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (CTCAEv4) and Organ Dysfunction Working Group: Mild: bilirubin >1.0-1·5 x ULN and any AST or bilirubin ≤ULN and AST >ULN; Moderate: bilirubin 1·5-3 x ULN, with any AST); Severe (bilirubin >3.0-10 x ULN, with any AST)

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