How to prioritize essential medicines for cancer

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Background

With citizens of the entire world as its constituents regarding matters of health, the challenges faced by the World Health Organization as it tries to help provide the best possible cancer care are understandably complex. Viewed by some as a personal tragedy but not a societal health challenge, the importance of cancer medicines was first addressed as a problem of low- and middle-income [LMI] countries in need of World Health Organization support in 1977 when the first essential medicines list was published including some essential medicines for cancer. Recognizing the diverse income structure of the world’s countries and the challenge a diagnosis of cancer presents to any human, the World Health Organization has tried, through its list of Essential Medicines, to highlight cancer therapies it considers valuable because they can meaningfully change outcomes for cancer patients throughout the world.

While in developed countries one often encounters a clamoring for the latest novel therapy that “cures” cancer, in fact as the data will show, with only rare exceptions, novel therapies are increasingly not novel and rarely curative; indeed, the majority provide only marginal benefits. Furthermore, it is often incorrectly assumed that developed countries, with well-funded health care systems can afford to pay for such novel therapies with marginal improvements at what many consider exorbitant prices. A long overdue reconciliation will soon force even the richest countries to confront the unavoidable truth that budgets are not infinite, much more public good can be reaped from many less expensive options and that investing in prevention and vaccinations can deliver much more, albeit in the future. These tenets, long recognized by the World Health Organization, provide the foundation for much of what follows.

With this monograph we hope to provide background that will help the reader understand some of the variables that must be considered in deciding what constitutes an Essential Medicine. It is designed to complement the report of a working group of international experts convened by the World Health Organization in its Geneva Headquarters on March 22/23 of 2018. The charge for that working group was to begin the process of identifying the cancer therapies that would be added to the 2019 Essential Medicines List and define guiding principles for EML candidates.

While cost or what is increasingly referred to as “value” is of necessity of utmost importance, this monograph will focus on the novelty and efficacy of cancer therapies. Decisions as to the worth of a therapeutic should be made on the basis of a body of evidence, not a single study or publication. And while regulatory bodies consider numerous attributes as measures of efficacy of a cancer therapeutic, prolongation of meaningful life will always be the most important attribute. To that end, the availability of
overall survival data as well as data from randomized clinical trials is considered most valuable. The use of surrogates, especially progression-free survival in diseases where its value as a surrogate is not established, are considered inadequate [Wilkerson and Fojo, 2009; Saad et al, 2010a; Saad et al, 2010b; Amir et al, 2012; Booth and Eisenhauer, 2012]. In addition, the actual conduct of the trial, looking especially at the problem of censoring and early ascertainment of efficacy and most importantly the impact of toxicity is very important. The latter, impactful to all patients in any economy takes on added importance in low and low to middle income countries where the cost of managing treatment complications can be especially onerous making toxicity a very important variable. In addition, we will also address emerging metrics in Europe and the United States for estimating “value” and address how they might inform decisions as to which therapies are included in the Essential Medicines List.

Cancer Therapeutics in the Essential Medicines List: Appropriately Timely or Outdated and Inadequate?

Because inclusion of a therapeutic in the Essential Medicines List requires robust, mature data, the Essential Medicines List may be seen by some as dated and lacking “cutting edge therapies”. However, as will become apparent, this apparent lack of “cutting edge therapies” that some criticize about the Essential Medicines List, is in fact an attribute not a flaw. The Essential Medicines List does not seek to be at the “cutting edge of therapy”. The data summarized below will unfortunately establish that the majority of “cutting edge therapies” provide only marginal benefits, are increasingly not novel and most importantly, often lack robust supporting data. Instead the Essential Medicines List seeks to confidently recommend therapeutics that will meaningfully change the survival of the majority of cancer patients who receive such a therapy in what worldwide will be highly diverse, and often very challenging environments. While at international meetings one often hears pronouncements that a given therapy should now be considered the new standard of care, in fact, effective standard of care therapies cannot be decreed based on a single clinical trial, take time to develop and must be ratified. Inclusion in the Essential Medicines List occurs only after the therapeutic strategy has been ratified in the community – in “real world settings”. Only then can consideration be given to deploying them worldwide for millions of patients. Below are three examples of many that underscore the need for mature data and that ratify why the approach of the World Health Organization for the inclusion of novel therapies in the Essential Medicines List is not only prudent but also supported by countless examples.

1. Targeting the epidermal growth factor receptor [EGFR] in colorectal cancer. In February 2004 the US FDA granted accelerated approval for the use of the anti-EGFR antibody, cetuximab [Erbitux®], in patients with a diagnosis of colorectal cancer. On MEDSCAPE five days later, the Editor noted “This ImClone–Bristol-Myers Squibb drug is being heralded as a major advance offering a sorely needed treatment option for patients with advanced disease”. The US FDA approval of cetuximab relied on three clinical trials [Cunningham et al, 2004; Saltz et al, 2001; Saltz et al, 2004] that enrolled patients with metastatic colorectal cancer expressing the EGFR, whose disease had progressed after an initial irinotecan-containing
regimen. The first trial was a randomized, controlled trial that enrolled 329 subjects who received cetuximab both as monotherapy and in combination with irinotecan [Cunningham, 2004]. The response rate of 22.9% [95% CI, 17.5-29.1%] in the combination-therapy group was significantly higher (P=0.007) than the 10.8% response rate in the monotherapy group [95% CI, 5.7-18.1%]. Similarly, the 4.1 months median time to progression observed in the combination-therapy group was significantly greater (P< 0.001) than the 1.5 months in the monotherapy group. However, the median survival times of 8.6 months in the combination-therapy group and 6.9 months in the monotherapy group were statistically indistinguishable (P=0.48). Furthermore, toxic effects were more frequent in the combination therapy group, although their severity and incidence were said to be similar to those that would be expected with irinotecan alone. A second trial [Saltz et al, 2001], an open-label, single-arm trial enrolled 138 subjects who received cetuximab in combination with irinotecan. Seventy-four of the 138 patients had documented progression with irinotecan. The overall response rate was 15% for the entire population and 12% for those whose tumors had progressed on irinotecan with median durations of response of 6.5 and 6.7 months, respectively. The third trial [Saltz et al, 2004], enrolled 57 patients who received cetuximab as a single agent in an open-label, single-arm study. A partial response was observed in five patients (9%; 95%CI, 3-19%); with 21 additional patients achieving stable disease or minor responses.

Although administered patients with chemotherapy-refractory colorectal cancer near the end of their lives the benefit of a median survival of 6.4 months in this single arm study remained uncertain. Furthermore, an acne-like skin rash, predominantly on the face and upper torso was observed in 86% of patients, 18% with grade 3, and a composite of asthenia, fatigue, malaise, or lethargy was seen in 56% including 9% with grade 3.

Four years later, in 2008, ratifying data first gathered in the early 1990’s that predicted tumors harboring K-ras mutations would not benefit from a strategy interdicting EGFR signaling, Australian investigators reported that “patients with a colorectal tumor bearing mutated K-ras did not benefit from cetuximab, whereas patients with a tumor bearing wild-type K-ras did benefit from cetuximab” [Karapetis et al, 2008]. Furthermore, analysis of the data available at the time showed that in fact those whose tumors harbored a K-ras mutation had shorter progression-free survivals [HR 1.27, 95%CI 1.09-1.48], demonstrating that not only had benefit not accrued, but that harm had occurred [Figure 1]. Between 2004 and 2008 as many as 200,000 Americans had received cetuximab of which about one half had tumors that harbored a mutant K-ras. Thus in 2004, the US FDA had approved a therapy that not only had uncertain overall survival benefit, but was likely harming a substantial fraction of recipients. Despite this, it was not until 2012 that the accelerated approval was modified when in July of that year the FDA granted approval to cetuximab for use in combination with FOLFIRI for the first line treatment of patients with KRAS mutation negative (wild type), EGFR expressing metastatic colorectal cancer as determined by an FDA-approved test for this use [FDA Approvals: Cetuximab + FOLFIRI KRAS WT/EGFR Expressing CRC + Therascreen]. The FDA also approved the TheraScreen KRAS RGQ PCR kit concurrently with this cetuximab approval. The approval was based on retrospective
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analyses in patient subsets according to KRAS mutation status in tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies [Bokemeyer et al, 2012]. The FDA noted that the addition of cetuximab to chemotherapy or best supportive therapy resulted in improved overall survival, progression-free survival and overall response rates in the subset with KRAS wild type tumors whereas there was no benefit or potential harm in patients with KRAS mutant tumors. Unfortunately, the retrenchment by the US FDA in 2012 did not acknowledge the 2004 accelerated approval eight years earlier had been excessively broad. Nor did it address the unreliability of data in patients whose tumors were undergoing characterization of only a single protein (KRAS) in a very complex pathway (the EGFR pathway) or the marginal outcomes in the studies that followed the initial FDA approval, with magnitudes of benefit that rendered outcomes vulnerable to patient selection in determining outcomes. As regards the pathway’s complexity, subsequent studies have found, not surprisingly, that mutations other than KRAS including NRAS, BRAF, PIK3CA and PTEN also impair response to agents targeting the EGFR [cetuximab and panitumumab] [Therkildsen et al, 2014; Hsu et al, 2016]. As regards both the complexity of the pathway and the marginal benefits achieved, the year before the US FDA modified its 2004 approval, the Medical Research Council (MRC) COIN trial published the results of a trial that sought to determine whether the benefit of adding cetuximab to chemotherapy in patients with colorectal cancer not previously treated for metastatic disease would hold up in a larger patient population [Maughan et al, 2011]. They randomized 1,630 patients to receive oxaliplatin plus either physician’s choice capecitabine or 5FU plus leucovorin with or without cetuximab. As expected, the addition of cetuximab to chemotherapy did not improve OS in patients with tumors harboring a KRAS mutation, with a median OS values of 14.8 and 13.6 months for those treated with chemotherapy alone or with cetuximab plus chemotherapy, respectively. But surprisingly it also did not prolong survival in patients whose tumors expressed wild-type KRAS - median OS 17.9 and 17.0 months with chemotherapy alone and with cetuximab plus chemotherapy, respectively. The addition of cetuximab to chemotherapy also did not improve the time to disease progression in patients with wild-type KRAS with median times to progression 8.6 months in both groups. Importantly, while treatment randomization had no effect on outcome, OS varied depending on the mutations the patient’s tumor harbored. Median OS with tumors harboring a mutated BRAF, NRAS or KRAS were 8.8, 13.8 months, and 14.4 months, respectively, whereas patients whose tumors did not have any of these mutations had a median OS of 20.1 months. This is an important observation repeated time and again in oncology where targeting an abnormality that confers a poorer outcome does not alter OS meaningfully. The addition of cetuximab, however, did increase skin and gastrointestinal side effects prompting the authors to conclude “This trial has not confirmed a benefit of addition of cetuximab to oxaliplatin-based chemotherapy in first-line treatment of patients with advanced colorectal cancer. Cetuximab increases response rate, with no evidence of benefit in progression-free or overall survival in KRAS wild-type patients or even in patients selected by additional mutational analysis of their tumours. The use of
cetuximab in combination with oxaliplatin and capecitabine in first-line chemotherapy in patients with widespread metastases cannot be recommended”.

Finally, the question as to the optimal choice of targeted therapy has been addressed by three studies, the phase III FIRE-3 (AIO KRK-0306) [Heinemann et al, 2014], the phase II PEAK [Schwartzberg et al, 2014; Rivera et al, 2017], and the phase III CALGB/SWOG 80405 trial [Venook et al, 2017], by directly comparing the addition of bevacizumab (discussed further below) versus cetuximab or panitumumab to FOLFOX/FOLFIRI. Unfortunately, none of these studies met their primary endpoint (response rate, progression-free survival or overall survival respectively), precluding a categorical decision of the optimal targeted treatment in the first-line setting for patients with mCRC. Putting aside the fact that the comparator, bevacizumab, has never been shown to improve overall survival in colorectal cancer when added to either mFOLFOX6 or FOLFIRI, the results prompted a further analysis that according to the authors, although not pre-planned found that with the addition of cetuximab, OS and PFS were prolonged in left sided cancers, but were poorer with right sided tumors – outcomes that prompted the authors to suggest that “for now, stratification in mCRC studies by R v L 1° sidedness is indicated”. The concept of sidedness has now blossomed into disagreements as to whether cetuximab or bevacizumab is the preferred option for left and right sided tumors, respectively, but ignores what is quite possibly the best option – neither! [Elez et al, 2015; Holch et al, 2017; Snyder et al, 2018]. That so many years after the first clinical trials with bevacizumab and cetuximab were launched even large meta-analyses cannot provide answers speaks to the marginal benefits achieved with these agents and ratifies the guarded approach of the World Health Organization.

We are thus now poised more than 15 years after the initial US FDA approval of cetuximab to further narrow the subset of patients with colorectal cancer that can be treated with an EGFR targeting agent – to a number that will soon approach at most 10 to 15% of all colorectal cancer patients – an enormous difference compared to the initial unrestricted FDA approval of 2004. Given this, it is not surprising that Dr. Len Saltz of Memorial Sloan Kettering Cancer Center who led the initial cetuximab trials the FDA cited in its 2004 approval recently concluded a Viewpoint with the question: “So I don’t use anti-EGFR agents up front. If you do, may I ask why?” [Saltz 2015].

2. Bevacizumab and Breast Cancer – the E2100 Outlier. A perceived lack of advances in the therapy of metastatic breast cancer (MBC) and heightened expectations for a drug that would target a key component of angiogenesis led to a proliferation of clinical trials combining bevacizumab with chemotherapy in the treatment of MBC. This enthusiasm accelerated with the publication of the E2100 study [Miller et al, 2007]. Designed to compare the efficacy of paclitaxel alone versus a combination of paclitaxel and bevacizumab, the study garnered widespread attention because of a benefit in progression-free survival (PFS), reported initially as a doubling from 5.9 to 11.8 months, despite a failure to demonstrate an overall survival (OS) advantage (25.2 vs. 26.7 months) and quickly led to an accelerated approval for bevacizumab in breast cancer in 2008. Breast cancer was not the first approval for bevacizumab,
as it had been approved by the US FDA in 2004 for the treatment of advanced colon cancer, and in 2006 for advanced lung cancer. Furthermore, the approval for metastatic breast cancer in 2008 was under the US FDA’s Accelerated Approval Program. Under the latter, the regulations allow drug approval based on its effect on a biomarker or surrogate endpoint, and in the case of E2100 the. Surrogate endpoint was progression-free survival. However, the regulations require additional clinical trials confirming meaningful clinical benefit to patients such as increased survival and in this bevacizumab faltered. Numerous other bevacizumab combinations followed, and these also achieved statistical improvement in PFS, albeit not as impressive as the results in E2100, but as with E2100, none were able to demonstrate an OS benefit. [O’Shaughnessy et al, 2009; Robert et al, 2009; Chan et al, 2010; Miles et al, 2010; Brufsky et al, 2011; Rosarri et al, 2012; Miller et al, 2018] Despite the lack of an OS advantage, the use of bevacizumab in the therapy of patients with MBC quickly gained wide acceptance, especially in the US and also in Europe. Oncologists eager to offer patients the latest advance began prescribing bevacizumab in combination with different chemotherapeutic agents, often continuing bevacizumab with a different chemotherapeutic agent even as they deemed the original combination with chemotherapy ineffective. For none of these practices was there supporting data.

Elsewhere in this monograph we address the issue of the use of PFS as a surrogate for OS, and breast cancer is a prime example of a cancer where this remains at best controversial. Data available at the time E2100 was published clearly demonstrated the near concordance of absolute gains in PFS and OS and the marked discordance in E2100 should have been a red flag to regulatory agencies. Figures 2 and 3, for example, demonstrates this for 59 phase III studies that had been published since the mid-1990’s in which either the PFS or the OS difference achieved statistical significance and for colorectal cancer trials over the two decades that bracketed the E2100 studies. For all cancers and for colorectal cancer, the slopes of the regression lines, 1.21 and 1.35, emphasize that the relationship between gains in PFS (△PFS) and gains in OS (△OS) are near unity. However, in the E2100 study, the 5.9 months gain in PFS initially reported far exceeded the 1.5 months gain in OS – a ratio of 3.93. What could have led to this? The possibility tumor growth accelerated following discontinuation of therapy cannot be discounted. However, the more likely explanation was that, in the E2100 study, either PFS or OS was wrong, and given the undisputed accuracy of OS, PFS was suspect. With rare exceptions, one expects measures of drug efficacy to be correlated. Therapies that shrink tumors should slow tumor growth and in turn delay the time to progression, usually assessed as PFS. Thus, one expects a correlation between overall response rate (ORR) and PFS. Such a correlation is not surprising since ORR and PFS are estimated using the same data – measures of tumor quantity on study. A high correlation between ORR and PFS (Figure 4, 5 and 6) could be found in phase II studies, with both “cytotoxic” or “targeted” therapies (Figure 4) [Wilkerson and Fojo, 2009; Fojo and Wilkerson, 2010], across a wide range of cancers and in breast cancer (Figure 5) and most pointedly in colorectal cancer (Figure 6) where studies over two decades showed a very high correlation –
There is disagreement as to the use of PFS as a surrogate for OS, and breast cancer is an example. Data available at the time E2100 was published clearly demonstrated the near concordance of absolute gains ($\Delta$) in PFS ($\Delta$PFS) and OS ($\Delta$OS). The marked discordance in E2100 should have been a red flag to regulatory agencies. The figure demonstrates this for 59 phase III studies that had been published since the mid-1990’s that bracketed the E2100 studies and in which either the PFS or the OS difference achieved statistical significance. For all cancers the slope of the regression line, 1.21, emphasizes that the relationship between gains in PFS ($\Delta$PFS) and gains in OS ($\Delta$OS) are near unity. However, in the E2100 study, the 5.9 months gain in PFS initially reported far exceeded the 1.5 months gain in OS – a ratio of 3.93.
Figure 3. There is disagreement as to the use of PFS as a surrogate for OS, and colorectal cancer is an example. Data clearly demonstrates the near concordance of gains (Δ) in PFS (ΔPFS) and OS (ΔOS). The marked discordance in E2100 should have been a red flag to regulatory agencies. The figure demonstrates this for colorectal cancer trials that had been published since the mid-1990’s in which either the PFS or the OS difference achieved statistical significance. For colorectal cancer, the slope of the regression line, 1.35, emphasizes that the relationship between gains in PFS (ΔPFS) and gains in OS (ΔOS) are near unity. However, in the E2100 study, the 5.9 months gain in PFS initially reported far exceeded the 1.5 months gain in OS – a ratio of 3.93.
Figure 4. Plots of median PFS (left) and median OS (right) as a function of percent PR + CR. Within each comparison, three groups are plotted. Cytotoxic refers to the group of studies where patients received cytotoxic therapy, targeted therapies refers to the group of studies where patients received targeted therapies and All refers to patients from both the cytotoxic and targeted therapies groups combined. In all plots, Percent PR + CR is significantly correlated (P < 0.0001) with both median PFS and median OS.

Figure 5. Analysis of data available at the time of the E2100 trial demonstrating a high correlation between response rate and PFS. Panel A shows the correlation across a broad range of malignancies. Panel B confines it to trials that enrolled breast cancer patients with the E2100 results highlighted with a circle around it. Panel C confines the analysis to other trails in breast cancer that employed bevacizumab. Panel D estimates what should have been the PFS in E2100 based on its response rate and points to the PFS result as the likely outlier.
Figure 6. Correlations Between Overall Response Rate and Progression-Free and Overall Survival. Therapeutic gains are highly correlated with a drugs’ activity as measured by the overall response rate (complete response + partial response) (top 4 graphs). No such correlation or even a negative correlation is seen for stable disease (bottom 2 graphs). In all panels, the slopes (solid lines) (95% CIs [dotted lines]) represent the gains or decreases in fractions of a month of progression-free or overall survival per 1% change in the overall response rate or rate of stable disease.

Jawed et al, JAMA Oncol. 2015;1:787-95
and this was true also for bevacizumab-containing regimens – with only E2100 as an outlier (Figure 5).

That E2100 was an outlier became abundantly clear and in June 28, 2001 after an at times contentious Public Hearing the FDA’s Oncologic Drugs Advisory Committee voted strongly against the use of bevacizumab in this setting with the agency stating that the clinical benefit in the E2100 trial was an outlier and that the risks of bevacizumab outweighed its benefits. The FDA recognized in a three-arm, randomized trial submitted by the sponsor as evidence in support of E2100, data that supported the FDA’s conclusion E2100 was an outlier [Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin). 2011]. Subsequently on November 18, 2011, the US FDA announced that breast cancer indication for bevacizumab had been withdrawn. The agency concluded the drug had not been shown to be safe nor effective for the treatment of breast cancer. The specific indication withdrawn was for the use of bevacizumab in metastatic breast cancer with paclitaxel. To this day the European Medicines Agency has maintained that approval, limiting the use of bevacizumab only with paclitaxel. The latter has been deemed necessary given that all trials with the closely-related docetaxel as well as numerous other chemotherapeutics did not achieve comparable PFS gains; and in no case was OS found to be statistically better with bevacizumab. However, the EMA decision underestimated the near identity in the therapy of breast cancer of paclitaxel and docetaxel and the incontrovertible evidence E2100 was an outlier – two facts that cannot support the continued use of bevacizumab for any reason in breast cancer. Indeed, in its written opinion the US FDA noted “Assertions that there is a unique interaction between Avastin and paclitaxel providing a rationale for the magnitude of PFS change observed only in E2100 has not been substantiated by either clinical or non-clinical evidence” [https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237171.pdf].

The World Health Organization does not include bevacizumab as one of its Essential Medicines, a decision that can be strongly defended by a critical review of the bevacizumab data not only in metastatic breast cancer but also in other approved cancer indications.

3. **EGFR inhibitors in non-small cell lung cancer.** Accounting for approximately 12-14% of all cancers, lung cancer has been the most common cancer in the world for several decades, with an estimated 1.8 million new cases in 2012, 58% in less developed regions [http://globocan.iarc.fr/old/FactSheets/cancers/lung-new.asp]. With 1.2 million new cases in men in 2012 (16.7% of all cancers) it remains the most common cancer in men worldwide. The highest estimated age-standardized incidence rates are found in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000), statistics driven by tobacco abuse; and not surprisingly, lower incidence rates in Middle and Western Africa (2.0 and 1.7 per 100,000 respectively). Differences in tobacco abuse explains the generally lower incidence rates in women and differences in geographical pattern - with the highest estimated rates in Northern America (33.8), Northern Europe (23.7) and Eastern Asia (19.2) and the lowest rates again in Western and Middle Africa (1.1 and 0.8
respectively). Lung cancer remains the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five (1.59 million deaths, 19.4% of the total). An overall mortality to incidence ratio of 0.87 and the relative lack of variability in survival in different world regions, has resulted in similar incidence and mortality rates across divergent geographical regions.

The past decade has seen the emergence of NSCLC as a major platform for development of targeted chemotherapeutics. This journey began with tyrosine kinase inhibitors (TKIs) targeting the epidermal growth factor receptor (EGFR), drugs that were initially evaluated in unselected patients. [Fukuoka et al, 2003; Giaccone et al, 2004; Shepherd et al, 2005; Thatcher et al, 2005; Kim et al, 2008: Mok et al, 2009]. However, after two landmark publications in 2004 reported somatic mutations in the EGFR predicted sensitivity and response to gefitinib [Lynch et al, 2004; Paez et al, 2004], their development evolved to assessments almost exclusively in patients whose tumors harbored specific mutations in the kinase domain of the EGFR [Mok et al, 2009; Maemondo et al, 2010; Mitsudomi et al, 2010; Rossell et al, 2012].

Gefitinib (Iressa®) was the first oral EGFR TKI approved in the USA. [http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110473.htm]. On May 2003, it was granted accelerated approval by the US FDA on the basis of the response rate observed in 142 patients with non-small cell lung cancer (NSCLC) whose tumors were considered refractory to both docetaxel and a platinum agent [Cohen et al, 2003; Cohen et al, 2004]. Following this approval, a larger phase III trial was undertaken, the Iressa Survival Evaluation in Lung Cancer (ISEL) [Thatcher et al, 2005]. The data showed a statistically significant improvement in objective response rate but gefitinib failed to prolong the median overall survival (OS) of the study population [5.6 versus 5.1 months for gefitinib and placebo, respectively, HR 0.89; p = 0.11]. And while prospective subgroup analyses suggested survival benefits in patients of Asian origin and those who never smoked, gefitinib did not prolong the OS of patients with adenocarcinoma, at that time emerging as a subset more likely to benefit from TKIs targeting the EGFR [median OS of adenocarcinoma patients 6.3 versus 5.4 months; HR 0.83, p = 0.07] [Thatcher et al, 2005]. As a result of this, in June 17, 2005, the FDA rescinded gefitinib’s approval, limiting its availability under the Iressa Access Program to patients benefiting from gefitinib and enrolled in clinical trials approved by an IRB prior to June 17, 2005 [http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126182.pdf]. In second line, gefitinib had also been compared with docetaxel in a non-inferiority trial (INTEREST), where it met predefined non-inferiority criteria with median OS values of 7.6 and 8.0 months, a HR of 1.02 [p= 0.62] [Kim et al, 2008].

Erlotinib, the second EGFR TKI evaluated in NSCLC, was initially approved by the U.S. FDA in November 2004, based on results of the BR.21 trial conducted by the National Cancer Institute of Canada Clinical Trials Group [Shepherd et al, 2005; http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110473.htm]. In this study patients with advanced NSCLC were randomized to erlotinib or placebo in second line. Median overall survivals were 6.7
and 4.7 months for erlotinib and placebo, respectively, resulting in a statistically significant HR of 0.70 [P<0.001]. Indications for erlotinib in NSCLC were subsequently extended in 2010 based on the SATURN trial that demonstrated improved survival in patients receiving maintenance erlotinib after induction chemotherapy [Capuzzo et al, 2010]. Consequently, in the United States, erlotinib is currently approved as maintenance therapy of locally advanced or metastatic NSCLC in patients whose disease has not progressed after platinum-based induction chemotherapy, as a single agent in second or third line after failure of a prior platinum based chemotherapy and for the first-line treatment of metastatic NSCLC patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations [http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021743s018lbl.pdf]. Fortunately its use is now almost exclusively guided by mutational analysis and it is not administered to tumors harboring wild type EGFR.

As noted, in 2004, two landmark publications reported somatic mutations in the EGFR predicted sensitivity and response to gefitinib [Paez et al, 2004; Lynch et al, 2004]. Subsequently, similar mutations were identified as important in the response of tumors to erlotinib, leading to the emergence of a paradigm that patients most likely to benefit from these therapies are those whose tumors harbor activating EGFR mutations. The presence of these mutations was reported increased in specific NSCLC populations, including women, patients of Asian origins and patients without a history of smoking. Importantly, retrospective analyses had identified these subgroups as those most likely to benefit from gefitinib and erlotinib while tumors lacking these mutations responded poorly or not at all, and had marginal benefits at best in subset analyses.

Based on these findings, gefitinib was tested in specific patient populations. The Phase III IPASS trial compared gefitinib to doublet chemotherapy in the first line setting and found a longer progression free survival (PFS) with gefitinib, especially in the 60% of patients whose tumors harbored EGFR mutations (P<0.001; HR, 0.48) [Mok et al, 2009]. Following the IPASS trial, three additional phase III trials compared a platinum doublet against gefitinib or erlotinib in patients whose tumors harbored EGFR mutations. All demonstrated longer PFS values in patients receiving the TKI with PFS values of 10.8 and 9.8 months in two trials conducted in Japan using gefitinib [Maemondo et al, 2010; Mitsudomi et al, 2010], and 9.7 months in a European study using erlotinib [Rosell et al, 2012].

Although not approved in the United States, gefitinib was approved in 36 countries by 2005. In Asia, gefitinib was approved in 2005 for second- and third-line therapy. In Europe, the European Medicines Agency (EMA) approved gefitinib in 2009 for use in locally advanced or metastatic NSCLC with activating EGFR mutations. A meta-analysis of forty-three phase 2 and phase 3 trials evaluating gefitinib or erlotinib in metastatic NSCLC that enrolled similar patient populations examined efficacy variables including progression-free survival, overall survival and response rate, and quantitated their toxicities and rates of doses reduction and discontinuation (Burotto et al, 2015, Figures 7 and 8). The data demonstrated similar efficacy across all patient populations and similar toxicities but lower rates of dose reduction and discontinuation for gefitinib leading to the clearly evident
Figure 7. A meta-analysis of forty-three phase 2 and phase 3 trials evaluating gefitinib or erlotinib in metastatic NSCLC that enrolled similar patient populations examined efficacy variables including progression-free and overall survival. The data demonstrated similar efficacy across all patient populations leading to the clearly evident conclusion of the comparability of gefitinib and erlotinib in patients with NSCLC. Similar efficacy data with afatinib underscore the issue of Me-Too therapies.

Burotto et al, The Oncologist. 2015; 20:400-10
Figure 8. Forest plot depicting the meta-analysis of the PFS HR outcome. An odds ratio of <1 indicates that the arm with the tyrosine kinase inhibitor performed better than the control. Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
conclusion of the comparability of gefitinib and erlotinib in patients with NSCLC. In 2016 the US FDA belatedly granted gefitinib FDA approval [Kazandjian et al, 2016]. Similar efficacy data with afatinib underscore the issue of Me-Too therapies discussed later.

However, the value to include EGFR inhibitors in the WHO EML could be considered and a resubmission to the EML is still possible for an evaluation of all available data.

The foregoing examples in three major cancers worldwide – colorectal, breast and lung cancer – help understand why the goal of the World Health Organization’s Essential Medicines List is to recommend valuable therapeutics only after robust evidence has been gathered. As there is no cancer therapeutic that does not have side effects, the administration of the foregoing therapies for the initial regulatory agency approved indications, meant that a meaningful fraction of patients was harmed and none or a smaller fraction accrued benefit. The examples, by no means unique, stand in support of the measured and thoughtful approach of the World Health Organization that seeks to ensure meaningful survival benefit is achieved with minimal harm. Requiring mature data for inclusion in the Essential Medicines List has the dual advantage of establishing a clear improvement in meaningful overall survival while hopefully leading to the identification of patients most likely to derive such a benefit. As the patients which will truly derive benefit are identified, one expects to see an improvement in survival.

That neither cetuximab nor the fully human panitumumab are included in the Essential Medicines List is but one example of why no matter how exciting or how desperate the population in need may seem “practice changing therapies” are almost never immediately obvious nor established. In the case of cetuximab, and panitumumab the balance sheet since 2004 is overwhelming. The measured approach of the World Health Organization has not kept a “practice changing” therapeutic from patients – but rather, unlike developed countries where its approval was rushed beginning in 2004, its deferred deployment has meant millions of colorectal cancer patients worldwide have been spared a therapeutic that the data clearly show is not just ineffective; its harmful. The lack of convincing, consistent evidence of an improvement in meaningful overall survival [Maughan et al, 2011] not only ratifies the measured approach of the World Health Organization but also explains why cetuximab has never been considered for inclusion in the Essential Medicines List. We would also note that the World Health Organization position is shared by many who question the benefit of cetuximab [Saltz 2015] especially when one considers its toxicity profile, a very difficult one, that has not seen a reduction in severity nor prevalence despite widespread use, as the fraction considered to harbor tumors potentially vulnerable to its effects has narrowed. Similarly, despite the initial enthusiasm, a prudent posture regarding the use of bevacizumab in breast cancer meant the drug was never added to the Essential Medicines List and no one was harmed by receiving an ineffective drug approved initially on the basis of a clinical trial that was an obvious outlier [Fojo and Wilkerson, 2010; Proposal to Withdraw Approval for the Breast Cancer Indication for Bevacizumab (Avastin), 2011]. As with cetuximab, bevacizumab has also never been included in the Essential Medicines List reflecting the lack of convincing data demonstrating an improvement in overall survival, an outcome that was ratified by the failure of
ramucirumab, an antivascular agent of the same class of bevacizumab [Mackey et al, 2015]. We would note here that the ramucirumab results ratify the decision of the US FDA to rescind the Avastin approval in metastatic breast cancer and argue even more strongly against the EMA posture of continued support for the use of Avastin in metastatic breast cancer. Given that the OS gains with bevacizumab in several cancers have either been at best marginal or none (lung cancer, colorectal cancer, and glioblastoma) it is difficult to argue against the position of the World Health Organization on this agent. As one example, a recent global cost-effectiveness analysis concluded “the cost-effectiveness of bevacizumab varies significantly between multiple countries. By conventional thresholds, bevacizumab is not cost-effective in metastatic colon cancer in the U.S., the U.K., Australia, Canada, and Israel” [Goldstein et al, 2017]. To argue that a drug that is not cost-effective in developed countries be deployed worldwide is indefensible. The one bevacizumab exception might be metastatic cervical cancer, a cancer that killed an estimated 266,000 women worldwide in 2012, accounting for 7.5% of all female cancer deaths with 87% in less developed regions of the world [Cervical Cancer Statistics Worldwide http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp]. Its use in this indication still awaits additional mature data. If eventually included in the Essential Medicines List as a therapy for cervical cancer, the approval will apply not only to the original bevacizumab product, Avastin®, but also to emerging biosimilars, a development that would allow individual countries the ability to hopefully negotiate more competitive prices [See list of Me-Too Therapies, Table 1].

Finally, as with cetuximab, the approvals of gefitinib and erlotinib began with broad indications, that experience clearly indicates were wrong. Wide approvals for marginal efficacy such as were achieved originally, assumes those who do not derive benefit are also not measurably harmed. This is an incorrect assumption. Because toxicity is independent of the mutational status of the tumor, those who receive a targeted therapy and have a tumor that does not harbor the mutation that makes the tumor vulnerable, accrue only toxicity and no efficacy. As has been noted, in resource-limited regions of the world, the occurrence of any toxicity can be enormously burdensome and it is for these reasons that the World Health Organization looks for mature data that demonstrates benefit of sufficient magnitude that tips the balance in favor of administration. Identification of increasingly smaller subsets with greater efficacy should help to tip this balance.

Unlike the cetuximab example, still a work in progress with uncertain meaningful survival benefit, the story of erlotinib and of gefitinib proceeded over time to a different conclusion. Erlotinib was chosen as an example of a therapy initially deployed for a large unselected population that was eventually shown to be effective only in tumors harboring mutations in the EGFR. This observation, regarded as a landmark in the development of truly targeted therapies, in turn led to meaningful improvements in overall survival when compared to chemotherapy. The data also showed that tumors harboring such mutations were as a group more sensitive to “traditional cytotoxic” chemotherapy, thus assigning value to more traditional approaches in these patients. However, demonstrating the challenges the World Health Organization must consider in its deliberations, neither erlotinib, nor gefitinib, nor for that matter, afatinib, have yet to be included in the Essential Medicines List. The most recent application in 2015
Table 1: Me-Too Therapies – These nearly identical competitors could be leveraged to reduce outlays

<table>
<thead>
<tr>
<th>Generic drug name [Trade name]</th>
<th>Company</th>
<th>United States FDA approval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDK4/6 INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Palbociclib [IBRANCE] Approval: 2015 | Pfizer | Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:  
• An aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or  
• Fulvestrant in women with disease progression following endocrine therapy. | Palbociclib was the original CDK4/6 inhibitor. Ribociclib and abemaciclib did not add anything to palbociclib. Clinical trial results are nearly indistinguishable as regards efficacy and very similar as regards toxicity. |
| Ribociclib [KISQALI] Approval: 2017 | Novartis | As initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor. |          |
| Abemaciclib [VERZENIO] Approval: 2017 | Eli Lilly | In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy  
• As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. |          |
| **PARP INHIBITORS**            |         |                             |          |
• Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for Lynparza.  
• Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.  
• Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.  
Breast cancer  
• In patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza. | Although the olaparib and talazoparib approvals are for breast cancer while others are for epithelial ovarian, fallopian tube or primary peritoneal cancer, this reflects the indication sought rather than differences in drug. In the laboratory PARP inhibitors differ markedly in their potency to trap PARP-DNA complexes, but these differences have not appeared to impact the clinical activity or toxicity profile. |
| Rucaparib [RUBRACA] Approval: 2016 | Clovis | Monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two |          |
or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.

[This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials]

Niraparib  
[ZEJULA]  
Approval: 2017  
Teso • Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Talazoparib  
[TALZENNA]  
Approval: 2018  
Pfizer • Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA.

### ALK INHIBITORS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>Pfizer</td>
<td>Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test. Control of extracranial sites of disease are comparable/However, ceritinib, alectinib, brigatinib, and lorlatinib have improved activity in the therapy of brain metastases compared with crizotinib, the first ALK inhibitor. Crizotinib has some activity, but in a high percentage of cases brain metastases appear during the course of therapy due to its poor blood-brain barrier penetration as it is a substrate of P-glycoprotein.</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Novartis</td>
<td>Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Roche</td>
<td>Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>Takeda</td>
<td>Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. [This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial]</td>
</tr>
</tbody>
</table>
| Lorlatinib            | Pfizer       | Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on:
• Crizotinib and at least one other ALK inhibitor for metastatic disease; or
• Alectinib as the first ALK inhibitor therapy for metastatic disease; or
• Ceritinib as the first ALK inhibitor therapy for metastatic disease. [This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial] |

### EGFR INHIBITORS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>AstraZeneca</td>
<td>First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations. All have activity against epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations. Osimertinib also approved for EGFR T790M</td>
</tr>
<tr>
<td>Drug</td>
<td>Approval</td>
<td>Manufacturer</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
</tbody>
</table>
| Erlotinib             | 2004     | Genentech/Roche                       | • Maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.  
  • Treatment of locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.  
  • First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.                                                                 | Evidence for starting with osimertinib versus instituting therapy when EGFR T790M mutation detected lacking.                                                                                       |
| Afatinib              | 2013     | Boehringer Ingelheim                  | • First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test.  
  • Limitation of Use: Safety and efficacy of GILOTRIF were not established in patients whose tumors have resistant EGFR mutations.  
  • Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy.                                                                                           |                                                                                                                                                                                                       |
| Osimertinib           | 2015     | AstraZeneca                           | • First-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.  
  • The treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.                      |                                                                                                                                                                                                       |
| Dacomitinib           | 2018     | Pfizer                                | • First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test.                                      |                                                                                                                                                                                                       |
| Abiraterone           | 2011     | Janssen                               | • Metastatic castration-resistant prostate cancer [with prednisone]  
  • Metastatic castration-sensitive prostate cancer [with prednisone]  
  Note: Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchectomy.                                      | Abiraterone is chemically different but clinically very similar. Enzalutamide, apalutamide and darolutamide have been evaluated in non-metastatic castration resistant prostate cancer and have achieved nearly identical results. These are very similar drugs. |
| Enzalutamide          | 2012     | Pfizer                                | • Treatment of patients with castration-resistant prostate cancer                                                                                                                                            |                                                                                                                                                                                                       |
| Apalutamide           |          | Janssen                               | • Treatment of patients with non-metastatic castration-resistant prostate cancer                                                                                                                             |                                                                                                                                                                                                       |
| Darolutamide          |          | Bayer                                 | • Approval expected: Treatment of patients with non-metastatic castration-resistant prostate cancer                                                                                                        |                                                                                                                                                                                                       |
| Vemurafenib + Cobimetinib | 2011  +  2015 | Genentech/Roche + Genentech/Roche | Vemurafenib [ZELBORAF]  
  • Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.  
  **Limitation of Use:** ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma.  
  • Treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.                                                                                                            | These three BRAF inhibitor + MEK inhibitor combinations for the treatment of melanoma with BRAF V600E mutation are indistinguishable in terms of activity and very |

**ANTI-ANDROGENS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval</th>
<th>Manufacturer</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Abiraterone           | 2011     | Janssen                               | • Metastatic castration-resistant prostate cancer [with prednisone]  
  • Metastatic castration-sensitive prostate cancer [with prednisone]  
  Note: Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchectomy.                                      | Abiraterone is chemically different but clinically very similar. Enzalutamide, apalutamide and darolutamide have been evaluated in non-metastatic castration resistant prostate cancer and have achieved nearly identical results. These are very similar drugs. |
| Enzalutamide          | 2012     | Pfizer                                | • Treatment of patients with castration-resistant prostate cancer                                                                                                                                            |                                                                                                                                                                                                       |
| Apalutamide           |          | Janssen                               | • Treatment of patients with non-metastatic castration-resistant prostate cancer                                                                                                                             |                                                                                                                                                                                                       |
| Darolutamide          |          | Bayer                                 | • Approval expected: Treatment of patients with non-metastatic castration-resistant prostate cancer                                                                                                        |                                                                                                                                                                                                       |

**BRAF INHIBITOR + MEK INHIBITOR**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval</th>
<th>Manufacturer</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Vemurafenib + Cobimetinib | 2011  +  2015 | Genentech/Roche + Genentech/Roche | Vemurafenib [ZELBORAF]  
  • Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.  
  **Limitation of Use:** ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma.  
  • Treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.                                                                                                            | These three BRAF inhibitor + MEK inhibitor combinations for the treatment of melanoma with BRAF V600E mutation are indistinguishable in terms of activity and very |

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<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Approval Year</th>
<th>Approval Agency</th>
<th>Description</th>
<th>Limitations of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib [TAFINLAR]</td>
<td>Trametinib [MEKINIST]</td>
<td>2013</td>
<td>Novartis</td>
<td>Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.</td>
<td>MEKINIST is not indicated for treatment of patients with wild-type BRAF melanoma who have progressed on prior BRAF-inhibitor therapy.</td>
</tr>
<tr>
<td>Encorafenib [BRAFTOVI]</td>
<td>Binimetinib [MEKTOVI]</td>
<td>2018</td>
<td>Array Biopharma</td>
<td>Treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.</td>
<td></td>
</tr>
<tr>
<td>Encorafenib</td>
<td></td>
<td>2018</td>
<td>Array Biopharma</td>
<td>BRAFTOVI is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.</td>
<td></td>
</tr>
<tr>
<td>Cobimetinib [COTELLIC]</td>
<td></td>
<td></td>
<td>Novartis</td>
<td>Treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.</td>
<td></td>
</tr>
</tbody>
</table>
**Binimetinib:**
- In combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

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**FILGRASTIN [G-CSF]**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim [NEUPOGEN]</td>
<td>Amgen</td>
<td></td>
</tr>
</tbody>
</table>
- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome) |
| tbo-filgrastim [GRANIX] | Teva | 
- Indicated for reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. |
| Filgrastim sndz [ZARXIO] | Sandoz | 
- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. |

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**SOMATOSTATIN RECEPTOR ANTAGONISTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
</table>
| Octreotide acetate for injectable suspension, for gluteal intramuscular use [SANDOSTATIN LAR DEPOT] | Sandoz | SANDOSTATIN LAR DEPOT is a somatostatin analogue indicated for: Treatment in patients who have responded to and tolerated Sandostatin Injection subcutaneous injection for:
- Acromegaly
- Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors |

Although SANDOSTATIN LAR DEPOT is not approved for "the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic"
• Profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors

gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival as is lanreotide it is widely used for this indication.

SOMATULINE DEPOT (lanreotide) Injection is a somatostatin analog indicated for:

• The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
• The treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

G-CSF [LEUCOCYTE GROWTH FACTOR]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Approval</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegfilgrastim</td>
<td>[NEULASTA]</td>
<td>2002</td>
<td>Amgen</td>
</tr>
<tr>
<td>Pegfilgrastim-jmdb</td>
<td>[FULPHILA]</td>
<td>2018</td>
<td>Mylan GmbH</td>
</tr>
<tr>
<td>Pegfilgrastim-cbqv</td>
<td>[UDENYCA]</td>
<td>2018</td>
<td>Coherus Bioscience</td>
</tr>
</tbody>
</table>

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.
- Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).

**Limitations of Use:**
FULPHILA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Biosimilars have essentially identical indications to the drug they emulate.

**Limitations of Use:**
UDENYCA is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

**PD-1 INHIBITORS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Approval</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>[OPDIVO]</td>
<td>2014</td>
<td>Bristol Meyers</td>
</tr>
</tbody>
</table>

- Patients with BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent.
- Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, as a single agent.
- Patients with unresectable or metastatic melanoma, in combination with ipilimumab.
- Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting.

**Non-small cell lung cancer**
- Patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

**Classical Hodgkin Lymphoma (cHL)**
- Adult patients with classical Hodgkin lymphoma that has relapsed or progressed after:
  - Autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, or
  - 3 or more lines of systemic therapy that includes autologous HSCT.

**Head and Neck Squamous Cell Cancer (HNSCC)**

- The strong similarities between the PD-1 inhibitors support their interchangeability. Differences reflect priorities in development. Despite claims of differences, to date these are difficult to discern with the two current leading drugs, nivolumab and pembrolizumab essentially interchangeable.
<table>
<thead>
<tr>
<th>Patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urothelial Carcinoma</strong></td>
</tr>
</tbody>
</table>
| Patients with locally advanced or metastatic urothelial carcinoma who:
| - Have disease progression during or following platinum-containing chemotherapy
| - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. |
| **Microsatellite Instability-High Cancer** |
| Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. |
| **Hepatocellular Carcinoma** |
| Patients with hepatocellular carcinoma who have been previously treated with sorafenib. |
| **Renal cell carcinoma** |
| Patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
| Patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab. |

aThis indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

bThis indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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<tr>
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<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
</tr>
</tbody>
</table>
| For the treatment of patients with unresectable or metastatic melanoma.
| For the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. |
| **Non-Small Cell Lung Cancer (NSCLC)** |
| In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
| In combination with carboplatin and either paclitaxel or nab-paclitaxel, as first-line treatment of patients with metastatic squamous NSCLC.
| As a single agent for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.
| As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK aberrations. |
genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

**Classical Hodgkin Lymphoma (cHL)**
- For the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.\(^1\)

**Head and Neck Squamous Cell Cancer (HNSCC)**
- For the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.\(^1\)

**Urothelial Carcinoma**
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.\(^1\)
- For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

**Microsatellite Instability-High Cancer**
- For the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient o Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options,\(^1\) or o Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.\(^1\)

**Limitations of Use:** The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

**Hepatocellular Carcinoma (HCC)**
- For the treatment of patients with HCC who have been previously treated with sorafenib.\(^1\)

**Primary Mediastinal Large B-Cell Lymphoma (PMBCL)**
- For the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.\(^1\)

**Limitations of Use:** KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

**Gastric Cancer**
- For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.\(^1\)

**Cervical Cancer**
| **Cemiplimab-rwlc** [LIBTAYO] | **Regeneron/Sanofi** | **Merkel Cell Carcinoma (MCC)**  
| | | - For the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.  
| | | 1This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.  
| | | - Metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation.  
| **PD-L1 INHIBITORS** |  
| Atezolizumab [TECENTRIQ] | **Roche** | **Urothelial Carcinoma**  
| | | - For the treatment of patients with locally advanced or metastatic urothelial carcinoma who:  
| | | o Are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or  
| | | o Are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or  
| | | o Have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.  
| | | [This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials].  
| | | - In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment, of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.  
| | | - For the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.  
| | | As with anti-PD-1 agents, the indications for the anti-PD-L1 agents are emerging with strong similarities again with differences reflecting priorities in development and the disincentive of competing against established anti-PD-1 agents in some of the more common indications. However, the data cannot yet defend an argument that both PD-1 and PDL-1 agents will have similar activities across all cancer indications. Data will also  
| Avelumab [Bavencio] | **Merck/Pfizer/Eli Lilly** | **Merkel Cell Carcinoma (MCC)**  
| | | - Adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).  
| | | [This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials].  
| | | - Patients with locally advanced or metastatic urothelial carcinoma (UC) who:  
| | | o Have disease progression during or following platinum-containing chemotherapy  
| | | o Have disease progression on FDA-approved therapy for UC harboring these aberrations prior to receiving TECENTRIQ.
Durvalumab [IMFINZI]
Approval: 2017

AstraZeneca/Medimmune

Urothelial Carcinoma
- Locally advanced or metastatic urothelial carcinoma who:
  - Have disease progression during or following platinum-containing chemotherapy
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

[This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials].

Non-Small Cell Lung Cancer
- Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
requested “addition of erlotinib to the Complementary List of the EML, with a square box as the representative of the pharmaceutical class, with gefitinib and afatinib available as alternatives, for the treatment of non-small cell lung cancer (NSCLC) in patients” with tumors harboring “activating mutations of epidermal growth factor receptor”. It was denied. At the time, a comprehensive review of NSCLC medicines was conducted and the Expert Committee “endorsed etoposide, carboplatin and paclitaxel (already included on the Complementary List) and recommended the addition of vinorelbine, gemcitabine and cisplatin to the Complementary List for this indication.” However, the Committee did not recommend addition of the tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib to the Complementary List. Although it was acknowledged that individual patients with tumors harboring drug-sensitive EGFR mutations “may derive a substantial extension of life, the average increase in progression-free survival was modest (3–4 months). But more importantly and highlighting the challenges alluded to previously, the Committee “also considered that substantial infrastructure would be required to establish routine and reliable molecular testing for EGFR mutations in NSCLC.” Consequently, “the Committee considered it was neither practical nor cost effective to establish molecular testing, and the use of TKIs as essential medicines for this disease could therefore not be supported”. The decision acknowledges that while sensitizing EGFR mutations can be found in as many as 30-50% of patients with NSCLC in countries such as Japan and Korea, often occurring in women without a personal history of smoking [Zhang et al, 2016], the incidence of such mutations in other parts of the world is substantially lower, less than 10%. The lower incidence means that a difficult to obtain and expensive mutation screening would be conducted widely at great expense largely in a population of patients lacking the sought-after mutations.

Importantly we would note the World Health Organization recognizes that truly transforming therapies may emerge and that these should not endure a prolonged wait before being listed in the essential Medicines List. As regards these therapeutics that appear promising but at the time of their initial consideration still lack the needed body of evidence with the follow up necessary to establish their ability to prolong life meaningfully, these can be considered for inclusion in a provisional list. Inclusion in this provisional list will ensure its future consideration while also highlighting to those involved in its development the need for additional supportive evidence.

**Advances in cancer therapeutics: Evaluating outcomes by looking beyond the hype**

The goal of this monograph is not to dispute claims of progress in the therapy of cancer, since progress has been clearly made, but rather to put this progress in perspective. It is important that this be put in perspective so that one can understand the composition of cancer therapeutics in the Essential Medicines List. Examination of the data demonstrates that despite claims of rapid advances in the therapy of cancer – claims that could tarnish the Essential Medicines List – in fact progress even in the modern era of next generation sequencing and immunotherapy remains slow. The National Cancer Institute Annual Report to the Nation in 2018 [Cronin et al, 2018; Negoita et al, 2018] highlighted that between 1999 and 2015, cancer death rates had declined – an average of 1.8 percent per year for men; and 1.4 percent per year for women (Figures 9 and 10). However, as the rates of new cases of cancer for men
Figure 9. Trends in age-standardized incidence (1999-2014) and mortality rates (1999-2015) are illustrated for all cancer sites combined, all races/ethnicities combined, and by sex. An asterisk indicates that the annual percent change (APC) or the average APC (AAPC) is statistically significantly different from zero (2-sided t test; P < .05). UNK indicates unknown. Rates were age-standardized to the 2000 US standard population (19 age groups; Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census 25-1130]). Scattered points indicate observed rates, and lines are fitted rates according to joinpoint regression. Incidence rates were delay-adjusted and covered 89% of the US population, and mortality covered the entire United States. The AAPC is a weighted average of the APCs over the fixed interval (2010-2014 for incidence; 2011-2015 for mortality) using the underlying Joinpoint model for the period from 1999 to 2014 for incidence and the period from 1999 to 2015 for mortality. Joinpoint models with up to 2 joinpoints for incidence and up to 3 joinpoints for mortality are based on rates per 100,000 persons age standardized to the 2000 US standard population (19 age groups; Census P25-1130).

Figure 10. Delay-adjusted incidence (1999-2014) and mortality (1999-2015) trends, 5-year survival estimates by stage (2007-2013), and stage distribution at diagnosis are illustrated for (A) female breast cancer, (B) colon and rectum cancer, (C) lung and bronchus cancer, and (D) melanoma of the skin. Rates were age-standardized to the 2000 US standard population (19 age groups; Bureau of the Census. Current Population Reports, Publication 25-1130. Washington, DC: US Government Printing Office; 2000 [Census P25-1130]). Scattered points indicate observed rates, and lines are fitted rates according to joinpoint regression. Incidence rates were delay-adjusted and covered 89% of the US population, and mortality covered the entire United States.

decreased an average of 2.2 percent per year during this same time, in fact the decline in cancer death rates amongst men was largely explained by lower incidence rates – driven mostly by successful smoking cessation campaigns – and not better therapies for established cancers. In contrast with women, because the cancer incidence rates remained stable the decrease in cancer death rates most likely reflects improvements in the therapy of cancer in women. Note here that one must be cautious in ascribing the reduced mortality from cancer in women to better cancer therapies. We cannot both conclude that in men there has been very little or no improvement in the therapy of cancer while in women substantive improvements have been made. With the exception of breast and ovarian cancer, most common cancers that occur in women also occur in men and no or only small gender differences exist in the therapy of these shared diseases. Thus, one would have to have an enormous improvement in the therapy of breast and ovarian cancer to support conclusions that the reduced mortality in women are due to improvements in the therapy of cancer.

Consider, for example, the incidence and mortality rates from cancer in the United States depicted in Table 2. And for several of the most common cancers look at the accompanying figures summarizing the mortality rates over time. Because none of these can be cured when metastatic disease develops, mortality rates have not changed appreciably. That patients with cancer survive longer can be attributed to non-curative therapies, but accurate estimates of the length of survival can be confounded by lead time bias and greater end of life support making it impossible to estimate the contribution of new therapies. We do not disagree that effective therapies have been developed and that for some patients these have translated into longer overall survivals, but the magnitude of that prolongation is increasingly difficult to ascertain. With confidence, however, one can expect the prolongation of life to not exceed that achieved in a clinical trial and more often to be less and occasionally much less than that.

**Marginal gains and me-too therapies**

In 2003, Andrew von Eschenbach, MD, at the time the director of the National Cancer Institute made the provocative and highly controversial statement that his goal was to "eliminate suffering and death" from cancer by 2015. In 2016, one year after the twelve-year deadline had passed, Dr. von Eschenbach acknowledged that statement as the biggest mistake of his life. He argued that he had been misunderstood. Regardless, in 2019, with sixteen years of additional experience and additional knowledge, it would be similarly unrealistic to set a goal of "eliminating suffering and death" from cancer in 2030.

Dr. von Eschenbach argues that he "didn't realize that people would not see [what I meant] as clearly as I did and what I wanted them to appreciate, because, if they did, we might be in a very different place today". Dr. von Eschenbach was criticized for not “appreciating how complex cancer was”. Nearly everyone understood this. But neither he nor the overwhelming majority of those who criticized him failed to appreciate two important facts: (1) the complexity of cancer would render it exceptionally difficult to treat and we would increasingly settle for marginal gains; and (2) pharmaceutical companies had by then effectively usurped the development of cancer medicines and henceforth profits would become the main driving force behind the drug development
### Table 2: Estimated new cases and deaths for the ten most common cancers in the United States

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>2019 Estimates - United States</th>
<th>2018 Estimates - Worldwide (% all sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>Breast Cancer (Female)</td>
<td>271,270</td>
<td>42,260</td>
</tr>
<tr>
<td>Lung and Bronchus Cancer</td>
<td>228,150</td>
<td>142,670</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>174,650</td>
<td>31,620</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>145,600</td>
<td>51,020</td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td>96,480</td>
<td>7,230</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>80,470</td>
<td>17,670</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>74,200</td>
<td>19,970</td>
</tr>
<tr>
<td>Kidney and Renal Pelvis Cancer</td>
<td>73,820</td>
<td>14,770</td>
</tr>
<tr>
<td>Uterine Corpus Cancer</td>
<td>61,880</td>
<td>12,160</td>
</tr>
<tr>
<td>Leukemia</td>
<td>61,780</td>
<td>22,840</td>
</tr>
<tr>
<td>Cancer of Any Site</td>
<td>1,762,450</td>
<td>606,880</td>
</tr>
</tbody>
</table>
enterprise. The latter would lead to increasingly large trials designed to achieved increasingly smaller but statistically positive outcomes and a proliferation of “me too therapies” (Table 1). The latter are rationalized as development of slightly better and slightly less toxic alternatives but in fact provide a safe and profitable drug development strategy, that has increasingly sapped the drug development resources in cancer as pharmaceutical companies seek safe paths to increase profits.

The consequences of overlooking or underestimating these two critically important factors can be seen in Figures 11 and 12 that depict graphically the gains in progression-free and overall survival achieved in all cancer therapeutics approved by the US FDA for the treatment of solid tumors. A median gain of just over two months in both progression-free and overall survivals is discouraging and even more so when one realizes half of all approvals were given to therapies that achieved even less than this. Even more important is the dearth of truly novel agents. While the US FDA has approved cancer therapeutics at a rate faster than ever, in fact the approvals have almost exclusively involved new indications with marginal gains for existing drugs, or approvals of “me-too therapies” often in similar indications - approvals that have done little to advance the therapy of cancer and that were never envisioned by Dr. von Eschenbach. (Tables 3 and 4)

This development by many pharmaceutical companies of therapeutics that are often nearly identical and in turn their approval by regulatory agencies is becoming increasingly common (Table 1). While subtle differences are often touted as important attributes, for the purposes of the Essential Medicines List, slight variations amongst several very similar therapeutics will not render one more valuable than the next. Indeed, the development of several highly similar therapeutics, especially in the very same indications, will be an important attribute given their redundancy will add to the totality of the data available for analysis. This will allow for the approval of one agent as an Essential Medicine while also at the same time allowing the recommendation of similar agents with highly similar activity and toxicity profiles that can be substituted. The value of this will be twofold: first as noted, it will allow for the accumulation of a greater body of evidence and second it will provide options that will allow individual countries greater leverage in negotiations with pharmaceutical companies. Additionally, as biosimilars of a therapeutic included in the Essential Medicines List are developed and approved by regulatory agencies these will be referenced in the Essential Medicines List, so as to provide individual countries greater leverage in the procurement of their essential medicines.

Metrics of success: A critical assessment of data, its collection and interpretation

As noted several times throughout this monograph, the World Health Organization views overall survival as the desired endpoint and a meaningful improvement in overall survival the desired outcome for inclusion in the Essential Medicines List. Unfortunately, in recent years, there has been increasing enthusiasm for using PFS as a “surrogate” for OS. [Lebwohl, 2009; Zhwang, 2009] While the debate as to the wisdom of PFS as a surrogate is likely to continue, we would note the correlation between PFS and OS arises because the magnitude of the PFS benefit mimics the magnitude of the OS benefit (Figure 4, 5 and 6) — the quantitative difference in PFS and OS between the control and experimental group are similar [Wilkerson, 2009]. We
Figure 11. Progression-free survival (PFS) gains for US FDA approved therapies. The 86 drugs approved by the US FDA between 2006 and 2017 had a **median PFS gain of 2.55 months**
Figure 12. Overall survival (OS) gains for US FDA approved therapies. The 86 drugs approved by the US FDA between 2006 and 2017 had a median OS gain of 2.45 months
### Table 3: 31 US FDA approvals in 2017 for solid tumors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Drug class / Target</th>
<th>Novelty T/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab (PERJETA)</td>
<td>+Trastuzumab + chemotherapy adjuvant HER2+ BC</td>
<td>HER2- targeting antibody</td>
<td>N/N</td>
</tr>
<tr>
<td>Nivolumab (OPDIVO)</td>
<td>Adjuvant melanoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Cabozantinib (CABOMETYX)</td>
<td>Advanced renal cell carcinoma</td>
<td>TKI (M)</td>
<td>N/N</td>
</tr>
<tr>
<td>Ogivri (trastuzumab-dkst)</td>
<td>Anti-HER2 biosimilar</td>
<td>HER2- targeting antibody</td>
<td>N/Y</td>
</tr>
<tr>
<td>Sunitinib malate (SUTENT)</td>
<td>Adjuvant renal cell carcinoma</td>
<td>TKI (M)</td>
<td>N/N</td>
</tr>
<tr>
<td>Alectinib (ALECENSA)</td>
<td>ALK+ NSCLC</td>
<td>ALK inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Vemurafenib (ZELBORAF)</td>
<td>Erdheim-Chester Disease BRAF V600E</td>
<td>BRAFT inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Abemaciclib (VERZENIO)</td>
<td>With fulvestrant in HR+ / HER2- BC</td>
<td>CDK4/6 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Nivolumab (OPDIVO)</td>
<td>Hepatocellular carcinoma (HCC)</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Pembrolizumab (KEYTRUDA)</td>
<td>Gastric/gastroesophageal adenocarcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Cabazitaxel (JEVTANA)</td>
<td>Lower dose of cabazitaxel in CRPC</td>
<td>MTA</td>
<td>N/N</td>
</tr>
<tr>
<td>Mvasi (bevacizumab-awwb)</td>
<td>Bevacizumab biosimilar</td>
<td>VEGF antibody</td>
<td>N/Y</td>
</tr>
<tr>
<td>Olaparib (LYNPARZA)</td>
<td>Maintenance EOC, FTC, or PPC with CR/PR to cisplatin</td>
<td>PARP inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Ibrutinib (IMBRUVICA)</td>
<td>Chronic GVHD</td>
<td>Bruton’s tyrosine kinase inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Nivolumab (OPDIVO)</td>
<td>dMMR and MSI-H CRC</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Neratinib (NERLYNX)</td>
<td>HER2+ BC &gt; trastuzumab</td>
<td>HER1/2/4 inhibitor</td>
<td>N/Y</td>
</tr>
<tr>
<td>Dabrafenib + trametinib (TAFINLAR + MEKINIST)</td>
<td>Metastatic NSCLC BRAF V600E</td>
<td>BRAFT inhibitor + MEK inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Ceritinib (ZYKADIA)</td>
<td>ALK+ NSCLC</td>
<td>ALK inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Pembrolizumab (KEYTRUDA)</td>
<td>dMMR and MSI-H CRC and other cancers</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Pembrolizumab (KEYTRUDA)</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Pembrolizumab (KEYTRUDA)</td>
<td>NSCLC + pemetrexed and carboplatin</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Avelumab (BAVENCIO)</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Durvalumab (IMFINZI)</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Brigatinib (ALUNBRIG)</td>
<td>ALK+ NSCLC</td>
<td>ALK inhibitor</td>
<td>N/Y</td>
</tr>
<tr>
<td>Regorafenib (STIVARGA)</td>
<td>HCC</td>
<td>TKI (M)</td>
<td>N/N</td>
</tr>
<tr>
<td>Palbociclib (IBRANCE)</td>
<td>With aromatase inhibitor in HR+ / HER2- BC</td>
<td>CDK4/6 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Osimertinib (TAGRISSO)</td>
<td>EGFR+ T790M NSCLC</td>
<td>EGFR inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Niraparib (ZEJULA)</td>
<td>Maintenance EOC, FTC, or PPC</td>
<td>PARP inhibitor</td>
<td>N/Y</td>
</tr>
<tr>
<td>Avelumab (BAVENCIO)</td>
<td>Merkel cell carcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/Y</td>
</tr>
<tr>
<td>Ribociclib (KISQALI)</td>
<td>+ Aromatase inhibitor HR+ / HER2- BC</td>
<td>CDK4/6 inhibitor</td>
<td>N/Y</td>
</tr>
<tr>
<td>Nivolumab (OPDIVO)</td>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
</tr>
</tbody>
</table>

**Novelty:** T, target; [Y = protein never targeted; N = previously targeted protein] D, drug [Y = 1st approval or approval in novel indication; N = previous approvals in similar indications]

Anaplastic lymphoma kinase; BC, breast cancer; BRAFT, proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B; CDK4/6, cyclin dependent kinase 4/6; dMMR, mismatch repair deficient; EGFR, epidermal growth factor receptor; EOC, epithelial ovarian cancer; FTC, fallopian tube cancer; HER2 human epidermal growth factor receptor 2; HCC, hepatocellular carcinoma; HR, hormone receptor; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; MEK, mitogen-activated extracellular signal-regulated kinase; MSI-H, microsatellite instability-high; MTA, microtubule-targeting agent; PARP, poly ADP ribose polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PPC, primary peritoneal cancer; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
Table 4: 36 US FDA approvals in 2018 for solid tumors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Drug class / Target</th>
<th>Novelty T/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib (LYNPARZA)</td>
<td>Deleterious/suspected deleterious gBRCAm, HER2(-) MBC &gt; chemotherapy</td>
<td>PARP inhibitor</td>
<td>N/Y</td>
</tr>
<tr>
<td>Aftatinib (GILOTRIF)</td>
<td>1st line NSCLC with non-resistant EGFR mutations</td>
<td>EGFR inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>I17Lutetium-dotatate (LUTATHERA)</td>
<td>SSTR(+) GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors</td>
<td>Radiolabeled SSTR analog</td>
<td>N/Y</td>
</tr>
<tr>
<td>Abiraterone acetate (ZYTIGA)</td>
<td>Metastatic high-risk castration-sensitive prostate cancer</td>
<td>Anti-androgen, inhibits steroid 17-alpha-hydroxylase</td>
<td>N/N</td>
</tr>
<tr>
<td>Apalutamide (ERLEADA)</td>
<td>Non-metastatic castration-resistant prostate cancer</td>
<td>Non-steroidal anti-androgen</td>
<td>N/Y</td>
</tr>
<tr>
<td>Durvalumab (IMFINZI)</td>
<td>Unresectable stage III NSCL &gt; platinum-based CRT</td>
<td>PD-L1 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Abemaciclib (VERZENIO)</td>
<td>1st line + aromatase inhibitor postmenopausal HR(+), HER2(-) A/M BC</td>
<td>CDK4/6 inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Rucaparib (RUBRACA)</td>
<td>Maintenance of recurrent EOC, FTC and PPC</td>
<td>PARP inhibitor</td>
<td>N/N</td>
</tr>
<tr>
<td>Nivolumab and ipilimumab (OPDIVO and YERVOY)</td>
<td>Poor risk / advanced RCC</td>
<td>PD-1 inhibitor and CTL4 inhibitor</td>
<td>N/N</td>
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<tr>
<td>Osimertinib (TAGRISSO)</td>
<td>1st line mNSCL with EGFR exon 19 deletion or exon 21 L858R</td>
<td>EGFR inhibitor</td>
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<tr>
<td>Dabrafenib + trametinib (TAFINLAR + MEKINIST)</td>
<td>Adjuvant treatment melanoma with BRAF V600E or V600K mutation</td>
<td>BRAF inhibitor + MEK inhibitor</td>
<td>N/N</td>
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<tr>
<td>Dabrafenib + trametinib (TAFINLAR + MEKINIST)</td>
<td>Anaplastic thyroid cancer with BRAF V600E mutation</td>
<td>BRAF inhibitor + MEK inhibitor</td>
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<tr>
<td>Retacrit (epoetin alfa-epbx)</td>
<td>Epoetin/Procrit (epoetin alfa) biosimilar</td>
<td>Erythropoiesis-stimulating biosimilar</td>
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<td>Fulphila (pegfilgrastim-jmd)</td>
<td>Neulasta (pegfilgrastim) biosimilar</td>
<td>Pegfilgrastim biosimilar</td>
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<tr>
<td>Pembrolizumab (KEYTRUDA)</td>
<td>PD-L1+ (CPS ≥1) recurrent/metastatic cervical cancer &gt; chemotherapy</td>
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<tr>
<td>Bevacizumab (AVASTIN)</td>
<td>+ Carboplatin and paclitaxel for EOC, FTC and PPC</td>
<td>VEGF inhibitor</td>
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<td>Ncorafenib and binimetinib (BRAFVTOI and MEKTOVI)</td>
<td>Unresectable/metastatic melanoma with mBRAFV600E or mBRAFV600K</td>
<td>BRAF inhibitor + MEK inhibitor</td>
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<tr>
<td>Ipilimumab (YERVOY)</td>
<td>+ nivolumab for MSI-H/dMMR mCRC &gt; fluoropyrimidine, oxaliplatin, and irinotecan</td>
<td>CTL4 inhibitor</td>
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<td>Enzalutamide (XTANDI)</td>
<td>Castrate-resistant prostate cancer</td>
<td>Anti-androgen; androgen receptor competitor</td>
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<tr>
<td>Ribociclib (KISQALI)</td>
<td>+ Aromatase inhibitor in pre/perimenopausal HR(+), HER2(-) LAMBC</td>
<td>CDK4/6 inhibitor</td>
<td>N/N</td>
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<td>Nivolumab (OPDIVO)</td>
<td>SCLC with progression &gt; platinum-based chemotherapy</td>
<td>Radiolabeled catecholamine</td>
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<td>Lenvatinib (LENVIMA)</td>
<td>1st line mCRC</td>
<td>VEGF inhibitor</td>
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<td>Pembrolizumab (KEYTRUDA)</td>
<td>Cisplatin ineligible urothelial cancer require FDA-approved companion diagnostic</td>
<td>PD-1 inhibitor</td>
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<td>Pembrolizumab (KEYTRUDA)</td>
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<td>Dacomitinib (VIZIMPRO)</td>
<td>1st line NSCLC with EGFR exon 19 deletion or exon 21 L858R</td>
<td>EGFR inhibitor</td>
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<td>Cemiplimab-rwlc (LIBTAYO)</td>
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<td>Talazoparib (TALZENNA)</td>
<td>gBRCAm, HER2(-) LAMBC</td>
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<td>Pembrolizumab (KEYTRUDA)</td>
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<td>Lorbatinib (LORBRENA)</td>
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<td>Larotrectinib (VITRAKVI)</td>
<td>Solid tumors with neurotrophic receptor tyrosine kinase (NTRK) gene fusion</td>
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<table>
<thead>
<tr>
<th>Drug &amp; Brand Name</th>
<th>Indication</th>
<th>Target</th>
<th>Previous Approvals</th>
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<tr>
<td>Atezolizumab (TECENTRIQ)</td>
<td>1st line NSCLC with bevacizumab, paclitaxel, and carboplatin</td>
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<td>Herzuma (trastuzumab-pkrb)</td>
<td>HER2-overexpressing breast cancer</td>
<td>Herceptin biosimilar</td>
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<td>Pembrolizumab (KEYTRUDA)</td>
<td>Merkel cell carcinoma</td>
<td>PD-1 inhibitor</td>
<td>N/N</td>
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<td>Olaparib (LYNPARZA)</td>
<td>Maintenance - EOC, FTC &amp; PPC with deleterious/suspected gBRCAm or sBRCAm</td>
<td>PARP inhibitor</td>
<td>N/N</td>
</tr>
</tbody>
</table>

**Novelty:** T, target; [Y = protein never targeted; N = previously targeted protein] D, drug [Y = 1st approval or approval in novel indication; N = previous approvals in similar indications]

ALK, anaplastic lymphoma kinase; A/M BC, advanced or metastatic breast cancer; BRAF, proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B; CDK4/6, cyclin dependent kinase 4/6; CPS, combine positive score; CSCC, cutaneous squamous cell carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CRT, chemotherapy and radiation therapy; dMMR, mismatch repair deficient; EGFR, epidermal growth factor receptor; EOC, epithelial ovarian cancer; FTC, fallopian tube cancer; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; gBRCAm, germline BRCA-mutated; HER2 human epidermal growth factor receptor 2; HCC, hepatocellular carcinoma; HR, hormone receptor; LAMBC, locally advanced or metastatic breast cancer; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; MEK, mitogen-activated extracellular signal-regulated kinase; MSI-H, microsatellite instability-high; NSqNSCLC, non-squamous non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PARP, poly ADP ribose polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PPC, primary peritoneal cancer; sBRCAm, somatic BRCA-mutated; SCLC, small cell lung cancer; SSTR, somatostatin receptor; VEGF, vascular endothelial growth factor
would argue the latter occurs because our therapies do not change the “biology” of metastatic cancer but only modify it while administered, and consequently all benefit accrues while a therapy is administered. Provided discontinuing treatment does not accelerate tumor growth, the magnitude of the “on-treatment” benefit – constrained by the inaccuracies of estimating PFS – is the magnitude of the benefit that accrues to OS. The limitations of surrogates and their inadequacy relative to OS [Wilkerson and Fojo, 2009; Saad et al, 2010a; Saad et al, 2010b; Amir et al, 2012; Booth and Eisenhauer, 2012] are discussed in an accompanying report [Booth Report for WHO 2019]

Real World Data

Increasingly data from the “real world” is being gathered after the deployment of a cancer therapeutic. While recognizing the limitations of such data, their value cannot be overlooked, and especially as one recommends deployment across diverse populations, data that establish the tolerability and hopefully also the efficacy of a therapeutic in patients, the majority of which would likely not be considered “trial eligible”, is very valuable (Figures 13 and 14). Where possible such data will be analyzed and the results considered in the decision regarding the inclusion of a therapeutic in the Essential Medicines List. Examples that allow one to compare real-world outcomes to those in the clinical trials that led to regulatory approvals are shown in Table 5.

In hepatocellular cancer (HCC), for example, a common and universally fatal disease in many parts of the world, Phase III trials [Llovet et al, 2008; Cheng et al, 2009] have previously shown improved survival of patients with a diagnosis of HCC treated with sorafenib. However, narrow trial eligibility criteria have raised concerns that the results may not be generalizable to a broader HCC population. Support for this concern has been provided in several publications [Sanoff et al, 2016; Doyle et al, 2016] including a trial that sought to evaluate the effectiveness of initial sorafenib versus no treatment among Medicare beneficiaries with advanced HCC [Sanoff et al, 2016]. Specifically, amongst 223 patients treated with initial sorafenib the median duration of sorafenib use was only 60 days (IQR, 30–107 days), and median OS from first prescription was 3 months (IQR, 1–8 months). Comparing outcomes using a propensity score (PS)-matched cohort, revealed median OS from a 60-day landmark of 3 and 2 months in sorafenib treated (n=223) and untreated (n=223) patients, respectively (adjusted HR, 0.95 [95%CI, 0.78–1.16]). Additionally, sorafenib administration did not reduce mortality at 3 months (44% versus 51%; adjusted RR, 0.88 [95% CI, 0.72–1.07]). The results led to the conclusion that published trial results are not generalizable and that given the minimal benefit accrued in the real world, the downsides of sorafenib use — including high drug-related symptom burden and high drug cost — cannot be ignored.

Similar concerns regarding applicability have emerged for the use of regorafenib monotherapy in patients with treatment-refractory, metastatic colorectal cancer (mCRC). Although the CORRECT and CONCUR trials [Grothey et al, 2013; Li et al, 2015] demonstrated survival benefits in treatment-refractory mCRC, the trial’s stringent eligibility criteria raised questions about its broad applicability. As with sorafenib in HCC, the concern with regorafenib has been ratified by several publications [Gotfrit et al, 2018; Patel et al, 2018; Angeles et al, 2018] concluding that patients
Figure 13. Published data often does not apply to “real world patients” who often would not satisfy eligibility criteria; Example: Renal Cell Carcinoma. Overall, 2210 patients with mRCC treated with VEGF-targeted therapy were included in this analysis. 768 (35%) of patients were deemed trial ineligible and 1442 (65%) were deemed trial eligible. Most common first-line therapy was sunitinib, followed by sorafenib, bevacizumab, and pazopanib. There were multiple reasons why patients were deemed ineligible. The most common reason was Karnofsky performance status (KPS) <70% in 13% of patients, nonclear histology in 11%, brain metastases in 8%, and low hemoglobin (≤9) in 8%. The majority of patients (605) were excluded due to one exclusion criteria while 140 patients met two exclusion criteria and one patient had five exclusion criteria. By definition, patients in the trial ineligible group had lower KPS, more anemia, hypercalcemia, brain metastases, and nonclear-cell histology. The median overall survival from first-line targeted therapy was 12.5 versus 28.4 months ($P < 0.0001$) in the trial ineligible versus trial eligible patients.

International Metastatic RCC Database Consortium, Heng et al Ann Oncol 2014;25:149-54
Figure 14. Published data often does not apply to real world patients. Example: Five-Year Data and Prognostic Factor Analysis of Oxaliplatin and Irinotecan Combinations for Advanced Colorectal Cancer [Study N9741] Fitness is an important factor. The top panel shows overall survival by baseline performance status (PS). In the lower panel is shown the relevant data as regards fitness and age from a multivariate prognostic factor analysis. ECOG PS, Eastern Cooperative Oncology Group performance status; Younger age invariably means more fit as does a better ECOG PS. These are linked.

Sanoff et al, J Clin Oncol 2008; 26:5721-7
Table 5: Selected examples of real-world data

Sorafenib in hepatocellular carcinoma (HCC)

Sanoff et al [2016]
- 1532 patients with a diagnosis of advanced HCC between 2008 and 2011 were identified from the SEER-Medicare database.
- Eligible patients received initial sorafenib or no therapy
- Sorafenib use and PS-matched sample used to compare the effectiveness of sorafenib versus no treatment by Cox proportional hazards and binomial regression, using a landmark requiring patients survive ≥60 days after diagnosis
- 414/1532 (27%) of patients received initial sorafenib
- Median duration of sorafenib use = 60 days ([IQR, 30–107 days)
- Median OS from first prescription = 3 months (IQR, 1–8 months)
- In the PS-matched cohort median OS = 3 months from the 60-day landmark in sorafenib treated (n=223) and 2 months in untreated (n=223) patients (adjusted HR, 0.95; 95%CI, 0.78–1.16).
- Sorafenib associated with nonsignificant reduction in mortality at 3 months (44% versus 51%; adjusted RR, 0.88; 95% CI, 0.72–1.07), but no reduction thereafter
- In newly diagnosed Medicare beneficiaries with HCC survival after starting sorafenib is exceptionally short, suggesting trial results are not generalizable to all HCC patients.
- The downsides of sorafenib use—high drug-related, symptom burden and high drug cost—must be considered in light of minimal benefit

Doyle et al [2016]
- Retrospective cohort study of medical records of 320 patients with a diagnosis of HCC treated with sorafenib
- Adverse effects in 79% of patients
- Dose reduction in 31% of patients
- Increased mortality rate with:
  - Child-Pugh C (HR 5.52, p=0.012)
  - ECOG PS 2-3 (HR 2.84, p=0.001)
  - Extrahepatic metastases (HR 1.54, p=0.04)
- Decreased mortality rate with:
  - AFP reduction ≥20% at 3 months (HR 0.38, p=0.001)
- Increased rate of radiological progression with:
  - ECOG PS 2-3 (HR 2.34, p=0.041)
- Decreased rate of radiological progression with
  - On-treatment diarrhea (HR 0.55, p=0.015)
- Poor survival when sorafenib used in patients with Child-Pugh C liver function or advanced functional impairment
- Routine use of sorafenib in Child-Pugh C liver function or advanced functional impairment does not appear justified, given the high rate of adverse effects.

Regorafenib in metastatic colorectal cancer (mCRC)

Angeles et al [2018]
- Patients at British Columbia Cancer Agency with mCRC with disease progression or intolerable toxicity and ≥2 lines of systemic therapy
- Aimed to examine treatment attrition rates and eligibility for regorafenib in routine practice determined using the CORRECT trial criteria
- Among 391 patients only 39% were eligible for regorafenib. Main reasons for ineligibility
  - ECOG PS >1 (69%)
  - Elevated total bilirubin (21%)
  - Thromboembolic events in the past 6 months (10%)
- Median OS for regorafenib-eligible and regorafenib-ineligible patients were 5.3 versus 2.1 months, respectively (P < 0.001) However, Cox proportional hazard analyses showed that only ECOG PS rather than trial eligibility was correlated with outcomes
- Strict eligibility criteria disqualify most patients with treatment-refractory mCRC for regorafenib therapy
- Future trials should broaden eligibility criteria to improve external validity
### Patel et al [2018]
- Analyzed retrospective data from the US Symphony Health Solutions’ Integrated Dataverse database for adults with a diagnosis of mCRC receiving FTD/TPI (1630) and regorafenib (1425) from OCT2014 - JUL2016.
- Patients receiving FTD/TPI were 80% more likely to have a medication possession ratio of ≥0.80 compared with the patients receiving regorafenib (OR, 1.80; P<.001)
- Patients receiving FTD/TPI were twice as likely to have a proportion of days covered of ≥0.80 (OR, 2.66; P<.001) at 3 months.
- Patients receiving FTD/TPI 37% less likely to discontinue treatment compared with patients administered regorafenib when using the 60-day gap (HR, 0.63; P<.001). Similar results using 45- and 90-day gaps
- Patients with a diagnosis of mCRC taking FTD/TPI significantly more likely to adhere to and comply with therapy compared with those taking regorafenib

### Gotfrit et al [2018]
- Retrospective review of patients with a diagnosis of mCRC treated with regorafenib at one institution from 2013-2015
- 48 patients offered regorafenib; 35 (73%) started treatment [57% men. median age 61 years, and PS 0-2.
- Time from diagnosis of mCRC to regorafenib treatment >18 months in 71%
- Starting doses: 160 mg (545), 120 (40), and 80 mg (6%)
- Dose reductions in 34%; dose interruptions in 29%
- Best response: PD (60%), SD (17%), and unknown (3%)
- Most common AE (any grade): Fatigue (57%), hyperbilirubinemia (43%), thrombocytopenia (37%), anorexia (31%), and hypertension (31%)
- Most common grade 3/4 AEs: Fatigue (29%), hypophosphatemia (17%), weight loss (11%), and hyperbilirubinemia (9%)
- Common reasons for discontinuing regorafenib: PD (51%) and toxicity (26%)
- With regorafenib PFS 2.4 months (95%CI, 1.8-3.3 months) and OS 5.6 months (95%CI 3.7-8.9 months)

### Bevacizumab in non-small cell lung cancer (NSCLC)

#### Yang et al [2010]
- Meta-analysis to evaluate the effectiveness and safety of bevacizumab in patients with unresectable NSCLC on the basis of evidence-based methodology. Four eligible studies including 2101 patients found
- Bevacizumab administered to 1237/2101 patients
- Neither high-dose (15 mg/kg) nor low-dose (7.5 mg/kg) bevacizumab increased 1-year OS rates compared with patients not treated with bevacizumab
- High-dose but not low-dose bevacizumab increased 2-year OS rate (RR=1.24; 95%CI 1.04, 1.49) and tumor response rate (RR=1.69; 95% CI 1.21, 2.35) compared with patients not treated with bevacizumab
- PFS significantly improved in both low- (HR=0.76; 95%CI 0.64, 0.90) and high-dose bevacizumab groups (HR=0.73; 95%CI 0.65, 0.81)
- Clear and significant increase in the rate of treatment-related death in high-dose group (RR=2.07; 95%CI 1.19, 3.59) but not in the low-dose group compared with patients not treated with bevacizumab

#### Low-dose bevacizumab may significantly improve PFS in patients with unresectable NSCLC
High-dose bevacizumab may increase 2-year OS rates, prolong PFS and improve tumor response rate
But these marginal gains come at the cost of higher treatment-related death
Larger well designed RCTs should be carried out to clarify the role of bevacizumab in the treatment of NSCLC

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<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Findings</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu et al [2012]</td>
<td>Retrospective cohort study of 4168 Medicare beneficiaries ≥65 years with stage IIIB/IV non–squamous cell NSCLC diagnosed in 2002-2007 in a SEER region</td>
<td>Patients were categorized into 3 cohorts: (1) diagnosis in 2006-2007 treated with bevacizumab + carboplatin + paclitaxel (BCP); (2) diagnosis in 2006-2007 and treated with carboplatin + paclitaxel (CP); or (3) diagnosis in 2002-2005 and treated with CP</td>
<td>Comparisons used Cox proportional hazards models and PS analyses including information about patient characteristics recorded in SEER-Medicare. Median OS were 9.7, months (IQR, 4.4-18.6) for BCP, 8.9 months (IQR, 3.5-19.3) for CP in 2006-2007, and 8.0 months (IQR, 3.7-17.2) for CP in 2002-2005. One-year survival probabilities were 39.6% (95%CI, 34.6%-45.4%) for BCP vs 40.1% (95% CI, 37.4%-43.0%) for CP in 2006-2007 and 36.6% (95% CI, 33.8%-37.5%) for CP in 2002-2005. Neither multivariable nor propensity score—adjusted Cox models demonstrated a survival advantage for BCP compared with CP cohorts. In propensity score-stratified models, the HR for OS for BCP compared with CP in 2006-2007 was 1.01 (95%CI, 0.89-1.16; P=.85) and compared with CP in 2002-2005 was 0.93 (95% CI, 0.83-1.06; P=.28). The propensity score–weighted model and propensity score–matching model similarly failed to demonstrate statistically significant superiority for BCP.</td>
</tr>
</tbody>
</table>

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**Bevacizumab in metastatic colorectal cancer (mCRC)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Findings</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyerhardt et al [2012]</td>
<td>SEER-Medicare used to assess outcomes in 2,526 patients with stage IV mCRC diagnosed between 2002 and 2007. All received first-line combination therapy with a fluoropyrimidine and either irinotecan (33%) or oxaliplatin (67%); 36% received bevacizumab with first-line therapy. Primary outcome was OS. Secondary outcomes were bevacizumab-associated toxicities, including incidence of stroke, myocardial infarction, and GI perforation.</td>
<td>OS advantage for bevacizumab seen only with irinotecan-based chemotherapy (HR, 0.80; 95%CI, 0.66 to 0.97) and not with oxaliplatin-based chemotherapy (HR, 0.96; 95%CI, 0.86 to 1.07). Combination chemotherapy with bevacizumab, versus combination chemotherapy without bevacizumab: Increased risk of stroke (4.9% v 2.5%, respectively; P&lt;.01) Increased risk of GI perforation (2.3% v 1.0%, respectively; P&lt;.01) No increased risk of cardiac events or venous thrombosis.</td>
<td>Confirming existing literature at the time: FOLFOX (mOS = 20.2 months shown to be superior to FOLFIRI (mOS 13.3 months) and IFL (mOS 13 months) OS advantage for bevacizumab seen only with irinotecan-based and not with oxaliplatin-based chemotherapy. Authors incorrectly concluded that addition of bevacizumab was associated with improved OS. An imbalance in the chemotherapy backbone was responsible for difference since a much larger percentage of bevacizumab-treated patients received the superior FOLFOX backbone.</td>
</tr>
</tbody>
</table>

Abbreviations: HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results; PS, propensity score; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mCRC, metastatic colorectal cancer; FDI/TPI, trifluridine/tipiracil; OR, odds ratio; HR, hazard ratio; PD, progressive disease; SD, stable disease; AE, adverse event; NSCLC, non-small cell lung cancer; RR, risk ratio.; BCP, bevacizumab + carboplatin + paclitaxel; CP, carboplatin + paclitaxel; mOS, median overall survival.
enrolled on regorafenib clinical trials do not emulate the majority of real-world patients; and tolerability as a whole is very poor.

The use of bevacizumab both in non-small cell lung cancer and in colorectal cancer provide one final example of therapies that have achieved clinical trial results of questionable value. Usually diagnosed at advanced stage (IIIB or IV), for non–small cell lung cancer (NSCLC) even in the era of immunotherapy cure is rarely attainable. Chemotherapy, long the first line option in the management of NSCLC and even in the era of immunotherapy an important component of management has unfortunately only achieved modest OS advantages with 1-year and 3-year survivals less than 50% and 25%, respectively. In 2006, the Eastern Cooperative Oncology Group conducted a randomized trial (ECOG 4599) of 878 patients with advanced NSCLC of non–squamous cell type that reported a significant survival benefit with the addition of bevacizumab to a carboplatin + paclitaxel regimen (HR for death 0.79; 95% CI, 0.67-0.92) [Sandler et al, 2006]. Hailed at the time as a major advance, the trial led in October 2006 to the approval by the US FDA of bevacizumab in combination with carboplatin and paclitaxel as treatment for advanced NSCLC. However, a subsequent meta-analysis of 4 randomized trials did not identify a significant improvement in 1-year overall survival when adding bevacizumab to standard chemotherapy [Yang et al, 2010]. Additionally, ECOG 4599 failed to demonstrate an OS advantage with bevacizumab (HR, 0.89; 95% CI, 0.70-1.14) among the 366 trial participants 65 years or older [Sandler et al, 2006]. The latter was subsequently confirmed by an analysis of SEER-Medicare data in which neither multivariable nor propensity score–adjusted Cox models demonstrated a survival advantage to adding bevacizumab to carboplatin + paclitaxel, leading the authors to conclude that adding bevacizumab was of no benefit amongst Medicare patients with advanced NSCLC. Similarly, in metastatic colorectal cancer, where a survival advantage with the addition of bevacizumab has only been demonstrated with the combination of irinotecan + fluorouracil + leucovorin (IFL), a combination no longer used, benefit in the Medicare population has not been shown [Meyerhardt et al, 2012, Figures 15 and 16]. Specifically, the results confirmed the literature existing at the time by demonstrating FOLFOX (median OS, 20.2 months) superior to FOLFIRI (median OS, 13.3 months) and IFL (median OS, 13 months) and reported an OS advantage for bevacizumab only with irinotecan-based and not with oxaliplatin-based chemotherapy. The authors incorrectly concluded that bevacizumab with chemotherapy was associated with improved OS in this Medicare population because an imbalance in the chemotherapy backbone was responsible for the putative difference since a much larger percentage of bevacizumab-treated patients received the superior FOLFOX backbone

The ASCO Value Framework and the ESMO-MCBS. A primer and how the World Health Organization can use it to inform decisions on the Essential Medicines List

Both the American Society of Clinical Oncology (ASCO) (Table 6) [https://www.asco.org/about-asco/press-center/news-releases/asco-value-framework-update; Schnipper et al, 2015; Schnipper et al, 2016] and the European Society of Medical Oncology (ESMO) (Table 7) [https://academic.oup.com/annonc/article/28/10/2340/4102112?searchresult=1#supplementary-data; Cherny et al, 2015; Cherny et al, 2017] have only recently begun attempts to better describe the "value" of the various therapeutics used in the
The authors erroneously concluded “Routine use of bevacizumab with chemotherapy for Medicare beneficiaries with mCRC is associated with a modest survival advantage and modest risk of perforation and stroke. On balance, elderly patients with mCRC can be counseled that including bevacizumab in first-line therapy regimens for mCRC seems to be no more than marginally effective”. But in fact there is absolutely no benefit from bevacizumab as seen in the two panels on the left. The “apparent benefit” seen in the upper right panel occurred simply because the better therapy [FOLFOX] was given more often with bevacizumab. The better outcomes had nothing to do with bevacizumab; they occurred because the better backbone that was used with bevacizumab.

Figure 16. The limited efficacy of bevacizumab in colorectal cancer found in randomized trials was emulated by the results in the Medicare population [Figure 15]. In the panel on the left the median duration of survival (indicated by the dotted lines) was 20.3 months in the group given irinotecan, fluorouracil, and leucovorin (IFL) plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 (P<0.001). However, this regimen is no longer used and this fact led NICE to rescind its recommendation for the use of bevacizumab in colorectal cancer. This is an example where the evolution to better therapies [FOLFIRI and FOLFOX] made the use of as second drug combined with a poorer backbone obsolete. The panel on the right shows the overall survival (intent to treat population) of patients enrolled in a randomized phase III study that examined bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer (MCRC) [XELOX, capecitabine and oxaliplatin; FOLFOX-4, infused fluorouracil, folinic acid, and oxaliplatin]. So that while the addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved PFS in this first-line trial in patients with MCRC, overall survival differences did not reach statistical significance, and response rate was not improved by the addition of bevacizumab. The lack of overall survival again was emulated by the results in the Medicare population [Figure 15].

### Table 6: American Society of Clinical Oncology - Defining Clinically Meaningful Outcomes

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Current OS Median [Months]</th>
<th>Improvement in OS, [Number of Months]</th>
<th>Percent of Current Median</th>
<th>Improvement in PFS, [Number of Months]</th>
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</thead>
<tbody>
<tr>
<td>PANCREATIC CANCER</td>
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</tr>
<tr>
<td>FOLFIRINOX-eligible</td>
<td>10-11</td>
<td>≥4</td>
<td>≥36-40</td>
<td>≥4</td>
</tr>
<tr>
<td>Gemcitabine or gemcitabine/nab-paclitaxel eligible</td>
<td>8-9</td>
<td>≥3</td>
<td>≥33-37.5</td>
<td>≥3</td>
</tr>
<tr>
<td>LUNG CANCER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous cell carcinoma</td>
<td>13</td>
<td>≥3.25</td>
<td>≥25</td>
<td>≥4</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10</td>
<td>≥2.5</td>
<td>≥25</td>
<td>≥3</td>
</tr>
<tr>
<td>BREAST CANCER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic triple negative, previously untreated for metastatic disease</td>
<td>18</td>
<td>≥4.5</td>
<td>≥25</td>
<td>≥4</td>
</tr>
<tr>
<td>COLON CANCER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression with all prior therapies; not candidate for standard second-line or third-line options</td>
<td>4-6</td>
<td>≥3</td>
<td>≥50-75</td>
<td>≥3</td>
</tr>
</tbody>
</table>
Table 7: ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE
THOUGHTFUL AND REASONED APPROACH
A GOOD START AND A HELPFUL BENCHMARK

Overestimating or overstating the benefits from new intervention can cause harm:
1. Confounds public policy decision making
2. Undermines the credibility of oncology research reporting
3. Harms patients who choose to undertake treatments based on exaggerated expectations that may subject them to either risk of adverse effects, inconvenience or substantial personal costs
4. In the public domain, they fuel sometimes inappropriate hype or disproportionate expectations about novel treatments and the need to allocate public or personal funds to provide them.

PROBLEM: IT ACCEPTS TRIAL RESULTS AT FACE VALUE
Many factors impact clinical trial results:
• Censoring
• Ascertainment bias
• Toxicity
• Early reporting before OS available – The lack of OS benefit and when if ever is it valuable?
management of patients with cancer in countries whose resources exceed most of the rest of the world. The ASCO Value Framework and the ESMO Magnitude of Clinical Benefit Scale (MCBS), described in greater detail below, are at this time best described as "works in progress". The challenges of establishing "value" for an organization such as the World Health Organization may be insurmountable given any assessment will vary depending on the country, its health care system, the disease under consideration and the segment of the patient population affected. While the definition of value is generally accepted as a measure of outcomes achieved per monetary expenditure in fact this omits so many critical variables that its worth is questionable. An often cited "method for defining value in healthcare using cancer care as a model" concluded that greater data could "lead to improved competition in the healthcare marketplace" and, as a result, "improved outcomes and decreased health expenditures" [Feeley et al, 2010]. For the World Health Organization and its Essential Medicines List it is unfortunately almost never about competition but about accessibility and affordability.

Although still works in progress, largely dependent on published clinical trials that in many cases lack the data needed to properly evaluate a therapeutic, both the ASCO Value Framework and the ESMO MCBS nevertheless provide valuable information that can be used in the assessment of a cancer therapeutic. Their reliance, indeed dependency, on published data limits their effectiveness and is further compounded by their lack of critical assessment of the results. This lack of critical assessment of a trial's outcomes is essential if "experts" are to meaningfully assess the "true value" of a therapeutic. Unexpected outcomes such as better or worse performance of the control arm, results that highlight a potential outlier without a rational explanation, inordinate censoring that appears informative, any imbalance in enrollment that might explain differences, excessive deviation from the real-world patient population, and many others will be overlooked if the numbers reported in a manuscript are simply entered into a from without careful thought given. The ASCO Value Framework for example, awards Bonus Points centered around toxicity/tolerability but penalties are not incurred for concerns that might arise from the data. The ESMO MCBS is similarly wanting. As an example, the use of bevacizumab in breast cancer garnered a score of 3 in the ESMO MCBS for its use in first line in women with HER-2 negative MBC in combination with capecitabine ignoring increasingly robust data that time and again have failed to demonstrate meaningful or any benefit of bevacizumab in the therapy of breast cancer [O'Shaughnessy et al, 2009; Robert et al, 2009; Chan et al, 2010; Miles et al, 2010; Brufsky et al, 2011; Rosarri et al, 2012; Miller et al, 2018].

Tables 6 and 7 provide summaries of the ASCO Value Framework (Table 6) and the ESMO Meaningful Clinical Benefit Scale (ESMO-MCBS, Table 7). For the World Health Organization these represent tools that can help assess treatment efficacy. The cost side of the equation while very important is less relevant when deciding the survival benefit of a therapeutic and whether it should be included in the Essential Medicines List. Consequently, in the summary that follows emphasis is given to the efficacy aspects of both metrics ignoring the cost considerations that factor into the analyses.

The ASCO Value Framework

The ASCO Value Framework had its origins in the ASCO Cancer Research Committee [Ellis et al, 2014] and was initially published in 2015. [Schnipper et al, 2015]
In assessing the value of a cancer therapeutic, the Value Framework considers clinical benefit, side effects, and improvements in patient symptoms or quality of life in the context of cost. An updated version was published on May 31, 2016. When initially deciding what metrics would be used to define value, ASCO, through the Value in Cancer Care Task Force, looked to the highly regarded Institute of Medicine (IOM) for guidance [Crossing the Quality Chasm, 2001; Delivering High-Quality Cancer Care, 2013]. The Institute of Medicine (IOM) had previously identified six elements it considered essential for quality health care delivery including safety, effectiveness, patient centeredness, timeliness, efficiency, and equity. Of these, the ASCO Task Force chose clinical benefit (effectiveness), toxicity (safety), and cost (efficiency) for its Value Framework feeling these were “readily measured, ascertainable from high-quality medical evidence, and central to the mission of the clinical oncologist”. Although the task force felt patient centeredness, timeliness, and equity are also essential it was felt they are unfortunately not as easy to measure and are only rarely captured and reported in clinical trials.

At the time of this writing the ASCO Value Framework is much more of a work in progress than the ESMO MCBS. It has two frameworks – the advanced disease framework and the curative framework. In the advanced disease framework, efficacy or clinical benefit is assigned a categorical 1 to 5 score. In the initial version, clinical benefit was based on fractional improvement in median overall survival (OS), median progression-free survival (PFS) or overall response rate (ORR). OS and PFS were scored if the new therapeutic has been compared with a standard-of-care regimen in a specific clinical scenario; while ORR was scored if neither OS or PFS were available or if a therapeutic was only evaluated in a single arm trial. Disappointingly, as discussed below, the revised version will pivot to hazard ratios. As noted by ASCO [ASCO Value Framework Update, 2016], it “modified the Net Health Benefit score — our weighted measure of a treatment’s benefits and side effects — to better reflect true differences between treatments. For example, to calculate the efficacy of a treatment, the updated framework uses hazard ratios, when available, rather than absolute survival measures. Hazard ratios provide a more complete assessment of the relative differences between therapies”. [italics added] The “weight” of each metric reflects the view of the Task Force, and indeed of all oncologists and especially the World Health Organization, that improvement in OS is the most desirable outcome. Thus, the categorical score for OS is weighted (i.e., multiplied) by 16, while the values for PFS and ORR are weighted by 11 and eight, respectively. These values, all arbitrarily chosen, reflect the feeling of the Task Force that PFS is a less clinically meaningful end point, not always a surrogate for OS, and that ORR is an even less reliable predictor of OS. The latter concerns are arguable, but welcomed, even though in some diseases both PFS and ORR but not stable disease (SD) correlate highly with OS. [Jawed et al, 2015] For the curative framework, categorical scores of 1 to 5 are assigned based on the hazard ratio (HR) for OS or disease-free survival (DFS) estimated in a comparison of the new therapeutic with the reference therapy. As with the advanced disease framework, the categorical scores are weighted by 16 for OS and a nearly identical 15 for DFS.

As regards toxicity, In both the advanced disease and curative frameworks, the toxicity of the new therapeutic is calculated relative to the reference regimen. Categorical values of -20 to +20 without multipliers are then assigned. Negative values
are assigned to less well tolerated, with -20 assigned very poorly tolerated regimens, and increasingly positive values to a maximum of +20 to therapeutics that are better tolerated than the reference. The original framework assigned values erroneously because it considered only the frequency of grade 3 to 5 toxicities as defined by the Common Terminology Criteria for Adverse Events. Despite the availability of data that substantiated the adverse impact of lower grade toxicities even in clinical trials [Prasad et al, 2014] the original version only acknowledged “that certain chronic, low-grade toxicities can be troubling to patients as well and should be incorporated into future versions of the framework if the relevant data are available”. The updated version “reflecting feedback from patients who emphasized that even mild side effects can have a major impact on quality of life” [ASCO Value Framework Update, 2016] now considers all side effects in the Net Health Benefit score, not just the most severe, high-grade toxicities.

Finally, in the advanced disease framework bonus points can be accrued for either palliation or for prolonging the treatment free-interval that follows. Bonus points are awarded for palliation if in a randomized trial the severity of any cancer-related symptom is statistically significantly improved and in the updated version if there is improvement in the quality of life. Bonus points for treatment-free interval are awarded if in a randomized trial a statistically significant improvement in treatment-free interval versus the reference can be achieved. The latter recognizes the importance of treatment-free intervals.

With both efficacy and toxicity estimated and bonus points assigned, the ASCO Value Framework then calculates a Net Health Benefit (NHB) score. The maximum NHB score is 130 [5 x 16 = 80 + 20 = 100 + 30 = 130] for the advanced disease framework and 100 [5 x 16 = 80 + 20 = 100] for the curative framework.

After publishing the initial version of the framework in 2015, ASCO invited public feedback during a 60-day comment period and received more than 400 comments from physicians, patients, patient advocates, the pharmaceutical industry, and others. An updated version of the ASCO Value Framework was published in the Journal of Clinical Oncology on May 31, 2016. [Schnipper et al, 2016] Some of the refinements, based on a review of the 400 comments have been alluded to. The major points can be summarized as follows:

- Modification of the Net Health Benefit score by using hazard ratios, when available, rather than absolute survival measures. The framework now will also recognize treatments that improve long-term disease control for a significant portion of patients. Significant is yet to be defined but this change is designed to value some of the merging immunotherapies that often lead to an increase in the fraction of patients comprising the “tails of the curves”.
- All side effects not just the most severe, high-grade toxicities are now considered in the Net Health Benefit score. Additional points are also given for improvements in quality of life.
- Only treatments evaluated in head-to-head prospective randomized clinical trials will be considered although ASCO agrees other comparisons will eventually be valuable.
- The focus will continue to be on cancer drugs, rather than other interventions. Although it is recognized the cost of drugs is but one component of overall cancer
care costs. It remains the most rapidly rising component and the biggest concern among patients who all too often must pay a significant share of these costs.

- ASCO hopes to add patient-reported outcomes (PROs) to the framework in the future as these data are more rigorously collected and reported.

**The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)**

Just as with the ASCO Value Framework, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) has undergone one revision. Originally published in May 2015 it had been validated and established as a reproducible tool to assess the magnitude of clinical benefit from new cancer therapies. The ESMO-MCBS was designed to be a dynamic tool with planned revisions and updates based upon recognition of expanding needs and the identification of any shortcomings.

The original version of the ESMO-MCBS noted as its goal “to assign the highest grade to trials having adequate power for a relevant magnitude of benefit, and to make appropriate grade adjustment to reflect the observed magnitude of benefit”. To achieve both the goals of relevant magnitude and grade adjustments, a dual rule was implemented, that one must now accept even while questioning its wisdom. The first, was to take for each study not the point estimate of the HR but rather the lower limit of the 95% confidence interval (CI) for comparisons with specified threshold values. The reason given for this maneuver was to take into account the variability of the estimated HR from a study; and secondly the observed absolute difference in treatment outcomes is compared was taken at face value – without concern for variability – and compared with the minimum absolute gain considered as beneficial.

In the original publication it was stated that “different candidate threshold values for HR and absolute gains for survival, DFS and PFS, adjusted to represent as accurately as possible the expert opinion of the oncology community” were explored through extensive simulations to yield the “finally implemented combined thresholds for the HR and the minimum observed benefit that could be considered as deserving the highest grade in both the curative and non-curative setting”.

Unlike the ASCO Value Framework that utilizes only two frameworks – the advanced disease framework and the curative framework – the ESMO-MCBS has five evaluation forms summarized below:

- **Evaluation Form 1**: For new approaches to adjuvant therapy or new potentially curative therapies.
  
  **Notes:**
  
  ⇒ Scale is graded A, B or C; A highest
  ⇒ Makes allowance for early high DFS data without mature OS; pending re-evaluation
  ⇒ Hyper mature data from studies un-blinded after compelling early results with subsequent access to the superior arm are contaminated and late intention to treat (ITT) follow-up data not evaluable
  ⇒ Pathological complete remission from neoadjuvant therapies not included because consistent evidence is lacking that is a valid survival surrogate

- **Evaluation Form 2a**: For therapies that are not likely to be curative with primary end point of OS with separate sheets for:
  
  - IF median OS with the standard treatment is ≤12 months
• IF median OS with the standard treatment >12 months, <24 months
• IF median OS with the standard treatment >24 months

Notes:
⇒ Graded 5, 4, 3, 2, 1; 5 maximum
⇒ Preliminary grading: HR + median and late survival gains on a 4-point scale
⇒ Higher score prevails when median and late survival gains discordant
⇒ Preliminary scores upgraded 1 point if QoL improved, QoL deterioration delayed or substantial reduction in G3/4 toxicity
⇒ Score of 5 only with optimal survival and QoL and reduction in toxicity

**Evaluation Form 2b:** For therapies that are not likely to be curative with primary end point PFS or TTP with separate sheets for:
• IF median PFS with standard treatment ≤6 months
• IF median PFS with standard treatment >6 months

Notes:
⇒ Maximal preliminary score = 3 because PFS and TTP are surrogate outcomes with a less reliable relationship to improved OS or QoL [Wilkerson and Fojo, 2009; Saad et al, 2010a; Saad et al, 2010b; Amir et al, 2012; Booth and Eisenhauer, 2012]
⇒ Consider when crossover allowed
⇒ Results of secondary outcomes can lead to upgrade (OS, QoL) or downgrade (toxicity, lack of QoL without OS) of preliminary score

**Evaluation Form 2c:** For therapies not likely to be curative with primary end point other than OS or PFS (i.e. QoL, toxicity or RR) or for equivalence (non-inferiority) studies.

**Evaluation Form 3:** For single-arm studies in ‘orphan diseases’ and for diseases with ‘high unmet need’ when primary outcome is PFS or ORR.

Applicable at present only to solid cancers, the ESMO-MCBS was successfully developed as a tool with broad applicability. It can be applied to comparative studies with outcomes as diverse as overall survival (OS), Quality of Life (QoL), and putative surrogates such as disease-free interval (DFI), event-free survival (EFS), time to response (TTR), progression-free survival (PFS) and time to progression (TTP) or treatment toxicity. Eligible studies include randomized or comparative cohort designs or a “meta-analysis which report statistically significant benefit from any one, or more of the evaluated outcomes”. Pre-planned subgroup analyses with a maximum of three but not un-planned (post hoc) subgroup can be scored with the exception of “studies that incorporate collection of tissue samples to enable re-stratification based on new genetic or other biomarkers” that can be scored.

The revision process for the ESMO-MCBS incorporates a nine-step process that carefully considers critiques, identifies shortcomings, proposes solutions, undergoes field testing and seeks feedback from ESMO Faculty and Guidelines Committee before final review and approval. Version 1.1 was published in 2017. Twelve issues were proposed for revision or amendment and proposed amendments were formulated for eight that were felt to identify shortcomings. In all 10 revision were executed. An important change was allowances for scoring of single-arm studies. All amendments were field tested in a wide range of studies comparing scores generated with
ESMOMCBS v1.0 and version 1.1 (v1.1) and these were shown to be very stable; with revisions in v1.1 altering the scores of only 12 out of 118 comparative studies but importantly facilitating the scoring of single-arm studies.

Limitations of ASCO Value Framework and the ESMO-MCBS and how the World Health Organization can use it to inform decisions on the Essential Medicines List

As noted above, for the World Health Organization both the ASCO Value Framework and the ESMO-MCBS represent tools that can help assess treatment efficacy. The cost side of the equation while very important is less relevant when deciding the survival benefit of a therapeutic and whether it should be included in the Essential Medicines List. For the uses envisioned by the World Health Organization the ESMO-MCBS appears more adaptable and will be preferred. However, decisions will not be made solely on the basis of the ESMO-MCBS score. A more critical look at the data will be essential. Similarly, the use of the scale may be adapted with, for example, the actual point estimate and not just the lower limit of the 95% CI explored in individual cases. In the case of deciding whether a therapeutic should be included in the Essential Medicines List, the World Health Organization will look beyond the reported result and interpret the data more critically aware of the special needs and circumstances of its constituents.

With the increasing use of hazard ratios in assessing new cancer therapeutics, the decision by the Working Group of the ESMO-MCBS to use the lower limit of the 95% CI instead of the point estimate in its calculations is of concern but fortunately a decision that can be ignored or remedied in assessing therapeutics for inclusion in the Essential Medicines List. In crafting v1.1, the point estimate decision was to have been addressed but unfortunately the MCBS Working Group demurred concluding the issue “had been reviewed extensively by the Working Group and subjected to extensive statistical modelling … and a decision was made not to subject this issue to revision”.

The concern arises because a confidence interval does not quantify variability. Rather a 95% confidence interval describes the range of values one can be 95% certain contains the true mean of the population. This is not the same as a range that contains 95% of the values. The width of a confidence interval decreases with increasing sample size because the standard error decreases and in a clinical trial as data mature and more data is captured the range diminishes. And while there has been no systematic analysis in cancer clinical trials of what happens to the point estimate as the data mature and the “sample size” increases, the ESMO-MCBS Working Group would be hard pressed to find examples where the point estimate approached the lower boundary of the 95% confidence interval as more data accrued and matured. Indeed, it is almost certain the opposite would happen. One can confidently expect that with more data, indeed as the “ideal large data set” is approached, the lower limit of the 95% CI comes increasingly closer to the point estimate; one does not expect the point estimate to move increasingly closer to the lower limit of the 95% CI. Hence using the lower boundary of the 95% CI in its estimate is a major but remediable concern.

Similarly, while the original ASCO Value Framework focused on fractional improvements in median OS or PFS, the revision pivoted to hazard ratios with the comments from the organization noting what might be argued is the “standard line” that “Hazard ratios provide a more complete assessment of the relative differences between
therapies” [ASCO Value Framework Update, 2016]. This recantation of statistical mantra betrays the true value of a therapy since hazard ratios say nothing about absolute benefit but only relative benefits and the ability to “provide a more complete assessment of the relative differences between therapies” does not mean this provides a better assessment of true efficacy. While one might argue a gain of one month might be considered meaningful in the therapy of a difficult to treat cancer such as pancreatic cancer but not a well differentiated neuroendocrine tumor, this thought process in effect sentences difficult to treat cancers to the achievement of marginal benefits that can be easily achieved without impacting survival in truly meaningful ways. The decision betrays a lack of consensus amongst the project’s participants, but also a lack of clarity. In a March 2018 Commentary in JAMA Oncology entitled “Are Value Frameworks Missing the Mark When Considering Long-term Benefits From Immuno-oncology Drugs?” Drs. Schnipper and Schilsky, the first and senior authors of the ASCO Value Framework manuscripts [Schnipper and Schilsky 2018; Schnipper et al, 2015; Schnipper et al, 2016] wrote: “Setting the bar higher is the direction in which we should be moving”. They noted that “reviews [Kumar et al, 2016] of drugs approved by the US Food and Drug Administration between 2014 and 2016 identified only 19% that met or exceeded the modest hazard ratio targets identified by the ASCO Cancer Research Committee as being clinically meaningful”. Interestingly while they argued for a higher bar, since they deem the current one a “modest” one, the current, admittedly “modest” bar was met or exceeded by only 19% of approved drugs. Setting the bar higher may incentivize the development of more meaningful therapies – but more likely it might also just reduce the fraction of approved therapeutics that meet the ASCO thresholds.

Indeed, the problem is not that therapies “surprisingly” underperform. They underperform because they were expected to (Figures 17 and 18). Large trials that enroll thousands of patients are designed to achieve outcomes many would consider marginal. Whether the ASCO and ESMO thresholds can incentivize the development of more effective therapeutics remains to be seen but if so it will take years to become a reality. As noted by Drs. Schnipper and Schilsky, a “recent overview [Del Paggio et al, 2017] found only 31% of 138 randomized clinical trials met the standards established by ESMO for meaningful clinical benefit”. It would appear not many are listening. Is a change in clinical trial conduct difficult to achieve? No. Very simply trial size has to be capped and academic oncologists and clinical trialists should refuse to participate in trials whose size exceeds such caps. No expertise in biostatistics is required to understand trial size. Large trials are designed to find marginal outcomes. Meaningful outcomes will only come from smaller trials. Indeed, one could argue that in cases where benefit is uncertain a small size trial conducted with input from the World Health Organization could rapidly answer the magnitude of benefit question and whether a drug should be included in the Essential Medicines List.

Finally, as regards ASCO, and for that matter ESMO, with ASCO envisioning a “user-friendly software tool for physicians to use with patients as part of broader discussions about treatment options and their value” the pivot to hazard ratios is ill advised. The thoughtful patient will not want to know only that ASCO has scored a therapy beneficial. The thoughtful patient will want to know, “how much longer will I live?” The clinician – the majority of whom do not understand hazard ratios – will have at his/her fingertips a hazard ratio. To quote that inquiring patient a hazard ratio but
Figure 17: The often marginal outcomes achieved in clinical trials are not a surprise, but rather the expected outcomes. Example: Clinical trials with ramucirumab. For each clinical trial the hazard ratio predicted from the statistical plan is shown as well as the hazard ratio achieved in the clinical trial. As can be seen both are very similar. The US FDA approved ramucirumab for gastric cancer, NSCLC and metastatic colorectal cancer. The latter two approvals were for indications indistinguishable from those previously garnered by bevacizumab and are examples of the “me-too” strategy employed by pharmaceutical companies. In this case these were not drugs in the pharmaceutical company’s “pipeline” but rather drugs that were purchased for the express purpose of developing them as “me-too” therapies. An interesting observation is that attempts to emulate bevacizumab were remarkably on target. The OS gains in colorectal and lung cancer were nearly identical to those achieved with bevacizumab and in breast cancer [ROSE-TRIO trial] ramucirumab like bevacizumab failed to achieved statistical gains.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Indication</th>
<th>Arms</th>
<th>#</th>
<th>Outcomes</th>
<th>Statistical Plan</th>
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<tbody>
<tr>
<td>REGARD</td>
<td>Advanced gastric cancer</td>
<td>R v PBO</td>
<td>355</td>
<td>OS HR 0.776</td>
<td>p=0.047 OS HR 0.6 (0.05)</td>
</tr>
<tr>
<td>RAINBOW</td>
<td>Previously treated advanced gastric cancer</td>
<td>PTX/R v PTX/PBO</td>
<td>665</td>
<td>OS HR 0.807</td>
<td>p=0.017 OS HR 0.75</td>
</tr>
<tr>
<td>REVEL</td>
<td>Stage IV NSCLC after platinum-based therapy</td>
<td>DTX/R v DTX/PBO</td>
<td>1253</td>
<td>OS HR 0.86</td>
<td>p=0.023 OS HR 0.816 (0.025)</td>
</tr>
<tr>
<td>ROSE-TRIO</td>
<td>Unresectable, locally recurrent, or metastatic breast cancer</td>
<td>DTX/R v DTX/PBO</td>
<td>1144</td>
<td>OS HR 1.01</td>
<td>PFS HR 0.75 PFS 8 v 6</td>
</tr>
<tr>
<td>RAISE</td>
<td>mCRC progressing on 1st line FOLFOX + bevacizumab</td>
<td>FOLFIRI/ R v FOLFIRI/ PBO</td>
<td>1072</td>
<td>OS HR 0.84</td>
<td>OS HR 125 v 10</td>
</tr>
</tbody>
</table>

Ramucirumab (R) Clinical Trials
Percent difference between the hazard ratio that was achieved in a clinical trial and that which was predicted based on the statistical plan.

**Figure 18:** The often marginal outcomes achieved in clinical trials are not a surprise, but rather the expected outcomes. Hazard ratios that are much less than one would like are found and unfortunately coincide with those that were planned. The graph depicts the percent difference between the planned hazard ratios and the achieved hazard ratios for therapies approved by the US FDA in the last decade where there was data for overall survival – specifically the hazard ratio for OS – and where in the literature one could find the planned for hazard ratio usually in the Statistical Plan accompanying the publication. As one can see statisticians have become very adept at predicting how good a therapy is and at predicting what the hazard ratio as a measure of efficacy will be. Where a bar is not seen the planned and achieved hazard ratios were identical. A positive value means the achieved was larger (worse) than the planned, negative means it was smaller (better) than the planned. The small differences indicates that the planned and the achieved hazard ratios are very similar.
have no idea of the magnitude of benefit of this therapy nor of the alternative will betray a glaring indifference to what is meaningful to a patient – the duration of life not a hazard ratio. And to claim that a one-month difference has been deemed of great value by this ASCO-designed program that prizes hazard ratios above all will leave the already embattled patient wondering who has been advocating for progress in the therapy of cancer patients? Hopefully not this organization that endorses marginal outcomes.

Attributes for inclusion in the Essential Medicines List and of the supporting evidence

The body of evidence available for a given therapeutic will be considered. Specifically, data from more than one trial will be necessary for a therapeutic to be considered. Data from randomized trials will be considered most important. The data will of necessity have to be mature to allow for assessing the impact of the therapeutic on overall survival. Multiple studies corroborating each other and especially studies across several indications or lines of therapy will be exceptionally valuable in supporting the inclusion of a therapeutic in the Essential Medicines List.

It is well recognized that the efficacy of therapies is less as disease progresses and that a therapeutic given in an advanced line is often but not always less effective that one given in first line. As the oncology therapeutics to be included in the Essential Medicines List must prolong survival meaningfully, therapeutics that have been shown to be effective in the first line setting are highly desirable. Therapeutics given to patients in first line are often most effective and are administered to an individual who is less likely to experience a toxicity. In contrast a therapeutic that has shown evidence in a second or latter line of therapy while potentially of some value is unlikely to achieve the magnitude of benefit desired for its inclusion in the Essential Medicines List. Although in this setting “statistically valid” differences in overall survival are at times attained in a randomized clinical trial, the magnitude of this benefit is usually small and often very small.

Additionally, the World Health Organization acknowledges the challenge of treating cancers such as hepatocellular carcinoma for which the available therapeutic options are few and their efficacy very limited. However, in deliberations involving such difficult to treat cancers the magnitude of benefit needed for inclusion in the Essential Medicines List will not be lowered, nor will additional toxicity be considered acceptable. All therapeutics added to the Essential Medicines List must be able to prolong life meaningfully, not only alter a surrogate of overall survival, and must be tolerable by the often less than optimal patient population envisioned as receiving the treatment.

As considerations are given to deploying cancer therapeutics to low- and middle-income countries and as the data is evaluated for the inclusion of the increasing number of therapeutics in the World Health Organizations Essential Medicines List the importance of conducting clinical trials to provide answers that can inform the wide deployment of these therapeutics in countries with varying degrees of financial challenges cannot be ignored. Included amongst these are:

1. Randomized trials that compare the efficacy of new regimens to currently used regimens not to available comparators that are not widely utilized. This is especially
important in cases where the regimen that is to be substituted has emerged as an affordable option in countries that face economic challenges.

2. Trials that address the need for maintenance therapy and specifically the length of that maintenance phase. Shorter and even much shorter durations of therapy that do not compromise efficacy or even that compromise efficacy only marginally but might substantially reduce outlays and allow more patients to receive a therapeutic are desperately needed.

3. Trials that demonstrate superiority. It should be recognized that for the endorsement of a therapy as an Essential Medicine, therapeutic superiority must be demonstrated not a lack of inferiority. While a better tolerated option that might not be inferior is attractive, the Essential Medicines List aims to improve the survival of patients, and demonstrating a drug is not inferior cannot be accepted given the often-broad inferiority margins allowed.

Conclusions

Unlike regulatory agencies that often grant a therapeutic a provisional approval, inclusion in the Essential Medicines List requires mature data that informs the impact of a therapeutic on overall survival. Special attention will be given to the available data and the scientific rigor of trial conduct. Where a therapeutic will be replacing an established regimen, randomized clinical trial(s) demonstrating its superiority over the established regimen will be sought as supporting evidence. Trials that have not reported overall survival will not be considered, even though they may have met pre-specified endpoints that relied on surrogates for their approval.

Inclusion of a therapeutic in the Essential Medicines List will occur after review of the accumulated data in a given indication and its inclusion by no means implies its endorsement for any indication other than the one that led to its inclusion. The approval of a therapeutic does not imply it will be similarly valuable in any other indication and its use should be restricted to the indication for which it has received consideration and approval. For example, breast cancer expressing the Her2 protein is the indication envisioned for trastuzumab; not its use in the therapy of gastrointestinal cancers. Thus, the focus in the approval process will be for specific indications where the totality of the available data has demonstrated the ability of a therapeutic to meaningfully prolong life in that indication.

Even though the cost of a therapeutic is not to influence the decision regarding its inclusion in the Essential Medicines List, it is recognized that any therapeutic added to the Essential Medicines List and eventually adopted by a country as one of its essential medicines in turn competes with all other medicines and indeed often with the entire health care needs for available funds. Thus, the Essential Medicines List seeks to include only therapies that prolong life meaningfully for the patients that receive them.

Finally, it must be recognized that the World Health Organization cannot and does not seek to dictate to governments what to consider as its essential medicines. The hope of the World Health Organization is that by generating a list of therapeutics that are truly beneficial, it will incentivize individual countries to more seriously consider the Essential Medicines List as its own goal to help improve the outcomes of their citizens struggling with a diagnosis of cancer.
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