The toxicity profile was acceptable-acceptable to whom?

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Title: The toxicity profile was acceptable-acceptable to whom?

Cancer drug trials frequently use general terms that downplay the harms despite increasing the incidence and risks of severe and serious toxicities.

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The clinical trial report of a new cancer drug called ribociclib for breast cancer patients mentions in its Discussion that "Most patients had an acceptable adverse-event profile".[1] A trial report of a new drug liposomal irinotecan in pancreatic cancer mentions in the concluding paragraph that it "has a manageable and mostly reversible safety profile."[2] Another report of a drug called tasquinimod trialed among patients with prostate cancer mentions "The tolerability of tasquinimod was good overall".[3] All three of these studies were published in top medical journals. Naturally, the readers would take these statements to be true. However, a look at the actual data for adverse events (AEs) doesn't paint as good a picture. In the first study of ribociclib that mentions acceptable adverse event profile, more than double number of patients in the ribociclib arm suffered grade 3 or higher AEs (*severe AEs*) compared with the control arm (271 of 334 versus 108 of 330 patients).[1] The incidence of treatment-related *serious AEs* (adverse events leading to death, life-threatening condition, hospitalization or prolongation of hospitalization, disability or permanent damage, congenital anomaly or birth defect, requiring intervention to prevent permanent impairment or damage, or any other adverse events that may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes[4]) was nearly 5 times (25 v 5). The second report of liposomal irinotecan that mentioned "manageable and mostly reversible" toxicities in fact shows that 5 patients died due to drug toxicities in the intervention arms due versus none in the control.[2] For the third report of tasquinimod that mentioned overall good tolerability, the incidences of severe AE and serious AE compared with control were 42.8% v 33.6% and 36.0% v 23.6% respectively.[3]

These three studies are only a few examples. The true risks of many new cancer drugs are hidden behind such general terms that downplay the harms of drugs. We therefore investigated how often the reports of cancer drug trials downplayed the harms. For our study, based on our prior experience with reading trial publications, we defined apriori the use of following terms or their derivates to describe adverse events profile as implying "downplaying of harms": tolerable, favorable, acceptable, manageable,

feasible and safe. We studied all the trial reports to find if any other terms were used that could imply downplaying of harms. Any dispute, or the discovery of any new term that seemed to downplay the toxicities, would be resolved by discussion and consensus among the authors. We also investigated the incidence and risks of toxicities with the cancer drugs in such trials.

From the five major medical journals that publish cancer drug trials (The New England Journal of Medicine, Lancet, Lancet Oncology, Journal of American Medical Association and Journal of Clinical Oncology), we extracted all phase 2 and phase 3 randomized controlled trials (RCTs) of cancer drugs published in the year 2016. We then studied the abstracts and full-texts of these articles to assess if the harms of the experimental arm were downplayed. We extracted the data on severe AEs, Serious AEs and FAEs for both the experimental and control cohorts from these RCTs and pooled them using random effects model to obtain an overall estimate of incidence and risk. Random effects model was chosen because of the obvious heterogeneity in pooling trials conducted among patients with different tumor types. All the study eligibility confirmations and data extractions were done twice: once by BG and once by KH, who remained blinded to each-other's extractions which was finally double checked by TS.

What terms did the trial reports use to downplay harms?

We found that the trial reports used a variety of terms –singly or in combination-to downplay the toxicities of the intervention arm. All these terms were within the list we had decided a priori; no new terms were discovered that could imply downplaying of harms. These terms and some arguments as to why their use is inappropriate, irrespective of whether the toxicities were increased or decreased, are listed in box 1.

How frequently do the trial reports of cancer drugs use such terms?

In the year 2016, a total of 122 phase 2 or 3 RCTs of cancer drugs were published in the major five journals. Of these, 53 RCT reports (43.4%) contained the terms downplaying the toxicities of the experimental arm and were included in our analysis.

How good was toxicity reporting in such trials that downplayed harms?

Of the 53 studies that downplayed harms, 14 (26.4%) had no data on severe AEs, 22 (41.6%) had no data on serious AEs and 2 (3.8%) had no data on FAEs. Severe AEs, serious AEs and fatal AEs constitute information of utmost importance for any shared decision making in the oncology clinic. Such underreporting of harms is common in oncology trials as previously reported.[5,6] However, for the trials that mention "acceptable or tolerable or favorable toxicity profile" for the experimental treatment arm not to report these data seems conflicting.

Were toxicities lower in the trials that downplayed the harms?

Of the trials that downplayed harms and provided data on toxicities, we found that the toxicities for the experimental arm were numerically higher than that for control arm for 77% of trials (30/39) with respect to severe AEs; 84% of trials (26/31) with respect to serious AEs and 66% of trials (34/51) with respect to FAEs. Thus, the drugs in majority of trial reports that downplay harms in fact increase toxicities compared to control arms.

What was the incidence of toxicities in trials that downplayed harms?

The overall incidence of severe AEs among the trials that downplayed toxicities were 50.6% (95% confidence interval CI : 41.5%-59.7%). A total of 21.9% (95% CI: 16.3%-28.7%) patients suffered serious AEs with the experimental drug whose harms were downplayed. Similarly, 1.6% patients (95% CI: 1.2% to 2.2%) died due to treatment related mortality with these drugs in these trials. To compare, the incidence of severe AEs, serious AEs and fatal AEs respectively in the control arm were: 43.7%(95% CI:

36.3%-51.5%), 15.7% (95% CI: 11.7%-20.6%) and 1.6% (95% CI: 1.1%-2.3%). This shows that in the intervention arm, there is an absolute increase in toxicities relative to the control cohort by 6.9% for severe AEs and 6.2% for SAEs. However, we don't mean to imply that the use of these terms is valid if the toxicities were lower than the control arms - such general downplaying terms shouldn't be used irrespective of the comparison (e.g. if fatal adverse event for a drug is 3% versus 5% for the control arm, the drug cannot still be said to be safe or well tolerated.)

By how much is the risk of toxicities higher in trials that downplay harms?

To estimate the increased risk, we calculated the risk ratio. Compared with control, the risk of severe AEs and serious AEs were significantly increased with the use of the cancer drugs that downplayed the harms. The risk for severe AEs were increased by 15% (RR 1.15, 95% CI: 1.04-1.27, p = 0.005) while the risk of serious AEs were increased by as much as 49% (RR 1.49, 95% CI: 1.26-1.77, p < 0.001). The risk of FAEs was similar across the experimental and control arms (RR 0.89, 95% CI: 0.72-1.11, p = 0.306).

Why is the downplaying of harms in trial reports problematic?

Downplaying the toxicities of cancer drugs is of particular concern because cancer drugs usually provide modest benefit at high costs- both figuratively in terms of toxicities and literally in terms of skyrocketing prices.[7] Hence, prescribing a cancer drug is always a risk-benefit trade-off. Downplaying toxicities can falsely convince the physicians and patients of better risk-benefit trade-off than that actually exists. Furthermore, all the downplaying terms we found were used either in the Abstract, Conclusion/Discussion or the "Research in context" Box (in Lancet/Lancet Oncology). These are the most widely read sections in any research paper thereby strengthening the impact of such messages. Most readers don't go through or don't remember the toxicities data from the tables but statements such as "the treatment was safe" make a lasting impression. Because in majority of cases the toxicities are

actually increased, use of such general terms falsely convinces the reader of better value with the drug. Therefore, use of such general terms to downplay the harms is a poor reporting practice.

We also believe that it is inappropriate for us to consider toxicities as acceptable or tolerable, irrespective of incidence and risks. Whether the toxicities are acceptable or not is for the patient to decide, not the physicians or the trial stakeholders. The threshold for tolerability to toxicities differs from person to person. It is unethical for a trial to report AEs as acceptable without collecting data from the patients. We are unaware of any standardized criteria or consensus to label toxicities as acceptable or tolerable. Without collecting data from patients on what they would acknowledge as acceptable or tolerable toxicities, we believe that we cannot put those labels unto the experiences of our patients. Furthermore, any cancer drug with a non-zero treatment related FAEs (i.e., some patients have died as a result of the drug) shouldn't be labeled as "safe" or as having "manageable toxicities"

Although we focused on RCTs for our study, the use of such terms downplaying the harms are also common in phase I or II non- randomized studies. We studied RCTs to compare the toxicities with a control arm. However, the use of such terms in non-randomized studies would be particularly concerning because the readers wouldn't have a control to make comparisons. Also, our pooling of toxicity data from trials of different drugs across different tumor types might seem as pooling apples and oranges together, but the main objective was not to provide an accurate data on increased risk of toxicities, but to highlight how important safety information remain hidden behind such generalized terms. We don't intend to promote or discourage a certain drug as safe or unsafe. Indeed, one RCT alone cannot provide enough data on safety and ongoing real-world data as well as physicians plus patients' experience with the use of a drug should dictate clinical practice. However, unambiguous and complete reporting of harms data in trial publications is the most important step to appropriate clinical

practice, more so in oncology where many new drugs are used that have inadequate safety signals from long term studies.

Any measures to control such reporting practices?

In fact, the CONSORT statement already recommends against such reporting practice. The CONSORT statement for reporting of harms has a table listing "Common poor reporting practices for harms-related data".[8] The first such poor practice listed reads: "Using generic or vague statements, such as "the drug was generally well tolerated" or "the comparator drug was relatively poorly tolerated". We have found that nearly 44% of cancer drug trials published in the major medical journals violate this suggestion from CONSORT to avoid the generic or vague statements in describing harms. We also showed that the proportion of patients who suffer severe, serious and fatal AEs with such drugs in these trials is substantial.

Summary and recommendations

Practice of evidence based medicine (EBM) requires correct interpretation of trial data, which in turn demands correct reporting of trial in publications. Many cancer trials do not report data on toxicities to make proper assessment of harms. Furthermore, a majority of trial reports use terms that downplay the harms. Most importantly, these terms are used in sections that are most impactful such as the abstracts. There is no threshold for harms that can be considered acceptable or tolerable. Labeling adverse effects from a drug as "acceptable" would only be acceptable if the patients who were enrolled were asked whether the toxicities were acceptable. If such data have not been collected, the use of vague terms such as "the treatment was safe" should be avoided. The physicians and patients would decide whether the side effects from any treatment are tolerable or not on a case by case basis.

Another share of responsibility to avoid such poor reporting practices also belongs to the medical journals that publish cancer drug trials. The use of such terms must be discouraged, especially in the abstracts and conclusions. The editors and reviewers should ask for detailed toxicities data and encourage reporting actual numbers or percentages rather than the vague general terms to describe the harms. As readers, the physicians and patients should look at the toxicities data in the tables rather than trust such generalized terms. Proper risk-benefit assessment of any cancer drug should be made with actual harms and efficacy data, and not based on general concepts of “safe” or “unsafe”, “tolerable” or “intolerable” etc.

Contributors and Sources

BG conceptualized the study. BG, TS and KH collected the data and all authors participated in data verification. BG performed the meta-analyses. All authors participated in discussion and interpretation. BG wrote the first draft of the manuscript which was revised and approved by all the authors. BG has a keen interest and has widely published in cancer policy. He also has an interest in clinical trial reporting of cancer drugs and hosts a monthly blog in ecancer critiquing on reporting practices of major cancer drug trials. The authors are also interested in safety reporting in cancer drug trials and have previously published together on serious and fatal adverse events of sorafenib.

Declaration of Competing Interests

We have read and understood the BMJ Group policy on declaration of interests and declare that BG is an adviser to the BMJ Analysis. YA has received research funding and personal fees from a number of pharmaceutical companies but none in relation with this work. Since this work critiques *against* the industry bias and poor reporting practices, none of the industry supports received by YA could be interpreted as affecting the results or interpretation of this work. A full ICMJE disclosure form for YA can be provided by the corresponding author upon request.

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BOX

Box 1: Terms used to downplay the harms of cancer drugs (*Italics represent some reasons as to why the use of such terms are inappropriate)*
1. Toxicities were acceptable. *(Acceptable to whom? Were the patients asked if the toxicities were acceptable to them?*) 2. Toxicities were manageable. (*SAEs and FAEs can never be considered manageable. Even manageable toxicities incur burden and decreased quality of life upon patients*) 3. Treatment was feasible. (*What would be the threshold for feasibility of a treatment? Will the mention of "the treatment is feasible" be enough to obtain patient's consent to a treatment?)* 4. It had a favorable toxicity profile. *(Favorable compared to what? Threshold of enduring toxicities and thus favorability is different from patient to patient)* 5. The side effects were tolerable or well-tolerated. (*Only the patient can decide whether any toxicity is tolerable or not.)* 6. The treatment was safe. *(Any cancer treatment that has a non-zero FAE cannot be considered safe)*

KEY MESSAGES

KEY MESSAGES
1. 4 of 10 cancer trial reports used general terms that downplayed harms, most in abstracts. 2. Many such trials had inadequate reporting of toxicity data. 3. The incidences of severe, serious and fatal adverse events were substantial in these trials. 4. Use of such general terms can mislead the risk-benefit assessment and provide false reassurance. 5. Such terms should be avoided in reporting of cancer drug trials.

Study	Safety N	Safety n	Sev.AE	Sev. AE control	SAE	SAE control	FAE	FAE control
Dimopoulos et al.	283	281	83%	74.7%	48.8%	42%	11	15
Goss et al.	959	954	Not reported		0	0	0	0
Maury et al.	105	104	96 per 100 p-y (Event 352)	92 per 100 p-y (Event 282)	Not reported		Not reported	
Moreau et al.	361	359	267	247	168	177	6	9
Hortobagyi et al.	334	330	271	108	25	5	2	0
Dreyling et al.	139	139	94	121	Not reported		8	11
Fehrenbacher et al.	142	135	16	52	50	46	1	3
Herbst et al.	339+343	309	43+55	109	Not reported		3+3	5
Ribrag et al.	128	129	Not reported		Not reported		6	7
Schoffski et al.	226	224	152	126	Not reported		1	0
D Tap et al.	64	65	43	36	14	17	0	6
Uesaka et al.	187	190	Not reported		Not reported		2	0
Wang Gilliams et al.	117+147	134	Not reported		56+90	60	5	0
Yao et al.	202	98	Not reported		Not reported		3	2
Zalcman et al.	222	224	158	139	Not reported		3	1
Zhang et al.	180	173	77	62	7	10	0	0
Ascierto et al.	247	246	147	128	92	69	5	3
Chanan-Khan et al.	287	287	222	212	150	125	19	18
Cristofanilli et al.	345	172	251	38	44	30	0	0
Dimopoulos et al.	463	456	339	305	224	162	18	16
Garcia-Manero et al.	184	91	145	62	111	54	3	0
Hironaka et al.	47	48+49	Not reported		18	8+20	0	0
Langer et al.	59	62	23	16	16	7	1	2
Ledermann et al.	136	128	15/32	1/5	30	11	1	0
Mateos et al.	62	63	Not reported		12%	3%	1	0

Mir et al.	76	41	55	17	20	0	3	0
Neal et al.	39+40	40					1+1	0
Park et al.	160	159	91	83	17	7	0	1
Quoix et al.	110	107	4	11	0	0	0	0
Rini et al.	202	132	116	62	Not reported		4	8
Rummel et al.	114	105	Not reported		23	23	0	0
Sehn et al.	194	198	132	123	74	65	3	5
Shore et al.	183	189	17	15	12	6	1	0
Sun et al.	239	238	174	128	Not reported		1	0
Trneny et al.	167	83	Not reported		Not reported		0	0
Vansteenkiste et al.	1515	757	246	122	29	8	0	1
Zelinkski et al.	277	284	Not reported		68	65	0	2
Pujade-Lauraine	54	55	33	17	Not reported		0	0
Demetri et al.	340	155	Not reported		Not reported		7	0
Amadori et al.	111	114	68	77	Not reported		19	23
Senan et al.	283	272	181	209	Not reported		5	3
Li et al.	176	91	Not reported		17	3	Not reported	
Penson et al.	197	198	70	72	58	56	6	6
Crump et al.	493	249	92	28	Not reported		0	0
Kurzeder et al.	77	76	69%	75%	Not reported		6	10
Cortes et al.	259	260	15%	11%	Not reported		8*	5*
Monk et al.	52	51	Not reported		Not reported		0	0
Sugiyama et al.	321	325	Not reported		Not reported		0	0
Pavlakis et al.	97	50	65	26	32%	18%	2	1
Sternberg et al.	830	411	355	138	299	97	27	15
Urata et al.	277	276	96	119	Not reported		0	3
Cheng et al.	126	65	53	12	11	1	2	0
Colleoni et al.	473	537	64	Not reported	Not reported		2	0

*Death within 30 days

Results

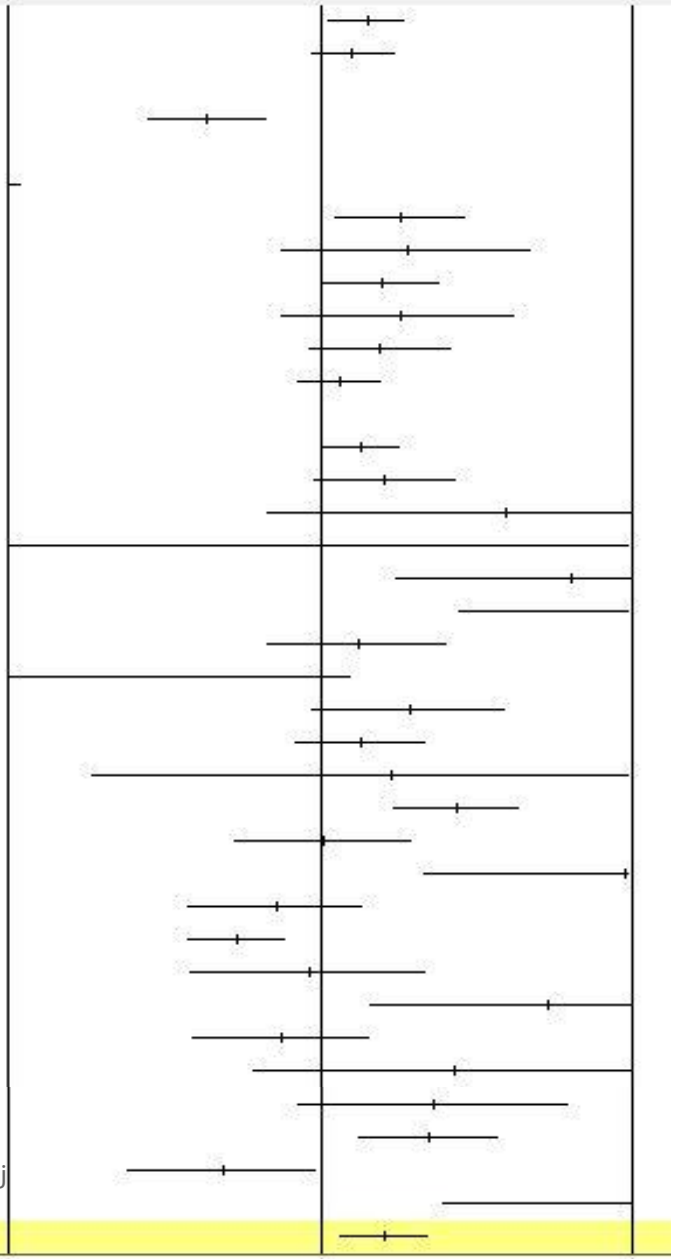
Incidence

	Incidence (95% Confidence Interval)	Control Incidence	Absolute increase in incidence
Severe Adverse Events (grade 3 or higher)	50.6% (41.5%-59.7%)	43.7%(36.3%-51.5%)	6.9%
Serious Adverse Events (SAEs)	21.9% (16.3%-28.7%)	15.7% (11.7%-20.6%)	6.2%
Fatal Adverse Events (FAEs)	1.6% (1.2%-2.2%)	1.6% (1.1%-2.3%)	0.0%

Risks of Severe AE (grade 3 or higher)

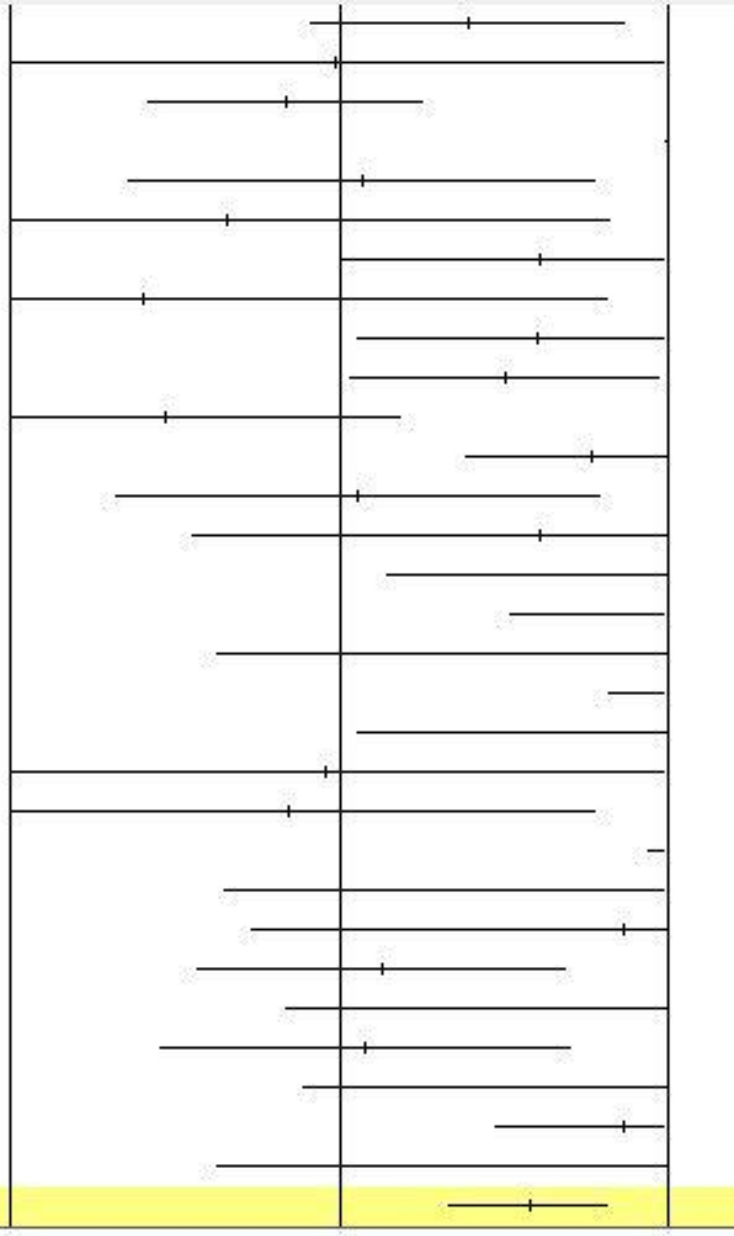
Model	Study name	Statistics for each study				
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
	Dimopoulos	1.111	1.020	1.211	2.402	0.016
	Moreau	1.075	0.980	1.179	1.528	0.126
	Hortobagyi	2.479	2.106	2.918	10.911	0.000
	Dreyling	0.777	0.681	0.886	-3.758	0.000
	Fehrenbach	0.293	0.176	0.486	-4.739	0.000
	Herbst	0.407	0.321	0.517	-7.413	0.000
	Schoffski	1.196	1.032	1.385	2.383	0.017
	D Tap	1.213	0.919	1.601	1.365	0.172
	Zalcman	1.147	1.005	1.309	2.031	0.042
	Zhang	1.194	0.919	1.550	1.327	0.184
	Ascierto	1.144	0.977	1.340	1.666	0.096
	Chanan-Kh	1.047	0.954	1.149	0.971	0.332
	Cristofanilli	3.293	2.469	4.392	8.112	0.000
	Dimopoulos	1.095	1.006	1.192	2.089	0.037
	Garcia	1.157	0.986	1.356	1.791	0.073
	Langer	1.511	0.890	2.564	1.528	0.127
	Ledermann	2.344	0.391	14.058	0.932	0.351
	Mir	1.745	1.183	2.576	2.804	0.005
	Neal	2.181	1.365	3.484	3.263	0.001
	Park	1.090	0.891	1.332	0.837	0.403
	Quoix	0.354	0.116	1.077	-1.830	0.067
	Rini	1.223	0.984	1.518	1.818	0.069
	Sehn	1.095	0.947	1.267	1.227	0.220
	Shore	1.170	0.603	2.273	0.465	0.642
	Sun	1.354	1.176	1.559	4.210	0.000
	Vansteenkis	1.008	0.826	1.229	0.074	0.941
	Pujade-Laur	1.977	1.262	3.097	2.977	0.003
	Amadori	0.907	0.746	1.102	-0.981	0.327
	Senan	0.832	0.746	0.928	-3.296	0.001
	Penson	0.977	0.751	1.272	-0.172	0.863
	Crump	1.660	1.118	2.462	2.516	0.012
	Kurzeder	0.918	0.752	1.119	-0.847	0.397
	Cortes	1.350	0.862	2.115	1.311	0.190
	Pavlakis	1.289	0.954	1.741	1.653	0.098
	Sternberg	1.274	1.089	1.491	3.019	0.003
	Urata	0.804	0.651	0.993	-2.028	0.042
	Cheng	2.278	1.314	3.951	2.932	0.003
Random		1.152	1.043	1.271	2.793	0.005

Risk ratio and 95% CI



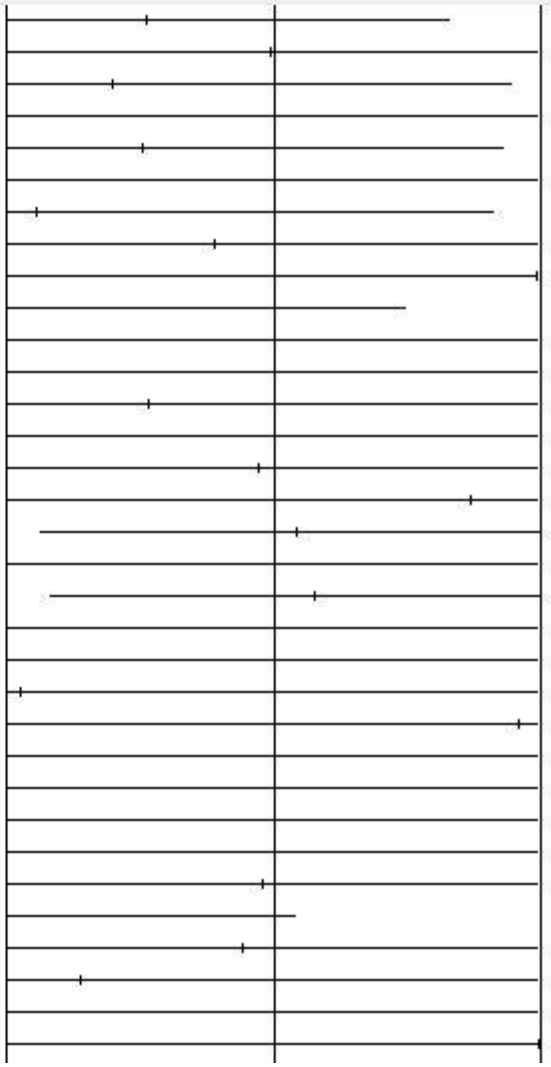
Risks of Serious AEs

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Dimopoulos	1.315	0.943	1.833	1.613	0.107
	Goss	0.995	0.020	50.185	-0.003	0.998
	Moreau	0.895	0.668	1.199	-0.743	0.458
	Hortobagyi	5.259	1.988	13.911	3.345	0.001
	Fehrenbach	1.052	0.641	1.725	0.199	0.842
	D Tap	0.791	0.351	1.778	-0.568	0.570
	Wang	1.526	1.005	2.318	1.981	0.048
	Zhang	0.660	0.245	1.774	-0.825	0.410
	Ascierto	1.523	1.042	2.225	2.172	0.030
	Chanan-Kh	1.419	1.021	1.971	2.086	0.037
	Cristofanilli	0.692	0.418	1.147	-1.429	0.153
	Dimopoulos	1.701	1.306	2.216	3.935	0.000
	Garcia	1.042	0.624	1.739	0.157	0.875
	Hironaka	1.530	0.734	3.187	1.135	0.256
	Langer	2.924	1.104	7.741	2.160	0.031
	Ledermann	3.010	1.437	6.304	2.922	0.003
	Mateos	3.882	0.773	19.482	1.648	0.099
	Mir	30.115	1.770	512.296	2.355	0.019
	Park	2.581	1.040	6.409	2.044	0.041
	Quoix	0.973	0.019	49.462	-0.014	0.989
	Rummel	0.901	0.470	1.727	-0.314	0.754
	Sehn	2.903	1.926	4.375	5.093	0.000
	Shore	2.140	0.786	5.829	1.489	0.137
	Vansteenkis	1.827	0.831	4.016	1.500	0.134
	Zelinski	1.096	0.743	1.618	0.463	0.644
	Li	3.136	0.894	10.998	1.786	0.074
	Penson	1.058	0.685	1.635	0.254	0.799
	Pavlakis	2.140	0.925	4.948	1.779	0.075
	Sternberg	1.823	1.394	2.383	4.388	0.000
	Cheng	6.122	0.773	48.504	1.716	0.086
Random		1.496	1.262	1.772	4.652	0.000



Risks of Fatal AEs

Model	Study name	Statistics for each study				
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Dimopoulos	0.717	0.323	1.590	-0.818	0.413
	Goss	0.995	0.020	50.185	-0.003	0.998
	Moreau	0.657	0.232	1.866	-0.788	0.431
	Hortobagyi	3.970	0.178	88.363	0.871	0.384
	Dreyling	0.711	0.277	1.824	-0.710	0.478
	Fehrenbach	0.312	0.032	3.037	-1.003	0.316
	Herbst	0.540	0.163	1.782	-1.012	0.311
	Ribrag	0.857	0.280	2.624	-0.270	0.787
	Schoffski	1.987	0.066	59.517	0.396	0.692
	D Tap	0.077	0.004	1.417	-1.725	0.085
	Uesaka	4.097	0.184	91.461	0.890	0.373
	Wang	5.154	0.280	95.054	1.103	0.270
	Yao	0.724	0.119	4.403	-0.351	0.725
	Zalcman	3.055	0.315	29.593	0.964	0.335
	Zhang	0.961	0.019	48.702	-0.020	0.984
	Ascierto	1.674	0.396	7.080	0.700	0.484
	Chanan-Kh	1.059	0.544	2.063	0.170	0.865
	Cristofanilli	0.498	0.010	25.196	-0.348	0.728
	Dimopoulos	1.112	0.560	2.209	0.304	0.761
	Garcia	3.000	0.149	60.529	0.717	0.474
	Hironaka	2.075	0.041	106.230	0.364	0.716
	Langer	0.517	0.046	5.860	-0.532	0.595
	Ledermann	1.889	0.063	56.790	0.366	0.714
	Mateos	2.049	0.068	62.208	0.412	0.680
	Mir	3.329	0.163	68.103	0.781	0.435
	Neal	2.052	0.090	46.591	0.451	0.652
	Park	0.495	0.016	14.869	-0.405	0.686
	Quoix	0.973	0.019	49.462	-0.014	0.989
	Rini	0.313	0.092	1.062	-1.864	0.062
	Rummel	0.921	0.018	46.820	-0.041	0.967
	Sehn	0.606	0.143	2.572	-0.679	0.497
	Shore	2.071	0.069	62.122	0.420	0.675
	Sun	1.996	0.067	59.773	0.398	0.690



Risks of Fatal AEs

Trneny	0.495	0.010	25.194	-0.350	0.726
Vansteenkis	0.250	0.008	7.448	-0.801	0.423
Zelinski	0.255	0.011	5.679	-0.863	0.388
Pujade-Laur	1.019	0.020	52.277	0.009	0.993
Demetri	6.495	0.366	115.185	1.275	0.202
Amadori	0.817	0.417	1.602	-0.588	0.556
Senan	1.613	0.382	6.815	0.650	0.516
Penson	1.005	0.319	3.172	0.009	0.993
Crump	0.505	0.010	25.504	-0.342	0.733
Kurzeder	0.558	0.192	1.620	-1.073	0.283
Cortes	1.625	0.525	5.036	0.842	0.400
Monk	0.981	0.019	50.375	-0.010	0.992
Sugiyama	1.012	0.020	51.181	0.006	0.995
Pavlakis	1.032	0.091	11.660	0.025	0.980
Sternberg	0.888	0.467	1.688	-0.363	0.716
Urata	0.165	0.008	3.300	-1.179	0.238
Cheng	2.081	0.092	46.816	0.461	0.645
Colleoni	4.556	0.205	101.286	0.958	0.338
Random	0.895	0.724	1.106	-1.024	0.306