Temporal Trends in Clinical Trials and the Benefit of New Cancer Therapies:
Identifying High Value Treatment for Patients

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INTRODUCTION

Cancer is now the most common cause of death in high-income countries (HICs) with a similar trajectory anticipated in low-middle (LMIC) countries. While efforts in primary prevention and secondary prevention/screening are urgently needed to reduce the future burden of cancer; effective treatments are needed to address to the surge in prevalent cases. The pillars of cancer therapy include locoregional treatment (i.e. surgery and radiotherapy), systemic therapy (i.e. chemotherapy, molecular targeted therapy, immunotherapy), and supportive care (i.e. symptom management, palliative care, psychosocial oncology). Although there have been important advances in each of these domains, in recent years a rising proportion of cancer health system budgets have been dedicated to systemic therapy for cancer [1-3]; this is potentially problematic when one considers that the dominant curative modalities for cancer are surgery and radiotherapy.

With the rapidly expanding number of systemic therapy options has come important considerations with regards to clinical/patient-reported toxicity and financial toxicity. It is therefore imperative that cancer systems carefully consider which treatments will offer the largest clinical benefit within a sustainable health care system. In recent years there have been two primary concerns with the expanding role of systemic therapy in cancer: 1) many therapies are associated with small clinical benefits; and 2) the financial cost of these therapies is very high and growing rapidly.

This report will provide an overview of a) temporal trends in clinical trial methodology and endpoints; b) magnitude of benefit of new cancer therapies; c) industry funding and reporting of trial results, d) progression-free survival as a surrogate endpoint; e) the value of new
anti-cancer therapies; and f) statistical significance versus clinically significance. It is hoped that this report will provide useful context for policymakers in prioritizing cancer therapies.

TEMPORAL TRENDS IN ONCOLOGY CLINICAL TRIALS

The design and conduct of multi-centred randomized controlled trials in oncology accelerated in the mid-20th century with the advent of cooperative trials groups in the United States. Thereafter, oncology drug development has followed a paradigm whereby promising agents from the laboratory first undergo safety and dose finding studies in phase I trials before moving to more a comprehensive study of safety and early efficacy in phase II trials. Ultimately, the gold standard for establishing the efficacy of new cancer therapies is a phase III randomized controlled trial. Results of RCTs thereafter move into the regulatory approval process and are incorporated into practice guidelines. More recently, there is growing interest in phase IV studies which use “real-world” data to explore the uptake of new therapies and effectiveness in the general population [4-6]. Real-world evidence will be briefly addressed in a later section of this report; herein we focus on phase III oncology trials.

Sample Size and Study Endpoints

Temporal trends in methodology of oncology RCTs have been reported by a number of bibliometric studies. Key observations are shown in Table 1. Booth and colleagues evaluated 321 systemic therapy RCTs in breast, colorectal, and non-small cell lung cancer published in six major journal during three decades 1975-2004 [7]. During the three study decades there was a marked increase in the median sample size (from 100 to 249 to 446 patients/trial). Intention-to-treat analysis became more common over time (from 33% to 54%, p<0.001). This report was subsequently updated with an additional 137 RCTs published during 2005-2009; median sample size continued to rise over time (from 446 to 772) [8]. While earlier RCTs tested cytotoxic
agents and hormonal therapies, in more recent years there has been a shift towards molecular targeted therapies (from 4% in 2005 to 29% in 2009, p<0.001). However, despite substantial interest in targeted therapy only half of trials evaluating these agents incorporated biomarkers into the trial design and the vast majority of these biomarkers related to traditional use of hormone receptors status and HER-2 expression in breast cancer.

Work by Booth et al and Kay et al have shown marked shifts in the primary endpoint of cancer clinical trials [7, 8]. Use of response rate as primary endpoint decreased from 54% in 1975-1984 to 6% in 2005-2009. While use of overall survival initially increased (from 21% of all trials in 1975-1985 to 51% in 1995-2004), its use has decreased in more recent years (36% in 2005-2009). This has been accompanied by a large increase in use of surrogate endpoints. Collectively, use of disease-free survival, progression-free survival, time-to-progression, and relapse-free survival increased substantially over time: 18% in 1975-1984, 11% in 1985-1994, 27% in 1995-2004, 53% in 2005-2009.

In their analysis of phase III RCTs (with ≥200 patients) of breast and colorectal cancer published 1975-2007, Seruga et al identified an increase in sample size as well as a marked shift to multicenter and international trials [9]. Over the three decade study period, RCTs become more likely to be conducted in the palliative setting rather than the adjuvant setting (from 24% to 50% and from 76% to 50%, p<0.01). The proportion of control arms that contained an active regimen increased from 48% in 1975-1985 to 59% in 1986-1995 to 81% in 1996-2007 (p<0.001). Two separate reports have explored temporal trends in phase III trials of advanced non-small cell lung cancer. Sacher and colleagues reviewed 203 RCTs published during 1980-2010 [10]. Fernandez-Lopez et al analyzed 76 trials published during 2000-2012 [11]. Both groups reported large increases in median sample size; from 152 to 413 and from 460 to 741
patients respectively. RCTs in the earlier years were primarily cytotoxic therapy; this shifted towards targeted therapies in more recent years. Sacher et al found that while OS remained the primary endpoint for most RCTs in advanced lung cancer, its use did decrease over time from 97% in 1980-1990 to 81% in 2001-2010; during this period there was a clear increase in use of PFS as the primary endpoint. Finally, Zer et al described phase II and III RCTs in soft-tissue sarcoma published during 1975-2014 [12]. Over time there was a substantial increase in the proportion of phase II trials (from 16% in 1974-1994 to 59% in 1995-2014, p<0.001). Intention-to-treat analysis was only clearly performed in only 10% and 49% of trials in the two study eras.

Quality of life is not well reported in oncology RCTs. In a review of 112 RCTs in patients with advanced cancer (≥150 patients) only 22% defined QOL or symptom control as the primary endpoint [13]. Among those trials that did report QOL and symptom control the analytic approach and reporting were generally of poor quality. More recently Schandelmaier and colleagues evaluated planning and reporting of QOL in 173 oncology RCTs reviewed by Research Ethics Boards in 3 countries during 2000-2003 [14]. Fifty-two percent of protocols specified QOL outcomes and only 20% actually reported QOL in a subsequent publication. This represents an important loss of valuable information to physicians and patients.

**Magnitude of Clinical Benefit**

Several reports have shown that the incremental gain of new cancer therapies is getting smaller over time. In their overview of RCTs published over three decades (1975-2004), Booth et al found that despite the median effect size showing a decreasing trend (HR 1.4, 1.2, 1.2), authors in the most recent decade became more likely to strongly endorse the novel treatment as the new standard of care (31% vs 39% vs 49%, p=0.017) [7]. Seruga and colleagues found that among RCTs of breast and colorectal cancer published during 1975-2007, the absolute benefits
of adjuvant therapy decreased over time [9]. Among palliative intent RCTs, there was no change in absolute benefit over time but monthly costs of new agents increased markedly. Among 203 RCTs of systemic therapy for advanced lung cancer Sacher et al found a decreasing trend in the absolute improvement in median survival (from 3.9 months during 1980-1990 to 2.5 months in 2001-2010, p=0.121) [10]. Despite this trend, the proportion of studies which were framed as “positive” by the study authors increased from 24% in 1991-2000 to 53% in 2001-2010 (p<0.001). Finally, Fojo et al all new drugs/indications approved by the Food and Drug Administration for solid tumours during 2002-2014 [15]. Among the 71 drug approvals, the median gain in PFS and OS were 2.5 and 2.1 months respectively.

**Funding**

Temporal analyses of oncology RCTs show a substantial increase in industry sponsorship. Booth et found that the proportion of RCTs with industry support increased from 4% in 1975-1984 to 78% in 2005-2009 (p<0.001) [7]. Their analysis also suggested evidence of sponsorship bias whereby authors of industry-funded RCTs were more likely to consider study results as “practice-changing” independent of effect size and statistical significance. Similar trends in funding were observed by Seruga et al (industry funding 10% in 1975-1985 and 58% in 1996-2007, p<0.001) and by Zer et al (industry funding 0% in 1974-1994 and 31% in 1995-2014, p<0.001) [9, 12]. In an overview of all RCTs registered in clinicaltrials.gov 1997-2011, Jairam and colleagues found marked differences in trial funding across treatment modalities; studies of chemotherapy or targeted therapy were much more likely to be funded by industry (32% and 48% respectively) compared to multimodality trials and RCTs of radiotherapy (5% and 4% respectively) [16]. In addition to the study by Booth et al, several other groups have described “sponsorship bias” in oncology RCTs [17-19]. Bourgeois and colleagues reported that
85% of industry oncology trials listed on clinicaltrials.gov reported positive outcomes compared to 50% of government funded studies [20].

**Biased reporting**

It is now recognized that reporting of trial results is subject to various forms of bias and spin. This phenomenon likely contributes to the increase in marginal gains seen in anti-cancer therapies by over-stating the benefit of novel treatments. Early forms of reporting bias included publication bias (i.e. whereby RCTs with “positive” results are more likely to be published than “negative” RCTs) and sponsorship bias (i.e. industry funded trials are more likely to be “positive” than trials funded by other sources) [7, 21, 22]. More recent studies have demonstrated that reporting of RCTs at major conferences and in peer-reviewed publications are subject to “spin”. Booth and colleagues reviewed abstracts presented at seven major cancer meetings related to 138 published RCTs [23]. In this review that found that 44% of related abstracts were presenting non-final results. Moreover, for 10% of RCTs they found evidence of major discordance (i.e. the recommendation to adopt/not adopt the experimental therapy) in the study conclusion between conference presentation and the subsequent full publication.

“Spin” within published reports of RCTs has described by several groups. Altwairgi et al reviewed 114 published RCTs of systemic therapy for lung cancer and found that bottom line recommendation from the abstract was fully discordant with the conclusion within the text of the manuscript in 10% of cases; in the vast majority of these cases the abstract vastly over-stated the benefits of the new therapy [24]. Vera-Badillo and colleagues found evidence of bias in reporting of study results among 164 RCTs of new therapies for breast cancer [25]. One third of studies showed bias in reporting of the primary endpoint and two-thirds of studies showed bias in reporting toxicity. More than half of studies with a negative result for the primary endpoint used
secondary endpoints to suggest benefit of the experimental therapy. Finally, it has been shown that oncology RCT reports consistently under-estimate the extent of toxicity experienced by patients [26, 27].

**PROGRESSION-FREE SURVIVAL**

The contemporary use of “progression” as a measurement in cancer dates to the World Health Organization in 1981 and subsequent revisions via the RECIST criteria in 2000 and 2009 [28-30]. The WHO and RECIST classified response to therapy as complete response, partial response, stable disease, or progressive disease (PD). Progression was classified based on an increase of >20% in the sum of diameters of target lesions and/or the appearance of new lesions. Progression-free survival is measured from date of treatment initiation to either date of PD or death (whichever happens first). However, it is critical to note that these criteria were designed to be used in clinical trials where response rate was the primary objective (i.e. phase II trial) and were not intended to infer meaningful changes in the trajectory of a patient’s clinical course or response to treatment. The thresholds for classification as PD are arbitrary; for example it is unlikely that there is any substantial difference in patient outcome if his/her disease increases 19 vs 21% or decreases 29 vs 31%; however, in the former this is the difference between stable disease and PD and the latter it is the difference between stable disease and partial response. This underscores the arbitrariness of the definitions; their intended use was to aid in identifying signals of benefit in drug development, not to convey that achieving these states has an intrinsic benefit for patients [31].

Despite these origins, PFS has become the most common primary endpoint in oncology RCTs and has been accepted by European and US regulators as an appropriate basis for new drug approval [32]. Trialists have gravitated towards PFS as it is postulated to serve as a
surrogate for overall survival that allows for an earlier signal of benefit (i.e. rather than waiting for deaths to occur) and may be less prone to confounding from subsequent lines of therapy (although there is very limited evidence to support this assertion) [31]. In recent years it has become apparent that: 1) PFS is now the default primary endpoint for trials of new cancer therapies in the palliative setting; and 2) the correlation between PFS and overall survival in most clinical scenarios is very low.

Prasad et al reported the results of a systematic review of trial-level meta-analyses that evaluated the surrogacy of PFS for overall survival [33]. The authors identified 36 articles which explore 65 specific correlations between a surrogate endpoint and survival; the vast majority of which were in the palliative setting with 27 specific analyses for PFS. Among the full study cohort, half (52%, 34/65) of correlations were of low strength (r < 0.07), one quarter (25%, 16/65) were of medium strength (0.7 < r < 0.08) and one quarter (23%, 15/65) were highly correlated (r ≥ 0.85). Among the 15 treatments for which there was high correlation, 6 were in the adjuvant setting, 3 were in the locally advanced setting, and 6 were in the metastatic setting. It is worth noting that for 4 of the 6 high correlations in the metastatic setting (i.e. breast and colon cancer), other studies had reported lesser correlations. In fact, in both metastatic breast cancer and metastatic colon cancer, the largest analyses found low correlation. The bottom line conclusion from this high profile review was that “the evidence supporting the use of surrogate endpoints in oncology is limited”.

Finally, it is worth noting that while patients value quantity of life (i.e. overall survival) and quality of life, there is no published data suggesting that patients intrinsically value PFS in the absence of improved OS or QOL. It is sometimes suggested that improvement in PFS may benefit patients by reducing cancer-related symptoms; if this is the case the trial should use
validated patient-reported measures of cancer symptoms and QOL to objectively measure such an improvement. In fact, a recent analysis failed to find an association between PFS and QOL independent of OS [34, 35]. Key observations regarding the use of PFS in oncology are summarized in Table 2.

**VALUE FRAMEWORKS**

The European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have recently developed unique frameworks to guide the conversation regarding benefit, cost, and the value of new cancer therapies [36, 37]. Both frameworks have undergone iterative revisions based on feedback from stakeholder communities [38, 39]. The ASCO Value Framework (VF) assigns points based on improvements in overall survival (or a surrogate endpoint) and subtracts points for toxicity. The ASCO-VF also allows for some adjustment based on QOL improvement, “tails” on survival curves, and treatment-free intervals. Using these inputs the ASCO-VF generates a numeric score (which can range from a negative score to >100; there is no “cut-point” threshold to define benefit and the intent of the score is to inform oncologist-patient decision-making when taking drug price into account. The ESMO-Magnitude of Clinical Benefit Scale (MCBS) also primarily considers improvement in outcome but does so using both the Hazard Ratio (HR) and the absolute gain in generating a final grade (ASCO-VF only considers the HR). The ESMO-MCBS can be upgraded or downgraded for toxicity/QOL and the most recent iteration allows single arm trials to be scored. The major difference between the ASCO-VF and the ESMO-MCBS relates to the output and how it is to be used: while ASCO-VF generates a continuous score to guide oncologist-patient decision-making at the individual level, the ESMO-MCBS generates a categorical grade (A, B, C for curative intent therapy and 1,2,3,4,5 for palliative therapies). Moreover, the ESMO-MCBS dichotomizes
high/substantial benefit (Score A,B or 4,5) and low/insubstantial benefit (Score C or 1,2,3). Finally, the architects of the ESMO-MCBS encourage comparison of “value” scores across treatments and disease settings.

Several groups have applied the ASCO-VF and ESMO-MCBS to published trials. Del Paggio et al identified 277 RCTs of systemic therapy in breast, lung, colorectal, and pancreas cancer published during 2011-2015 [40]. Among these trials, half (50%, 138/277) showed a statistically significant difference in favor of the experimental arm; among these “positive” trials, only 31% (43/138) of studies identified treatment with “substantial” clinical benefit. Accordingly, these data suggest that among all published RCTs of new cancer therapies, only ~15% identify a treatment with clinically meaningful benefit. In a separate analysis, Del Paggio and authors also applied the ASCO-VF to the same cohort of 277 RCTs [41]. In this analysis they found that agreement between scores via ASCO-VF and ESMO-MCBS were only fair. They also found that there was a negative correlation between magnitude of benefit and drug cost (i.e. drugs with the smallest clinical benefit had the highest price). Similar work by Cheng et al found only weak-moderate correlations between the ASCO-VF and the ESMO-MCBS [42].

The value frameworks have also been applied to new therapies recently approved by regulatory agencies. Vivot et al applied the ESMO-MCBS to 37 new drugs approved by the FDA during 2000-2015; only one third (13/37) met the threshold for substantial clinical benefit (i.e. score 4 or 5) [43]. Tibau et al scored 105 RCTs related to 63 drugs approved by the FDA during 2006-2016 for 118 indications [44]. In their analysis only 44% (46/105) met the ESMO-MCBS threshold for meaningful benefit. Grossman and colleagues performed a similar analysis for 38 cancer drugs approved by the European Medicines Agency (EMA) during 2001-2016 and found only 21% met the threshold for substantial benefit [45]. Finally, Davis and colleagues found that
among the 48 cancer drugs (68 indications) approved by the EMA in 2009-2013, only one third evaluated overall survival and 12% were single arm trials [46]. Among those studies with overall survival data, only half of therapies were associated with substantial benefit. Several other groups have related studies; each of them with consistent results – only a small minority of new cancer therapies (including those approved by the FDA and EMA) are associated with meaningful benefit for patients. Key observations related to the use of value frameworks in oncology are shown in Table 3.

**STATISTICAL AND CLINICAL SIGNIFICANCE: THE SOCIETAL PERSPECTIVE**

While there have been important advances in cancer treatment in the past several decades and noticeable improvements in patient outcomes, the literature reviewed in this report demonstrate that the incremental gain of new therapies has decreased over time and that there is no relationship between drug cost and magnitude of benefit. The fundamental goal of medicine is to help patients live longer and better lives. It is therefore worrisome that the majority of new cancer drugs are approved based on modest improvements in progression-free survival (or other surrogate outcomes) which have very limited correlation with OS or QOL. This becomes even more problematic when one considers that the magnitude of benefit reported in RCTs is very likely to be further attenuated in routine practice where patients are older and with greater comorbidity. In the era of mega-trials which are powered to detect very small differences in outcome between treatments, tension arises between the competing concepts of statistical significance and clinical significance; the value frameworks from ASCO and ESMO are important steps forward to better understand this dichotomy. Potential pitfalls of poorly designed RCTs are summarized in Table 4.
There is currently great interest in using real world data to better understand how novel therapies are adopted in routine practice and whether the outcomes observed in RCTs are translated into benefit in the general population. To date, most studies show that there is a substantial efficacy-effectiveness gap which suggests that the already modest gains from new cancer therapies observed in RCTs may become even smaller (and perhaps negligible) in routine practice. It is worth highlighting that using observational data from the “real world” to establish treatment efficacy is fraught with bias [6]; recent interest in using this data for regulatory decisions as a substitute for RCTs is therefore very worrisome. The oncology RCT should remain the gold standard to establish efficacy of new cancer therapies; while population-based data can augment this knowledge but is not a replacement [5].

To date, the patient voice has been largely absent from the “value debate”. Anecdotally, many patients (and the lay public) assume that cancer therapies are associated with much larger benefits than they actually offer. Studies to date suggest that patients would expect larger gains from palliative therapies than are typically observed in RCTs. The 2.1 month median gain in overall survival associated with new FDA approvals is far less than gains expected by patients. In a study of patients with advanced lung cancer who had completed chemotherapy, the median survival threshold for accepting chemotherapy was 5-9 months [47]. Only 22% (18/81) would accept chemotherapy for an increase in survival of 3 months. Jenkins et al conducted serial interviews with 120 patients on chemotherapy for advanced cancer and found that as the severity of side effects increased, drugs that controlled cancer for short periods were not viewed as worthwhile [48]. An expert panel of oncologists assembled by the ASCO Cancer Research Committee proposed treatment thresholds that were deliberately modest; only 42% (30/71) of
treatments recently approved by the FDA would meet these minimum conservative thresholds [49].

The issue of clinical benefit has relevance at the micro-level for individual patients who seek to balance improvements in longevity with quality of life. The issue also has relevance at the macro-level as cancer health systems worldwide balance competing priorities within a sustainable health care budget. This is important in both high-income and low-middle income countries.

CONCLUSIONS

Although the treatment of cancer has changed considerably in the past few decades, what patients want (i.e. to live longer and better lives) has not changed. The temporal evolution of oncology RCTs offers important insights into where the field has come from and where it is going. It is clear that while many elements of trial design have improved, in the era of mega-trials, most studies are increasingly powered to detected differences in outcome that may not be considered important by patients. This becomes further limited when endpoints other than overall survival or QOL are used. The substantial clinical toxicity and financial toxicity of new cancer therapies has necessitated the cancer system to ask itself some hard questions. The ASCO and ESMO value frameworks are important (albeit imperfect) tools to guide this conversation. In the era of high quality and sustainable cancer care oncologists, trialists, and policy-makers need to ensure that we seek to identify new therapies that offer substantial and meaningful benefit to our patients.
Table 1. Key observations from temporal trends in oncology RCTs.

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<tr>
<td>1.</td>
<td>There has been a marked increase in sample size of oncology RCTs over time; this has led to an increase in the proportion of “statistically significant” results.</td>
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<td>2.</td>
<td>Experimental arms of RCTs have shifted from cytotoxic/hormone therapies to targeted/immunotherapy agents; most of these are studied with no/little biomarker evaluation.</td>
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<td>3.</td>
<td>In recent years there has been a major shift away from overall survival as a primary endpoint. Surrogate endpoints (i.e. PFS) are now the most common primary endpoint in oncology trials.</td>
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<td>4.</td>
<td>Quality of life is not well reported in oncology RCTs. Many trials do not describe QOL outcomes and among those that do, the methodology is often poor.</td>
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<td>5.</td>
<td>The incremental gain of the experimental arm compared to the control arm has decreased over time. Despite this, authors of modern RCTs are more likely to consider the results “positive”.</td>
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<td>6.</td>
<td>The vast majority of oncology RCTs are now funded by industry. Industry-funded trials are more likely to be “positive” than trials funded by other sources.</td>
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<td>7.</td>
<td>Results of RCTs reported at major conferences and in peer-reviewed publications are often presented with “spin” which overstates the benefit of new therapies.</td>
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Table 2. Key observations related to use of progression-free survival (PFS) in oncology RCTs.

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<tr>
<td>1.</td>
<td>PFS was developed as a tool to guide studies of drug development (i.e. phase II trials) and was never intended to imply therapeutic benefit nor guide treatment decision-making.</td>
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<td>2.</td>
<td>Measurement of PFS is subject to bias and is subject to inherently arbitrary dichotomous cut-points.</td>
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<td>3.</td>
<td>PFS is now the most common endpoint in oncology trials and the most common endpoint upon which new drugs are approved by the US FDA and EMA.</td>
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<td>4.</td>
<td>PFS is postulated to be a surrogate endpoint for overall survival; the evidence that this is the case is very limited and for the most part contradicts this assumption.</td>
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<td>5.</td>
<td>There is no evidence that PFS is a useful surrogate for QOL. There is also no data to suggest that patients value PFS in the absence of improved survival or QOL.</td>
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**Table 3.** Key observations related to use of value frameworks to new oncology therapeutics.

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<tr>
<td>1.</td>
<td>The ASCO-Value Framework (VF) and the ESMO-Magnitude of Clinical Benefit Scale (MCBS) assign points/grades for the magnitude of survival improvement (or surrogate endpoint).</td>
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<tr>
<td>2.</td>
<td>ASCO-VF and ESMO-MCBS add/subtract points/grades for toxicity and QOL. The ASCO-VF also allows adjustment for “tails” on survival curves and treatment-free intervals.</td>
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<td>3.</td>
<td>While the ASCO-VF assigns points based on the Hazard ratio for survival (or surrogate), ESMO-MCBS considers both the HR and the absolute gain.</td>
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<td>4.</td>
<td>ASCO-VF generates a continuous score; ESMO-MCBS generates a categorical grade (A-C for curative therapy and 1-5 for palliative therapies).</td>
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<td>5.</td>
<td>ESMO-MCBS dichotomizes high value/substantial benefit from low value/insubstantial benefit.</td>
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<td>6.</td>
<td>When ASCO-VF and ESMO-MCBS have been applied to cohorts of oncology RCTs the agreement is only fair.</td>
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<td>7.</td>
<td>Among contemporary RCTs, only 15% will identify a new treatment that offers “substantial” benefit to patients.</td>
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<td>8.</td>
<td>Among cancer drugs that have been approved by the FDA and EMA, only 21-44% meet the ESMO-MCBS threshold for “substantial” benefit.</td>
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**Table 4.** Potential threats posed by poorly design oncology RCTs*

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<td>Well-designed RCTs can prevent bias in comparing treatments and provide a sound basis for changes in clinical practice.</td>
<td>BUT, poorly-designed RCTs may:</td>
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<td>Ask questions of commercial rather than clinical interest</td>
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<td>Be based on inadequate preclinical and early clinical studies</td>
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<td></td>
<td>Use surrogate endpoints that do not reflect patient benefit</td>
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<td></td>
<td>Show statistically significant but clinically irrelevant results</td>
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<td>Underestimate toxicity of new treatments</td>
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<td>Be subject to biased reporting</td>
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<td>Select patients who do not represent those seen in every-day practice</td>
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*Adapted from Tannock et al Lancet Oncology 2016*
REFERENCES