

CORRESPONDENCE

Open Access

# Clinically meaningful benefit: real world use compared against the American and European guidelines

Jessica J. Dreicer<sup>1</sup>, Sham Mailankody<sup>2</sup>, Farhad Fakhrejahani<sup>3</sup> and Vinay Prasad<sup>4,5,6</sup>

Although some cancer drugs offer large, indisputable benefits<sup>1</sup>, many drugs improve outcomes only marginally<sup>2</sup>. Recognizing the need to develop therapies of meaningful benefit to our patients, both the American Society of Clinical Oncology (ASCO)<sup>3</sup> and the European Society of Medical Oncology (ESMO)<sup>4</sup> have issued expert guidelines stating the magnitude of benefit that is clinically meaningful. These groups define clinically meaningful as whether drugs meet benchmarks of improvements in overall and progression free survival. For example, the ASCO guidelines propose that a new chemotherapeutic result in a relative increase in the median OS of at least 20% or 2.5–6 months<sup>3</sup>.

Prior groups have compared approved drugs<sup>5</sup> and randomized trials<sup>6</sup> against the ASCO and ESMO thresholds; however, to our knowledge, no analysis has compared the ASCO and ESMO thresholds against oncologist's use of the phrase "meaningful benefit" in the published literature.

We sought biomedical articles where authors explicitly endorsed or stated that some numerical improvement in a clinical outcome seen in a randomized controlled trial constituted a meaningful benefit for a particular cancer indication.

We searched Google Scholar with the terms "meaningful benefit" and "oncology" or "meaningful benefit" and "cancer," and limited our results to 2014 and 2015, as we were concerned with recent usage. Each article was reviewed by J.J.D. who identified the claim of meaningful benefit. Our study was conducted between November 2015 and March 2016.

Articles were excluded if: the article did not pertain to the field of oncology, the authors did not refer to a specific drug or combination, the authors were not claiming a meaningful benefit (i.e., they were saying a meaningful benefit does not exist), or the article did not reference a randomized trial and no such trial could be found.

We extracted changes in overall survival (OS), progression free survival, or other clinical endpoints between intervention and control arms that were deemed meaningful benefit. Descriptive statistics is provided. We

**Table 1** Cancer types where meaningful benefit was used

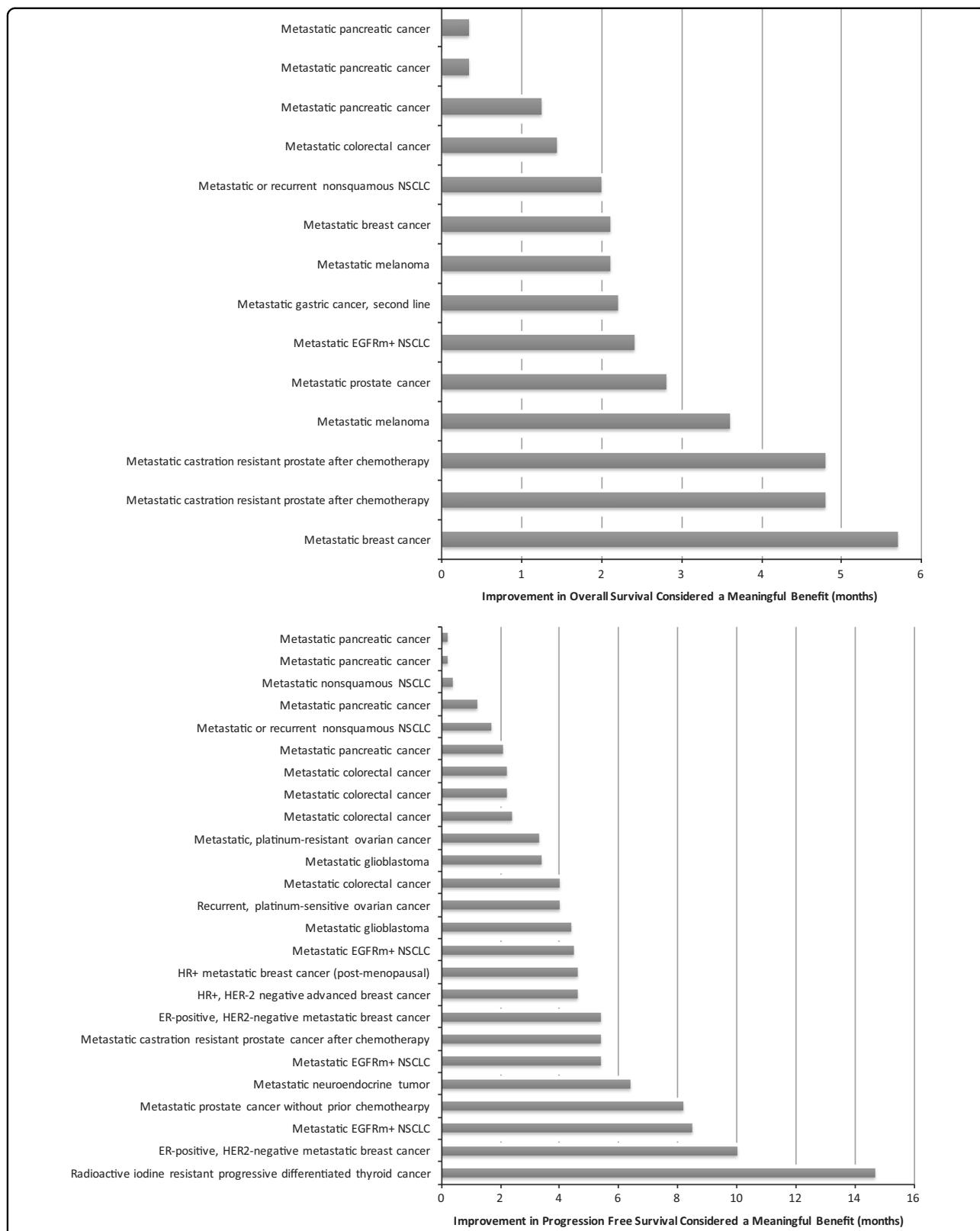
Cancer type	Instances
Pancreatic	8
Breast	7
Non-small cell lung	7
Prostate	6
Colorectal	6
Myeloproliferative neoplasm	3
Melanoma	2
Thyroid	2
Glioblastoma	2
Ovarian	2
Gastric	1
Neuroendocrine	1
Acute myeloid leukemia	1
Germ-cell	1

Correspondence: Vinay Prasad (prasad@ohsu.edu)

<sup>1</sup>Department of Medicine/OHSU, Portland, OR 97239, USA

<sup>2</sup>Myeloma Service/Memorial Sloan Kettering Cancer Center, New York City, NY, USA

Full list of author information is available at the end of the article



**Fig. 1** Top panel. Magnitude of improvement in median overall survival deemed a meaningful benefit. Bottom Panel. Magnitude of improvement in progression free survival deemed a meaningful benefit

compared author's usage against the ESMO and ASCO guidelines.

We used the method of Kumar et al.<sup>5</sup> for cancers not included in ASCO initial guidelines. Specifically, the group sought to adhere to the spirit of ASCO guidelines and gave credit for a PFS or OS of 2.5 months accompanied by a relative improvement of 25%.

We reviewed 559 articles in 2014 and 2015, and identified 53 claims of meaningful benefit in randomized studies. One was in the adjuvant setting (NSCLC), three were neoadjuvant (1 rectal, 2 urothelial), 49 were in the advanced or metastatic setting.

Of the 49 claims in the advanced/metastatic setting, 25 described median PFS improvement, 14 described median OS improvement, and 10 used another measure of benefit. These claims concerned 14 different tumor types (Table 1).

The median improvement in OS thought to constitute a meaningful benefit was 2.2 months (range 0.33–5.7 months). These are shown in Fig. 1 top panel. The median improvement in PFS thought to be meaningful was 4.0 month (range 0.2–14.7 months). These are shown in Fig. 1 bottom panel.

Among 14 claims of meaningful benefit based on median OS, 6 (43% 95% CI 18–71%) met ASCO and 4 (29% 95% CI 8–64%) met ESMO guidelines. Among 25 claims of meaningful benefit based on PFS, 17 (68% 95% CI 47–85%) met ASCO and 17 (68% 95% CI 47–85%) met ESMO guidelines.

Our results suggest that academic oncologists occasionally use the phrase "meaningful benefit" to describe a gain that does not meet expert, consensus guidelines. This happens 32% of the time for progression free survival and 57% and 71% of the time for overall survival, based on American and European standards, respectively. Given that the ASCO and ESMO thresholds are modest, we believe real world usage that falls short of this is setting the bar too low for our patients.

Future research should explore what magnitudes of benefit patients consider meaningful benefit, and whether

these might serve as an externally valid metric for professional societies.

#### Author details

<sup>1</sup>Department of Medicine/OHSU, Portland, OR 97239, USA. <sup>2</sup>Myeloma Service/Memorial Sloan Kettering Cancer Center, New York City, NY, USA. <sup>3</sup>National Cancer Institute/National Institutes of Health, New York City, NY, USA. <sup>4</sup>Division of Hematology Oncology/Knight Cancer Institute/Oregon Health and Science University, Portland, OR 97239, USA. <sup>5</sup>Department of Public Health and Preventive Medicine/Oregon Health and Science University, Portland, OR 97239, USA. <sup>6</sup>Senior Scholar in the Center for Health Care Ethics/Oregon Health and Science University, Portland, OR 97239, USA

#### Competing interests

Dr. Dreicer and Fahkrehjani—none; Dr Mailankody reported serving as a principal investigator for clinical trials with research funding from Juno Therapeutics and Takeda Oncology. Dr Mailankody reported receiving personal fees for speaking at the Wedbush Pacgrow Healthcare Conference 2016. Dr Prasad's research is funded by the Laura and John Arnold Foundation. Dr Mailankody is supported in part by support grant/core grant P30 CA008748 from the National Cancer Institute Memorial Sloan Kettering Cancer Center.

#### Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 17 August 2017 Accepted: 23 August 2017

Published online: 14 December 2017

#### References

1. Druker, B. J. et al. Five-year follow-up of patients receiving imatinib for chronic myeloid Leukemia. *N. Engl. J. Med.* **355**, 2408–2417 (2006).
2. Fojo, T., Mailankody, S. & Lo, A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley lecture. *JAMA Otolaryngol–Head Neck Surg.* **140**, 1225–1236 (2014).
3. Ellis, L. M. et al. American society of clinical oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J. Clin. Oncol.* **32**, 1277–1280 (2014).
4. Cherny, N. I. et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann. Oncol.* **26**, 1547–1573 (2015).
5. Kumar, H., Fojo, T. & Mailankody, S. A. N. Appraisal of clinically meaningful outcomes guidelines for oncology clinical trials. *JAMA Oncol.* **2**, 1238–1240 (2016).
6. Del Paggio, J. C. et al. Do contemporary randomized controlled trials meet ESMO thresholds for meaningful clinical benefit? *Ann. Oncol.* **28**, 157–162 (2017).