| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Amsacrine** | Amsacrine is extensively metabolised in the liver to inactive metabolites. Amsacrine and its metabolites are predominantly excreted in feces (bile) and to a lesser extent in urine (42%). | **MHRA**:<br>Renal impairment: 70-80% of the original dose (60- 75mg/m2 )<br>HD: not studied | GFR <60 ml/min: 70-80% of the original dose<br><br>HD: 70-80% of the original dose may be considered | **MHRA**:<br>Hepatic impairment: 70-80% of the original dose (60- 75mg/m2 ) | Mild and moderate: 70-80% of the original dose<br><br>Severe: not recommended | SPC Amsidine[8] |
| **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). | **FDA/EMA:**<br>CLcr ≥ 30 ml/min: no dose adjustment is needed CLcr < 30 ml/min: dose reduction may be warranted<br>HD: not studied<br><br>**Firkin et al.**<br>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.<br><br>**Sweeney et al.**<br>CLcr ≤ 30ml/min: mean $AUC_{0-t}$ of $AS^{III}$ 40% higher compared to patients with normal renal function after multiple doses.<br><br>**Perrault et al.**<br>HD: dialysed (approximately 38% removed). Arsenic trioxide 10 mg three times weekly post-dialysis was safe and effective. | GFR≥ 30 ml/min: no need for dose adjustment is expected<br>GFR < 30 ml/min: consider 50% of the original dose<br><br>HD: consider 10 mg three times weekly post-dialysis | **FDA:**<br>Child-Pugh A and B: no dose adjustment is needed<br>Child-Pugh C: $AUC_{0-24h}$ increased by 40% compared to normal hepatic function.<br><br>**EMA:**<br>Mild and moderate: no accumulation of arsenious acid en arsenic acid was observed following twice weekly infusion.<br>Severe: limited information | Child-Pugh A and B: no need for dose adjustment is needed. Use with caution due to risk of hepatotoxicity<br>Child-Pugh C: consider 50% of the original dose | Trisenox label[1]<br>SPC Trisenox[2]<br>Firkin et al. [10]<br>Sweeney et al.[11]<br>Perrault et al. [12] |
| **Asparaginase** | Asparaginase is thought to be degraded within the reticulo-histiocytic system and by serum proteases. No renal clearance. | **EMA:**<br>Renal impairment: no dose adjustment<br>HD: not studied | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA:**<br>Mild and moderate: no dose adjustment<br>Severe: contraindicated | Mild and moderate:<br>no dose adjustment is needed<br>Severe: not recommended due to hepatotoxicity | SPC spectrila [2] |
| **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:**<br>Renal impairment: no initial dose adjustment is needed<br><br>**Laille et al.**<br>CLcr < 30 ml/min/1·73m2: $AUC_{0-inf}$: 141·2% (90% CI 92·2-216 ·2%)<br><br>**Ham *et al.***<br>HD: no initial dose adjustment is needed | Renal impairment: no dose adjustment is needed<br><br>HD: no dose adjustment is needed | **EMA/FDA:**<br>Hepatic impairment: not studied<br>Contraindicated: albumin <30 g/l, advanced malignant hepatic tumours | Mild or moderate:<br>no need for dose adjustment is expected<br><br>If albumin <30 g/L/or advanced malignant hepatic tumours: not reccomended | Vidaza label[1]<br>SPC Vidaza[2]<br><br>Laille et al.[15]<br>Ham et al. [16] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr > 39 ml/min: No dose adjustment is needed<br>CLcr ≤ 39 ml/min: not studied<br>HD: not studied | GFR> 39 ml/min: no dose adjustment is needed<br>GFR < 39 ml/min: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild: no dose adjustment is needed<br>Moderate and severe: not studied | Mild: no dose adjustment is needed Moderate and severe: not recommended | Beleodaq label[1] |
| **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:**<br>CLcr 30-80 ml/min: no dose adjustment is needed<br>CLcr < 30 ml/min: not studied, contraindicated<br><br>**EMA:**<br>CLcr > 10 ml/min: no dose adjustment is needed<br>HD: no dose adjustment is needed | Renal impairment: no dose adjustment is needed<br><br>HD: no dose adjustment is needed | **FDA:**<br>Mild: no dose adjustment is needed<br>Moderate and severe: not studied, contraindicated<br><br>**EMA:**<br>Mild (bilirubin <20 µmol/L): no dose adjustment is needed<br>Moderate (bilirubin 20-51 µmol/L: 70% of the original dose<br>Severe (bilirubin >51µmol/L: not studied, contraindicated | Mild (bilirubin <20 µmol/L): no dose adjustment is needed<br><br>Moderate (bilirubin 20-51 µmol/L: 70% of the original dose<br><br>Severe (bilirubin >51µmol/L: not recommended | Treanda label[1]<br>SPC Levact[8] |
| **Bevacizumab** | Bevacizumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>Not studied in patients with renal impairment.<br><br>**Ganier-Viougeat et al.**<br>HD: 50% of the dose resulted in dose proportional AUC reduction, bevacizumab is not dialysed | Renal impairment: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Not studied in patients with hepatic impairment | Hepatic impairment: no need for dose adjustment is expected | Avastin label[1]<br>Garnier-Viougeat et al. [17] |
| **Bleomycin** | Bleomycin is widely distributed to normal tissues and inactivated by bleomycin hydrolases.<br>Bleomycin is excreted in urine (approximately 67% unchanged). | **MHRA:**<br>GFR > 50 ml/min: no dose adjustment<br>GFR 10-50 ml/min: 75% of the original dose<br>GFR < 10 ml/min: 50% of the original dose<br><br>**Crooke et al.**<br>HD: bleomycin is not dialysed | GFR > 50 ml/min: no dose adjustment is needed<br>GFR 10-50 ml/min: 75% of the original dose<br>GFR < 10 ml/min: 50% of the original dose<br><br>HD: 50% of the original dose may be considered | **MHRA:**<br>Not studied in patients with hepatic impairment | Hepatic impairment: no need for dose adjustment is expected | SPC Bleomycin[8]<br>Crooke *et al*. [19] |
| **Blinatumomab** | Blinatumomab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>CLcr: 30-89 ml/min: Values within the range observed in normal renal function.<br>CLcr <30 ml/min: not studied.<br>HD: not studied. | GFR ≥ 30 ml/min: no dose adjustment is needed<br>GFR <30 ml/min: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Not studied in patients with hepatic impairment<br><br>**Zhu et al.**<br>No association between blinatumomab clearance and baseline ALT or AST levels | Hepatic impairment: no need for dose adjustment is expected | Blincyto label[1]<br>SPC blincyto[2]<br>Zhu et al. 2016[20] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Bortezomib** | Bortezomib is metabolised in the liver. The elimination of bortezomib and its metabolites is unknown, but is believed to be hepatically. | **EMA/FDA:**<br>No dose adjustment is needed<br>HD: no dose adjustment is needed, administer after dialysis<br>**Leal et al.**<br>Bortezomib pharmacokinetics are not influenced by CLcr. | No dose adjustment is needed<br><br>HD: no dose adjustment is needed | **EMA/FDA:**<br>Mild: no dose adjustment<br>Moderate: 54% of the original dose (0·7 mg/m$^2$)<br>Severe: 54% of the original dose (0·7 mg/m$^2$)<br><br>**LoRusso et al.**<br>Mild: $AUC_{0\text{-last}}$ 90·2% (90% CI 66·2-122 ·8)<br>Moderate: $AUC_{0\text{-last}}$ 146 ·8% (90% CI 104 ·7-205 ·7)<br>Severe: $AUC_{0\text{-last}}$ 158 ·1%(90% CI 116 ·8-214 ·0) | Mild: no dose adjustment<br>Moderate/severe: 54% of the original dose (0·7 mg/m$^2$) | Velcade label[1]<br>SPC Velcade[2]<br>LoRusso et al.[21]<br>Leal et al.[22] |
| **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:**<br>CLcr 51-80 ml/min: no dose adjustment is needed<br>CLcr 30-50 ml/min: 300 mg QD (newly diagnosed) 400 mg QD (pretreated)<br>CLcr < 30 ml/min: 200mg QD (newly diagnosed) 300 mg QD (pretreated)<br>HD: not studied<br><br>**Abbas et al.**<br>CLcr 30-50 ml/min:135·02% (98·53–185·01)<br><br>CLcr < 30 ml/min: AUC 159·76 % (90 % CI 115·52–220·92) | GFR >50 ml ml/min: no dose adjustment is needed<br>GFR < 50 ml/min: 75% of the original dose<br>HD: 75% of the original dose may be considered | **EMA/FDA:**<br>Child-Pugh A, B and C: 200 mg QD<br><br>**Abbas et al.**<br>Child-Pugh A: AUC 225% (90% CI 160-315)<br>Child-Pugh B: AUC 200% (90% CI 143-281)<br>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]<br>SPC Bosulif[2]<br>Abbas et al.[23]<br>Abbas et al. [24] |
| **Brentuximab vedotin** | The anti-CD30 antibody is catabolized 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:**<br>CLcr 50-80 ml/min: no dose adjustment<br>CLcr 30-50 ml/min: no doseadjustment<br>CLcr < 30 ml/min: not recommended<br>HD: not studied<br><br>**EMA:**<br>CLcr < 30 ml/min: approximately 67% (1.2mg/kg)<br>Zhao et al.<br>CLcr 51-80 ml/min: MMAE AUC0-inf 0·85 (90% CI 0·39- 1·84)<br>Clcr 30-50ml/min: MMAE AUC0-inf 1·09 (90% CI 0·49- 2·42)<br>CLcr < 30 ml/min: MMAE AUC0-inf 1·90 (90% CI 0·85- 4·21) | GFR ≥ 30 ml/min: no dose adjustment is needed<br>GFR < 30 ml/min:<br>67% of the original dose<br><br>HD: 67% of the original dose | **FDA:**<br>Child-Pugh A: 67 or75% of the original dose (0·9 or 1·2mg/kg)<br>Child-Pugh B and C: not recommended<br><br>**EMA:**<br>Child-Pugh A/B/C: 67% of the original dose (1·2mg/kg)<br><br>**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<br><br>Child-Pugh B and C: not recommended | Adcetris label [1]<br>SPC Adcentris[2]<br>Zhao et al. [25] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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<br><br>**Masauzi et al.**<br>Busulfan clearance comparable to normal<br>patients on non-HD day, accelerated clearance on HD day. | Renal impairment: no dose adjustment is needed, dosing is based on busulfan plasma levels<br><br>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.<br>Severe: not recommended | Busulfex label[1]<br>SPC Busulfan Fresenius Kabi[2]<br>Masauzi et al. [26] |
| **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:**<br>CLcr: 51-80 ml/min: no dose adjustment<br>CLcr 30-50 ml/min: 75% of the original dose<br>CLcr <30 ml/min: not recommended<br>HD: not studied<br><br>**Poole et al.**<br>No effect of renal impairment on the systemic exposure of capecitabine or 5-FU. Based on safety data:<br>CLcr 30-50 ml/min 75% of original dose<br>CLcr < 30 ml/min: not recommended. | GFR: 51-80 ml/min: no dose adjustment is needed<br>GFR 30-50 ml/min: 75% of the original dose<br>GFR <30 ml/min:<br>not recommended<br>HD: not recommended | **EMA/FDA:**<br>Mild and moderate due to liver metastases: AUC and Cmax of capecitabine increased by 60%, AUC of 5- FU was unaffected.<br>severe: not studied<br><br>**Joerger et al.**<br>Normal – severe: no dose adjustment is needed, although hepatic impairment was associated with low clearance of capecitabine.<br><br>**Twelves et al.**<br>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:<br>No dose adjustment is needed | Xeloda label[1]<br>SPC Xeloda [2]<br>Poole et al.[30]<br>Joerger et al. [31]<br>Twelves et al. [32] |
| **Carboplatin** | Carboplatin is not metabolised. It is highly protein-bound (87%) and is primarily excreted in urine | **MHRA:**<br>Dose according to Calverts formula: dose [mg]=target AUC*(GFR +25).<br><br>**Watanabe et al.**<br>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<br><br>HD: dose according to Calverts formula with GFR equals 0. Perform HD between 12 and 24 hours after administration. | **MHRA:**<br>Not studied in patients with hepatic impairment | Hepatic impairment:<br>No need for dose adjustment is expected | SPC Carboplatin[8]<br>Calvert et al. [33]<br>Watanabe et al.[34] |
| **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:**<br>Renal impairment: no dose adjustment is needed<br>HD: no dose adjustment is needed, dose after dialysis<br><br>**Badros et al.**<br>No difference in carfilzomib $AUC_{0\text{-}inf}$ and CL in patients with renal impairment (CLcr 15-80 ml/min) or HD.<br><br>**Quach et al.**<br>HD: $AUC_{0\text{-}inf}$ 138·1% (90% CI 102·8-185·5) | Renal impairment: no dose adjustment is needed<br><br>HD: no dose adjustment is needed | **EMA/FDA:**<br>Mild/moderate: 75% of the original dose<br>Severe: not studied<br><br>**Brown et al.**<br>27 mg/$m^2$<br>Mild: $AUC_{0\text{-}inf}$ 151·84% (90% CI 113·59-202·96)<br>Moderate: $AUC_{0\text{-}inf}$ 143·53% (90% CI 103·28-199·45)<br><br>56 mg/m2<br>Mild: $AUC_{0\text{-}inf}$ 181·90% (90% CI 96·4-343·24)<br>Moderate: $AUC_{0\text{-}inf}$ 152·59% (90% CI 74·87-310·96) | Mild and moderate: 75% of the original dose.<br>Severe: not recommended | Kyprolis label [1]<br>SPC Kyprolis[2]<br>Badros et al.[35]<br>Quach et al. [36]<br>Brown et al.[37] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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 CO2. | **FDA:**<br>Do not administer to patients with compromised renal function<br><br>**EMA:**<br>Reduce dose if GFR is reduced, CLcr < 10 ml/min: contraindicated<br><br>**Kintzel et al.**<br>CLcr 60 ml/min: 80%<br>CLcr 45 ml/min: 75%<br>CLcr < 30 ml/min: not recommended<br>HD: not studied | GFR 46-60 ml/min: 80% of the original dose<br>GFR 31-45 ml/min: 75% of the original dose<br>GFR < 30 ml/min: not recommended<br>HD: not recommended | **EMA/FDA:**<br>Hepatic impairment: no advise given | Mild and moderate: no need for dose adjustment is expected<br><br>Severe: not recommended | Bicnu label[1]<br>SPC Carmustine Obvius[2]<br>Kintzel et al.[38] |
| **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:**<br>CLcr 30-89 ml/min: no dose adjustment<br>CLcr <30 ml/min: not studied HD: not studied | GFR 30-89 ml/min: no dose adjustment is needed<br>GFR < 30 ml/min: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Child-Pugh A: no dose adjustment (18% increase in $AUC_{0\text{-}inf}$)<br>Child-Pugh B: no dose adjustment (2% increase in $AUC_{0\text{-}inf}$)<br>Child-Pugh C: 67% of the original dose (66%increase in $AUC_{0\text{-}inf}$) | Child-Pugh A and B: no dose adjustment is needed<br><br>Child-Pugh C: 67% of original dose | Zykadia label[1]<br>SPC Zykadia[2] |
| **Cetuximab** | Cetuximab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>Not studied in patients with renal impairment<br><br>**Inauen et al.**<br>HD: not dialysed, no dose adjustment needed | Renal impairment: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Not studied in patients with hepatic impairment | Hepatic impairment: no need for dose adjustment is expected | Erbitux label[1]<br>SPC Eribtux[2]<br>Inauen et al. [39] |
| **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:**<br>Renal impairment: no dose adjustment is needed<br>HD: not dialysable, no dose adjustment needed (FDA) | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Not studied in patients with hepatic impairment; consider dose reduction in severe hepatic impairment. | Mild and moderate: no need for dose adjustment is expected<br><br>Severe: not recommended | Leukeran label[1]<br>SPC Leukeran[8] |
| **Chlormethine** | Chlormethine is rapidly metabolised after administration. Its metabolites are mainly excreted in urine. | **FDA:**<br>Renal impairment/HD: no advise given | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA:**<br>Hepatic impairment: no advise given | Mild: no need for dose adjustment is expected Moderate and severe: not recommended | Label mustargen[1] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Cisplatin** | Cisplatin is not metabolised. It is highly protein bound (90%) and is excreted predominantly in urine and to a minimal extent in feces. | **FDA:**<br>CLcr < 60 ml.min: contraindicated<br>**MHRA;**<br>dose should be reduced adequately<br><br>**Watanabe et al.**<br>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.<br><br>**Kintzel et al.**<br>GFR 60 ml/min: 75% of the original dose<br>GFR 45 ml/min: 50% of the original dose<br>GFR 30 ml/min: not recommended | Curative<br>GFR 50-59 ml/min: 75% of the original dose<br>GFR 40-49 ml/min: 50% of the original dose<br>GFR < 40 ml/min: not recommended HD: 50% of the original dose may be considered<br><br>Palliative<br>GFR 50-59 ml/min: 75% of the original dose<br>GFR < 50 ml/min: not recommended HD: not recommended, consider carboplatin | **FDA/MHRA:**<br>No advise given | Hepatic impairment: no need for dose adjustment is expected | Cisplatin label[1]<br>SPC Cisplatin[8]<br>Watanabe et al.[40]<br>Kintzel et al. [38] |
| **Cladribine** | The prodrug cladribine is metabolised intracellularly to its active metabolite. Cladribine is mainly excreted in urine (15-18% unchanged) | **EMA:**<br>CLcr ≤ 50 ml/min: not studied, contraindicated<br><br>**Crews et al.**<br>Half-life increased approximately 2-fold in a child on CVVH/HD | GFR ≤ 50 ml/min: not recommended<br><br>HD: not recommended | **EMA:**<br>Child-Pugh A: not studied, no dose adjustment<br>Child-Pugh B and C: not studied, contraindicated | Child-Pugh A: no need for dose adjustment is expected<br>Child-Pugh B and C: not recommended | SPC Litak[2]<br>Crews et al.[41] |
| **Clofarabine** | The prodrug clofarabine is metabolised intercellulary to its active metabolite. Clofarabine is mainly excreted in urine (60% unchanged) | **EMA/FDA:**<br>CLCcr 30-59 ml/min: 50% of the original dose<br>CLcr <30 ml/min: not studied<br>HD: not studied<br><br>**Benitez et al.**<br>HD: clofarabine was not effectively dialysed during intermittent HD, $T_{1/2}$ interdialytic and on hemodialysis was approximately 2·5-3 times higher than in patients without renal impairment. | GFR 30-59 ml/min: 50% of the dose<br>GFR <30 ml/min: not recommended<br><br>HD: not recommended | **FDA:**<br>Not studied in patients with hepatic impairment<br><br>**EMA:**<br>No experience in patients with hepatic impairment (serum bilirubin > 1.5 x ULN plus AST and ALT > 5 x ULN)<br>Severe: contraindicated | Mild and moderate: no need for dose adjustment is expected<br>Severe: not recommended | Cloclar label[1]<br>SPC Evoltra[2]<br>Benitez et al.[42] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Cytarabine (high-dose ≥ 1 g/m2)**<br><br>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 urine (90% as metabolites, 5·8% unchanged) | **MHRA:**<br>Renal impairment: use with caution and at reduced dose. HD: dialysed<br><br>**Kintzel et al.**<br>CLcr 60 ml/min: 60% of the original dose<br>CLcr 45 ml/min: 50% of the original dose<br>CLcr 30ml/min: not recommended<br><br>**Radeski et al.**<br>HD: no dose adjustment, HD initiated 6 h after administration of 1 g/m2 resulted in 63% Ara-U removal. | GFR ≥ 60 ml/min: no dose adjustment is needed<br>GFR 31-59 ml/min: 50% of the original dose<br>GFR < 30 ml/min: not recommended<br><br>HD: 50% of the original dose, start HD 4-5 h after administration | **MHRA:**<br>Hepatic impairment: use with caution and at reduced dose<br><br>**Barker et al.**<br>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<br>Severe: consider 25-50% of the original dose and increase if tolerated | Cytarabine 100 mg/ml, Pfizer Ltd.[8]<br>Kintzel et al. [38]<br>Smith et al.[49]<br>Radeski et al.[50]<br>Barker et al. [51] |
| **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:<br>Mild and moderate without hepatic impairment: no dose adjustment<br>Severe: no advice<br>In patients with combined renal and hepatic impairment elimination is prolonged<br>HD: not studied | GFR ≥30 ml/min without hepatic impairment: no dose adjustment is needed<br>GFR <30 ml/min: 70% of the original dose may be considered<br>HD: 70% of the original dose may be considered | **MHRA:**<br>Mild and moderate without renal impairment: no dose adjustment<br>Severe: no advice<br>in patients with combined renal and hepatic impairment elimination is prolonged | Mild and moderate without renal impairment: no dose adjustment is needed<br>Severe: not recommended | SPC Dacarbazine[8] |
| **Dactinomycin** | Dactinomycin is minimally metabolised. Approximately 30% of the dose is excreted in urine and feces. | **FDA/MHRA:**<br>Not studied in patients with renal impairment<br>HD: not studied | Renal impairment: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **FDA/MHRA:**<br>Not studied in patients with hepatic impairment | Mild and moderate: no need for dose adjustment is expected<br><br>Severe: not recommended | Cosmegen label[1]<br>SPC cosmegen[8] |
| **Daratumumab** | Daratumumabis catabolised by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **FDA:**<br>CLcr: 15-89 ml/min: no dose adjustment is needed<br>**EMA:**<br>Renal impairment: no dose adjustment needed | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild/moderate :no dose adjustment needed<br>Severe: not studied<br><br>**EMA:**<br>Hepatic impairment: no dose adjustment needed | Hepatic impairment: no dose adjustment is needed | Darzalex label [1]<br>SPC Darzalex[2] |
| **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:<br>Creatinine clearance had no clinically relevant effect on the pharmacokinetics<br>HD: not studied | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>No initial dose adjustment is needed<br>Child-Pugh-A: not studied<br>Child-Pugh B: 8% decrease in mean AUC<br>Child-Pugh C: 28% decrease in mean AUC | Child-Pugh A-C: no dose adjustment is needed | Label Sprycel [8]<br>SPC Sprycel[2] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Serum creatinine 105-265 µmol/L: 75% serum creatinine > 265 µmol/L: 50%<br><br>**Krashin et al.**<br>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<br><br>GFR < 30 ml/min: 50% of the original dose<br><br>HD: 50% of the original dose | **MHRA:**<br>Serum bilirubin 20-50 µmol/L: 75% of the original dose<br>Serum bilirubin > 50 µmol/L: 50% of the original dose | Bilirubin 20-50 µmol/L: 75% of the original dose<br>Bilirubin > 50 µmol/L: 50% of the original dose | SPC Daunorubicin[8]<br>Krashin et al. [53] |
| **Decitabine** | Decitabine is converted intracellularly to its active metabolite. Decitabine is metabolised by cytidine deanimase in, among others, the liver and kidneys.<br>Decitabine and its metabolites are excreted in urine (90%, 4% unchanged). | **EMA/FDA:**<br>renal impairment: not studied. Exposure not likely to be affected in patients with impaired renal function (EMA).<br><br>**Levine et al.**<br>Retrospective safety data:higher incidence of grade ≥ 3 cardiac and respiratory toxicities in group with CLcr< 60ml/min compared to CLcr ≥60ml/min. | Renal impairment: no need for dose adjustment at start is expected, close monitoring for toxicity is recommended<br>HD: not recommended | **EMA/FDA:**<br>Hepatic impairment: not studied | Hepatic impairment: no need for dose adjustment is expected | Dacogen label[1]<br>SPC Dacogen[2]<br>Levine et al.[54] |
| **Docetaxel** | Docetaxel is metabolised in the liver. Docetaxel and its metabolites are mainly excreted in feces (75%) and to a lesser extend with urine (6%), mostly as metabolites. | **EMA/FDA**<br>not studied<br><br>**Dimopoulos et al.**<br>Full dose was tolerated in 11 patients with CLcr <10- 39ml/min.<br><br>**Hochegger et al.**<br>HD: not dialysed | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA**<br>If bilirubin > ULN or AST and/or ALT > 1·5 x ULN concomitant with AP > 2·5 x ULN: avoid<br><br>**EMA**<br>AST and/or ALT > 1·5 x ULN concomitant with AP > 2·5 x ULN: reduce to 75 mg/m2<br><br>Serum bilirubin > ULN and/or ALT and AST > 3·5 x ULN concomitant with AP > 6 x ULN: only use on strict indication<br><br>**Bruno *et al*.**<br>PopPK: 27% decrease in CL in patients with ALT or AST > 1·5 X ULN and AP>2·5 X ULN<br><br>**Syn et al.**<br>AP, AST and/or AST ≤ 5 x ULN and bilirubin < 1 x ULN: 75% of the original dose<br>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 AUC0-inf.<br><br>**Minami *et al.***<br>popPK: AP > 2·5 x ULN and AST/ALT >2·5 - 5·0 x ULN<br>22% decrease in CL, suggesting a 20% dose reduction<br>AP > 2·5 x ULN and AST/ALT<br>>5·0 - 20·0 x ULN 38%<br>decrease in CL, suggesting a 40% dose reduction | AST and/or ALT > 1·5-5 x ULN concomitant with AP > 2·5 – 5·0 x ULN and normal bilirubin: consider 75% of the original dose<br><br>AST or ALT >1·5-5 x ULN concomitant with AP ≤ 2·5-6 x ULN and/or bilirubin ≤ 1-1·5 x ULN: consider 50% of the original dose<br><br>Bilirubin > 1·5 x ULN or AST/ALT > 10 x ULN or AP > 6 x ULN: not recommended | Taxotere label[1]<br>SPC taxotere[2]<br>Dimopoulos et al[55]<br>Hochegger et al. [56]<br>Bruno et al.[57]<br>Syn et al.[58]<br>Minami et al.[59]<br>Eckmann et al.[60] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | **Eckmann et al.**<br>A dose of 25 mg/m2(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) | | |

| | | **Renal impairment** | | **Hepatic impairment** | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Renal impairment: no advice given<br><br>**MHRA**<br>eGFR < 10ml/min: 75% of the dose<br><br>**Yoshida et al.**<br>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<br><br>GFR < 10ml/min: no need for dose adjustment is expected<br>HD: 75% of the original dose may be considered | **FDA/ MHRA:**<br>Serum bilirubin 20-50 µmol/L: 50% of the original dose<br>Serum bilirubin 50 µmol/L – 85.5 µmol/ : 25% of the original dose<br>Serum bilirubin > 85.5 µmol/: contraindicated (FDA)<br>Child-Pugh C: contraindicated | Bilirubin 20-50 µmol/L: 50% of the original dose<br><br>Bilirubin 51 µmol/L – 86 µmol/ : 25% of the original dose<br><br>Bilirubin > 86 µmol/L or Child-Pugh C: not recommended | Doxorubicin label[1]<br>SPC doxorubicin[2]<br>Yoshinda et al.[61] |
| **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:**<br>No dose adjustment is needed | Renal impairment: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **EMA:**<br>Bilirubin < ULN and normal<br>AST: no dose adjustment<br>Bilirubin < ULN and raised<br>AST: consider a 25% dose reduction<br>Bilirubin > ULN but < 50 µmol/l: 50% dose reduction<br>Bilirubin >50 µmol/l: avoid if possible, otherwise 75% dose reduction | AST > ULN: 75% of the original dose<br>Bilirubin 20-50 µmol/L: 50% of the original dose<br>Bilirubin 51 µmol/L – 86 µmol/L : 25% of the original dose<br>Bilirubin > 86 µmol/L or Child-Pugh C: not recommended | SPC Myocet[2] |
| **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:**<br>No information<br>**EMA:**<br>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<br><br>HD: no need for dose adjustment is expected | **FDA:**<br>Bilirubin ≥ 1·2 mg/dL: a dose reduction is needed<br>**EMA:**<br>Bilirubin ≥ 1·2-3·0 mg/dl:<br>75% of the original dose Bilirubin is > 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<br>Bilirubin > 86 µmol/L: not recommended | Doxil label[1]<br>SPC Caelyx label[2] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Elotuzumab** | Elotuzumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>Renal impairment/HD: no dose adjustment needed<br><br>**Berdeja et al.**<br>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<br><br>HD: no dose adjustment is needed | **EMA/FDA:**<br>mild: no dose adjustment is needed.<br>moderate and severe: not studied. | Mild: No dose adjustment is needed<br>Moderate and severe: no need for dose adjustment is expected | Empliciti label[1]<br>SPC Empliciti (2)<br>Berdeja et al.[62] |
| **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:**<br>CLcr > 30 ml/min: no clinically meaningful effect on PK<br>CLcr < 30 ml/min: not studied | GFR ≥ 30 ml/min: no dose adjustment is needed<br><br>GFR < 30 ml/min: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild: no clinically meaningful effect on PK<br>Moderate and severe: not studied | Mild: No dose adjustment is needed<br>Moderate: 50% of the original dose may be considered<br>Severe: not recommended | Label Idhifa[1] |
| **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:**<br>serum creatinine < 5 mg/dL: no clinically relevant effect on PK, no dose adjustment serum creatinine > 5 mg/dL: not studied, consider dose reduction<br>HD: not studied (FDA) not dialysed (MHRA)<br><br>**Gori et al.**<br>HD: 30 mg/m2 weekly was tolerated | GFR ≥ 10 ml/min:<br>No dose adjustment is needed<br>GFR < 10 ml/min: no need for dose adjustment is expected.<br>HD: no need for dose adjustment is expected, consider weekly schedule | **FDA:**<br>Bilirubin 1·2-3 mg/dL or AST 2-4 ULN: 50% of the original dose<br>Bilirubin > 3 mg/dL or AST > 4x ULN: 25% of the original dose<br><br>**MHRA:**<br>Elevated bilirubin/AST: lower doses are recommended Severe: contraindicated<br><br>**Twelves et al.**<br>25 mg/m2 once weekly was tolerated in breast cancer patients with liver metastases and AST > 2 x ULN or bilirubin > ULN<br><br>**Dobbs et al.**<br>Proposed dosing scheme ranging from 20 – 90mg/m2based on AST levels and target AUC. | Bilirubin 21-51 µmol/L or AST 2-4 x ULN: consider 50% of the original dose<br><br>Bilirubin > 51 µmol/L or AST > 4x ULN: consider 25% of the original dose<br><br>Bilirubin > 86 µmol/L or Child-Pugh C: not recommended | Ellence label[1]<br>SPC Epirubicin[8]<br>Gori et al.[64]<br>Dobbs et al.[65]<br>Twelves et al.[66] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr > 50 ml/min: no dose adjustment<br>CLcr 15-50 ml/min: 75% of the original dose<br>CLcr <15ml/min: not studied, consider further dose reduction<br>HD: not dialysed (MHRA)<br><br>**Watanabe et al.**<br>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<br>GFR 10-50 ml/min: 75% of the original dose, increase if tolerated<br>HD: not dialysed, consider 75% of the original dose | **FDA:**<br>Not reported. Total body clearance correlated with albumin concentration.<br><br>**MHRA:**<br>Total body clearance of etoposide is not reduced in adult patients with liver dysfunction<br><br>**Stewart et al.**<br>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<br><br>Bilirubin ≥ 50 µmol/L or decreased albumin levels: consider 50% of the dose, increase if tolerated | Etophos label[1]<br>SPC Etophos[2]<br>Stewart et al.[72]<br>Watanabe et al. [40] |
| **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:**<br>Renal impairment: no dose adjustment<br>HD: not studied<br><br>**Thiery-Vuillemin et al.**<br>HD: not dialysed | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA/FDA: (original dose 10 mg QD)**<br>Child-Pugh A: 7·5 mg QD<br>Child-Pugh B: 5 mg QD<br>Child-Pugh C: 2·5 mg QD<br><br>**Peveling-Oberhag et al.**<br>Child-Pugh A: $AUC_{0\text{-}inf}$ 1·84 (90%CI: 1·36-2·50)<br>Child-Pugh B: $AUC_{0\text{-}inf}$ 3·15 (90%CI: 2.36-4.21)<br>Child-Pugh C: $AUC_{0\text{-}inf}$ 3·64 (90%CI: 2·64-5·00) | Child-Pugh A: 75% of the original dose<br>Child-Pugh B: 50% of the original dose<br>Child-Pugh C: 25% of the original dose | Afinitor label[1]<br>SPC Afinitor [2]<br>Thiery-Vuillemin et al.[73]<br>Peveling-Oberhag et al.[74]<br>Kovarik et al. [75] |
| **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:**<br>Although renal impairment increases exposure to exemestane, no dose adjustment is necessary<br><br>**Jannuzzo et al.**<br>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$^2$ | Renal impairment:<br>Due to large therapeutic index no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **FDA/MHRA:**<br>Child-Pugh A: not studied<br>Child-Pugh B and C: Although hepatic impairment increases exposure to exemestane, no dose adjustment is necessary<br><br>**Jannuzzo et al.**<br>Child-Pugh B and C: 2-3 fold increase in $AUC_{0\text{-}inf}$ compared with normal hepatic function | Hepatic impairment:<br>Due to large therapeutic index no dose adjustment is needed | Aromasin label[1]<br>SPC Aromasin[8]<br>Januzzo et al.[76] |
| | | | | | | |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr ≥ 80 ml/min: no dose adjustment<br>CLcr 50-79 ml/min: 20 mg/m$^2$<br><br>CLcr 30-49 ml/min: 15 mg/m$^2$<br>CLcr < 30 ml/min: do not administer<br>HD: not studied<br><br>**MHRA:**<br>CLcr 30-70 ml/min: reduce up to 50% of the original dose<br>CLcr < 30 ml/min: contraindicated<br><br>**Lichtman et al.**<br>The following dose adjustments resulted in similar F-ara-A exposure ($AUC_{0\text{-}24h}$) levels:<br>CLcr > 70 ml/min/1·73m$^2$: 25 mg/m$^2$<br>CLcr 30-70 ml/min/1·73 m$^2$: 20 mg/m$^2$<br>CLcr < 30 ml/min/1·73m2: 15 mg/m$^2$<br><br>**Kielstein et al.**<br>HD: Average dialysis clearance was 25% of clearance in patients with normal renal function (dialysis 12h after administration of 40mg/m$^2$). | GFR > 70 ml/min: no dose adjustment is needed<br>GFR 30-70 ml/min: 80% of the original dose<br>GFR < 30 ml/min: not recommended<br><br>HD: 80% of the original dose. Start dialysis 12h after administration. | **MHRA/FDA:**<br>not studied | Hepatic impairment: no need for dose adjustment is expected | Fludarabine phophate Sandoz label[1]<br>SPC Fludara[8]<br>Lichtman et al. [77]<br>Kielstein et al. [78] |
| **Fluorouracil** | Fluorouracil (FU) is converted intracellularly mainly by dihydropyrimidine dehydrogenase (DPD) to inactive metabolites. A small part of fluourouracil is excreted unchanged in urine (15%). The remainder is metabolised in the liver. Metabolites are mainly excreted in urine. | **FDA:**<br>No advice given<br>**MHRA:**<br>Renal impairment: dose should be reduced by 33- 50%.<br><br>**Fleming et al.**<br>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.<br><br>**Rengelshausen et al.**<br>HD: not dialysed. PK of 5-FU comparable to patients with normal renal function. Higher levels of the potentially toxic metabolite fluoro-beta-alanine (FBAL) were observed. | Renal impairment: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **FDA:**<br>No advice given<br>**MHRA:**<br>Hepatic impairment: dose should be reduced by 33- 50%.<br><br>**Fleming et al.**<br>full dose (2600 mg m/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<br>Severe: not recommended | Fluorouracil, injection USP[1]<br>Fluorouracil 25 mg/ml injection Hospira Uk Ltd[8]<br>Rengelshausen et al. [79]<br>Fleming et al.[80] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Renal impairment: CLcr >20ml/min: no clinically relevant effect on PK. No dose adjustment (EMA)<br><br>**Shinagawa et al.**<br>Not dialysed | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Hepatic impairment due to liver metastases: PK not altered<br>Child Pugh A, B or C due to cirrhosis: increased plasma exposure (40, 263 and 166% respectively).<br><br>**Horak et al.**<br>Child-Pugh A: $AUC_{0\text{-}inf}$: 1·40<br>Child-Pugh B: $AUC_{0\text{-}inf}$: 3·63<br>Child-Pugh C: $AUC_{0\text{-}inf}$: 2·66<br>Hepatic impairment due to liver metastases: no significant difference in PK parameters | Hepatic impairment due to metastasis and Child Pugh A: no dose adjustment is needed.<br><br>Child-Pugh B and C: 50% of the original dose | Iressa label[1]<br>SPC Iressa[2]<br>Shinagawa et al.[82]<br>Horak et al.[83] |
| **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:**<br>Renal impairment: not studied. GFR 30-80ml/min: no significant effect on PK (MHRA)<br><br>**Venook et al.**<br>No statistical significant difference in gemcitabine pharmacokinetics in patients with renal impairment, however tolerance might be decreased.<br><br>**Kiani et al.**<br>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<br>GFR < 30 ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected. Start HD 6-12 h after administration. | **MHRA/FDA:**<br>Not studied<br><br>**Venook et al.**<br>No statistical significant differences in gemcitabine PK in patients with total bilirubin ≤1·6mg/dL and AST ≤2xULN or bilirubin 1·6 -7·0 mg/dl. However increased risk for hepatotoxicity in patients with elevated bilirubin.<br><br>**Joerger et al.**<br>Hepatic impairment (cohorts wild mild/moderate/severe) associated with lower clearance, not with DLT.<br><br>**Teusink et al.**<br>Retrospective safety data: full dose can be given safely in patients with severe hepatic impairment (total bilirubin ≥ 4·5 mg/dL) | Total bilirubin < 27 µmol/L: no dose adjustment is needed<br><br>Total bilirubin ≥ 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]<br>SPC Gemzar [2]<br>Venook et al[84]<br>Kiani et al.[85]<br>Joerger et al. [31]<br>Teusink et al. [86] |
| **Gemtuzumab ozogamicin** | Gemtuzumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. The metabolic pathway of gemtuzumab ozogamicin is anticipated to be therelease of N-acetyl-gamma- calicheamicin dimethylhydrazide by hydrolytic cleavage, which is further metabolised via non- enzymatic reduction. | **EMA/FDA:**<br>CLcr ≥ 30 ml/min: no dose adjustment<br>CLcr < 30 ml/min: not studied | GFR ≥ 30 ml/min: no dose adjustment is needed<br>GFR <30ml/min: no need for dose adjustment is expected.<br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild: no dose adjustment moderate and severe: not studied<br>**EMA:**<br>Bilirubin ≤ 2 × ULN and AST/ ALT≤ 2·5 × ULN: no dose adjustment<br>Bilirubin > 2× ULN and AST/ ALT > 2·5 × ULN: postpone until recovery | Mild: no dose adjustment is needed<br>Moderate and severe: no need for dose adjustment is expected | Mylotarg label[1]<br>SPC Mylotarg[2] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Hydroxycarbamide (Hydroxyurea)** | Hydroxycarbamide is for up to 60% metabolised in the liver. Hydroxycarbamide and its metabolites are excreted in urine (up to 80%). | **FDA:**<br>CLcr < 60 ml/min: 50% of the original dose<br>HD: 50% of the original dose following dialysis<br>**MHRA:**<br>Renal impairment: consider dose reduction<br><br>**Yan et al.**<br>CLcr 60-89 ml/min: $AUC_{0\text{-}inf}$ 188%<br>CLcr 30-59 ml/min:$AUC_{0\text{-}inf}$ 170%<br>CLcr 15-29 ml/min:$AUC_{0\text{-}inf}$ 162%<br>CLcr < 15 ml/min: $AUC_{0\text{-}inf}$ 180%<br>HD: $AUC_{0\text{-}inf}$ 152% | GFR < 60 ml/min: 50% of the original dose<br>HD: 50% of the original dose | **FDA/ MHRA:**<br>Not studied | No need for dose adjustment is expected. Monitor for hematological toxicity | Siklos label[1]<br>SPC Hydrea[8]<br>Yan et al.[87] |
| **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) and with minimally in urine (<10%). | **EMA/FDA:**<br>CLcr> 25 ml/min: no dose adjustment<br>CLcr < 25 ml/min: not studied<br>HD: not studied<br><br>**Filanovsky et al.**<br>full dose (560 mg) was tolerated in a patient with CLcr 13 ml/min. | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Child-Pugh A: 280 mg (EMA) 140 mg (FDA)<br>Child-Pugh B: 140 mg (EMA) 70 mg (FDA)<br>Child-Pugh C: avoid<br><br>**de Jong et al.**<br>Child-Pugh A: $AUC_{0\text{-}inf}$ 265·20% (90% CI 138·34-508·41)<br>Child-Pugh B: $AUC_{0\text{-}inf}$ 795·84%(90% CI 456·87-1386·31)<br>Child-Pugh C: $AUC_{0\text{-}inf}$ 956·46%(90% CI 529·69-1691·15) | Child-Pugh A: 50% of the dose<br>Child-Pugh B: 12·5% of the dose.<br>Child-Pugh C: not recommended | Imbruvica label[1]<br>SPC Imbruvica [2]<br>Filanovsky et al.[88]<br>de Jong et al.[89] |
| **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**<br>Creatinin > ULN: consider dose reduction<br>HD: not studied, unlikely to be dialysed<br><br>**MHRA**<br>Renal impairment:<br>Severe (creatinine >2mg/dL): contraindicated<br><br>**Tsuchiya et al.**<br>HD: 67% of the original dose was tolerated and effective | GFR ≥ 30 ml /min: no need for dose adjustment is expected<br>GFR < 30 ml/min: consider 67% of the original dose<br>HD: consider 67% of the original dose | **FDA :**<br>Bilirubin > ULN: consider dose reduction<br>Bilirubin > 5 mg/dL: not recommended<br>Patients with bilirubin 2·6-5 mg/dL received 50% of the original dose<br><br>**MHRA:**<br>Bilirubin ≥1·2-2 mg/dL: 50% of the original dose<br>Severe (bilirubin > 2 mg/dL): contraindicated | Bilirubin 45 - 86 µmol/L: 50% of the original dose<br>Bilirubin > 86 µmol/L: not recommended | Idamycin PSF label[1]<br>SPC Zavedos [8]<br>Tsuchiya et al.[90] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr ≥ 15 ml/min: no dose adjustment is needed<br>HD: not studied<br><br>**Jin et al.**<br>CLcr 15-29 ml/min: $AUC_{0\text{-}inf}$ 127% (90% CI 92-176) | Renal impairment: No dose adjustment is needed<br>HD: no need for dose adjustment is expected | FDA<br>ALT or AST or bilirubin > ULN: no dose adjustment AST or ALT > 2·5 x ULN or bilirubin > 1·5 x ULN: limited information<br>EMA:<br>Child-Pugh A and B: no dose adjustment, intensified monitoring<br>Child-Pugh C: limited information<br>Jin et al.<br>Child-Pugh B: AUC0-inf 158% (90% CI 125-199%)<br>Child-Pugh C: AUC0-inf 159% (90%CI 121-208%) | Child-Pugh A or B: no dose adjustment is needed<br>Child-Pugh C: start with 50% of the original dose (150 mg QD), increase if tolerated | Zydelig label[1]<br>SPC Zydelig[2]<br>Jin et al.[91]<br>Jin et al.[92] |
| **Ifosfamide** | Ifosfamide (prodrug) is metabolised in the liver to its active metabolites, one of which is the cytotoxic and urotoxic acrolein.<br>Ifosfamide and its metabolites are mainly excreted in urine (70- 86%unchanged fraction depending on the dose) and minimally in feces. | **FDA:**<br>Not studied, monitor for toxicity and consider dose reduction.<br>HD: dialysed<br><br>**MHRA**<br>Impaired renal function: contraindicated<br>HD: dialysed<br><br>**Carlson et al.**<br>HD: Mean decrease of ifosfamide, chloroacetaldehyde and 4-hydroxyifosfamide concentrations of 86·9%, 77·2% and 36·2% respectively following dialysis in an anephric 20-month old infant. | GFR ≥50 ml/min: no dose adjustment is needed<br>GFR < 50 ml/min or HD: not recommended | **FDA**<br>not studied, give cautiously.<br><br>**MHRA**<br>Hepatic impairment: contraindicated | Mild and moderate: no need for dose adjustment is expected.*<br><br>Severe: not recommended, due to risk of reduced efficacy*<br><br>*due to limited information extrapolated from cyclophosphamide | Ifex label[1]<br>SPC Ifosfamide injection 1g[8]<br>Carlson et al. [93] |
| **Imatinib** | Imatinib is metabolised in the liver. The active metabolite CGP74588 contributes to the clinical effect. Imatinib and its metabolitesare predominantly excreted in feces (68%, 20% unchanged) and to a lesser extent in urine (13%, 5% unchanged). | **FDA:**<br>CLcr ≥ 60 ml/min: no dose adjustment<br>CLcr 40-59 ml/min: no dose adjustment, max 600 mg<br>CLcr 20-39 ml/min: 50% of the dose, max 400 mg<br>CLcr < 20 ml/min: 100 mg<br><br>**EMA:**<br>Renal impairment or HD: minimum of 400mg/day as starting dose<br><br>**Gibbons et al.**<br>CLcr 40-59ml/min and CLcr 20-39ml/min: significantly greater AUC0-inf compared to normal renal function, no increase in toxicity. No requirement for initial dose adjustment in these patients.<br><br>**Pappas et al.**<br>HD: no change in imatinib and CGP74588 PK compared to normal renal function. | Renal impairment: no dose adjustment is needed.<br><br>HD: no dose adjustment is needed | **FDA:**<br>mild an moderate: no dose adjustment<br>severe hepatic impairment : 75% of the original dose<br><br>**EMA:**<br>Hepatic impairment: minimum of 400 mg/day as starting dose<br><br>**Ramanathan et al.**<br>mild and moderate: no change in AUC<br>severe: approximately a1·5 increase of AUC for imatinib and CGP74588. | Hepatic impairment: no dose adjustment is needed | Gleevec label[1]<br>Glivec SPC[2]<br>Gibbons et al.[94]<br>Pappas et al. [95]<br>Ramanathan et al.[96] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Inotuzumab ozogamicin** | Inotuzumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. N-acetyl-gamma-calicheamicin dimethylhydrazide is metabolised via non-enzymatic reduction | **EMA/FDA:**<br>CLcr 15-89 ml/min: no change in CL<br>HD: not studied | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Mild: no dose adjustment Moderate and severe: not studied<br>Serious ongoing hepatic liver disease (e.g. cirrhosis): contraindicated | Hepatic impairment: no need for dose adjustment is expected | Besponsa label[1]<br>SPC Besponsa[2] |
| **Ipilimumab** | Ipilimumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>CLcr ≥ 30 ml/min: no dose adjustment<br>CLcr < 30 ml/min: no dose adjustment (FDA) not studied (EMA) | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>mild: no dose adjustment<br>moderate and severe: not studied | Hepatic impairment: no need for dose adjustment is expected | Yervoy label[1]<br>SPC Yervoy [2] |
| **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:**<br>Renal impairment: not studied, use with caution HD: not recommended<br><br>**MHRA:**<br>Not recommended in renal impairment.<br><br>**Czock et al., Stemmler et al. (weekly)**<br>HD: minimally dialysed, low clearance of SN-38. Dose escalation from 50 mg/m2 to 80 mg/m2 was tolerated.<br><br>**Fujita et al. (weekly/2- weekly)**<br>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.<br><br>**Venook et al. (3-weekly)**<br>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 creatinine <1·5mg/dL. | GFR ≥ 10 ml/min: no need for dose adjustment is expected<br><br>GRF < 10 ml/min: start with 50-66% of the original dose, increase if tolerated<br><br>HD: start with 50- 66% of the original dose, increase if tolerated | **FDA:**<br>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).<br><br>**MHRA (3-weekly):**<br>Bilirubin <1·5 x ULN: no dose adjustment<br>Bilirubin 1·5 -3 x ULN: 200 mg/m².<br>Bilirubin > 3 x ULN: contraindicated<br><br>**Raymond et al. (3-weekly)**<br>Reduced irinotecan clearance in hepatic impairment. Hyperbilirubinmi a associated with exponential decrease in clearance and increase in dose normalized AUC.<br>Dose advice: bilirubin <1·5 x ULN: 350 mg/m², bilirubin ≥1·5 to 3 x ULN: 200 mg/m².<br><br>**Schaaf et al. (weekly)**<br>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 : 60 mg/m2;<br>Bilirubin 3·1-5·0 x ULN and ALT/AST ≤5·0 x ULN 50 mg/m2;<br>bilirubin 1·5-3·0 x ULN and ALT/AST 5·1-20·0 x ULN: 40 mg/m2.<br>Similar SN-38 exposure and observed toxicities with these dose reductions compared to patients with normal liver function (despite lower irinotecan $AUC_{0\text{-}24h}$). | **3-weekly**<br>Bilirubin ≥1·5 to 3 x ULN: 200 mg/m²<br>Bilirubin > 3 x ULN: not recommended<br><br>**Weekly**<br>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<br>Bilirubin 3·1-5·0 x ULN and ALT/AST ≤ 5·0 x ULN: 50 mg/m2<br>Bilirubin 1·5-3·0 x ULN and ALT/AST 5·1-20·0 x ULN: 40 mg/m2 | Camptosar label[1]<br>SPC Campto[2]<br>Czock et al. [97]<br>Stemmler et al. [98]<br>Fujita et al. [99]<br>Raymond et al. [100]<br>Schaaf et al.[101]<br>Venook et al. [102] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr ≥ 30 ml/min: no dose adjustment<br>CLcr < 30 ml/min: 3 mg QD<br>HD: 3 mg QD, not dialysed<br><br>**Gupta et al.**<br>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<br>GFR <30 ml/min: 75% of the original dose<br>HD: 75% of the original dose | **EMA/FDA:**<br>Mild: no dose adjustment Moderate and severe: 3 mg QD<br><br>**Gupta et al.**<br>Moderate (2·3 mg): dose-normalized $AUC_{0\text{-}last}$ 1·27 (90% CI 0·77-2·11)<br>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]<br>SPC Ninlaro[2]<br>Gupta et al.[103]<br>Gupta et al.[104] |
| **Lapatinib** | Lapatinib is metabolised in the liver. Lapatinib is predominantly excreted in feces (27% unchanged). Less than 2% is eliminated in urine. | **FDA/EMA:**<br>Mild/moderate: no dose adjustment<br>Severe: not studied<br>HD: unlikely to be dialysed | GFR ≥ 30 ml/min: no dose adjustment is needed<br><br>GFR < 30 ml/min: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **FDA:**<br>Child-Pugh A: not studied, no dose adjustment<br>Child-Pugh B: 14% increase in AUC, no dose adjustment Child-Pugh C: 63% increase in AUC: 750mg QD (HER2-positive metastatic breast cancer) or 1000mg QD (hormone receptor and HER2-positive breast cancer)<br><br>**EMA:**<br>Child-Pugh A: not studied<br>Child-Pugh B: 56% increase in AUC<br>Child-Pugh C: 85% increase in AUC | Child-Pugh A and B: no dose adjustment is needed<br><br>Child-Pugh C: 750mg QD (HER2 positive metastatic breast cancer) or 1000mg QD (hormone receptor and HER2-positive breast cancer) | Tykerb label[1]<br>SPC Tyverb[2] |
| **Lomustine** | Lomustine is rapidly metabolised to its active metabolites. Its metabolites are mainly excreted in urine. | **FDA:**<br>Renal impairment: not studied<br>HD: not studied<br><br>**MHRA:**<br>Severe: contraindicated<br><br>**Kintzel et al.**<br>CLcr 60 ml/min: 75% of the original dose<br>CLcr 45 ml/min: 70% of the original dose<br>CLcr 30 ml/min: not recommended | GFR > 50 ml/min: no dose adjustment is needed<br>GFR 30-50 ml/min: 75% of the original dose<br>GFR < 30 ml/min: not recommended<br>HD: not recommended | **FDA/ MHRA:**<br>Hepatic impairment: not studied | Mild and moderate: no need for dose adjustment is expected<br>Severe: not recommended | Gleostine label[1]<br>SPC lomustine medac[8]<br>Kintzel et al. [38] |
| **Melphalan** | Melphalan is hydrolyzed in plasma to inactive metabolites. Approximately 10% is excreted in urine unchanged. | **FDA/MHRA**<br>Oral: no dose advice given<br>HD: not dialysed<br><br>**FDA: (IV)**<br>Consider 50% of the dose if Blood Urea Nitrogen ≥ 30mg/dL for palliative treatment<br><br>**MHRA: (IV)**<br>CLcr 30-50ml/min: 50% of the original dose<br>CLcr < 3 0ml/min: high-dose melphalan contraindicated<br><br>**Kergueris et al.**<br>PK parameters correlated with creatinine clearance. Renal impairment did not result in a large decrease in CL compared to inter-individual variation in CL. | Conditioning treatment:<br>Renal impairment/HD: no need for dose adjustment is expected<br><br>Palliative treatment GFR 30-50 ml/min: consider 50% of the dose<br>GFR < 30 ml/min or HD: not recommended | **FDA/MHRA:**<br>Hepatic impairment: not studied | Hepatic impairment: no need for dose adjustment is expected | Evomela/ Alkeran label[1]<br>SPC Alkeran/Melphlan hydrochloride [8]<br>Kergueris et al. [106] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Not studied, consider dose reduction, starting at the low end of dosing range, or increasing the dosing interval to 36-48 hours.<br>HD: no clearance expected | GFR ≥ 30 ml/min: no need for dose adjustment is expected<br>GFR < 30 ml/min: increase dosing interval to 48 hours<br>HD: not recommended | EMA/FDA:<br>Not studied, consider dose reduction, starting at the low end of dosing range. | Mild : no need for dose adjustment is expected<br>Moderate: consider starting with a lower dose or increase dosing interval.<br>Severe: not recommended | Purinethol/Purixan label[1]<br>SPC Xaluprine[2] |
| **Methotrexate** | Methotrexate is partly metabolised in the liver. Methotrexate and its metabolites are mainly excreted in urine by glomerular filtration and active tubular secretion (80-90% unchanged). Excretion in feces is minimal (10% or less). | **FDA**<br>Reduced clearance in renal impairment. No dose advice given.<br><br>**MHRA:**<br>CLcr > 50 ml/min: no dose adjustment<br>CLcr 20-50 ml/min: 50% of the dose<br>CLcr < 20 ml/min: not recommended<br>Conventional HD and peritoneal dialysis: not dialysed<br><br>**Wall et al.**<br>HD: approximately 63% of infused methotrexate removed by 6 hours of high-flux dialysis initiated 1 hour after administration | GFR ≥ 50 ml/min: no dose adjustment is needed<br>GFR 20-50 ml/min: 50% of the original dose<br>GFR < 20 ml/min not recommended. If unavoidable consider hemodialysis<br>HD: not recommended, if unavoidable 50% of the original dose, can be dialysed with daily high flux dialysis. | **FDA**<br>No advice given<br><br>**MHRA:**<br>bilirubin > 5 mg/dL: contraindicated | Hepatic impairment: no need for dose adjustment is expected<br><br>Bilirubin > 86 µmol/L: avoid, due to hepatotoxicity | Methotrexate injection USP label[1]<br>methotrexate concentration for solution for infusion[8]<br>Wall et al. [107] |
| **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%). | **FDA/EMA:**<br>CLcr ≥ 30 ml/min: no clinically meaningful effect on PK, no dose adjustment CLcr < 30 ml/min: not studied<br><br>**Tollkuci et al.**<br>HD: full dose was tolerated and effective | GFR ≥ 30ml/min: no dose adjustment is needed<br>GFR < 30ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild/moderate: no clinically meaningful effect on PK Severe: not studied<br><br>**EMA:**<br>Child-Pugh A and B: no dose adjustment<br>Child-Pugh C: not studied | Mild, moderate, Child-Pugh A and B,: no dose adjustment<br>Severe or Child- Pugh C: not recommended | Rydapt Label[1]<br>SPC Rydapt[2]<br>Tollkuci et al.[108] |
| **Mitomycin** | Mitomcyin is metabolised and inactivated in the liver but also in other tissues. Excretion is mainly in feces and to a lesser extent in urine (approximately 10% unchanged) | **MHRA:**<br>Renal impairment: not studied | GFR ≥ 30 ml/min: no need for dose adjustment is expected<br>GFR < 30 ml/min or HD: not recommended due to nephrotoxicity | **MHRA:**<br>Hepatic impairment: not studied | Mild and moderate: no need for dose adjustment is expected<br>Severe: consider 50% of the original dose | Mitomycin-C Kyowa SPC[8] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Renal impairment: no advice given<br><br>**EMA:**<br>Mild/moderate: exercise caution, monitor mitotane plasma levels<br>Severe: not recommended | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | EMA/FDA:<br>Hepatic impairment: not studied, use with caution Monitor mitotane plasma levels (EMA)<br>Severe: not recommended (EMA) | Mild and moderate: no need for dose adjustment is expected.<br>Severe: not recommended | Lysodren label[1]<br>SPC lysodren [2] |
| **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:**<br>Renal impairment: not studied, use with caution HD: not studied<br><br>**Boros et al.**<br>HD: not dialysed | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **MHRA:**<br>Hepatic impairment: not studied, use with caution<br><br>**Savaraj et al.**<br>Total clearance in patients with liver dysfunction or ascites was less than 50% of that observed in patients without liver dysfunction or ascites. | Mild/moderate: no need for dose adjustment is expected<br>Severe: consider 50% of the original dose | SPC Mitoxantrone 2 mg/ml concentrate for solution for infusion (Accord Healthcare Limited[8]<br>Boros et al. [109]<br>Savaraj et al.[110] |
| **Mogamulizumab** | Mogamulizumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **FDA:**<br>Renal impairment: no clinically significant PK changes<br><br>**Yoshihara et al.**<br>HD: not dialysed, no dose adjustment is needed | Renal impairment: no dose adjustment is needed<br><br>HD: no dose adjustment is needed | **FDA:**<br>mild and moderate: no clinically significant changes in PK<br>severe: not studied | Mild and moderate: no dose adjustment is needed<br><br>Severe: no need for dose adjustment is expected | Label Potelegeo[1]<br>Yoshihara et al. [111] |
| **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:**<br>Renal impairment:<br>CLcr ≥ 50ml/min: no dose adjustment<br>CLcr < 50ml/min: not studied<br>HD: not studied | Renal impairment:<br>no need for dose adjustment is expected.<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>hepatic impairment: not studied | Hepatic impairment: no need for dose adjustment is expected | Arranon label[1]<br>Atriance SPC[2] |
| **Nilotinib** | Nilotinib is metabolised in the liver. Nilotinib and its metabolites are predominantly excreted in feces (93-94%, 69% unchanged). | **EMA/FDA:**<br>Renal impairment: not studied<br><br>**Onaka et al.**<br>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<br>HD: no need for dose adjustment is expected | **FDA:**<br>Newly diagnosed Ph+ Chronic Myelogenous Leukemia (CML)<br>Child-Pugh A-C: start at 200 mg BID, max 300 mg BID<br>Resistant or chronic phase Ph+ CML<br>Child-Pugh A-B: start at 300 mg BID, max 400 mg<br>BID Child-Pugh C: start at200 mg BID, max 400 mg BID<br><br>**EMA:**<br>No dose adjustment is needed<br><br>**Yin et al.**<br>Child-Pugh A: $AUC_{0\text{-}inf}$: 1·35 (90% CI 0·91-2·02)<br>Child-Pugh B: $AUC_{0\text{-}inf}$: 1·35 (90% CI 0·89-2·07)<br>Child-Pugh C: $AUC_{0\text{-}inf}$: 1·19 (90% CI 0·80-1·78) | Hepatic impairment: no dose adjustment is needed | Tasigna label[1]<br>Tasigna SPC[2]<br>Onaka et al.[112]<br>Yin et al.[113] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Nivolumab** | Nivolumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>GFR ≥ 30 ml/min: no dose adjustment<br>GFR < 30 ml/min: no dose adjustment (FDA), not studied (EMA) | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>mild: no dose adjustment<br>Moderate: no dose adjustment (FDA), not studied (EMA)<br>Severe: not studied | Mild and moderate: no dose adjustment is needed<br><br>Severe: no need for dose adjustment is expected | Label Opdivo [1]<br>SPC Opdivo[2] |
| **Obinutuzumab** | Obinutuzumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **FDA:**<br>No effect of baseline CLcr on PK.<br><br>**EMA:**<br>CLcr 30-89ml/min: no dose adjustment<br>CLcr <30ml/min: not studied | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Not studied in patients with hepatic impairment | Hepatic impairment: no need for dose adjustment is expected | Label Gazyva[1]<br>SPC Gazyvaro[2] |
| **Ofatumumab** | Ofatumumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>CLcr > 30 ml/min: no dose adjustment<br>CLcr ≤ 30 ml/min: not studied | GFR ≥ 30 ml/min: no dose adjustment is needed<br>GFR < 30 ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Hepatic impairment: not studied | Hepatic impairment: no need for dose adjustment is expected | Label Arzerra[1]<br>SPC Arzerra [(2)] |
| **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**<br>CLcr 30-80 ml/min: no dose adjustment<br>CLcr < 30 ml/min: 65 mg/m$^2$<br>(FDA), contraindicated (MHRA)<br><br>**Gori et al., Watayo et al.**<br>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.<br><br>**Takimoto et al.**<br>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<br>GFR < 30 ml/min: consider 50% of the original dose<br>HD: consider 50% of the original dose, HD within 1·5 hour after administration. | **FDA/MHRA:**<br>Hepatic impairment: not studied<br><br>**Synold et al.**<br>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]<br>SPC Eloxatin[2]<br>Gori et al.[118]<br>Watayo et al.[119]<br>Takimoto et al.[120]<br>Synold et al.[121] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Paclitaxel** | Paclitaxel is metabolised in the liver. Paclitaxel and its metabolites are predominantly excreted in feces (71%) and to a lesser extent in urine (14%). | **FDA:**<br>No advise given<br><br>**MHRA:**<br>Renal impairment: not studied, no dose advise given HD: pharmacokinetic properties in one patient undergoing HD in range with non-dialysis patients<br><br>**Tomita et al.**<br>Paclitaxel is not dialysed. AUC and Cmax were comparable to values reported in patients with normal renal function.<br><br>**Gelderblom et al.**<br>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<br>HD: no need for dose adjustment is expected | **FDA:**<br>**24-hour infusion:**<br>Transaminase <2 x ULN and bilirubin ≤1·5 mg/dL: no dose reduction (135 mg/m$^2$)<br>Transaminase 2- <10 x ULN and bilirubin ≤1·5 mg/dL: 74% of original dose (100mg/m$^2$)<br>Transaminase <10 x ULN and bilirubin 1·6-7.5 mg/dL: 37% of original dose (50 mg/m$^2$)<br>Transaminase ≥10 x ULN or bilirubin >7·5 mg/dL: not recommended<br><br>**3-hour infusion:**<br>Transaminase <10 x ULN and bilirubin ≤1·25 x ULN: no dose reduction (175 mg/m$^2$)<br>Transaminase <10 x ULN and bilirubin 1·26-2 x ULN: 77% of original dose (135mg/m$^2$)<br>Transaminase <10 x ULN and bilirubin 2·01-5xULN: 51% of orginal dose (100mg/m$^2$)<br>Transaminase ≥10 x ULN or bilirubin >5 x ULN: not recommended<br><br>**MHRA:**<br>Mild/moderate: not studied, no dose advise given<br>Severe: contraindicated<br><br>**Briasoulis et al.**<br>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.<br><br>**Joerger et al.**<br>Total bilirubin 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$^2$. | 24-hour infusion:<br>Transaminase <2 x ULN and bilirubin ≤26 µmol/l: no dose adjustment is needed (135mg/m$^2$)<br>Transaminase 2-10 x ULN and bilirubin ≤26 µmol/l: 74% of original dose (100mg/m$^2$)<br>Transaminase < 10 x ULN and bilirubin 27-128 µmol/l: 37% of orginal dose (50mg/m$^2$)<br>Transaminase ≥10 x ULN or bilirubin | Taxol label[1]<br>Paclitaxel SPC[2]<br>Briasoulis et al[123]<br>Tomita et al[124]<br>Gelderblom et al[125]<br>Joerger et al[126] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr ≥ 30 ml/min: no dose adjustment is needed<br>CLcr < 30 ml/min or HD: not studied<br><br>**Sharma et al.**<br>Panobinostat $AUC_{0\text{-}inf}$ geometric mean ratios compared to CLcr> 80ml/min:<br>CLcr 50-79 ml/min: 0·67 (90% CI 0·39-1·17)<br>CLcr 30-49 ml/min: 1·05 (90% CI 0·58-1·91)<br>CLcr < 30 ml/min: 0·63 ( 0·33-1·20)<br><br>**Sekiguchi et al.**<br>HD: dialysable. Elimination of panobinostat by HD 14·1- 36·3%. | Renal impairment: no need for dose adjustment is expected.<br>HD: no need for dose adjustment is expected. | **EMA/FDA:**<br>Mild: 75% of original dose (15mg)<br>Moderate: 50% of original dose (10mg)<br>Severe: avoid use<br><br>**Slingerland et al.**<br>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<br>Moderate: 50% of original dose<br>Severe: not recommended | FDA label Farydak[1]<br>SPC Farydak[2]<br>Sharma et al[128]<br>Slingerland et al[129]<br>Sekiguchi[130] |
| **Pegaspargase** | Pegylated L-asparaginase is degraded by proteolytic degradation. No renal or hepatic clearance. | **FDA:**<br>No advise given<br><br>**EMA:**<br>Renal impairment: no dose adjustment is needed | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **FDA:**<br>No advise given<br><br>**EMA:**<br>No dose adjustment is needed | Hepatic impairment: no dose adjustment is needed | FDA label Oncaspar[1]<br>SPC Oncaspar[2] |
| **Pembrolizumab** | Pembrolizumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>eGFR: 15-89 ml/min/1·73m$^2$: no clinically important effect on clearance<br>HD: not studied | Renal impairment: no dose adjustment is needed<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>mild: no clinically important effect on clearance (FDA), no dose adjustment (EMA)<br>moderate and severe: not studied | Mild: no dose adjustment is needed<br><br>Moderate and severe: no need for dose adjustment is expected | Label Keytruda[1]<br>SPC Keytruda[2] |
| **Pemetrexed** | Pemetrexed undergoes intracellular polyglutamation and is primarily excreted unchanged in urine (70-90%). Hepatic metabolism is minimal. | **EMA/FDA:**<br>CLcr ≥45 mL/min: no dose adjustment<br>CLcr < 45 mL/min: no dose recommendations (FDA), not recommended (EMA)<br><br>**Hill et al.**<br>CLcr 30-45 ml/min: 80% of dose was tolerated without grade ≥3 hematological toxicity<br><br>**Mita et al.**<br>Increased drug exposures in patients with renal impairment, GFR ≥ 40 mL/min: no dose adjustment needed<br>**Brandes et al.**<br>HD: not dialysed | GFR ≥ 40 ml/min: no dose adjustment is needed<br><br>GFR 30-40 ml/min: 80% of the original dose<br><br>GFR <30 ml/min: not recommended<br><br>HD: not recommended | **EMA/FDA:**<br>Not studied in patients with hepatic impairment | Mild and moderate: no need for dose adjustment is expected<br><br>Severe: not recommended, based on the risk of pemetrexed induced liver dysfunction | Label Alimta [1]<br>SPC Alimta[2]<br>Mita et al.[132]<br>Brandes et al.[133]<br>Hill et al. [134] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Pentostatin** | Only a small amount of pentostatin is metabolised. Pentostatin is predominantly excreted unchanged in urine (90%). | **MHRA:**<br>Ambiguous advice: CLcr < 60 ml/min: contraindicated.<br>However a study with 13 renally impaired patients suggest the following dose adjustments:<br><br>CLcr 40-59 ml/min: 75% of original dose (3 mg/m$^2$) CLcr 35-39ml/min: 50% of original dose (2mg/m$^2$)<br><br>**Lathia et al.**<br>Pentostatin $AUC_{0\text{-}inf}$ was comparable when treated with 4mg/m$^2$ in patients with CLcr > 60ml/min, 3mg/m$^2$ in patients with CLcr 41-60ml/min and 2mg/m$^2$ in one patient with CLcr 35- 40mg/m$^2$. | GFR 40-59 ml/min: 75% of original dose<br>GFR 35-39 ml/min: 50% of original dose GFR < 35 ml/min: not recommended<br>HD: not recommended.<br>If unavoidable consider 50% of the original dose, start HD 1-2 h after administration | **MHRA:**<br>Limited experience, treat with caution | Hepatic impairment: No need for dose adjustments is expected | SPC Nipent[8]<br>Lathia et al[135] |
| **Pixantrone** | Only a small amount of pixantrone is metabolised. Pixantrone is mainly excreted unchanged in bile with minimal excretion in urine (<10% ). | **EMA:**<br>Use with caution in patients with renal impairment | Renal impairment or HD: no need for dose adjustment is expected | **EMA:**<br>Mild/moderate: use with caution<br>Severe: contraindicated | Mild/moderate: no need for dose adjustment is expected<br>Severe: not recommended | SPC Pixuvri[2] |
| **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:**<br>Renal impairment: not studied<br><br>**EMA:**<br>CLcr ≥ 50ml/min: no dose adjustment needed<br>CLcr < 50ml/min/ESRD:<br>caution is recommended | GFR ≥ 50 ml/min: no dose adjustment is needed<br>GFR <50 ml/min or HD: no need for dose adjustment is expected | **FDA:**<br>Child-Pugh A/B/C: 67% of original dose (30mg QD)<br><br>**EMA:**<br>No dose reduction needed for hepatic impairment<br><br>**Narasimhan et al.**<br>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 C ($AUC_{0\text{-}inf}$ 79.4%) respectively. | Child-Pugh A/B/C: No need for dose adjustment is expected | FDA label Iclusig[1]<br>SPC Iclusig[2]<br>Narasimhan et al[136] |
| **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:**<br>eGFR ≥ 30 ml/min/1·73m$^2$: no dose reduction needed<br>eGFR 15-29ml/min/1·73m$^2$: 50% of the original dose (15 mg/m$^2$)<br>eGFR < 15 ml/min/1·73m$^2$ or<br>HD: (relatively) contraindicated<br><br>**Kelly et al.**<br>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<br>GFR 15-29 ml/min: 50% of the original dose (15 mg/m$^2$)<br>GFR < 15 ml/min: not recommended<br>HD: not recommended | **FDA:**<br>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. | FDA label Folotyn[1]<br>Kelly et al[137] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>CLcr < 10 ml/min: contraindicated | GFR ≥10ml/min: no dose adjustment is needed<br>GFR < 10ml/min: not recommended<br>HD: not recommended | **MHRA:**<br>Severe hepatic impairment: contraindicated | Hepatic impairment: No need for dose adjustments is expected | SPC Procarbazine[8] |
| **Regorafenib** | Regorafenib is metabolised in the liver. The M-2 and M-5 metabolite contribute to the clinical effect. Regorafenib and its metabolites are predominantly excreted in feces (71%, 47% unchanged) and to a lesser extent in urine (19%). | **FDA/EMA:**<br>Renal impairment: no dose adjustment recommended<br>HD: not studied | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild/moderate: no dose adjustment recommended, close monitoring<br>Severe: not studied, not recommended<br><br>**EMA:**<br>Child-Pugh A: no dose adjustment is needed<br>Child-Pugh B: limited data indicate similar exposure<br>Child-Pugh C: not studied | Mild, moderate or Child-Pugh A: no dose adjustment is needed<br>Child-Pugh B: no need for dose adjustment is expected<br>Child-Pugh C: not recommended | FDA Label Stivarga[1]<br>SPC Stivarga[2] |
| **Rituximab** | Rituximab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>Renal impairment: not studied<br><br>**Jillella et al.**<br>HD: not dialysed, comparable plasma levels | Renal impairment: no need for dose adjustment is expected<br><br>HD: no dose adjustment is needed | **EMA/FDA:**<br>Hepatic impairment: not studied | Hepatic impairment: no need for dose adjustment is expected | Rituxan label[1]<br>SPC MabThera[2]<br>Jillella et al.[139] |
| **Romidepsin** | Romidepsin is extensively metabolised in the liver. Romidepsin's route of excretion is unknown. | **FDA:**<br>Pharmacokinetics not affected by mild, moderate or severe renal impairment End-stage renal disease: not studied | Renal impairment or HD: no need for dose adjustment is expected | **FDA:**<br>Mild: no influence on pharmacokinetics, no advise given<br>Moderate/severe: not studied, treat with caution | Mild: no need for dose adjustment is expected<br>Moderate: consider 50% of the original dose, increase if tolerated<br>Severe: not recommended | FDA label Istodax[1] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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 etabolites. | **FDA:**<br>CLcr 15-59 ml/min and platelet count > 150x109/L: no dose adjustment<br>CLcr 15-59 ml/min and platelet count 100-150x109/L: 10 mg BID<br>CLcr 15-59 ml/min and platelet count 50 – 99x109/L: 5 mg QD<br>CLcr 15-59 ml/min and platelet count < 50 x 109/L: avoid<br><br>HD with platelet count 100- 200x109/L: 15 mg after dialysis, on dialysis days<br>HD with platelet count >200x 109/L: 20 mg after dialysis, on dialysis days<br><br>**EMA:**<br>CLcr ≥ 30 ml/min: no dose adjustment<br>CLcr < 30 ml/min: approximately 50% of the dose based on platelet count HD with Platelet count 100- 200x109/L: 15 mg QD after dialysis<br>HD with Platelet count >200x 109/L: 20 mg QD after dialysis<br><br>**Chen et al.**<br>eGFR 50-80 ml/min/1·73m$^2$: $AUC_{0\text{-}inf}$ 1·10 (90% CI 0·90- 1·36 )<br>eGFR 30-49 ml/min/1.73m$^2$: $AUC_{0\text{-}inf}$ 1·22 (90% CI 0·99- 1·50)<br>eGFR <30 ml/min/1.73m$^2$: $AUC_{0\text{-}inf}$ 1·03 (90% CI 0·84- 1·27)<br>HD: $AUC_{0\text{-}inf}$ 0·93 (90% CI 0·72-1·19) | Renal impairment:<br>Adjust the dose according to FDA recommendations | **FDA:**<br>Child-Pugh A-C and platelet count:<br>>150 x109/L: no dose adjustment<br>100-150 x109/L: 10 mg BID<br>50-100 x109/L: 5 mg QD<br>< 50 x 109/L: avoid<br><br>**EMA:**<br>Child-Pugh A-C:<br>approximately 50% of the original daily dose based on platelet count, divided in two doses<br><br>**Chen et al.**<br>Child-Pugh A: $AUC_{0\text{-}inf}$ 1·87(90% CI 1·29-2·71)<br>Child-Pugh B: $AUC_{0\text{-}inf}$ 1·28 (90% CI 0·88-1·85 )<br>Child-Pugh C: $AUC_{0\text{-}inf}$ 1·65(90% CI 1·14-2·40) | Child-Pugh A-C:<br>Adjust the dose according to FDA recommendations | Jakafi label[1]<br>SPC Jakafi[2]<br>Chen et al.[140] |
| **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:**<br>Renal impairment: no dose adjustment is needed<br>HD: not studied<br><br>**Miller et al.**<br>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.<br><br>**Kennoki et al.**<br>Not dialysed. An increased incidence of adverse events was observed in patients with hemodialysis, however $AUC_{0\text{-}10}$ was lower than reported values in patients with normal renal function. | GFR > 40 ml/min: no dose adjustment is needed<br>GFR 20-39 ml/min: 200 mg BID, dose- escalation based on tolerability<br>GFR < 20 ml/min or HD: 200 mg QD, dose-escalation based on tolerability | **EMA/FDA:**<br>Child-Pugh A/B: no dose adjustment needed<br>Child-Pugh C: not studied<br><br>**Miller et al.**<br>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<br>Child-Pugh C: starting dose of 200mg QD, dose-escalation based on tolerability | FDA label<br>Nexovar[1]<br>SPC Nexovar[2]<br>Miller et al[142]<br>Kennoki et al [143] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>GFR 45-60 ml/min: 50% of original dose<br>GFR 31-44 ml/min: evaluation risk/benefits<br>GFR ≤ 30 ml/min: contraindicated | Renal impairment:<br>GFR 46-60 ml/min: 50% of original dose GFR 31-45 ml/min: not recommended, if unavoidable consider 25% of the original dose.<br>GFR ≤ 30 ml/min or HD: not recommended | **MHRA:**<br>Consider dose reduction | Hepatic impairment: no need for dose adjustment is expected | Zanosar SPC[8] |
| **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<br><br>**Langenegger et al.**<br>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<br><br>**Floren et al.**<br>Tamoxifen dose was adjusted based on tamoxifen and N-desmethyltamoxifen levels in a patient with acute hepatic decompensation (total bilirubin 340 µmol/L, AST 99UI/L, INR 3·0) after transjugular intrahepatic portosystemic shunt placement. | Mild/ moderate: no dose adjustment is needed<br>Severe: not recommended | FDA label<br>Nolvadex[1]<br>SPC Nolvadex[8]<br>Langenegger et al[9]<br>Floren et al. [147] |
| **Tegafur/gimeracil/oteracil** | Tegafur is a prodrug, which is converted in the liver to the active metabolite 5-fluoruracil (5-FU). 5-FU is converted intracellularly to inactive metabolites by dihydropyrimidine-dehydrogenase (DPD). Tegafur and its metabolites are excreted in urine (83-91%, of which 3·8- 4·2% unchanged). | **EMA**<br>CLcr 51-80 ml/min: no dose adjustment recommended CLcr 30-50 ml/min: 80% of original dose (20 mg/m$^2$ twice daily)<br>CLcr: < 30 ml/min: not recommended due to increased adverse events<br>HD: not studied<br><br>**Booka et al.**<br>Moderate correlation between 5-FU $AUC_{0-24h}$ and CLcr in 16 patients with varying degrees of renal impairment.<br><br>**Tomiyama et al.**<br>Comparable 5-FU $AUC_{0-24h}$ in a patient undergoing HD receiving 40mg and reported 5-FU $AUC_{0-24}$h in patients receiving 100mg. | GFR > 50 ml/min: no dose adjustment is needed<br>GFR 30-50 ml/min: 80% of original dose (20mg/m2 twice daily)<br>GFR < 30 ml/min or HD: 40% of the original dose (20 mg/m2 QD) | **EMA:** no dose adjustment recommended<br><br>**Yoon et al.**<br>Maximal tolerated dose:<br>Mild hepatic impairment (bilirubin 1-1·5xULN and AST>ULN): 80mg/m$^2$/day<br>Moderate hepatic impairment (bilirubin 1·5-3 x ULN): 70 mg/m2/day<br>Severe hepatic impairment (bilirubin > 3 x ULN): 50 mg/m2/day | Hepatic impairment: no dose adjustment is needed | Teysuno SPC[2]<br>Booka et al.[148]<br>Tomiyama et al.[149] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Temozolomide** | Temozolomide is spontaneously hydrolyzed, 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%). | **FDA:**<br>CLcr ≥ 36 ml/min: no dose adjustment needed<br>CLcr < 36 ml/min: no dose advise given, exercise caution<br>HD: not studied<br><br>**EMA:**<br>Renal impairment: dose reductions probably not necessary. Exercise caution. | Renal impairment: GFR ≥36 ml/min: no dose adjustment is needed<br>GFR < 36 ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment expected | **FDA:**<br>Child-Pugh A/B: no dose adjustment needed<br>Child-Pugh C: no dose advise given, exercise caution<br><br>**EMA:**<br>Mild/moderate: no dose adjustment needed<br>Severe: dose reductions probably not necessary | Child-Pugh A/B: no dose adjustment is needed<br>Child-Pugh C: no need for dose adjustment is expected | FDA label Temodal[1]<br>SPC Temodal[2] |
| **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%). | **FDA/EMA:**<br>Renal impairment: no dose adjustment recommended HD: not studied<br><br>**Lunardi et al.**<br>(tem)sirolimus pharmacokinetics not significantly altered by hemodialysis compared to controls with normal renal function | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **FDA:**<br>Bilirubin 1-1·5 x ULN or AST >ULN but bilirubin ≤ ULN): 60% of original dose (15mg/week)<br>Bilirubin >1·5xULN: contraindicated<br><br>**EMA:**<br>Renal cell carcinoma (RCC), if platelet count ≥ 100 x 109/l:<br>Mild/moderate (bilirubin ≤ 3 x ULN with AST > ULN) or Child-Pugh A/B: no dose adjustment is needed<br>Severe (bilirubin >3 x ULN with AST >ULN)or Child-Pugh C: 40% of original dose (10 mg/week)<br><br>Mantel cell lymphoma (MCL):<br>Mild: no dose adjustment recommended<br>Moderate/severe: contraindicated | RCC<br>Child-Pugh A or B or mild or moderate: no dose adjustment is needed<br>severe or Child-Pugh C: 40% of the original dose<br><br>MCL<br>Mild: no dose adjustment<br>Moderate/severe: not recommended | FDA label Torisel[1]<br>SPC Torisel[2]<br>Lunardi et al[150] |
| **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<br>HD: no need for dose adjustment is expected | **FDA**: insufficient data, dose adjustment may be necessary | Mild/moderate: no need for dose adjustment is expected<br>Severe: not recommended | FDA label Vumon[1] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Moderate/severe renal impairment: more extensive monitoring indicated.<br><br>**EMA:**<br>Mild/moderate renal impairment: not studied. No need for dose adjustment<br><br>**Ekhart et al:**<br>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<br>GFR < 30 ml/min: consider 70% of the original dose, increase if tolerated<br>HD: consider 70% of the original dose, increase if tolerated | **FDA:**<br>Mild (bilirubin <1·5xULN): similar clearance compared to normal liver function.<br>Moderate (bilirubin 1·5- 3xULN and any AST): 1·6-1·8 fold increase of thiotepa AUC. More extensive monitoring indicated.<br>Severe (bilirubin >3xULN and any AST): unknown. More extensive monitoring indicated.<br><br>**EMA:**<br>Dose modification not recommended for transient alterations of hepatic parameters. Exercise caution in patients with pre-existing hepatic impairment, especially severe. | Bilirubin <1·5xULN: no dose adjustment is needed<br>Bilirubin 1·5- 3 x ULN: intensify monitoring<br>Bilirubin > 3 x ULN: not recommended | Tepadina FDA label[1]<br>Tepadina SPC[2]<br>Ekhart et al[151] |
| **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<br>**MHRA:** consider dose adjustment | Renal impairment or HD: no need for dose adjustment is expected | **FDA:** no advise given<br>**MHRA:** consider dose adjustment | Hepatic impairment: no need for dose adjustment is expected | FDA label Tabloid[1]<br>SPC Tioguanine[8] |
| **Topotecan** | Topotecan undergoes pH dedendent hydrolysis to a pharmacologically active lactone form. Topotecan is to a lesser extent eliminated (<10%) by metabolization to a N- demethylated metabolite.<br>Topotecan and its metabolites are predominantly excreted in urine (54%) and to a lesser extent in feces (20%). | **Intravenous:**<br>**FDA/EMA**: CLcr ≥ 40 ml/min: no dose adjustment needed CLcr 20-39ml/min: 50% of original dose (0·75mg/m$^2$) CLcr <20ml/min: not studied, not recommended<br><br>**O'Reilly et al.**<br>Significantly reduced clearance of topotecan in patients with mild and moderate renal impairment:<br>CLcr ≥ 60ml/min: 0·4±0·18 L/min/m$^2$<br>CLcr 40-59ml/min: 0·27±0·11 L/min/m$^2$<br>CLcr 20-39ml/min: 0·14±0·05 L/min/m$^2$<br><br>**Herrington et al.**<br>Case report, almost fourfold increase of topotecan clearance on dialysis compared to off dialysis<br><br>**Oral:**<br>**FDA:**<br>CLcr > 50 ml/min: no dose adjustment<br>CLcr 30-49 ml/min: 65% of original dose (1·5mg/m$^2$)<br>CLcr < 30 ml/min: 26% of original dose (0·6mg/m$^2$) | (Oral and intravenous)<br>GFR ≥ 40 ml/min: no dose adjustment is needed<br>GFR 20-39 ml/min: 50% of original dose<br>GFR < 20 ml/min: not recommended, if unavoidable consider 25% of the original dose<br><br>HD: not recommended, if unavoidable consider 25% of the original dose | **Intravenous:**<br>**FDA:** no differences in pharmacokinetics in patients with hepatic impairment.<br><br>**EMA:**<br>Bilirubin 1·5-10 mg/dl: insufficient data to make dose recommendations Bilirubin >10 mg/dl: not recommended<br><br>**O'Reilly et al.**<br>No statistically significant pharmacokinetic differences of total topotecan or topotecan lactone between patients with normal hepatic function (bilirubin ≤1·2mg/dl) and hepatic impairment (bilirubin >1·2mg/dl).<br><br>**Oral:**<br>**FDA:** no differences in pharmacokinetics in patients with hepatic impairment.<br><br>**EMA:**<br>Mild/moderate hepatic impairment (bilirubin 1·5-10 mg/dl): insufficient data to make recommendations<br>Severe hepatic impairment: not recommended | (Oral and intravenous)<br>Bilirubin ≤171 µmol/l: no need for dose adjustment is expected<br>Bilirubin >171 µmol/l: not recommended | FDA label<br>Hycamtin[1]<br>SPC Hycamtin[2]<br>O'Reilly et al.[152]<br>Devriese et al.[153]<br>O'Reilly et al.[154]<br>Herrington et al.[155] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | **EMA:**<br>CLcr >50 ml/min: no dose adjustment<br>CLcr 30-49 ml/min: 83% of original dose (1·9mg/$m^2$)<br>CLcr < 30 ml/min: limited data<br><br>**Devriese et al.**<br>CLcr 50-79ml/min: $AUC_{0\text{-}inf\ f}$: 1·61 (90% CI 1·14-2·28)<br>CLcr 30-49ml/min: $AUC_{0\text{-}inf}$ 2·48 (90% CI 1·72-3·56)<br>CLcr < 30 ml/min: $AUC_{0\text{-}inf}$ 3·98 (2·64-6·01) | | | | |

| | | **Renal impairment** | | **Hepatic impairment** | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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. | **FDA/EMA:**<br>CLcr ≥ 30 ml/min: no dose adjustment<br><br>CLcr < 30 or HD: not studied/contraindicated<br><br>**Thariat et al.**<br>$AUC_{0\text{-}inf}$ of normal dose trabectedin in patient on hemodialysis was 2-fold that of the control population, although within 95%-CI. | GFR ≥30ml/min: no dose adjustment is needed<br>GFR < 30 ml/min: no need for dose adjustment is expected<br>HD: No need for dose adjustment is expected | **FDA:**<br>Moderate (bilirubin 1·5-3 x ULN and AST and ALT <8 x ULN): 60% of original dose (0·9 mg/$m^2$)<br>Severe: contraindicated<br><br>**EMA:**<br>Bilirubin >ULN: contraindicated<br><br>**Calvo et al.**<br>Hepatic impairment (bilirubin 1·5 – 3 x ULN, AST and ALT ≤ 8 xULN ): dose normalized $AUC_{0\text{-}last}$ 1·97 (90% CI 1·20-3·22) | Mild hepatic impairment (bilirubin <1·5xULN): no need for dose adjustment is expected<br><br>Moderate hepatic impairment (bilirubin 1·5-3 x ULN, AST and ALT ≤ 8 x ULN): 60% of original dose (0·9mg/$m^2$)<br><br>Severe hepatic impairment (bilirubin > 3 x ULN): not recommended | FDA label Yondelis<br>SPC Yondelis[2]<br>Thariat et al[158]<br>Calvo et al. [159] |
| **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. | **FDA/EMA**<br>GFR 30-89 ml/min/1·73m2: no dose adjustment is needed<br>GFR < 30 ml/min/1·73m2 or HD: not studied<br><br>**Park et al. comparable**<br>Cmax in a dialysed patient receiving a reduced dose (1mg OD) of trametinib compared to previously reported concentrations at that dose. | GFR ≥ 30 ml/min: no dose adjustment is needed<br>GFR < 30 ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA/EMA:**<br>mild hepatic impairment: no dose adjustment<br>Moderate/severe hepatic impairment: not studied | Mild: no dose adjustment is needed<br>Moderate: consider 50% of the original dose<br>Severe: not recommended | SPC Mekinist[2]<br>FDA label Mekinist[1]<br>Park et al[52] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **Trastuzumab emtansine** | Trastuzumab is catabolized 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:**<br>CLcr: 30-89 ml/min: No dose adjustment is needed<br>CLcr <30 ml/min: not studied | Renal impairment:<br>GFR ≥ 30 ml/min: no dose adjustment is needed<br>GFR <30ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>Child-Pugh A: no dose adjustment<br>Child-Pugh B: no dose adjustment<br>Child-Pugh C: not studied | Child-Pugh A/B:No dose adjustment is needed<br><br>Child-Pugh C: not recommended | Label Kadcyla[1]<br>SPC Kadcyla[2] |
| **Trastuzumab** | Trastuzumab is catabolized by proteolytic degradation to smaller peptides. No renal or hepatic clearance. | **EMA/FDA:**<br>CLcr: 30-90 ml/min: no clinically significant differences in PK<br>HD: not studied | Renal impairment:<br>GFR ≥ 30 ml/min: no dose adjustment is needed<br><br>GFR <30 ml/min: no need for dose adjustment is expected<br><br>HD: no need for dose adjustment is expected | **EMA/FDA:**<br>hepatic impairment: not studied | Hepatic impairment: no need for dose adjustment is expected | Label Herceptin[1]<br>SPC Herceptin[2] |
| **Treosulfan** | Treosulfan (prodrug) is spontaneously converted to an active monoepoxide intermediate and finally tot L- diepoxibutane. Treosulfan is renally excreted, with cumulative renal elimination of 5-49% of unchanged treosulfan. | **MHRA:**<br>Renal impairment: careful monitoring of blood counts | GFR ≥ 50 ml/min: no need for dose adjustment is expected<br>GFR < 50ml/min: consider the use of busulfan and dose according to busulfan plasma levels<br>HD: not recommended | **MHRA:** no advise | Hepatic impairment: no need for dose adjustment is expected, however due to limited knowledge about treosulfan pharmacokinetics careful monitoring is advised. | SPC treosulfan[8] |
| **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:**<br>CLcr 60-89 ml/min: no dose adjustments is needed<br>CLcr 30-59 ml/min: no dose adjustments is needed<br>CLcr < 29 ml/min: not sufficiently studied<br><br>**EMA:**<br>Mild/moderate renal impairment (CLcr > 40 ml/min): no dose adjustment is needed | Renal impairment:<br>GFR ≥ 30/ml/min: no dose adjustment is needed<br>GFR < 30 ml/min: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild/moderate (total bilirubin <3 x ULN): no dose adjustment recommended Severe: limited data<br><br>**EMA:**<br>No need for dose adjustment in patients with hepatic impairment. Close monitoring warranted in moderate/severe hepatic impairment. | Mild/moderate: no dose adjustment is needed<br>Severe: no need for dose adjustment is expected, monitor liver biochemistry twice a week. | FDA Label vemurafenib[1]<br>SPC vemurafenib[2] |
| **Vinblastine sulfate** | Vinblastine is extensively metabolised in the liver to the more active desacetylvinblastine. It is excreted slowly in urine and feces. | **MHRA:**<br>Renal impairment: no dose adjustment is needed | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **MHRA:**<br>direct serum bilirubin<br>> 3 mg/dl: 50% dose reduction is recommended. | Bilirubin > 51 µmol/L: 50% of the original dose | SPC vinblastine sulphate[8] |

| | | Renal impairment | | Hepatic impairment | | |
|---|---|---|---|---|---|---|
| **Agent** | **PK summary** | **Available evidence** | **Author's recommendations** | **Available evidence** | **Author's recommendations** | **References** |
| **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:**<br>Renal impairment: not studied | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA/MHRA:**<br>Direct serum bilirubin >3 mg/dl: 50% dose reduction is recommended.<br><br>**MHRA:**<br>Direct serum bilirubin >3 mg/dl: 50% dose reduction is recommended. | Bilirubin > 51 µmol/l: 50% of original dose | SPC vincristine sulfate[2]<br>Vincristine sulfate label[1] |
| **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:**<br>Renal impairment: not studied | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA (liposomal vincirstine)**<br>Child-Pugh A: not studied<br>Child-Pugh B: AUC and $C_{max}$ were comparable to normal hepatic function<br>Child-Pugh C: not studied<br><br>**Bedikian et al:**<br>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 and B: no dose adjustment is needed<br>Child-Pugh C: consider a 50% dose reduction | FDA label<br>Marqibo[1]<br>Bedikian et al[161] |
| **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:**<br>No information<br><br>**MHRA:**<br>Not studied, no dose adjustment is needed | Renal impairment: no dose adjustment is needed<br>HD: no need for dose adjustment is expected | **FDA: (IV)**<br>Serum total bilirubin ≤ 2·0 mg/dl: no dose adjustment Serum total bilirubin 2·1-3·0 mg/dl: 50% of starting dose Serum total bilirubin > 3·0 mg/dl: 25% of starting dose<br><br>**MHRA: (IV)**<br>Mild/moderate: no dose adjustment<br>Severe: reduced dose of 20mg/m2 is recommended<br>**Oral:**<br>Mild: 60 mg/m2/week<br>Moderate: 50 mg/m2/week Severe: not recommended<br><br>**Kitzen et al.**<br>No pharmacokinetic differences between patients with mild and moderate liver dysfunction compared to patients with normal hepatic function. | **IV/Oral**<br>Mild/moderate: no dose adjustment is needed<br>Severe: consider 66% of original dose | Navelbine label[1]<br>SPC Navelbine injection[8]<br>SPC Navelbine 80 mg soft capsule[8]<br>Kitzen et al[164] |
| **Vorinostat** | Vorinostat is metabolised in the liver. Excretion is mainly though metabolism with < 1% of unchanged vorinostat excreted in urine. | **FDA:**<br>Renal impairment: not studied, treat with caution HD: not studied | Renal impairment: no need for dose adjustment is expected<br>HD: no need for dose adjustment is expected | **FDA:**<br>Mild and moderate: treat with caution<br>Severe: contraindicated<br><br>**Ramalingam et al.**<br>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<br>Moderate: 50% of the original dose<br>Severe: 25% of the original dose | Zolinza label[1]<br>Ramalingam et al.[166] |

*Abbreviations:* ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; AUC0-inf, area under the plasma concentration time profile of the drug of interest from time zero to infinity; AUC0-last, area under the plasma concentration time profile of the drug of interest from time zero to last measured concentration; AUC0- 24h, area under the plasma concentration time profile of the drug of interest from time 0 to 24 hours; BID, twice a day; CI, confidence interval; CL, clearance; CLcr, creatinine clearance; Cmax, maximum concentration; Ctrough, trough concentration; CVVH, Continuous venovenous hemofiltration; DLT, dose limiting toxicity; EMA, European Medicines Agency; ESRD, end-stage renal disease; FDA, Food and Drug Administration; GGT, Gamma-glutamyltransferase; (e)GFR, estimated glomerular filtrating rate; HD, hemodialysis; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; 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; 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)

**References**


1. Drugs@FDA: FDA Approved Drug Products. 2018. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed 15/11 2018).
2. European public assesment reports for human medicines. 2018. https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine (accessed 15/11 2018).
3. Marbury T, Lawitz E, Stonerock R, et al. Single-dose pharmacokinetic studies of abiraterone acetate in men with hepatic or renal impairment. *Journal of clinical pharmacology* 2014; **54**(7): 732-41.
4. Wiebe S, Schnell D, Kulzer R, et al. Influence of Renal Impairment on the Pharmacokinetics of Afatinib: An Open-Label, Single-Dose Study. *European journal of drug metabolism and pharmacokinetics* 2017; **42**(3): 461-9.
5. Schnell D, Buschke S, Fuchs H, et al. Pharmacokinetics of afatinib in subjects with mild or moderate hepatic impairment. *Cancer chemotherapy and pharmacology* 2014; **74**(2): 267-75.
6. Imai H, Kaira K, Naruse I, et al. Successful afatinib treatment of advanced non-small-cell lung cancer patients undergoing hemodialysis. *Cancer chemotherapy and pharmacology* 2017; **79**(1): 209-13.
7. Morcos PN, Cleary Y, Sturm-Pellanda C, et al. Effect of Hepatic Impairment on the Pharmacokinetics of Alectinib. *Journal of clinical pharmacology* 2018.
8. Medicines Information: SPC & PILs. 2018. http://www.mhra.gov.uk/spc-pil/index.htm?IdcService=SS_GET_PAGE&nodeId=%3C%25%3D%2BnodeId%2B%25%3E&searchFiled&SubmitSearch=Search (accessed 15/11 2018).
9. Langenegger T, Wahl P, Schiesser D, Thurlimann B. Plasma levels of tamoxifen, N-desmethyl tamoxifen and anastrozole in a patient with metastatic breast cancer and chronic hemodialysis. *Breast cancer research and treatment* 2006; **100**(2): 177-81.
10. Firkin F, Roncolato F, Ho WK. Dose-adjusted arsenic trioxide for acute promyelocytic leukaemia in chronic renal failure. *European journal of haematology* 2015; **95**(4): 331-5.
11. Sweeney CJ, Takimoto C, Wood L, et al. A pharmacokinetic and safety study of intravenous arsenic trioxide in adult cancer patients with renal impairment. *Cancer chemotherapy and pharmacology* 2010; **66**(2): 345-56.
12. Perreault S, Moeller J, Patel K, et al. Use of arsenic trioxide in a hemodialysis-dependent patient with relapsed acute promyelocytic leukemia. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners* 2016; **22**(4): 646-51.
13. Thiery-Vuillemin A, Orillard E, Mouillet G, et al. Hemodialysis does not impact axitinib exposure: clinical case of a patient with metastatic renal cell carcinoma. *Cancer chemotherapy and pharmacology* 2017; **79**(6): 1273-6.
14. Tortorici MA, Toh M, Rahavendran SV, et al. Influence of mild and moderate hepatic impairment on axitinib pharmacokinetics. *Investigational new drugs* 2011; **29**(6): 1370-80.
15. Laille E, Goel S, Mita AC, et al. A phase I study in patients with solid or hematologic malignancies of the dose proportionality of subcutaneous Azacitidine and its pharmacokinetics in patients with severe renal impairment. *Pharmacotherapy* 2014; **34**(5): 440-51.
16. Ham JC, Hoogendijk-van den Akker JM, Verdonck LF. A hemodialysis patient with higher-risk myelodysplastic syndrome treated with standard-dose azacitidine. *Leukemia & lymphoma* 2012; **53**(12): 2521-2.
17. Garnier-Viougeat N, Rixe O, Paintaud G, et al. Pharmacokinetics of bevacizumab in haemodialysis. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2007; **22**(3): 975.
18. Ito F, Goya N, Nakazawa H, et al. A study of plasma bicalutamide concentrations in hemodialysis patients. *Urologia internationalis* 2012; **89**(2): 162- 5.
19. Crooke ST, Luft F, Broughton A, Strong J, Casson K, Einhorn L. Bleomycin serum pharmacokinetics as determined by a radioimmunoassay and a microbiologic assay in a patient with compromised renal function. *Cancer* 1977; **39**(4): 1430-4.
20. Zhu M, Wu B, Brandl C, et al. Blinatumomab, a Bispecific T-cell Engager (BiTE((R))) for CD-19 Targeted Cancer Immunotherapy: Clinical Pharmacology and Its Implications. *Clinical pharmacokinetics* 2016; **55**(10): 1271-88.
21. LoRusso PM, Venkatakrishnan K, Ramanathan RK, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: phase I NCI Organ Dysfunction Working Group Study NCI-6432. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2012; **18**(10): 2954-63.
22. Leal TB, Remick SC, Takimoto CH, et al. Dose-escalating and pharmacological study of bortezomib in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. *Cancer chemotherapy and pharmacology* 2011; **68**(6): 1439-47.
23. Abbas R, Hsyu PH. Clinical Pharmacokinetics and Pharmacodynamics of Bosutinib. *Clinical pharmacokinetics* 2016; **55**(10): 1191-204.
24. Abbas R, Chalon S, Leister C, El Gaaloul M, Sonnichsen D. Evaluation of the pharmacokinetics and safety of bosutinib in patients with chronic hepatic impairment and matched healthy subjects. *Cancer chemotherapy and pharmacology* 2013; **71**(1): 123-32.
25. Zhao B, Chen R, O'Connor OA, et al. Brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive haematologic malignancies and hepatic or renal impairment. *British journal of clinical pharmacology* 2016; **82**(3): 696-705.
26. Masauzi N, Higa T, Nakagawa S, et al. Pharmacokinetic study of busulfan in an AML patient treated with regular hemodialysis. *Annals of hematology* 1998; 77(6): 293-4.
27. Azaro A, Rodon J, Machiels JP, et al. A phase I pharmacokinetic and safety study of cabazitaxel in adult cancer patients with normal and impaired renal function. *Cancer chemotherapy and pharmacology* 2016; **78**(6): 1185-97.
28. Sarantopoulos J, Mita AC, He A, et al. Safety and pharmacokinetics of cabazitaxel in patients with hepatic impairment: a phase I dose-escalation study. *Cancer chemotherapy and pharmacology* 2017; **79**(2): 339-51.

29. Nguyen L, Holland J, Ramies D, et al. Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Cabozantinib. *Journal of clinical pharmacology* 2016; **56**(9): 1130-40.
30. Poole C, Gardiner J, Twelves C, et al. Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. *Cancer chemotherapy and pharmacology* 2002; **49**(3): 225-34.
31. Joerger M, Huitema AD, Koeberle D, et al. Safety and pharmacology of gemcitabine and capecitabine in patients with advanced pancreatico-biliary cancer and hepatic dysfunction. *Cancer chemotherapy and pharmacology* 2014; **73**(1): 113-24.
32. Twelves C, Glynne-Jones R, Cassidy J, et al. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. *Clinical cancer research : an official journal of the American Association for Cancer Research* 1999; **5**(7): 1696-702.
33. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1989; **7**(11): 1748-56.
34. Watanabe M, Aoki Y, Tomita M, et al. Paclitaxel and carboplatin combination chemotherapy in a hemodialysis patient with advanced ovarian cancer. *Gynecologic oncology* 2002; **84**(2): 335-8.
35. Badros AZ, Vij R, Martin T, et al. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. *Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK* 2013; **27**(8): 1707-14.
36. Quach H, White D, Spencer A, et al. Pharmacokinetics and safety of carfilzomib in patients with relapsed multiple myeloma and end-stage renal disease (ESRD): an open-label, single-arm, phase I study. *Cancer chemotherapy and pharmacology* 2017; **79**(6): 1067-76.
37. Brown J, Plummer R, Bauer TM, et al. Pharmacokinetics of carfilzomib in patients with advanced malignancies and varying degrees of hepatic impairment: an open-label, single-arm, phase 1 study. *Experimental hematology & oncology* 2017; **6**: 27.
38. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer treatment reviews* 1995; **21**(1): 33-64.
39. Inauen R, Cathomas R, Boehm T, et al. Feasibility of using cetuximab and bevacizumab in a patient with colorectal cancer and terminal renal failure. *Oncology* 2007; **72**(3-4): 209-10.
40. Watanabe R, Takiguchi Y, Moriya T, et al. Feasibility of combination chemotherapy with cisplatin and etoposide for haemodialysis patients with lung cancer. *British journal of cancer* 2003; **88**(1): 25-30.
41. Crews KR, Wimmer PS, Hudson JQ, Howard SC, Ribeiro RC, Razzouk BI. Pharmacokinetics of 2-chlorodeoxyadenosine in a child undergoing hemofiltration and hemodialysis for acute renal failure. *Journal of pediatric hematology/oncology* 2002; **24**(8): 677-80.
42. Benitez LL, Gharibian K, Frame D, Mody R, Mora E. Clofarabine Dosing in a Patient With Acute Myeloid Leukemia on Intermittent Hemodialysis: Case Report and Review of the Literature. *Journal of pediatric hematology/oncology* 2017; **39**(6): 481-4.
43. Tan W, Yamazaki S, Johnson TR, et al. Effects of Renal Function on Crizotinib Pharmacokinetics: Dose Recommendations for Patients with ALK- Positive Non-Small Cell Lung Cancer. *Clinical drug investigation* 2017; **37**(4): 363-73.
44. El-Khoueiry AB, Sarantopoulos J, O'Bryant CL, et al. Evaluation of hepatic impairment on pharmacokinetics and safety of crizotinib in patients with advanced cancer. *Cancer chemotherapy and pharmacology* 2018; **81**(4): 659-70.
45. Wang LH, Lee CS, Majeske BL, Marbury TC. Clearance and recovery calculations in hemodialysis: application to plasma, red blood cells, and dialysate measurements for cyclophosphamide. *Clinical pharmacology and therapeutics* 1981; **29**(3): 365-72.
46. Haubitz M, Bohnenstengel F, Brunkhorst R, Schwab M, Hofmann U, Busse D. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. *Kidney international* 2002; **61**(4): 1495-501.
47. Juma FD, Rogers HJ, Trounce JR. Effect of renal insufficiency on the pharmacokinetics of cyclophosphamide and some of its metabolites. *European journal of clinical pharmacology* 1981; **19**(6): 443-51.
48. Juma FD. Effect of liver failure on the pharmacokinetics of cyclophosphamide. *European journal of clinical pharmacology* 1984; **26**(5): 591-3.
49. Smith GA, Damon LE, Rugo HS, Ries CA, Linker CA. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1997; **15**(2): 833-9.
50. Radeski D, Cull GM, Cain M, Hackett LP, Ilett KF. Effective clearance of Ara-U the major metabolite of cytosine arabinoside (Ara-C) by hemodialysis in a patient with lymphoma and end-stage renal failure. *Cancer chemotherapy and pharmacology* 2011; **67**(4): 765-8.
51. Barker JA, Marini BL, Bixby D, Perissinotti AJ. Successful use of high-dose cytarabine in a patient with acute myeloid leukemia and severe hepatic dysfunction. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners* 2016; **22**(6): 811-5.
52. Park JJ, Boddy AV, Liu X, et al. Pharmacokinetics of dabrafenib in a patient with metastatic melanoma undergoing haemodialysis. *Pigment cell & melanoma research* 2017; **30**(1): 68-71.
53. Krashin E, Dolberg OJ, Hellmann I, Huitema AD, Rosing H, Ellis M. Cytosine arabinoside and daunorubicin induction therapy in a patient with acute myeloid leukemia on chronic hemodialysis. *Anti-cancer drugs* 2016; **27**(8): 800-3.
54. Levine LB, Roddy JV, Kim M, Li J, Phillips G, Walker AR. A comparison of toxicities in acute myeloid leukemia patients with and without renal impairment treated with decitabine. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners* 2018; **24**(4): 290-8.
55. Dimopoulos MA, Deliveliotis C, Moulopoulos LA, et al. Treatment of patients with metastatic urothelial carcinoma and impaired renal function with single-agent docetaxel. *Urology* 1998; **52**(1): 56-60.
56. Hochegger K, Lhotta K, Mayer G, Czejka M, Hilbe W. Pharmacokinetic analysis of docetaxel during haemodialysis in a patient with locally advanced non-small cell lung cancer. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2007; **22**(1): 289-90.
57. Bruno R, Hille D, Riva A, et al. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1998; **16**(1): 187-96.
58. Syn NL, Wang L, Wong AL, et al. Dose modifications in Asian cancer patients with hepatic dysfunction receiving weekly docetaxel: A prospective pharmacokinetic and safety study. *Cancer science* 2016; **107**(2): 173-80.
59. Minami H, Kawada K, Sasaki Y, et al. Population pharmacokinetics of docetaxel in patients with hepatic dysfunction treated in an oncology practice.
*Cancer science* 2009; **100**(1): 144-9.
60. Eckmann K, Michaud LB, Rivera E, et al. Pilot study to assess toxicity and pharmacokinetics of docetaxel in patients with metastatic breast cancer and impaired liver function secondary to hepatic metastases. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners* 2014; **20**(2): 120-9.
61. Yoshida H, Goto M, Honda A, et al. Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis. *Cancer chemotherapy and pharmacology* 1994; **33**(6): 450-4.

62. Berdeja J, Jagannath S, Zonder J, et al. Pharmacokinetics and Safety of Elotuzumab Combined With Lenalidomide and Dexamethasone in Patients With Multiple Myeloma and Various Levels of Renal Impairment: Results of a Phase Ib Study. *Clinical lymphoma, myeloma & leukemia* 2016; **16**(3): 129-38.
63. Krauwinkel W, Noukens J, van Dijk J, et al. A comparison of the pharmacokinetics and safety of enzalutamide in subjects with hepatic impairment and matched healthy subjects. *Journal of clinical pharmacy and therapeutics* 2017; **42**(3): 268-75.
64. Gori S, Rulli A, Mosconi AM, Sidoni A, Colozza M, Crino L. Safety of epirubicin adjuvant chemotherapy in a breast cancer patient with chronic renal failure undergoing hemodialytic treatment. *Tumori* 2006; **92**(4): 364-5.
65. Dobbs NA, Twelves CJ, Gregory W, Cruickshanka C, Richards MA, Rubens RD. Epirubicin in patients with liver dysfunction: development and evaluation of a novel dose modification scheme. *European journal of cancer* 2003; **39**(5): 580-6.
66. Twelves CJ, O'Reilly SM, Coleman RE, Richards MA, Rubens RD. Weekly epirubicin for breast cancer with liver metastases and abnormal liver biochemistry. *British journal of cancer* 1989; **60**(6): 938-41.
67. Tan AR, Sarantopoulos J, Lee L, et al. Pharmacokinetics of eribulin mesylate in cancer patients with normal and impaired renal function. *Cancer chemotherapy and pharmacology* 2015; **76**(5): 1051-61.
68. Devriese LA, Witteveen PO, Marchetti S, et al. Pharmacokinetics of eribulin mesylate in patients with solid tumors and hepatic impairment. *Cancer chemotherapy and pharmacology* 2012; **70**(6): 823-32.
69. O'Bryant CL, Haluska P, Rosen L, et al. An open-label study to describe pharmacokinetic parameters of erlotinib in patients with advanced solid tumors with adequate and moderately impaired hepatic function. *Cancer chemotherapy and pharmacology* 2012; **69**(3): 605-12.
70. Togashi Y, Masago K, Fukudo M, et al. Pharmacokinetics of erlotinib and its active metabolite OSI-420 in patients with non-small cell lung cancer and chronic renal failure who are undergoing hemodialysis. *J Thorac Oncol* 2010; **5**(5): 601-5.
71. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of erlotinib for solid tumors in patients with hepatic or renal dysfunction: CALGB 60101. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007; **25**(21): 3055-60.
72. Stewart CF, Arbuck SG, Fleming RA, Evans WE. Changes in the clearance of total and unbound etoposide in patients with liver dysfunction. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1990; **8**(11): 1874-9.
73. Thiery-Vuillemin A, Curtit E, Maurina T, et al. Hemodialysis does not affect everolimus pharmacokinetics: two cases of patients with metastatic renal cell cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2012; **23**(11): 2992-3.
74. Peveling-Oberhag J, Zeuzem S, Yong WP, et al. Effects of hepatic impairment on the pharmacokinetics of everolimus: a single-dose, open-label, parallel-group study. *Clinical therapeutics* 2013; **35**(3): 215-25.
75. Kovarik JM, Sabia HD, Figueiredo J, et al. Influence of hepatic impairment on everolimus pharmacokinetics: implications for dose adjustment. *Clinical pharmacology and therapeutics* 2001; **70**(5): 425-30.
76. Jannuzzo MG, Poggesi I, Spinelli R, Rocchetti M, Cicioni P, Buchan P. The effects of degree of hepatic or renal impairment on the pharmacokinetics of exemestane in postmenopausal women. *Cancer chemotherapy and pharmacology* 2004; **53**(6): 475-81.
77. Lichtman SM, Etcubanas E, Budman DR, et al. The pharmacokinetics and pharmacodynamics of fludarabine phosphate in patients with renal impairment: a prospective dose adjustment study. *Cancer investigation* 2002; **20**(7-8): 904-13.
78. Kielstein JT, Stadler M, Czock D, Keller F, Hertenstein B, Radermacher J. Dialysate concentration and pharmacokinetics of 2F-Ara-A in a patient with acute renal failure. *European journal of haematology* 2005; **74**(6): 533-4.
79. Rengelshausen J, Hull WE, Schwenger V, Goggelmann C, Walter-Sack I, Bommer J. Pharmacokinetics of 5-fluorouracil and its catabolites determined by 19F nuclear magnetic resonance spectroscopy for a patient on chronic hemodialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2002; **39**(2): E10.
80. Fleming GF, Schilsky RL, Schumm LP, et al. Phase I and pharmacokinetic study of 24-hour infusion 5-fluorouracil and leucovorin in patients with organ dysfunction. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2003; **14**(7): 1142-7.
81. Anjum S, Swan SK, Lambrecht LJ, et al. Pharmacokinetics of flutamide in patients with renal insufficiency. *British journal of clinical pharmacology* 1999; 47(1): 43-7.
82. Shinagawa N, Yamazaki K, Asahina H, Agata J, Itoh T, Nishimura M. Gefitinib administration in a patient with lung cancer undergoing hemodialysis. *Lung cancer* 2007; **58**(3): 422-4.
83. Horak J, White J, Harris AL, et al. The effect of different etiologies of hepatic impairment on the pharmacokinetics of gefitinib. *Cancer chemotherapy and pharmacology* 2011; **68**(6): 1485-95.
84. Venook AP, Egorin MJ, Rosner GL, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2000; **18**(14): 2780-7.
85. Kiani A, Kohne CH, Franz T, et al. Pharmacokinetics of gemcitabine in a patient with end-stage renal disease: effective clearance of its main metabolite by standard hemodialysis treatment. *Cancer chemotherapy and pharmacology* 2003; **51**(3): 266-70.
86. Teusink AC, Hall PD. Toxicities of gemcitabine in patients with severe hepatic dysfunction. *The Annals of pharmacotherapy* 2010; **44**(4): 750-4.
87. Yan JH, Ataga K, Kaul S, et al. The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *Journal of clinical pharmacology* 2005; **45**(4): 434-45.
88. Filanovsky K, Shvidel L. Safety and efficacy of ibrutinib in a patient with severe renal impairment. *Hematology reports* 2017; **9**(3): 7078.
89. de Jong J, Skee D, Hellemans P, et al. Single-dose pharmacokinetics of ibrutinib in subjects with varying degrees of hepatic impairment<sup/>. *Leukemia & lymphoma* 2017; **58**(1): 185-94.
90. Tsuchiya Y, Ubara Y, Suwabe T, et al. Successful treatment of acute promyelocytic leukemia in a patient on hemodialysis. *Clinical and experimental nephrology* 2011; **15**(3): 434-7.
91. Jin F, Robeson M, Zhou H, Hisoire G, Ramanathan S. The pharmacokinetics and safety of idelalisib in subjects with severe renal impairment. *Cancer chemotherapy and pharmacology* 2015; **76**(6): 1133-41.
92. Jin F, Robeson M, Zhou H, Hisoire G, Ramanathan S. The pharmacokinetics and safety of idelalisib in subjects with moderate or severe hepatic impairment. *Journal of clinical pharmacology* 2015; **55**(8): 944-52.
93. Carlson L, Goren MP, Bush DA, et al. Toxicity, pharmacokinetics, and in vitro hemodialysis clearance of ifosfamide and metabolites in an anephric pediatric patient with Wilms' tumor. *Cancer chemotherapy and pharmacology* 1998; **41**(2): 140-6.
94. Gibbons J, Egorin MJ, Ramanathan RK, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of renal dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008; **26**(4): 570-6.

95. Pappas P, Karavasilis V, Briasoulis E, Pavlidis N, Marselos M. Pharmacokinetics of imatinib mesylate in end stage renal disease. A case study. *Cancer chemotherapy and pharmacology* 2005; **56**(4): 358-60.
96. Ramanathan RK, Egorin MJ, Takimoto CH, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: a study by the National Cancer Institute Organ Dysfunction Working Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008; **26**(4): 563-9.
97. Czock D, Rasche FM, Boesler B, Shipkova M, Keller F. Irinotecan in cancer patients with end-stage renal failure. *The Annals of pharmacotherapy* 2009; 43(2): 363-9.
98. Stemmler J, Weise A, Hacker U, Heinemann V, Schalhorn A. Weekly irinotecan in a patient with metastatic colorectal cancer on hemodialysis due to chronic renal failure. *Onkologie* 2002; **25**(1): 60-3.
99. Fujita K, Sunakawa Y, Miwa K, et al. Delayed elimination of SN-38 in cancer patients with severe renal failure. *Drug metabolism and disposition: the biological fate of chemicals* 2011; **39**(2): 161-4.
100. Raymond E, Boige V, Faivre S, et al. Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2002; **20**(21): 4303-12.
101. Schaaf LJ, Hammond LA, Tipping SJ, et al. Phase 1 and pharmacokinetic study of intravenous irinotecan in refractory solid tumor patients with hepatic dysfunction. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2006; **12**(12): 3782-91.
102. Venook AP, Enders Klein C, Fleming G, et al. A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2003; **14**(12): 1783-90.
103. Gupta N, Hanley MJ, Harvey RD, et al. A pharmacokinetics and safety phase 1/1b study of oral ixazomib in patients with multiple myeloma and severe renal impairment or end-stage renal disease requiring haemodialysis. *British journal of haematology* 2016; **174**(5): 748-59.
104. Gupta N, Hanley MJ, Venkatakrishnan K, et al. Pharmacokinetics of ixazomib, an oral proteasome inhibitor, in solid tumour patients with moderate or severe hepatic impairment. *British journal of clinical pharmacology* 2016; **82**(3): 728-38.
105. Shumaker R, Aluri J, Fan J, Martinez G, Pentikis H, Ren M. Influence of hepatic impairment on lenvatinib pharmacokinetics following single-dose oral administration. *Journal of clinical pharmacology* 2015; **55**(3): 317-27.
106. Kergueris MF, Milpied N, Moreau P, Harousseau JL, Larousse C. Pharmacokinetics of high-dose melphalan in adults: influence of renal function. *Anticancer research* 1994; **14**(6a): 2379-82.
107. Wall SM, Johansen MJ, Molony DA, DuBose TD, Jr., Jaffe N, Madden T. Effective clearance of methotrexate using high-flux hemodialysis membranes. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 1996; **28**(6): 846-54.
108. Tollkuci E, Seddon A, Geswein L, Mulseh M. Midostaurin administration in two hemodialysis patients. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners* 2018: 1078155218801067.
109. Boros L, Cacek T, Pine RB, Battaglia AC. Distribution characteristics of mitoxantrone in a patient undergoing hemodialysis. *Cancer chemotherapy and pharmacology* 1992; **31**(1): 57-60.
110. Savaraj N, Lu K, Manuel V, Loo TL. Pharmacology of mitoxantrone in cancer patients. *Cancer chemotherapy and pharmacology* 1982; **8**(1): 113-7.
111. Yoshihara M, Kubota Y, Fukuda M, et al. Mogamulizumab treatment in a hemodialysis patient with adult T-cell leukemia/lymphoma. *Turkish journal of haematology : official journal of Turkish Society of Haematology* 2014; **31**(4): 424-5.
112. Onaka T, Takahashi N, Miura M, Yonezawa A, Imada K, Sawada K. Pharmacokinetics of nilotinib in imatinib-resistant/intolerant chronic myeloid leukemia patients on hemodialysis for chronic renal failure. *American journal of hematology* 2012; **87**(4): 451.
113. Yin OQ, Gallagher N, Tanaka C, et al. Effects of hepatic impairment on the pharmacokinetics of nilotinib: an open-label, single-dose, parallel-group study. *Clinical therapeutics* 2009; **31 Pt 2**: 2459-69.
114. Marzin K, Kretschmar G, Luedtke D, et al. Pharmacokinetics of Nintedanib in Subjects With Hepatic Impairment. *Journal of clinical pharmacology* 2017.
115. Okusaka T, Otsuka T, Ueno H, et al. Phase I study of nintedanib in Japanese patients with advanced hepatocellular carcinoma and liver impairment. *Cancer science* 2016; **107**(12): 1791-9.
116. Pilla Reddy V, Bui K, Scarfe G, Zhou D, Learoyd M. Physiologically Based Pharmacokinetic Modeling for Olaparib Dosing Recommendations: Bridging Formulations, Drug Interactions, and Patient Populations. *Clinical pharmacology and therapeutics* 2018.
117. Tamura T, Takagi Y, Okubo H, et al. Plasma concentration of osimertinib in a non-small cell lung cancer patient with chronic renal failure undergoing hemodialysis. *Lung cancer* 2017; **112**: 225-6.
118. Gori S, Lunardi G, Inno A, et al. Pharmacokinetics of oxaliplatin in a hemodialyzed patient: chemotherapy dose adjustment and timing of dialysis. *Clinical colorectal cancer* 2014; **13**(4): 260-3.
119. Watayo Y, Kuramochi H, Hayashi K, Nakajima G, Kamikozuru H, Yamamoto M. Drug monitoring during FOLFOX6 therapy in a rectal cancer patient on chronic hemodialysis. *Japanese journal of clinical oncology* 2010; **40**(4): 360-4.
120. Takimoto CH, Remick SC, Sharma S, et al. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute Organ Dysfunction Working Group Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003; **21**(14): 2664-72.
121. Synold TW, Takimoto CH, Doroshow JH, et al. Dose-escalating and pharmacologic study of oxaliplatin in adult cancer patients with impaired hepatic function: a National Cancer Institute Organ Dysfunction Working Group study. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2007; **13**(12): 3660-6.
122. Biakhov MY, Kononova GV, Iglesias J, et al. nab-Paclitaxel in patients with advanced solid tumors and hepatic dysfunction: a pilot study. *Expert opinion on drug safety* 2010; **9**(4): 515-23.
123. Briasoulis E, Karavasilis V, Tzamakou E, Piperidou C, Soulti K, Pavlidis N. Feasibility study and pharmacokinetics of low-dose paclitaxel in cancer patients with severe hepatic dysfunction. *Anti-cancer drugs* 2006; **17**(10): 1219-22.
124. Tomita M, Kurata H, Aoki Y, Tanaka K, Kazama JJ. Pharmacokinetics of paclitaxel and cisplatin in a hemodialysis patient with recurrent ovarian cancer. *Anti-cancer drugs* 2001; **12**(5): 485-7.
125. Gelderblom H, Verweij J, Brouwer E, et al. Disposition of [G-(3)H]paclitaxel and cremophor EL in a patient with severely impaired renal function. *Drug metabolism and disposition: the biological fate of chemicals* 1999; **27**(11): 1300-5.
126. Joerger M, Huitema AD, Huizing MT, et al. Safety and pharmacology of paclitaxel in patients with impaired liver function: a population pharmacokinetic-pharmacodynamic study. *British journal of clinical pharmacology* 2007; **64**(5): 622-33.
127. Krens LL, Baas JM, de Jong FA, Guchelaar HJ, Gelderblom H. Pharmacokinetics of panitumumab in a patient with liver dysfunction: a case report. *Cancer chemotherapy and pharmacology* 2014; **73**(2): 429-33.
128. Sharma S, Witteveen PO, Lolkema MP, et al. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of renal function. *Cancer chemotherapy and pharmacology* 2015; **75**(1): 87-95.
129. Slingerland M, Hess D, Clive S, et al. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function. *Cancer chemotherapy and pharmacology* 2014; **74**(5): 1089-98.

130. Sekiguchi Y, Takizawa H, Inano T, et al. Three cases of relapsed/refractory multiple myeloma under hemodialysis treated with panobinostat/bortezomib/dexamethasone (FVD). *International journal of hematology* 2017; **106**(4): 581-7.
131. Shibata SI, Chung V, Synold TW, et al. Phase I study of pazopanib in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute Organ Dysfunction Working Group study. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2013; **19**(13): 3631-9.
132. Mita AC, Sweeney CJ, Baker SD, et al. Phase I and pharmacokinetic study of pemetrexed administered every 3 weeks to advanced cancer patients with normal and impaired renal function. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(4): 552-62.
133. Brandes JC, Grossman SA, Ahmad H. Alteration of pemetrexed excretion in the presence of acute renal failure and effusions: presentation of a case and review of the literature. *Cancer investigation* 2006; **24**(3): 283-7.
134. Hill J, Vargo C, Smith M, Streeter J, Carbone DP. Safety of dose-reduced pemetrexed in patients with renal insufficiency. *Journal of Oncology Pharmacy Practice* 2018: 1078155218780507.
135. Lathia C, Fleming GF, Meyer M, Ratain MJ, Whitfield L. Pentostatin pharmacokinetics and dosing recommendations in patients with mild renal impairment. *Cancer chemotherapy and pharmacology* 2002; **50**(2): 121-6.
136. Narasimhan NI, Dorer DJ, Davis J, Turner CD, Marbury TC, Sonnichsen D. Evaluation of pharmacokinetics and safety of ponatinib in subjects with chronic hepatic impairment and matched healthy subjects. *Cancer chemotherapy and pharmacology* 2014; **74**(2): 341-8.
137. Kelly KR, Gabrail N, Weitman S, et al. Phase 1 study evaluating the safety and pharmacokinetics of pralatrexate in relapsed/refractory advanced solid tumors and lymphoma patients with mild, moderate, and severe renal impairment. *Cancer chemotherapy and pharmacology* 2016; **78**(5): 929-39.
138. Judson I, Maughan T, Beale P, et al. Effects of impaired renal function on the pharmacokinetics of raltitrexed (Tomudex ZD1694). *British journal of cancer* 1998; **78**(9): 1188-93.
139. Jillella AP, Dainer PM, Kallab AM, Ustun C. Treatment of a patient with end-stage renal disease with Rituximab: pharmacokinetic evaluation suggests Rituximab is not eliminated by hemodialysis. *American journal of hematology* 2002; **71**(3): 219-22.
140. Chen X, Shi JG, Emm T, et al. Pharmacokinetics and pharmacodynamics of orally administered ruxolitinib (INCB018424 phosphate) in renal and hepatic impairment patients. *Clin Pharmacol Drug Dev* 2014; **3**(1): 34-42.
141. Horsmans Y, Zhou J, Liudmila M, et al. Effects of Mild to Severe Hepatic Impairment on the Pharmacokinetics of Sonidegib: A Multicenter, Open- Label, Parallel-Group Study. *Clinical pharmacokinetics* 2018; **57**(3): 345-54.
142. Miller AA, Murry DJ, Owzar K, et al. Phase I and Pharmacokinetic Study of Sorafenib in Patients With Hepatic or Renal Dysfunction: CALGB 60301.
*Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009.
143. Kennoki T, Kondo T, Kimata N, et al. Clinical results and pharmacokinetics of sorafenib in chronic hemodialysis patients with metastatic renal cell carcinoma in a single center. *Japanese journal of clinical oncology* 2011; **41**(5): 647-55.
144. Khosravan R, Toh M, Garrett M, et al. Pharmacokinetics and safety of sunitinib malate in subjects with impaired renal function. *Journal of clinical pharmacology* 2010; **50**(4): 472-81.
145. Izzedine H, Etienne-Grimaldi MC, Renee N, Vignot S, Milano G. Pharmacokinetics of sunitinib in hemodialysis. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2009; **20**(1): 190-2.
146. Bello CL, Garrett M, Sherman L, Smeraglia J, Ryan B, Toh M. Pharmacokinetics of sunitinib malate in subjects with hepatic impairment. *Cancer chemotherapy and pharmacology* 2010; **66**(4): 699-707.
147. Floren LC, Hebert MF, Venook AP, Jordan VC, Cisneros A, Somberg KA. Tamoxifen in liver disease: potential exacerbation of hepatic dysfunction.
*Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 1998; **9**(10): 1123-6.
148. Booka E, Imamura CK, Takeuchi H, et al. Development of an S-1 dosage formula based on renal function by a prospective pharmacokinetic study. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 2016; **19**(3): 876-86.
149. Tomiyama N, Hidaka M, Hidaka H, et al. Safety, efficacy and pharmacokinetics of S-1 in a hemodialysis patient with advanced gastric cancer. *Cancer chemotherapy and pharmacology* 2010; **65**(4): 807-9.
150. Lunardi G, Armirotti A, Nicodemo M, et al. Comparison of temsirolimus pharmacokinetics in patients with renal cell carcinoma not receiving dialysis and those receiving hemodialysis: a case series. *Clinical therapeutics* 2009; **31**(8): 1812-9.
151. Ekhart C, Kerst JM, Rodenhuis S, Beijnen JH, Huitema AD. Altered cyclophosphamide and thiotepa pharmacokinetics in a patient with moderate renal insufficiency. *Cancer chemotherapy and pharmacology* 2009; **63**(2): 375-9.
152. O'Reilly S, Rowinsky EK, Slichenmyer W, et al. Phase I and pharmacologic study of topotecan in patients with impaired renal function. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1996; **14**(12): 3062-73.
153. Devriese LA, Witteveen PE, Mergui-Roelvink M, et al. Pharmacodynamics and pharmacokinetics of oral topotecan in patients with advanced solid tumours and impaired renal function. *British journal of clinical pharmacology* 2015; **80**(2): 253-66.
154. O'Reilly S, Rowinsky E, Slichenmyer W, et al. Phase I and pharmacologic studies of topotecan in patients with impaired hepatic function. *Journal of the National Cancer Institute* 1996; **88**(12): 817-24.
155. Herrington JD, Figueroa JA, Kirstein MN, Zamboni WC, Stewart CF. Effect of hemodialysis on topotecan disposition in a patient with severe renal dysfunction. *Cancer chemotherapy and pharmacology* 2001; **47**(1): 89-93.
156. A PROPOSED standard system of nomenclature of human mitotic chromosomes. *Lancet* 1960; **1**(7133): 1063-5.
157. Anttila M, Laakso S, Nylanden P, Sotaniemi EA. Pharmacokinetics of the novel antiestrogenic agent toremifene in subjects with altered liver and kidney function. *Clinical pharmacology and therapeutics* 1995; **57**(6): 628-35.
158. Thariat J, Etienne-Grimaldi MC, Launay-Vacher V, et al. Pharmacokinetics of trabectedin on hemodialysis: an application for the management of cancer patients with end-stage renal disease. *Cancer chemotherapy and pharmacology* 2011; **68**(5): 1363-7.
159. Calvo E, Azaro A, Rodon J, et al. Hepatic safety analysis of trabectedin: results of a pharmacokinetic study with trabectedin in patients with hepatic impairment and experience from a phase 3 clinical trial. *Investigational new drugs* 2018; **36**(3): 476-86.
160. Weil A, Martin P, Smith R, et al. Pharmacokinetics of vandetanib in subjects with renal or hepatic impairment. *Clinical pharmacokinetics* 2010; **49**(9): 607-18.
161. Bedikian AY, Silverman JA, Papadopoulos NE, et al. Pharmacokinetics and safety of Marqibo (vincristine sulfate liposomes injection) in cancer patients with impaired liver function. *Journal of clinical pharmacology* 2011; **51**(8): 1205-12.
162. Isambert N, Delord JP, Tourani JM, et al. How to manage intravenous vinflunine in cancer patients with renal impairment: results of a pharmacokinetic and tolerability phase I study. *British journal of clinical pharmacology* 2014; **77**(3): 498-508.
163. Delord JP, Ravaud A, Bennouna J, et al. Phase I and pharmacokinetic study of IV vinflunine in cancer patients with liver dysfunction. *Investigational new drugs* 2013; **31**(3): 724-33.

164. Kitzen JJ, Puozzo C, de Jonge MJ, Brandely M, Verweij J. Mild to moderate liver dysfunction does not require dose reduction of oral or intravenous vinorelbine: results of a pharmacokinetic study. *European journal of cancer* 2010; **46**(2): 266-9.
165. Abou-Alfa GK, Lewis LD, LoRusso P, et al. Pharmacokinetics and safety of vismodegib in patients with advanced solid malignancies and hepatic impairment. *Cancer chemotherapy and pharmacology* 2017; **80**(1): 29-36.
166. Ramalingam SS, Kummar S, Sarantopoulos J, et al. Phase I study of vorinostat in patients with advanced solid tumors and hepatic dysfunction: a National Cancer Institute Organ Dysfunction Working Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010; **28**(29): 4507-12.