

Targeted Oncology

Posterior reversible encephalopathy syndrome with angiogenesis inhibitors for solid tumours: clues from a disproportionality analysis of the FDA Adverse Event Reporting System and pharmacodynamics

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Table S1. Information about PRES associated with mABs, TKIs, and aflibercept reported in FDA and EMA labels

		FDA				EMA			
Drug class	Drug	Warnings and precautions	Frequency	Adverse drug reactions	Frequency	Special warnings and precautions for use	Frequency	Undesirable effects	Frequency
mAB	Bevacizumab	✓	<0.5% of patients across clinical studies	✓	⊗	✓	Rare reports	✓	Rare Across clinical trials, 8 cases of PRES have been reported
	Ramucirumab	✓	<0.1% of patients enrolled in six clinical studies	✓	⊗	✓	Cases of PRES, including fatal cases, have been rarely reported	✓	Rare (reported in clinical trials and through postmarketing reporting)
	Ranibizumab	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗
TKI	Axitinib	✓	In a controlled clinical study for the treatment of patients with RCC, was reported in <1% of patients. Two additional reports in other clinical trials	✓	⊗	✓	⊗	✓	Uncommon (reported in clinical trial)
	Cabozantinib	✓	⊗	✓	<15% of patients in Clinical Trial Experience	✓	⊗	✓	Uncommon Reported in one patient in a clinical study and in one patient in another study. PRES has been rarely reported in other clinical trials (0.04%)
	Fruquintinib	✓	In one patient with mCRC	✓	In clinical trials occurred in 0.2% of patients	✓	PRES has been reported in 1 patient (0.1%) treated in clinical studies	✓	Uncommon One case (0.1%) of PRES was reported in patients in monotherapy in clinical studies. PRES has also been reported in post-marketing experience
	Lenvatinib	✓	Across clinical studies occurred in 0.3%	✓	⊗	✓	<1%	✓	Uncommon (reported in clinical trials and through postmarketing reporting)
	Nintedanib	⊗	⊗	✓	⊗	✓	Some cases of PRES have been reported postmarketing	✓	Not known
	Pazopanib	✓	⊗	✓	⊗	✓	⊗	✓	Rare
	Regorafenib	✓	Occurred in one patient across all clinical trials	✓	⊗	✓	⊗	✓	Rare
	Sorafenib	⊗	⊗	✓	Uncommon	⊗	⊗	✓	Uncommon
	Sunitinib	✓	<1% of patients, some of which were fatal	✓	⊗	✓	⊗	✓	Rare
	Tivozanib	✓	⊗	✓	⊗	✓	In clinical studies, one case of PRES was confirmed after treatment	✓	Rare
	Vandetanib	✓	⊗	✓	⊗	✓	⊗	⊗	⊗
	Aflibercept	⊗	⊗	⊗	⊗	⊗	⊗	⊗	⊗

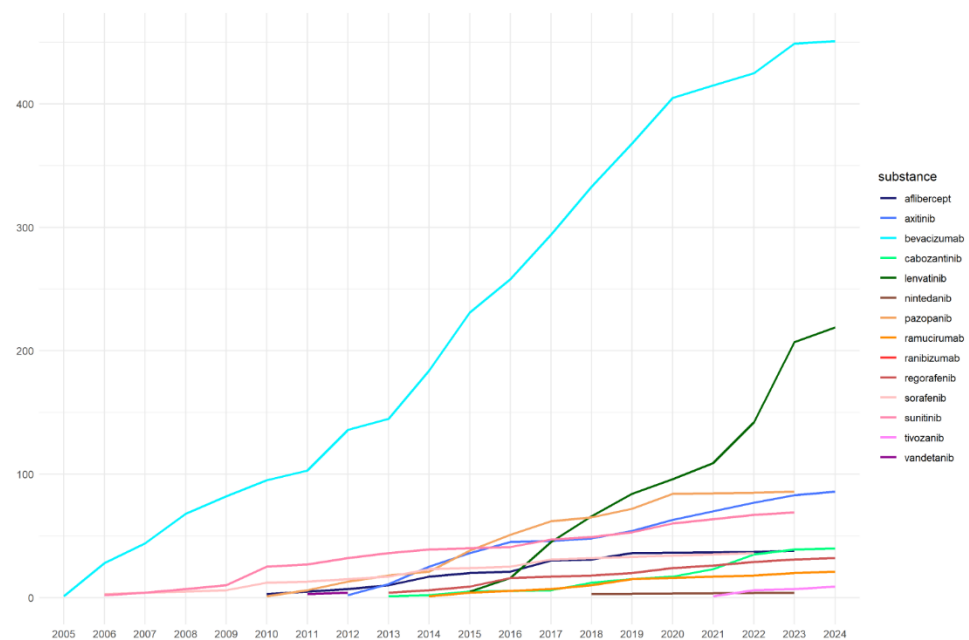


Figure S1- Evolution of cumulative number of reports by reporting year

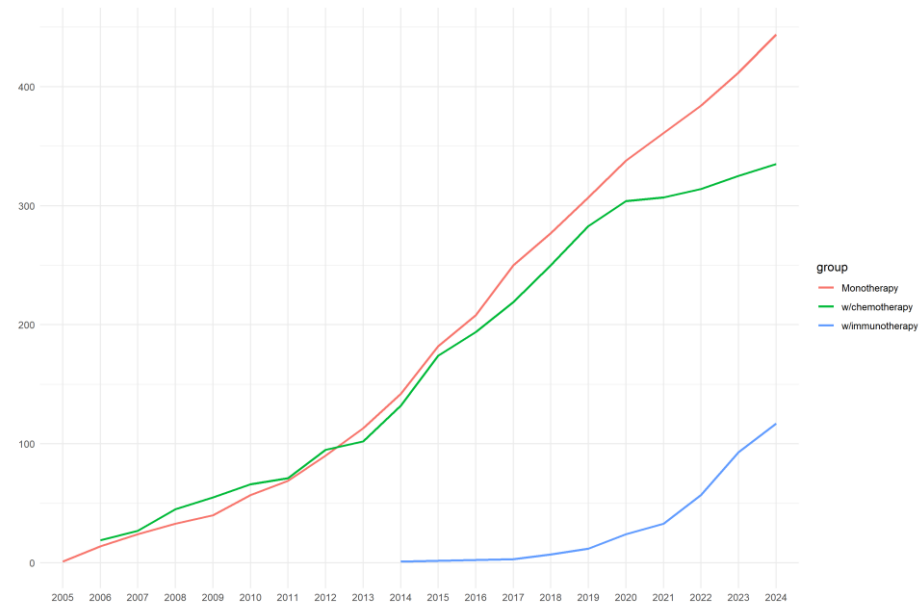


Figure S2 – Evolution of the cumulative number of reports by reporting year, divided by monotherapy or combination with chemotherapy or immunotherapy.

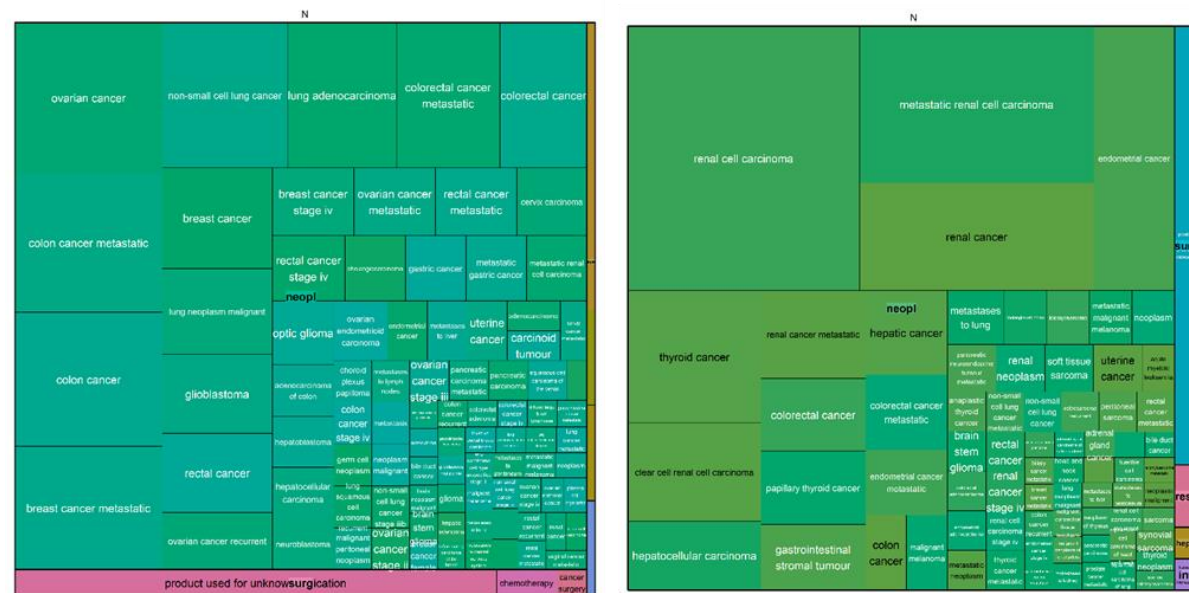


Figure S3. Indications of VEGFR MAB on the left and indications of VEGFR TKI on the right. Indications are presented at the PT level and grouped by HLT level (color-coded).

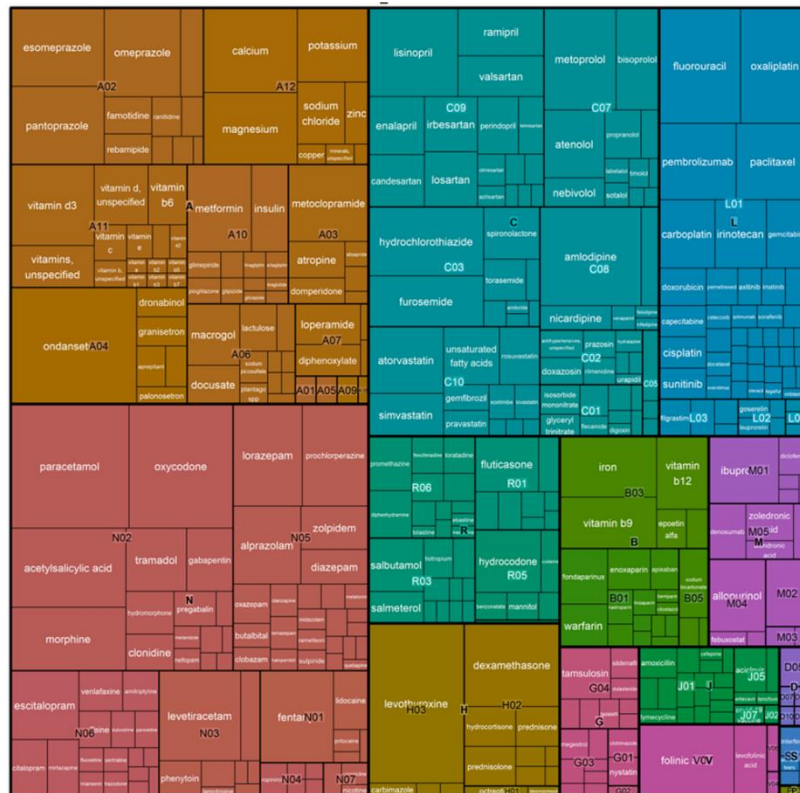


Figure S4 – Treemap of concomitant drugs. Drugs are presented at the ATC 5 level and grouped by ATC 2 level (color-coded).

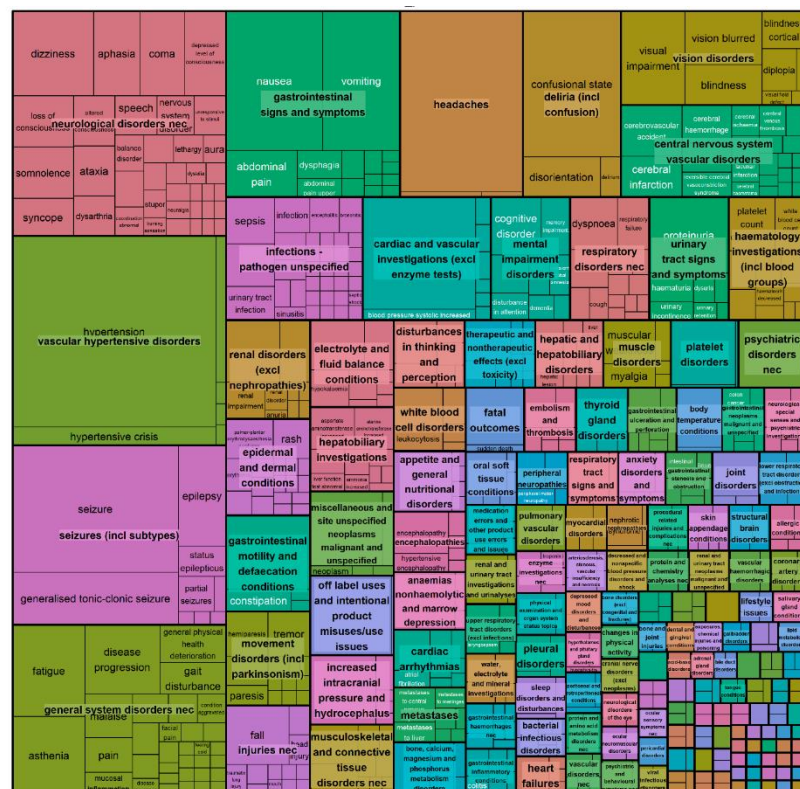


Figure S5 – PRES co-occurrent events. Events are presented at the PT level and grouped by HLT level (color-coded).

Table S2. Main Disproportionality Analysis

Substance	D_E	D_nE	D	nD_E	E	nD_nE	IC (95% CI)
bevacizumab	393	83204	83597	6814	7207	13889064	3.17 (3-3.29)
lenvatinib	132	25474	25606	7075	7207	13946794	3.27 (2.98-3.48)
axitinib	72	14575	14647	7135	7207	13957693	3.17 (2.77-3.45)
pazopanib	70	20804	20874	7137	7207	13951464	2.64 (2.24-2.93)
sunitinib	59	35646	35705	7148	7207	13936622	1.65 (1.22-1.96)
cabozantinib	33	32727	32760	7174	7207	13939541	0.94 (0.36-1.35)
sorafenib	26	19538	19564	7181	7207	13952730	1.32 (0.66-1.78)
aflibercept	26	19282	19308	7181	7207	13952986	1.34 (0.68-1.8)
regorafenib	24	9438	9462	7183	7207	13962830	2.18 (1.5-2.66)
ramucirumab	20	4375	4395	7187	7207	13967893	2.88 (2.13-3.41)
tivozanib	9	1030	1039	7198	7207	13971238	3.19 (2.05-3.95)
vandetanib	4	1561	1565	7203	7207	13970707	1.78 (0.01-2.86)
nintedanib	2	19480	19482	7205	7207	13952788	-2.08 (-4.67--0.69)
ranibizumab	1	20082	20083	7206	7207	13952186	-2.86 (-6.64--1.17)
fruquintinib	0	267	267	7207	7207	13972001	-0.36 (-10.68-1.62)

IC: Bayesian Information Component

D_E: events of PRES related to the drug

D_nE: other events different from PRES and related to the drug

D: total number of events related to the drug

nD_E: events of PRES related to all other drugs recorded in FAERS

E: total number of events of PRES, recorded in FAERS

nD_nE: all other events different from PRES and related to all other drugs recorded in FAERS

Table S3. Disproportionality Analysis restricted to antineoplastic drugs

substance	D_E	D_nE	D	nD_E	E	nD_nE	IC (95% CI)
bevacizumab	393	83204	83597	3386	3779	1874565	1.28 (1.11-1.4) [393]
lenvatinib	132	25474	25606	3647	3779	1932295	1.41 (1.12-1.61) [132]
axitinib	72	14575	14647	3707	3779	1943194	1.33 (0.94-1.61) [72]
pazopanib	70	20804	20874	3709	3779	1936965	0.79 (0.39-1.07) [70]
sunitinib	59	35646	35705	3720	3779	1922123	-0.22 (-0.66-0.09) [59]
cabozantinib	33	32727	32760	3746	3779	1925042	-0.93 (-1.51--0.52) [33]
sorafenib	26	19538	19564	3753	3779	1938231	-0.53 (-1.19--0.07) [26]
aflibercept	26	19282	19308	3753	3779	1938487	-0.51 (-1.17--0.05) [26]
regorafenib	24	9438	9462	3755	3779	1948331	0.38 (-0.3-0.86) [24]
ramucirumab	20	4375	4395	3759	3779	1953394	1.19 (0.44-1.71) [20]
tivozanib	9	1030	1039	3770	3779	1956739	1.92 (0.78-2.68) [9]
vandetanib	4	1561	1565	3775	3779	1956208	0.35 (-1.41-1.43) [4]
nintedanib	2	19480	19482	3777	3779	1938289	-3.93 (-6.53--2.54) [2]
fruquintinib	0	267	267	3779	3779	1957502	-1.03 (-11.35-0.95) [0]

Table S4. Disproportionality Analysis based on treatment context

SUBSTANCE	MONO IC (95% CI) [N]	CHEMO IC (95% CI) [N]	IMMUNO IC (95% CI) [N]
bevacizumab	1.35 (1.02-1.58) [104]	1.01 (0.79-1.17) [225]	0.13 (-0.85-0.8) [12]
lenvatinib	2.32 (1.9-2.62) [64]	0.27 (-1.5-1.35) [4]	2.16 (1.69-2.49) [51]
pazopanib	2.58 (2.16-2.88) [63]	1.06 (-0.35-1.97) [6]	-0.72 (-11.04-1.26) [0]
axitinib	2.87 (2.42-3.19) [55]	-0.96 (-11.29-1.02) [0]	2.12 (1.18-2.77) [13]
sunitinib	1.58 (1.13-1.91) [53]	-0.07 (-2.14-1.14) [3]	2.09 (0.02-3.3) [3]
cabozantinib	0.69 (0.03-1.15) [26]	-0.86 (-11.19-1.12) [0]	0.43 (-0.87-1.29) [7]
regorafenib	2.26 (1.58-2.74) [24]	-1.27 (-11.59-0.71) [0]	-0.57 (-10.89-1.41) [0]
sorafenib	1.23 (0.53-1.72) [23]	-0.91 (-3.5-0.49) [2]	-0.3 (-10.62-1.68) [0]
tivozanib	3.24 (2.1-4) [9]	-0.16 (-10.49-1.82) [0]	-0.06 (-10.39-1.92) [0]
ramucirumab	1.69 (0.48-2.49) [8]	-0.07 (-1.63-0.92) [5]	0.81 (-2.97-2.5) [1]
vandetanib	1.47 (-0.6-2.68) [3]	0.4 (-3.38-2.09) [1]	-0.01 (-10.33-1.97) [0]
nintedanib	-2 (-4.59--0.61) [2]	-3.02 (-13.35--1.04) [0]	-0.59 (-10.91-1.39) [0]
ranibizumab	-4.36 (-14.68--2.38) [0]	-0.57 (-4.35-1.12) [1]	-0.01 (-10.34-1.97) [0]
aflibercept	-4.3 (-14.63--2.32) [0]	-1.08 (-1.73--0.62) [26]	-0.04 (-10.36-1.94) [0]
fruquintinib	-0.34 (-10.66-1.64) [0]	-0.09 (-10.42-1.89) [0]	-0.02 (-10.34-1.96) [0]

Table S5 – Affinity data extracted from ChEMBL and IUPHAR databases

MOLECULE	AlogP	Vd (L)	VEGFR 1	VEGFR 2	VEGFR 3	PDGFR alpha	PDGFR beta	EGFR erbB1	FGFR 1	FGFR 2	FGFR 3	FGFR 4	RET
AXITINIB	4.64	160	9.12	9.03	8.39	9.29	7.82	5.43	6.75	6.96	6.68	-	6.52
CABOZANTINIB	5.54	349	6.75	8.33	8.48	-	-	6.39	7.95	-	-	-	7.65
LENVATINIB	4.07	97	7.66	8.69	8.28	7.29	6.96	-	-	-	-	-	8.11
NINTEDANIB	3.62	1050	7.44	8.11	7.94	8.27	7.67	-	7.06	7.11	6.96	6.06	7.92
PAZOPANIB	3.14	11.1	7.67	7.96	7.41	7.22	7.53	-	6.61	6.77	6.17	5.55	6.27
REGORAFENIB	5.69	88	8.36	8.48	8.08	-	8.82	-	7.76	-	-	-	7.86
SORAFENIB	5.55	-	7.15	7.69	7.44	6.53	7.37	7.04	6.38	5.57	5.50	-	7.63
SUNITINIB	3.33	2230	8.26	7.56	7.64	7.93	7.93	5.78	5.96	6.26	6.30	5.68	7.48
TIVOZANIB	5.64	123	8.61	8.39	8.82	8.57	5.62	-	-	-	-	-	7.92
VANDETANIB	4.43	7450	6.64	7.10	6.70	6.72	6.32	7.26	5.54	5.61	5.86	5.64	7.01
FRUQUINTINIB	3.85	46	7.48	7.46	9.30	-	-	-	6.74	-	-	-	6.89

Table S6 – Pharmacovigilance-pharmacodynamic regression models

Model	beta	p
model_vdL	-0.0486	0.9
model_vegfr1	0.03053	0.138
model_vegfr2	0.1459	0.206
model_vegfr3	-0.03411	0.821
model_pdgfrA	0.03198	0.889
model_pdgfrB	-0.1336	0.541
model_egfr_erb_b1	-0.5434	0.30126
model_fgfr_1	-0.07823	0.676
model_fgfr_2	-0.0758	0.694
model_fgfr_3	-0.1109	0.452
model_fgfr_4	-0.10709	0.0014
model_ret	-0.05433	0.672

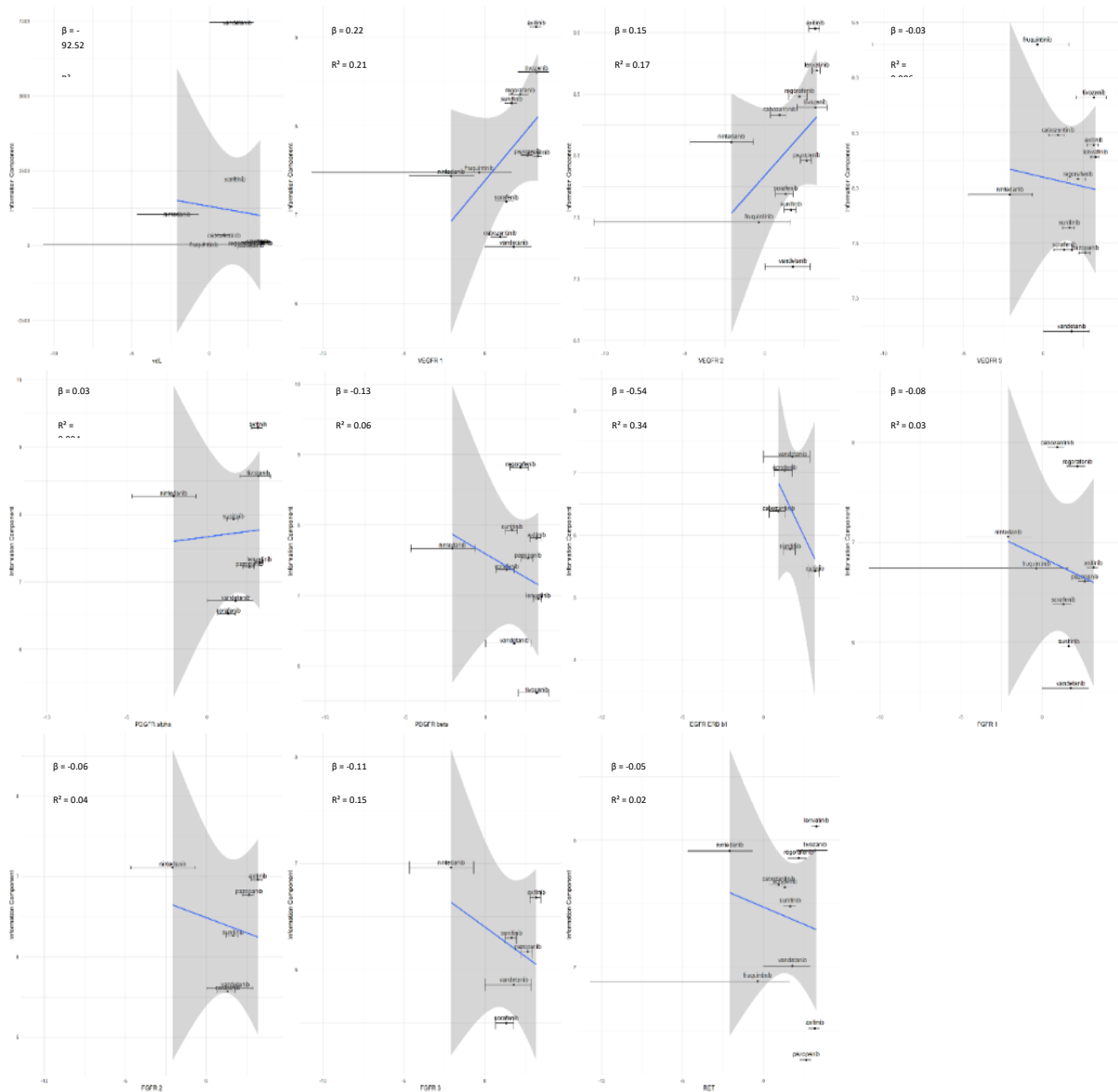


Figure S6 - Relationship between median IC (displayed with 95% CI) and all receptors other than FGFR4.

The READUS-PV checklist

Section and topic	Item #	Checklist item	Location where the item is reported
Title			
	1a	<i>If disproportionality analyses are a prominent component of the published study, the study should be identified as a “disproportionality analysis”. The type of data and name of the database(s) should be specified.</i>	Title page
	1b	<i>Report the name of adverse event(s) and/or drug(s) under study, when applicable.</i>	Title page
Introduction			
Background	2a	<i>Describe the drug(s) and their utilization, the nature of the adverse event(s) under study, their frequency, and the existing knowledge on the drug-event combination.</i>	Section 1, Introduction, paragraphs 1 and 2
	2b	<i>Specify the rationale for performing the analysis, e.g., as part of routine pharmacovigilance, to investigate an overall safety profile, or to assess a pre-specified hypothesis.</i>	Section 1, Introduction, paragraph 3
	2c	<i>Explain why ICSR databases and disproportionality analysis are suitable to fill the knowledge gap.</i>	Section 1, Introduction, paragraph 4
Objectives	3	<i>State specific objectives, identifying the adverse event(s), the drug(s), and the reference group, including any pre-specified hypothesis, if applicable.</i>	Section 1, Introduction, paragraph 5
Methods			
Study design	4a	<i>Identify the study (i.e., “disproportionality analysis”) and the type of data used (e.g., “individual case safety reports”).</i>	Section 2, Materials and Methods, Study Design and Data sources
	4b	<i>Provide an outline of the entire study design, including primary and sensitivity analyses performed, and other designs such as case-by-case analysis or literature review.</i>	Section 2, Materials and Methods, Study Design and Data sources
Data description, access, and pre-processing	5a	<i>Specify the name of the database(s), the database(s) custodian, and the coverage. Specify the type/number of drugs included within the database and the thesaurus, taxonomies, or ontologies used for coding drugs and events.</i>	Section 2, Materials and Methods, Study Design and Data sources
	5b	<i>Specify the extraction dates and describe and justify all choices used for data pre-processing, including any data transformation or exclusion, if appropriate.</i>	Section 2, Materials and Methods, Study Design and Data sources
Variables definition	6a	<i>Describe the study population, including any restrictions.</i>	Section 2, Materials and Methods, Study Design and Data

			<i>sources</i>
	6b	<i>Describe the nature and the meaning of key variables assessed in the work.</i>	<i>Section 2, Materials and Methods, Study Design and Data sources</i>
	6c	<i>Specify and justify any grouping of drugs or events. For drugs, specify and justify whether active ingredients/trade names/salts were considered and/or the selected role.</i>	<i>Section 2, Materials and Methods, Study Design and Data sources</i>
	6d	<i>Describe any additional data sources used, the type of data, and how they interact with ICSRs.</i>	<i>Section 2, Materials and Methods, Study Design and Data sources</i>
Statistical methods	7a	<i>Present any descriptive analysis performed, specifying variables investigated, statistical tests, and significance thresholds.</i>	<i>Section 2, Materials and Methods, Descriptive analysis</i>
	7b	<i>Describe the measure(s) selected for the disproportionality analysis, including any threshold used to identify signals of disproportionate reporting. Explain the reason for this choice if applicable.</i>	<i>Section 2, Materials and Methods, Disproportionality analysis</i>
	7c	<i>Clearly describe any sensitivity analysis and any tool to control confounding, including any restriction, subgroup, stratification, adjustment, or interaction.</i>	<i>Section 2, Materials and Methods, Disproportionality analysis</i>
	7d	<i>Specify the variables and methods used for the case-by-case analysis, including any algorithm or criteria used to assess causality</i>	<i>NA</i>
	7e	<i>Specify any statistical methods used for other data sources.</i>	<i>Section 2, Materials and Methods, Pharmacovigilance-pharmacodynamic analysis</i>

Results			
Participants	8a	<i>Specify the number of individual case safety reports included at each stage, including reasons for exclusion.</i>	<i>Section 3, Results, paragraphs 1</i>
	8b	<i>Provide key demographic and clinical characteristics of cases, if possible, comparing cases with any appropriate reference group.</i>	<i>Section 3, Results, paragraphs 2-6</i>
Disproportionality analysis	9	<i>Present all results, including confidence intervals. Present also the results of sensitivity analyses, if performed.</i>	<i>Section 3, Results, paragraphs 7-10</i>
Case-by-case analysis	10	<i>Present the case-by-case analysis of key variables. Present the causality assessment, if applicable.</i>	<i>NA</i>
Discussion			
Key results	11	<i>Discuss key results with reference to study objectives and contextualize them within the current literature and other consulted sources. Clearly discriminate between expected reactions and emerging safety signals.</i>	<i>Section 4, Discussion</i>
External validity	12a	<i>Discuss the external validity of the results to the general population.</i>	<i>Section 4, Discussion</i>
	12b	<i>Discuss the potential relevance of results in clinical practice</i>	<i>Section 4, Discussion</i>
	12c	<i>Propose further study designs if applicable</i>	<i>Section 4, Discussion</i>
Limitations	13	<i>Present general limitations, making clear that disproportionality analysis alone cannot prove causation or measure incidence, and specific limitations, including confounding and reporting bias and efforts to mitigate them.</i>	<i>Section 4, Discussion, Strengths and limitations</i>
Declarations			
	14a	<i>Provide the source of funding/sponsorship and the role of the funders/sponsors for the present study and for any original study on which the present article is based.</i>	<i>Section on funding information</i>
	14b	<i>Clearly identify potential commercial and intellectual conflicts of interest (e.g., link to any drug/event investigated, whether financial, legal action, or software used).</i>	<i>Section on conflict of interest statement</i>
	14c	<i>Declare any institutional approval needed or granted in the investigation.</i>	<i>NA</i>
	14d	<i>Include a statement on data availability, code availability (including the version of the statistical software used), and protocol registration.</i>	<i>Section on data availability statement</i>