Supplementary material

In order to provide a global safety perspective, we queried the FAERS, a consolidated spontaneous reporting database in oncology gathering more than 15 million reports worldwide [1]. To this aim, DILI reports of clinical interest were retained using two established Standardized MedDRA Queries (Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions; Hepatitis, non-infectious). First, demographic (sex, age), pharmacological (co-reported ICI) and clinical features (time to onset, seriousness, death) were described, with a focus on potentially hepatotoxic drugs according to the classification by Bjornsson et al. [2]. Then, a disproportionality approach, through the so-called case/non-case approach [3], was performed to assess whether suspected DILI events (cases) are differentially reported with MET inhibitors, as compared to other adverse events (non-cases). To this aim, the frequentist Reporting Odds Ratio (ROR, deemed significant by a lower limit of the 95% confidence interval>1) and the Bayesian Information Component (IC, deemed significant by a lower limit of the credibility interval IC025>0) were estimated. Different comparators (all drugs in FAERS, anticancer drugs, protein kinase inhibitors) were *a priori* selected to assess the robustness of the signal and provide a clinical perspective (Supplementary material). Moreover, sensitivity analyses were conducted on a population likely naïve to previous immunotherapy by removing reports (i.e., cases and non-cases) where ICIs were co-reported with MET inhibitors.

References

[1] Raschi E, Gatti M, Gelsomino F, Ardizzoni A, Poluzzi E, De Ponti F. Lessons to be Learnt from Real-World Studies on Immune-Related Adverse Events with Checkpoint Inhibitors: A Clinical Perspective from Pharmacovigilance. Target Oncol. 2020 Aug;15(4):449-466. doi: 10.1007/s11523-020-00738-6. PMID: 32725437; PMCID: PMC7434791.

[2] Björnsson ES, Hoofnagle JH. Categorization of drugs implicated in causing liver injury: Critical assessment based on published case reports. Hepatology. 2016 Feb;63(2):590-603. doi: 10.1002/hep.28323. Epub 2015 Dec 21. PMID: 26517184.

[3] Faillie JL. Case-non-case studies: Principle, methods, bias and interpretation. Therapie. 2019 Apr;74(2):225-232. doi: 10.1016/j.therap.2019.01.006. Epub 2019 Jan 31. PMID: 30773344.

Table 2. Disproportionality analyses. FAERS: Food and Drug Administration Adverse Event Reporting System; CI: Confidence Interval; IC: Information Component; ROR: Reporting Odds Ratio. NC: not calculated due the low number of cases (<3), which makes the ROR estimate unreliable. * Statistically significant disproportionality (95%CI>1 or $IC0_{25}$>0).

	Capmatinib			**Tepotinib**		
Comparator (N)	**N. cases/non cases**	**ROR (95%CI)**	**IC (IC_{025}-IC_{075})**	**N. cases/non cases**	**ROR (95%CI)**	**IC (IC_{025}-IC_{075})**
Primary Analysis						
All drugs recorded in FAERS (1,776,208)	43/875	3.20 (2.29-4.34) *****	1.59 (1.08-1.95) *****	2/103	NC	0.30 (-2.30-1.69)
Anticancer Drugs (359,861)	43/875	1.55 (1.11-2.11) *****	0.60 (0.09-0.96) *****	2/103	NC	-0.58 (-3.17-0.82)
Protein Kinase Inhibitors (124,834)	43/875	1.72 (1.23-2.35) *****	0.74 (0.23-1.10) *****	2/103	NC	-0.45 (-3.04-0.94)
Secondary Analysis (naive population without immunotherapy)					NC	
All drugs recorded in FAERS (1,776,208)	37/851	2.83 (1.97-3.93) *****	1.42 (0.88-1.81) *****	2/102	NC	0.31 (-2.29-1.7)
Anticancer Drugs (359,861)	37/851	1.37 (0.96-1.91)	0.43 (-0.12-0.82)	2/102	NC	-0.56 (-3.16-0.83)
Protein Kinase Inhibitors (124,834)	37/851	1.52 (1.06-2.12) *****	0.57 (0.02-0.96) *****	2/102	NC	-0.44 (-3.03-0.96)