TITLE: IQ DILI CONSENSUS OPINION: BEST PRACTICES FOR RECHALLENGE FOLLOWING SUSPECTED DRUG-INDUCED LIVER INJURY IN CLINICAL TRIALS

JOURNAL: Drug Safety

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Electronic Supplementary Materials # 1

Table 1 Oncology drugs with Liver Monitoring Guidelines in the Label

Oncology – Kinase Inhibitors				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
Votrient (pazopanib) *USPI December/2021* *https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022465s031s032lbl.pdf*	✓	✓	✓	**Pre-existing Hepatic impairment -** **Recommended Dosage Modification at initiation of treatment:** None Not recommended in patients with moderate (total bilirubin > 1.5 to 3 × ULN and any ALT value) and severe (total bilirubin > 3 × ULN and any ALT value) **Recommended Rechallenge Dosage** Reduced dose no more than 400 mg QD
BOSULIF (bosutinib) *USPI October/2021* **https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203341s020lbl.pdf**	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment:** Child-Pugh A, B, or C starting dose reduced to 200 mg daily **Recommended Rechallenge Dosage** Reduced dose 400 mg QD
ZYDELIG (idelalisib) *USPI October /2020* **https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205858s014lbl.pdf**	✓	✓	✓	**Pre-existing Hepatic Impairment Recommended Dosage Modification at initiation of treatment:** None **Recommended Rechallenge Dosage** Reduced dose 100 mg BID

Oncology – Kinase Inhibitors				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
NEXAVAR (sorafenib) *USPI July/2020* *https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021923s024lblrpl.pdf*	✓	✓	-	**Pre-existing Hepatic Impairment - Recommended Dosage Modification at initiation of treatment:** Child-Pugh A or B hepatic impairment: None Child-Pugh C: pharmacokinetics not studied
TASIGNA (nilotinib) *USPI September/2021* **https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022068s035s036lbl.pdf**	✓	✓	✓	**Pre-existing Hepatic Impairment - Recommended Dosage Modification at initiation of treatment:** If possible, consider alternative therapies. If TASIGNA must be administered, consider reduced dose **Recommended Rechallenge Dosage** Reduced dose - Adults 400 mg QD - Pediatric 230 mg QD
STIVARGA (regorafenib) *USPI June/2020* https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203085s013lbl.pdf	✓	✓	✓	**Pre-existing Hepatic Impairment- Recommended Dosage Modification at initiation of treatment:** Mild or moderate hepatic impairment: None Severe hepatic impairment: Not recommended **Recommended Rechallenge Dosage** Reduced dose 120 mg QD

Oncology – Kinase Inhibitors				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
GLEEVEC (imatinib mesylate) *USPI August/2022* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021588s062lbl.pdf	✓	✓	✓	**Pre-existing hepatic Impairment -Recommended Dosage Modification at initiation of treatment:** Mild or Moderate hepatic impairment: None Severe hepatic impairment: Reduce recommended dose by 25% **Recommended Rechallenge Dosage** Reduced dose - Adults reduced daily dose (dose varies based on prior dose per indication) - Pediatrics reduced dose to 260mg/m^2/day
TARCEVA (erlotinib) *USPI October/2016* *https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf*	✓	✓	✓	**Pre-existing hepatic Impairment- Recommended Dosage Modification at initiation of treatment:** None **Recommended Rechallenge Dosage** Reduced dose by 50 mg decrements
TYKERB (lapatinib *USPI March/2022* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022059s031lbl.pdf	✓	✓	-	**Pre-existing hepatic Impairment- Recommended Dosage Modification at initiation of treatment:** dose reduction should be considered in patients with severe preexisting hepatic impairment, **Recommended Rechallenge Dosage** Not specified Discontinue and do not restart TYKERB if patients experience severe changes in liver function tests

Oncology - Immunomodulators				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
REVLIMID (lenalidomide) *USPI: May/2022* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021880s065lbl.pdf	✓	✓	✓	**Pre-existing hepatic impairment – Recommended Dosage Modification at initiation of treatment:** None **Recommended Rechallenge Dosage** Reduced dose (restart at next lower dose)
Pomalyst (pomalidomide). USPI December/2020 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204026s028lbl.pdf	✓	✓	✓	**Pre-existing Hepatic impairment Dosage Recommended Dosage Modification at initiation of treatment:** Child-Pugh A, B or C hepatic impairment**:** Reduced starting dose **Recommended Rechallenge Dosage** Reduced dose
KEYTRUDA® (pembrolizumab) *USPI December/ 2022* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s127lbl.pdf	✓ ✓	✓ ✓	✓ ✓	**Pre-existing hepatic impairment - Recommended Dosage Modification at initiation of treatment:** Mild- No clinically important effect on CL. Moderate or severe unknown **Recommended Rechallenge Dosage** **KEYTRUDA + Axitinib** Single drug or sequential rechallenge with both drugs

Oncology – Checkpoint Inhibitors				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
YERVOY (Ipilimumab) *USPI May/2022* https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125377s130lbl.pdf	✓	✓	✓	**Pre-existing Hepatic impairment -Recommended Dosage Modification at initiation of treatment:** None specified **Recommended Rechallenge Dosage** Dose reductions not recommended – withhold or discontinue as appropriate **Clinical Trial Experience with Rechallenge** Additional information on rechallenge with Vervoy as single agent and in combination with nivolumab in clinical trials provided on label
Oncology – Miscellaneous				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
GEMZAR (gemcitabine) Neucloside metabolic inhibitor *USPI August/2019* https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020509s082lbl.pdf	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment:** None specified **Recommended Rechallenge Dosage** Not specified
MYLOTARG (gemtuzumab) CD33- antibody *USPI September/2017*	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment:** None specified **Recommended Rechallenge Dosage**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf				Not specified; withhold or discontinue as appropriate
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
Methotrexate *USPI March/2022* **https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214121s001lbl.pdf**	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment**: Not specified; Avoid in patients with chronic liver disease, unless benefits clearly outweigh the risks. **Recommended Rechallenge Dosage** Not specified; Withhold or discontinue as appropriate.
Cyclophosphamide Alkylating Agent *USPI September/2021* **https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212501s002lbl.pdf**	-	-	-	**Pre-existing Hepatic impairment – Recommended Dosage Modification at initiation of treatment**: Not specified
SOLTAMOX (tamoxifen) selective estrogen receptor modulator (SERM) *USPI: September 2018* **https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021807s005lbl.pdf**	✓	-	-	**Pre-existing Hepatic impairment – Recommended Dosage Modification at initiation of treatment**: Not specified

USPI: United States prescribing information **ULN:** upper limit of normal **ALT:** alanine aminotransferase

QDL: once daily **BID:** twice daily

Table 2 Liver Disease Treatments with Liver Monitoring Guidelines in the Label

Liver Disease (non-oncology)				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
OCALIVA (obeticholic acid) farnesoid X receptor (FXR) agonist) for PCB ***USPI* February 2022** **https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207999s008lbl.pdf**	✓	✓	-	**Pre-existing Hepatic impairment –** **Recommended Dosage Modification at initiation of treatment** : None specified Contraindicated for -decompensated cirrhosis (e.g., Child-Pugh Class B or C) - a prior decompensation event - compensated cirrhosis with evidence of portal hypertension - complete biliary obstruction
URSO (ursodiol) – Bile Acid Primary biliary cholangitis (PBC). ***USPI January 2023*** https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020675s028lbl.pdf	✓	✓	-	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment**: None specified Contraindicated for complete biliary obstruction
CHOLBAM (cholic acid) - Bile acid ***USPI October 2020*** **https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205750s003lbl.pdf**	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment**: None specified **Recommended Rechallenge Dosage** Consider restarting at a lower dose when

Liver Disease (non-oncology)				
Product	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
BYLVAY (odevixibat) - Ileal bile acid transporter (IBAT) inhibitor *USPI October/2022* *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215498s002lbl.pdf*	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment**: None specified **Recommended Rechallenge Dosage** consider restarting at the lowest dose of 40 mcg/kg and increase as tolerated if appropriate.
Viekira Pak (dasabuvir, ombitasvir, paritaprevir, ritonavir and ribavirin) *USPI December 2014*	✓	✓	-	**Pre-existing Hepatic impairment –** **Recommended Dosage Modification at initiation of treatment** : None specified Contraindicated in patients with severe hepatic impairment (Child-Pugh C) Liver Transplant Recipients: In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks.

Table 3 Drugs for Other Indications with Liver Monitoring Guidelines in the Label

Other Indications				
Product/ Dose	**Routine Monitoring**	**Stopping Rules**	**Rechallenge**	**Comment**
Zocor (simvastatin) *USPI May/2022* *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/019766s102lbl.pdf*	✓	✓	-	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment**: Not specified contraindicated in patients with acute liver failure or decompensated cirrhosis

Isoniazid *USPI July 2016* https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008678s028lbl.pdf	✓	✓	✓	**Pre-existing Hepatic impairment - Recommended Dosage Modification at initiation of treatment**: Not specified contraindicated in patients acute liver disease of any etiology **Recommended Rechallenge Dosage** Very small and increasing doses

USPI: United States prescribing information **ULN:** upper limit of normal **ALT:** alanine aminotransferase

QDL: once daily **BID:** twice daily