Special Communication

Unintended Consequences of Expensive Cancer Therapeutics—The Pursuit of Marginal Indications and a Me-Too Mentality That Stifles Innovation and Creativity

The John Conley Lecture

Tito Fojo, MD, PhD; Sham Mailankody, MD; Andrew Lo, PhD

Cancer is expected to continue as a major health and economic problem worldwide. Several factors are contributing to the increasing economic burden imposed by cancer, with the cost of cancer drugs an undeniably important variable. The use of expensive therapies with marginal benefits for their approved indications and for unproven indications is contributing to the rising cost of cancer care. We believe that expensive therapies are stifling progress by (1) encouraging enormous expenditures of time, money, and resources on marginal therapeutic indications and (2) promoting a me-too mentality that is stifling innovation and creativity. The modest gains of Food and Drug Administration–approved therapies and the limited progress against major cancers is evidence of a lowering of the efficacy bar that, together with high drug prices, has inadvertently incentivized the pursuit of marginal outcomes and a me-too mentality evidenced by the duplication of effort and redundant pharmaceutical pipelines. We discuss the economic realities that are driving this process and provide suggestions for radical changes to reengineer our collective cancer ecosystem to achieve better outcomes for society.

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Author Affiliations: Medical Oncology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland (Fojo, Mailankody); Sloan School of Management, Massachusetts Institute of Technology, Cambridge (Lo).

Corresponding Author: Tito Fojo, MD, PhD, Center for Cancer Research, National Cancer Institute, 9000 Rockville Pike, Bldg 10, Rm 12N226, Bethesda, MD 20892 (fojot@mail.nih.gov).

Despite continued progress in the therapy of some malignancies, cancer remains a major health and economic problem worldwide.[1] Advances in the therapy of cardiovascular disease and the aging of the American population will soon make cancer the number 1 cause of death in Americans, and a challenge going forward.[2] According to the American Society of Clinical Oncology (ASCO), "it is projected that by 2030, the number of new cancer cases in the United States will increase by 45%—from 1.6 million to 2.3 million cases annually."[3(p4)] A recent report by the International Agency for Research on Cancer noted that, as a single entity, cancer is the biggest cause of mortality worldwide, with an estimated incidence of 14.1 million and 8.2 million cancer deaths in 2012. Furthermore, cancer cases worldwide are forecast to rise by 75% and reach close to 25 million over the next 2 decades.[4]

The economic burden imposed by cancer is growing, with several factors contributing to the increase.[5-7] Among these, the cost of cancer drugs is rising most rapidly, with new cancer therapies costing more than $10 000 per month.[5] We argue that the use of expensive therapies with often only marginal benefits for their approved indications and the use of expensive therapies with marginal benefits for unproven indications ("off label") are important contributors to the rising cost of cancer care in the United States. And although the spiraling cost of cancer therapies has no single villain, responsibility must be borne by academia, professional societies, scientific journals, practicing oncologists, regulators, patient advocacy groups, and the biopharmaceutical industry.

The current problem of escalating drug prices will not be easily solved. We are reaping the seeds that we sowed and are sowing seeds that in the years to come will not solve but instead exacerbate our problems. We will argue that expensive therapies are stifling progress by (1) encouraging enormous expenditures of time, money, and resources on therapeutic indications that are arguably marginal and (2) stifling innovation and creativity by promoting a "me-too" mentality.

The Pursuit of Marginal Indications

Let us begin by addressing the issue of how expensive therapies are stifling progress by encouraging enormous expenditures of time, money, and resources on therapeutic indications that many might argue are of limited value. Many cite the high number of Food and Drug Administration (FDA) drug approvals as evidence of progress in the therapy of cancer. To be sure, some very effective therapies have been approved for cancers regarded as refractory—BRAF inhibitors for melanoma, as 1 example. But if one looks in **Table 1** and **Figure 1** at the therapies approved for solid tumors between 2002 and 2014, the median gains in progression-free and overall survival (OS) were a very modest 2.5 and 2.1 months, respectively. While any patient facing imminent death from cancer might welcome the respite that 2 months might bring, in fact, time and again surveys have indicated that patients expect much more.[8] That most oncologists also consider this

Table 1. Food and Drug Administration (FDA) Drug Approvals in Solid Tumors 2002 Through 2014[a,b]

Agent	Approval Date	Enrolled, No.	Cancer Indication	Gain, mo		Would Have Met ASCO Committee Criteria[d]
				PFS[c]	OS	
Imatinib[10]	2/1/2002	147	First-line GIST	NA	NA	Yes
Fulvestrant[11,12]	4/25/2002	400/451	Second-line breast cancer	0.4/2	NA	No
Oxaliplatin[13]	8/9/2002	NA	Second-line mCRC	2.8	1.5	No
Oxaliplatin[13]	1/9/2004	531	First-line mCRC	2.8	5.6	Yes
Pemetrexed[14]	2/4/2004	456	First-line mesothelioma	1.8	2.8	Yes
Bevacizumab[15]	2/26/2004	813	First-line mCRC	4.4	4.7	Yes
Cetuximab[16]	2/12/2004	1198	Refractory CRC	1.5	3.5	Yes
Docetaxel[17]	5/19/2004	1006	Hormone-refractory prostate cancer	NA	0.9-2.4	No
Gemcitabine[18]	5/19/2004	266	First-line breast cancer	2.8	2.16	No
Erlotinib[19]	11/18/2004	731	Second/third-line NSCLC	0.46	2	No
Abraxane[20]	1/7/2005	460	Refractory breast cancer	1.4	2.1-2.2	No
Erlotinib[21]	11/2/2005	569	First-line pancreatic cancer	0.2	0.33	No
Sorafenib[22,23]	12/20/2005	903	Second-line renal cell carcinoma	2.7	2.6	Yes
Sunitinib[24]	1/26/2006	312	Second-line GIST	4.2	NR	Uncertain
Sunitinib[25,26]	1/26/2006	750	Metastatic renal cell carcinoma	6	4.6	Yes
Cetuximab[27]	3/1/2006	424	With RT in SCCHN	4.7	19.7	Yes
Docetaxel[28]	3/22/2006	445	First-line gastroesophageal cancer	1.9	0.6	No
Topotecan[29]	6/14/2006	364	First-line cervical cancer	1.7	2.9	No
Bevacizumab[30]	6/20/2006	829	Second-line mCRC	2.6	2.1	No
Gemcitabine[31]	7/14/2006	356	With carboplatin in ovarian cancer	2.8	0.7	No
Panitumumab[32]	9/27/2006	463	Refractory mCRC	0.16	0	No
Bevacizumab[33]	10/11/2006	878	First-line NSCLC	1.7	2	No
Docetaxel[34]	10/17/2006	358	Unresectable SCCHN	2.8	4.3	Yes
Lapatinib[35,36]	3/17/2007	324	Refractory breast cancer	1.9	0.3	No
Temsirolimus[37]	5/30/2007	626	Advanced renal cell carcinoma	2.4	2.6	Yes
Ixabepilone[38,39]	10/16/2007	752	Second-line breast cancer	1.6	1.8	No
Sorafenib[40]	11/16/2007	602	First-line hepatocellular carcinoma	2.7	2.8	Yes
Pemetrexed[41]	9/26/2008	1725	First-line NSCLC	0	−0.3	No
Bevacizumab[42,43]	5/5/2009	215	Second-line glioblastoma	NA	NA	No
Everolimus[44,45]	3/30/2009	410	Advanced renal cell carcinoma	3	0.4	No
Pemetrexed[46]	7/2/2009	663	Maintenance NSCLC	1.7	2.8	Yes
Bevacizumab[47,48]	7/31/2009	649	First-line renal cell carcinoma	4.8	2	No
Pazopanib[49]	10/19/2009	435	Advanced renal cell carcinoma	5	−0.6	Uncertain
Lapatinib[50,51]	1/29/2010	1286	With letrozole in breast cancer	5.2	1	No
Erlotinib[52]	4/16/2010	1949	Maintenance NSCLC	0.28	1	No
Sipuleucel-T[53]	4/29/2010	127	Hormone-refractory prostate cancer	0.39	4.5	Yes
Cabazitaxel[54]	6/17/2010	755	Second-line prostate cancer	1.4	2.4	No
Trastuzumab[55]	10/20/2010	594	Advanced gastroesophageal cancer	1.2	2.7	Yes
Eribulin[56]	11/15/2010	762	Third-line breast cancer	1.5	2.5	Yes
Ipilimumab[57]	3/25/2011	502	First-line melanoma	0	2.1	Uncertain
Vandetanib[58]	4/6/2011	331	Advanced medullary thyroid carcinoma	11.1[e]	NA	Yes
Abiraterone[59]	4/28/2011	1195	Second-line CRPC	2	3.9	Yes
Everolimus[60]	5/5/2011	429	Advanced PNET	5.1	NR	Uncertain
Sunitinb[61]	5/20/2011	171	Advanced PNET	5.9	NR	Uncertain
Vemurafenib[62]	8/17/2011	675	First-line BRAF-mutated melanoma	3.7	NA	Yes
Cetuximab[63]	11/7/2011	220	First-line SCCHN	2.3	2.7	No
Axitnib[64]	1/27/2012	723	Second-line renal cell carcinoma	2	NA	No
Pazopanib[65]	4/26/2012	369	Soft-tissue sarcoma	3	NA	Uncertain
Pertuzumab[66]	6/8/2012	808	HER2-positive breast cancer	6.1	NA	Yes
Cetuximab[67]	7/6/2012	1217	First-line K-ras wild-type, EGFR-expressing CRC	1.4	4	Yes

(continued)

Table 1. Food and Drug Administration (FDA) Drug Approvals in Solid Tumors 2002 Through 2014[a,b] (continued)

Agent	Approval Date	Enrolled, No.	Cancer Indication	Gain, mo		Would Have Met ASCO Committee Criteria[d]
				PFS[c]	OS	
Ziv-Aflibercept[68]	8/3/2012	1226	Second-line mCRC; with FOLFIRI	2.2	1.44	No
Everolimus[69]	8/30/2012	724	HER2-positive breast cancer	4.6	NA	No
Enzalutamide[70]	8/31/2012	1199	Second-line CRPC	NA	4.8	Yes
Regorafenib[71]	9/27/2012	760	mCRC	0.3	1.4	No
Nab-paclitaxel[72]	10/11/2012	1052	First-line NSCLC; with carboplatin	NA	NA	Uncertain
Cabozantinib[73]	11/29/2012	330	Advanced medullary thyroid carcinoma	7.2	NA	Yes
Abiraterone[74]	12/10/2012	1088	First-line CRPC	NA	5.2	Yes
Bevacizumab[75]	1/23/2013	820	Second-line CRC	NA	1.4	No
TDM-1[76]	2/22/2013	991	HER2-positive metastatic breast cancer	NA	4.2	Yes
Regorafenib[77]	2/25/2013	199	Imatinib- and sunitinib-resistant GIST	3.9	NA	No
Erlotinib[78]	5/14/2013	174	First-line NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution	5.2	NA	Yes
Radium-223[79]	5/15/2013	809	CRPC with bone metastases but no visceral metastases	NA	2.8	Yes
Dabrafenib[80]	5/29/2013	250	Unresectable and/or metastatic melanoma	2.4	NA	Yes
Trametinib[81]	5/29/2013	322	Unresectable and/or metastatic melanoma	3.3	NA	Yes
Afatinib[82]	8/12/2013	345	NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution	6.7	NS	Uncertain
Nab-paclitaxel[83]	9/6/2013	861	Metastatic pancreatic cancer; with gemcitabine	1.8	1.8	No
Crizotinib[84,85,86]	11/20/2013	347	NSCLC expressing *ALK* gene	4.7	NA	Yes
Sorafenib[87]	11/22/2013	417	Metastatic and/or differentiated thyroid cancer	5	NA	Yes
Trametinib + Dabrafenib[88]	1/10/2014	162	Unresectable and/or metastatic melanoma	NA	NA	No
Ramucirumab[89]	4/21/2014	355	Stomach and/or esophageal junction cancer	0.8	1.4	No
Ceritinib[90]	4/29/2014	163	Second-line ALK-positive NSCLC	NA	NA	Uncertain
Total		**44 218**				
Mean		**632**				
Median		**582**		**2.5**	**2.1**	

Abbreviations: ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; CRC, colorectal cancer; CRPC, castration-refractory prostate cancer; FOLFIRI, folinic acid, fluorouracil, and irinotecan; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor 2; mCRC, metastatic colorectal cancer; NA, not available; nab-paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation; NR, median not reached; NS, not significant; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; PNET, pancreatic neuroendocrine tumor; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; TDM-1, ado-trastuzumab emtansine.

[a] Adapted and expanded from Fojo and Noonan, 2012.[91]

[b] Presented are the 71 drug approvals by the FDA for the treatment of metastatic and/or advanced and/or refractory solid tumors between 2002 and 2014. Adjuvant and neo-adjuvant approvals are not included. Approvals for hematologic malignancies (lymphoma, myeloma, leukemia) are also not included.

[c] In some reported as time to progression.

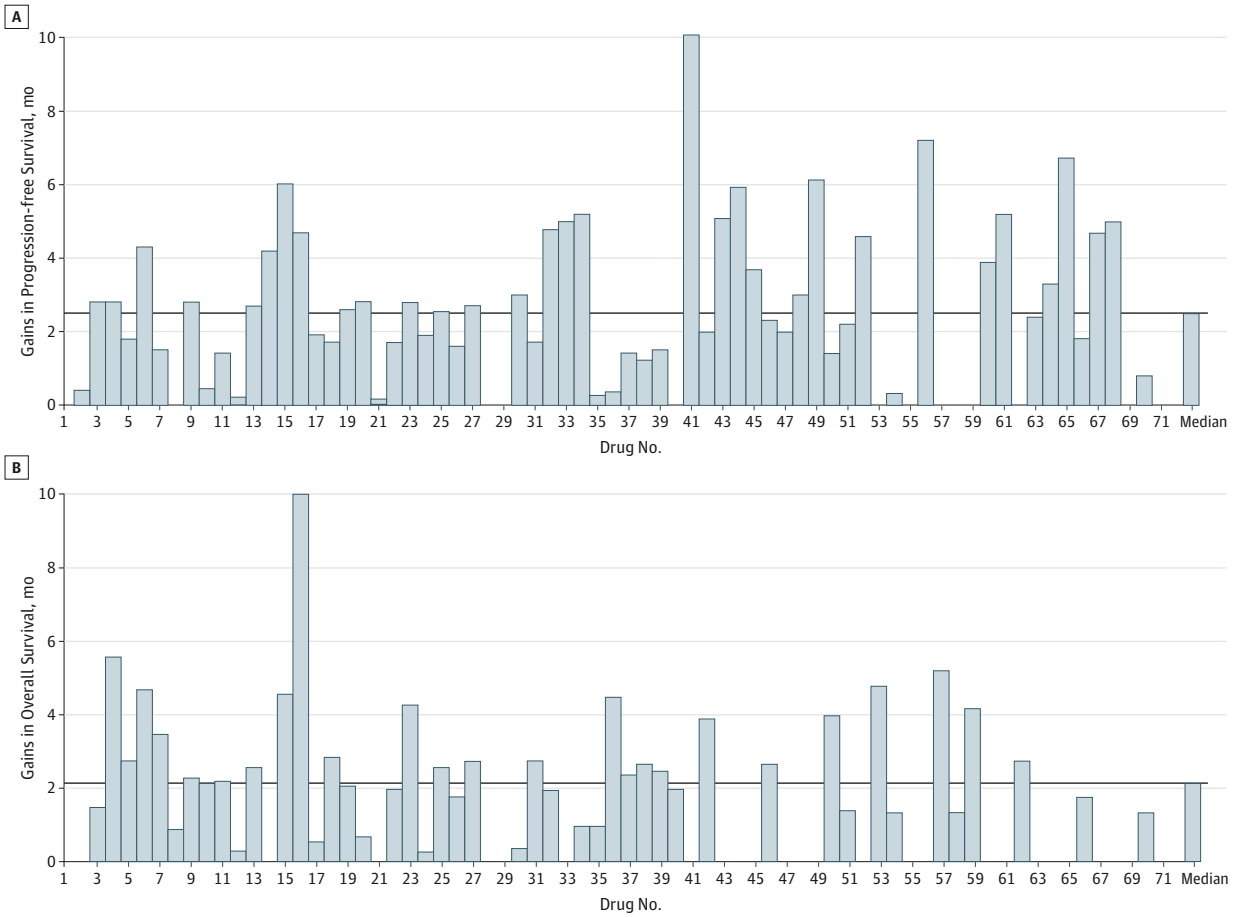
[d] Indicates how many of the 71 therapies approved by the FDA in the past 12 years would have met the criteria deemed to be "clinically meaningful to patients" by 4 disease-specific working groups (pancreatic, lung, breast, and colon cancers) convened by the ASCO Cancer Research Committee. For cancers other than pancreatic, lung, breast, and colon, we tried as fairly as possible to adhere to similar guidelines, setting 2.5 months and at least 25% to 30% as minimum gains in OS—values similar to those proposed by the ASCO working groups.

[e] Estimated.

magnitude of benefit unacceptable can be gleaned from a recent publication reporting the recommendations of 4 disease-specific working groups convened by the ASCO Cancer Research Committee "to consider the design of future clinical trials that would produce results that are clinically meaningful to patients (ie, significantly improved survival, quality of life [QOL], or both)."[9(p1277)] The recommendations, summarized in **Table 2**, were deliberately chosen as modest and thus attainable to ensure their relevance. If we then ask how many of the 71 therapies approved by the FDA in the last 12 years would have met these or similar standards, we can see that only 30 of 71 approvals, or 42%, can be considered "clinically meaningful improvements" according to the very modest goals of the ASCO Committee. We believe that this highlights the fact that 1 important reason for the rise in the number of FDA approvals has been a lowering of the efficacy bar—a lowering that, while providing a greater number of options for patients, has resulted in the approval of therapies that many would argue did not achieve clinically meaningful improvement. Furthermore, we would argue that this has had the unintended fallout of encouraging the pursuit of drugs and the conduct of clinical trials that will never achieve clinically meaningful improvements. Evidence for the latter is a median enrollment of 582 patients in the trials in Table 1. Such large numbers of patients were enrolled to ensure statistical validity because the margins of benefit were expected to be low and indeed they were.

As publicly traded for-profit entities subject to shareholder oversight, pharmaceutical companies are required to focus on maximiz-

Figure 1. Graphical Representation of the Results in Table 1: Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for the 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors



The horizontal lines represent the median values for PFS (A) and OS (B) of 2.5 and 2.1 months, respectively. The oldest approval (imatinib in gastrointestinal stromal tumor, February 1, 2002) is at the left, and the most recent (ceritinib in ALK-positive non–small cell lung cancer, April 29, 2014), at the right. In 3 cases the "gains" were 0 months. In all others where a bar does not appear, it is because for this indication either PFS or OS was not a prespecified end point (or neither was an end point for drugs 29 and 55). Because these were not end points, the values were not reported in the FDA approval announcement and in most cases have also not been published.

ing shareholder value, which typically means pursuing targets with the largest profit potential per unit risk. The enormous investment required to develop an approved drug—currently estimated at between $1.2 and $1.8 billion[92,93]—implies that once an initial indication is approved, there are substantial economic incentives to securing additional indications, known as supplemental approvals, rather than pursuing an entirely new program, even if they offer marginal or no clinically meaningful improvements. In particular, the combination of skyrocketing prices and health care insurance reimbursement policies has conspired to make these marginally beneficial alternatives increasingly profitable, diverting substantial amounts of time, money, and other resources away from the development of riskier but potentially transformative therapies.

To highlight the problem of pursuing marginal improvements in supplemental approvals, consider the 2 examples shown in **Table 3** and **Table 4** demonstrating the pursuit of outcomes that many may not regard as clinically meaningful improvements. Bevacizumab was originally approved in 2004 in the first-line therapy of metastatic colorectal cancer (mCRC).[94] Subsequently, BRiTE, a retrospective trial, reported a dramatic 9.7 months' OS advantage with a "bevacizumab beyond progression" strategy.[95] Many saw an improvement of this magnitude as an exaggerated result of a study encumbered by the biases that so often plague retrospective analyses, and a prospective, confirmatory, registration trial was launched. The investment paid off when on January 23, 2013, the US FDA approved bevacizumab "for use in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed on a first-line bevacizumab-containing regimen."[96] The trial on which the approval was granted enrolled 820 patients with mCRC whose disease progressed during or within 3 months of discontinuation of bevacizumab-based combination chemotherapy with fluoropyrimidine-oxaliplatin or fluoropyrimidine-irinotecan in the first line.[75] Patients were randomly allocated to receive the regimen that they had not received in first line without bevacizumab or with bevacizumab continued until dis-

Table 2. American Society of Clinical Oncology Cancer Research Committee Summary of Recommended Targets for Meaningful Clinical Trial Goals[a]

Patient Population	Current OS, Median Months	Clinically Meaningful Increase in OS		Improvement in PFS, Months, No.
		Months, No.	Percent of Current Median	
Pancreatic cancer				
FOLFIRINOX-eligible	10-11	≥4	≥36-40	≥4
Gemcitabine or gemcitabine/ nab-paclitaxel-eligible	8-9	≥3	≥33-37.5	≥3
Lung cancer				
Non-squamous cell carcinoma	13	≥3.25	≥25	≥4
Squamous cell carcinoma	10	≥2.5	≥25	≥3
Breast cancer				
Metastatic triple negative, previously untreated for metastatic disease	18	≥4.5	≥25	≥4
Colon cancer				
Disease progression with all prior therapies; not candidate for standard second-line or third-line options	4-6	≥3	≥50-75	≥3

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; nab-paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation; OS, overall survival; PFS, progression-free survival.

[a] Adapted from Ellis et al, 2014.[9]

Table 3. Colorectal Cancer Survivals a Decade Apart

Continuation of Bevacizumab Therapy After First Progression in Metastatic Colorectal Cancer (ML18147)

Group Assignment	Enrollment Period	First-Line PFS		Second-Line PFS		OS From Study Randomization		OS From Start of First-Line Therapy	
		Median (95% CI), mo	HR (95% CI); *P* Value	Median (95% CI), mo	HR (95% CI); *P* Value	Median (95% CI), mo	HR (95% CI); *P* Value	Median (95% CI), mo	HR (95% CI); *P* Value
Continuing bevacizumab (n = 409)	2/2006-6/2010	NA		5.7 (5.2-6.2)	0.68 (0.59-0.78); <.001	11.2 (10.4-12.2)	0.81 (0.69-0.94); .006	23.9 (22.2-25.7)	0.9 (0.77-1.05); .17
Stopping bevacizumab (n = 411)		NA		4.1 (3.7-4.4)		9.8 (8.9-10.7)		22.5 (21.4-24.5)	

FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study

Group Assignment	Enrollment Period	First-Line PFS		Second-Line PFS		OS	
		Median (95% CI), mo	*P* Value	Median (95% CI), mo	*P* Value	Median (Range), mo	*P* Value
FOLFIRI then FOLFOX6 (n = 133)	12/1997-9/1999	8.5 (7.0-9.5)	.26	4.2 (3.7-5.2)	.003	21.5 (16.9-25.2)	.99
FOLFOX6 then FOLFIRI (n = 113)		8.0 (6.2-9.4)		2.5 (2.1-3.3)		20.6 (17.7-24.6)	

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin; HR, hazard ratio; NA, not available; OS, overall survival; PFS, progression-free survival.

ease progression or unacceptable toxic effects occurred. The primary efficacy end point—OS from the time of enrollment—was a median 11.2 vs 9.8 months for patients receiving chemotherapy plus bevacizumab vs those given chemotherapy alone, respectively, a marginal 1.4 months' difference that achieved statistical significance. Progression-free survival was also similarly statistically improved, with median durations of 5.7 and 4.0 months, a marginal 1.7 months' difference in patients receiving bevacizumab compared to those receiving chemotherapy alone. Notably, the median OS from the start of first-line treatment (although not a primary end point and retrospectively documented) was statistically insignificant, with values of 23.9 months with bevacizumab plus chemotherapy and 22.5 months with chemotherapy alone—the same 1.4 months' difference that achieved statistical significance in the shorter time interval of the primary end point: OS from the time of randomization. Furthermore, the confidence intervals for the OS values from the start of first-line treatment overlapped those in a GERCOR (Groupe Cooperateur Multidisciplinaire en Oncologie) trial a decade earlier[97] that enrolled 226 patients and did not use bevacizumab, raising the question, in mCRC, how far have we really come if 10 years and thousands of patients later we find ourselves with such limited progress?

Similarly, one can look to "nonmutated" non–small cell lung cancer (NSCLC). The approval of pemetrexed disodium as a first-line therapy in NSCLC in September 2008 fueled attempts to extend its indications.[98] Less than a year later in July 2009, this well-tolerated drug garnered approval as maintenance therapy for NSCLC even as attempts were being made to demonstrate its superiority to paclitaxel in first-line treatment.[99] PointBreak, a study conducted between December 2008 and February 2012, attempted to demon-

Table 4. Nonmutated Non–Small-Cell Lung Cancer (NSCLC): Survivals 8 Years Apart

PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab vs Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer

Group Assignment	Enrollment Period	PFS		OS	
		Median (95% CI), mo	HR (95% CI); *P* Value	Median (95% CI), mo	HR (95% CI); *P* Value
Pemetrexed + carboplatin + bevacizumab (n = 472)	12/2008-2/2012	6.0 (5.6-6.9)	0.83 (0.71-0.96); .01	12.6 (11.3-14.0)	1.00 (0.86-1.16); .95
Paclitaxel + carboplatin + bevacizumab (n = 467)		5.6 (5.4-6.0)		13.4 (11.9-14.9)	

[ECOG 4599] Paclitaxel-Carboplatin Alone or With Bevacizumab for Non–Small-Cell Lung Cancer

Group Assignment	Enrollment Period	PFS		OS	
		Median, mo	HR (95% CI); *P* Value	Median, mo	HR (95% CI); *P* Value
Paclitaxel + carboplatin (n = 444)	7/2001-4/2004	10.3	0.66 (0.57-0.77); <.001	6.2	0.79 (0.67-0.92); .003
Paclitaxel + carboplatin + bevacizumab (n = 434)		12.3		4.5	

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

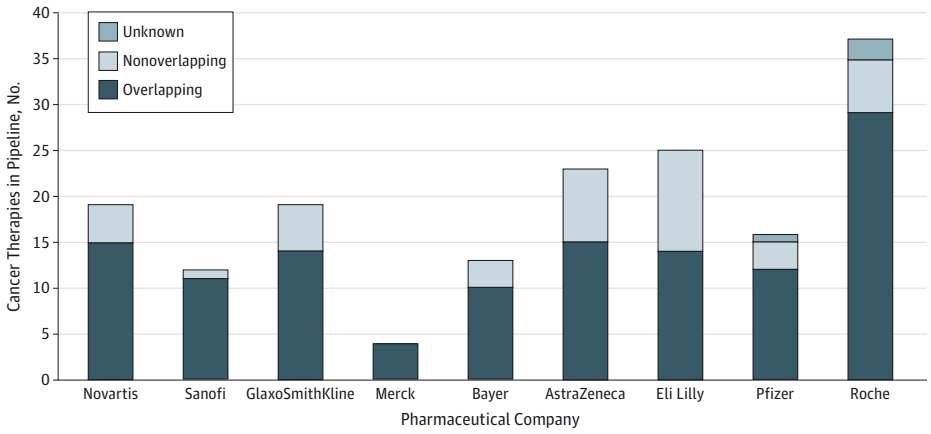
strate the superiority of pemetrexed over paclitaxel, also adding maintenance pemetrexed to continued bevacizumab in first line.[100] PointBreak randomly assigned 939 patients with previously untreated stage IIIB or IV nonsquamous NSCLC to either pemetrexed or paclitaxel with carboplatin and bevacizumab with maintenance pemetrexed plus bevacizumab or single-agent bevacizumab. The primary end point of this superiority study, OS, was not met, with median OS values of 12.6 and 13.4 months for patients assigned to pemetrexed and paclitaxel, respectively. Importantly, the 13.4 months' OS of the paclitaxel arm was similar to the 12.3 months' OS in ECOG 4599[33] 8 years earlier—again raising the question, in nonmutated NSCLC, how far have we really come if 8 years and thousands of patients later we find ourselves without meaningful progress?

Me-Too Strategies and Mentality

With pharmaceutical companies now developing the majority of cancer drugs, a fallout of expensive therapies even more disconcerting than the search for supplemental approvals has been the stifling of innovation and creativity that has occurred as a consequence of me-too strategies or a me-too mentality. For both validated and what we might term "speculative targets," all too often duplicative efforts exist, a phenomenon that we are currently witnessing as "immune therapies" replace "targeted therapies" as "must haves" in pharmaceutical company portfolios. That the eventual revenue from such therapies rather than their need has been a driving force cannot be doubted. What else could explain such an intense interest in inhibitors of the anaplastic lymphoma kinase (ALK), the product of a gene initially described in anaplastic large-cell lymphoma?[101] In NSCLC, where *ALK* is fused distal to the *EML4* gene, a successful therapy emerged from Pfizer, Inc. Although *ALK* fusions are found in only 3% to 5% of NSCLC, the discovery of crizotinib activity in patients with NSCLC established ALK inhibition as a very effective and a very tolerable therapeutic strategy.[84] An FDA-approved fluorescence in situ hybridization (FISH) test was codeveloped to detect the fusion gene in tumors and can guide who should receive this treatment.[102,103] Crizotinib rapidly became the most expensive cancer therapeutic and heightened interest in ALK. The number of pharmaceutical companies involved in the development of small molecules for this target had quickly expanded, and Novartis Pharmaceuticals Corporation became the first competitor to succeed, getting an accelerated approval for its drug ceritinib in April 2014.[104] Ceritinib then quickly assumed the top spot in the drug cost ladder, at a premium of 12.6% over crizotinib (Red Book Average Wholesale Price: ceritinib, $16 197; crizotinib, $14 383). While ceritinib is currently approved only for those whose cancer has progressed during crizotinib therapy, ongoing studies are comparing ceritinib directly to crizotinib to determine if ceritinib can replace crizotinib in the first line. And while ceritinib may succeed in replacing crizotinib, the development of ceritinib and that of similar drugs by at least half a dozen other companies raises questions: Do we need such enormous efforts on this target—a target found in a few thousand patients in the United States and for which, importantly, a very effective and tolerable drug already exists—or might our resources be better spent elsewhere? Is this really our most effective anticancer strategy, or is this what pharmaceutical companies see as safe and profitable investments?

And while the ALK inhibitor example has at least involved the pursuit of a "validated" target with what are expected to be very similar drugs, such safe bets are not the only example of the duplication of efforts that now too often makes up our drug development enterprise. For example, the hope that we would starve tumors by targeting their blood vessels led to more than 50 small-molecule vascular endothelial growth factor–tyrosine kinase inhibitors (VEGF-TKIs) entering clinical trials, the majority before a single VEGF-TKI had been approved, an expenditure of billions that has led to 5 drug approvals in renal cell, colorectal, gastrointestinal stromal tumor, and

Figure 2. Comparison of Cancer Therapies in the Pipelines of Pharmaceutical Companies According to Their Putative Mechanisms of Action



For this analysis we began by identifying the top 10 pharmaceutical companies based on 2013 earnings. Because Johnson & Johnson does not provide details of its pipeline, only 9 companies were included in this analysis totaling 168 agents in their oncology pipelines. We defined *overlapping* as a pharmaceutical agent whose mechanism of action is similar to that of a Food and Drug Administration (FDA)–approved agent and/or that of an agent in the pipeline of another top-10 company. *Nonoverlapping* was defined as a pharmaceutical agent whose mechanism of action is not similar to that of an FDA-approved drug and also not similar to that of a drug in the pipeline of another top-10 company. However, this does not exclude the possibility that the mechanism is similar to that of a drug in the pipeline of a company that is not in this list. With these somewhat arbitrary definitions, we found that 124 oncology agents (74%) in the pipelines of the 9 companies examined have an overlapping mechanism of action, 41 (24%) have a nonoverlapping mechanism of action, and 3 (2%) have a mechanism of action that is unknown since it is not listed on the company website. The drugs and companies, as well as the assignments, are summarized in the eTable in the Supplement.

well-differentiated thyroid cancers, all with modest improvements in OS and the 4 approvals in renal cell carcinoma clearly redundant. Similarly, because many thought that microtubule-targeting drugs such as paclitaxel (Taxol) killed cells by inhibiting mitosis, 25 drugs targeting mitosis were developed and entered clinical trials, all without prior evidence of efficacy in humans. The "achievement" of this multibillion-dollar effort was a response rate of approximately 1% in more than 2000 solid tumors.[105] The "investment" did succeed in establishing unequivocally that mitosis is not a valid anticancer drug target and, with neutropenia as the dose-limiting toxic effect, provided evidence of the prowess and expertise of pharmaceutical companies and the chemists that they employ.

A review of pharmaceutical company pipelines shows the extent of the me-too problem and why, as we stated at the outset, we are now sowing the seeds that in the years to come will not solve but instead exacerbate our problems. Our analysis summarized in **Figure 2** found that 124 oncology agents (74%) in the pipelines of the 9 companies examined have an "overlapping" mechanism of action, with 41 (24%) having a nonoverlapping mechanism of action, a remarkable duplication of effort (eTable in the Supplement).

The Economics and Emotion of Drug Development

The economics of drug development is a complex subject involving multiple stakeholders, each motivated by a different set of incentives. Therefore, to understand the motivation behind the development of "me-too therapies," we must first consider the objectives and constraints of publicly traded pharmaceutical companies, through which the vast majority of drugs are currently brought to market.

While pharmaceutical company executives are undoubtedly motivated by a genuine desire to ease the burden of disease, as stewards of publicly traded companies, their mandate is to maximize shareholder value. In crude terms, this directive translates into increasing the company's stock price over time. Because stock prices are determined by the purchases and sales of investors in the stock market, investor preferences ultimately dictate the decisions of corporate executives, all of whom act in the best interests of their shareholders. A central tenet of modern financial economics is that investors prefer higher returns, holding other factors constant, and investors prefer lower risk, holding other factors constant.[106] This principle implies that it is possible to increase a company's stock price by either increasing the expected return of its earnings, reducing the riskiness of its earnings, or both. Accordingly, a company's decision to invest in a radically new breakthrough therapy may eventually lead to much higher expected earnings, but if this strategy is so risky that investors lose confidence and sell their shares, the company's stock price will drop. Similarly, even if the development of an additional indication does not lead to clinically meaningful improvements, the lower risk associated with such products might still be viewed quite favorably by investors, leading to higher stock prices. And there is little doubt that developing additional indications for an approved drug is considerably less risky than developing an entirely new therapy from concept to approval by regulatory agencies.

Of course, undertaking lower-risk projects does not necessarily imply higher stock prices—the expected profitability of such projects must also be considered. If a me-too drug is less risky to develop but of little incremental benefit to patients, why would it generate any profit at all? For cancer therapeutics, one answer lies in how drugs are paid for. One of the largest payers in the health insurance industry is Medicare, and through a series of complex legal mandates, it is re-

Table 5. Annual Change in Price of Oncology Sterile Injectable Drugs[a]

	Change in Price Over Period, %			
	Drugs Experiencing a Shortage Since 2008 (n = 44)		Drugs Not Experiencing a Shortage Since 2008 (n = 28)	
Period	Mean (SD)	Median	Mean (SD)	Median
Q1 2006-Q1 2008	−26.5 (19.1)	−21.4	0.6 (10.9)	2.5
Q1 2008-Q1 2011	−6.3 (113.7)	−19.4	2.6 (32.0)	0.5
Q1 2006-Q1 2011	−27.4 (94.4)	−49.1	3.2 (24.4)	0.3

Abbreviation: Q, quarter.

[a] Adapted from Table 2 of Haninger, Jessup, and Koehler, 2011.[109] The table is restricted to the J9000-J9999 series of HCPCS codes with greater than 100 services in Q1 2006 and an average of more than 1000 services annually. Mean and median changes are weighted by volume of services in Q1 2006. Changes in prices are based on prices in 2011 dollars.

quired to reimburse patients for any drug used in an "anti-cancer chemotherapeutic regimen"—regardless of its incremental benefit over other drugs—as long as the use is "for a medically accepted indication" (commonly interpreted as "approved by the FDA").[107] Moreover, to ensure continued beneficiary access to certain drugs, Medicare will pay 106% of the average sales price of drugs covered under Part B. This policy has the unintended consequence of providing guaranteed revenues for me-too drugs as long as they can be successfully marketed to physicians, irrespective of their marginal benefits, which reduces the risk and increases the expected return of developing such drugs. A number of states impose similar policies on private-sector health insurers.[107] Although a small number of courageous institutions have begun to push back on these policies—for example, Memorial Sloan Kettering Cancer Center in New York recently, and quite publicly, refused to administer aflibercept (Zaltrap), a new colorectal cancer drug that costs $11 063 per month on average, more than twice the price of bevacizumab (Avastin), which yields comparable benefits[108]—the majority of payers are still obligated to pay for any FDA-approved and physician-prescribed cancer therapeutic regardless of cost and magnitude of benefit.

A concrete illustration of the importance of such pricing policies can be found at the opposite extreme of the price range: when prices for drugs of proven efficacy fall below a certain threshold, suppliers stop producing the drug altogether, causing severe shortages.[109] In a recent survey of 214 oncologists, "82.7% were unable to prescribe the preferred chemotherapy agent because of shortages at least once during the previous 6 months"[110(p2464)] and more than 75% indicated that these shortages led to major changes in the course of treatment. What could account for this unfortunate state of affairs? An economic analysis conducted by the US Department of Health and Human Services found that among a sample of sterile injectable oncology drugs, the ones experiencing shortages since 2008 exhibited a median price decline of 49.1% between the first quarter of 2006 and the first quarter of 2011, whereas the ones with no shortages exhibited a median price increase of 0.3% during the same period (**Table 5**, adapted from Haninger et al, 2011).[109] Drug manufacturers respond to basic economic incentives, as their shareholders demand.

By giving consumers maximum flexibility of choice, limiting price competition, and creating guaranteed revenues for cancer drugs irrespective of their incremental benefits, we have inadvertently incentivized the pharmaceutical industry to develop too many drugs of similar efficacy, supply too few drugs that have life-saving potential but yield little or no profit, and shy away from truly transformative medicine because the risks are simply too great for their shareholders.

However, economic incentives are not the only factors responsible for the status quo. Underlying the business forces and regulatory constraints are powerful emotional and ethical factors that conspire to create incentives for pharmaceutical companies to allocate resources toward safer but less transformative therapeutics. Because access to new therapies is almost always a highly emotionally charged issue—especially in oncology, where life-and-death decisions are not uncommon and the current standard of care is unfortunately so poor for many cancers—the ability to limit costs or forgo marginally beneficial drugs inevitably becomes a complex discussion. Moreover, as a society we are loathe to make trade-offs in which time and money are balanced against human lives, despite the fact that government policy must do so regularly; eg, setting the highway speed limit at 65 mph has yielded 3% more fatalities than at 55 mph.[111] Therefore, any discussion about limiting a dying patient's options because of cost can easily be mischaracterized as heartless and immoral. Until we can engage in a rational debate about how best to balance cost against therapeutic efficacy—as other countries such as the United Kingdom have done—it may be impossible to avoid gross misallocation of precious drug-discovery resources.

Conclusions

We can look back on the 1990s as a watershed, a time when pharmaceutical companies began to gradually participate in and then rapidly came to dominate cancer drug development. While it allowed for an effort that was more robust than what we had or could have had with the limited resources in academia, it also meant the fundamentals of cancer drug development shifted radically. As publicly traded companies increasingly dominated drug development, profits and shareholder value quickly and then dramatically became important, if not prime, considerations in decision making. In certain respects, this has been beneficial. For example, competition and the drive to be first to market have energized and accelerated cancer drug development to a pace none would have predicted. It is hard to imagine a government or academic institution developing BRAF and ALK inhibitors as rapidly as pharmaceutical companies developed them.

However, corporate accountability to shareholders, stock analysts, and the public has also meant an increasing number of decisions are now driven by the economics and emotion of drug devel-

opment, an approach that many might not consider a socially optimal drug development strategy. The rapid rise in drug costs is one, if not the principal, culprit in this evolution. Our stated thesis, for which we have provided examples, is that the rapidly rising cost of cancer therapies, the regulations governing their adoption by public and private insurers, and the increasing economic risk of drug development have had the unintended consequence of stifling progress by diverting enormous amounts of time, money, and other resources toward therapeutic indications that are arguably marginal. Why else would we pursue gains of a few weeks to a few months with a new drug or as an expanded indication? And rapidly rising costs have also stifled innovation and creativity by promoting a me-too mentality. Why else would the portfolios of companies overlap so greatly with drugs so similar and with differences that either do not exist or that will only be discernible with trials that enroll hundreds if not thousands of patients, the numbers needed to establish statistical significance for nearly imperceptible differences? While competition yields many benefits and can lead to the development of better products faster, cancer drugs are not computers or cell phones and the fundamentals that inform the development of other consumer products simply do not apply to the highly regulated, life-and-death context of cancer therapeutics.

A more systematic approach to cancer therapeutics—with the primary goal of truly clinically meaningful cancer therapeutics rather than maximizing shareholder value—would likely look quite different than the current biopharmaceutical ecosystem. Multiple shots on goal would be diversified across a broad spectrum of pathways, mechanisms, targets, and potential therapies, and data from each shot would be shared among the entire network of teams so as to encourage cross-fertilization and idea generation. However, the reality is that the profit motive is a powerful organizing force capable of focusing tremendous amounts of capital for long periods on solving big challenges such as cancer. The real question is how to maintain the profit motive while limiting the cost spiral. We began by acknowledging that the spiraling cost of cancer therapies has no single villain; academia, professional societies, scientific journals, practicing oncologists, regulators, patient advocacy groups, and the biopharmaceutical industry—all bear some responsibility. However, all too often when many are responsible, no one is responsible, and that is an unacceptable conclusion.

Going forward, we propose several steps that can be taken:

1. Academicians must avoid participating in the development of marginal therapies and acknowledge the marginal nature of an outcome when the gains are such that we ourselves would be dismayed as patients to discover that that was all the benefit we would receive. Beyond a few mutations, the promise of "personalized or precision medicine" in oncology remains a promise yet to be fully realized, and we cannot rationalize developing marginal therapies by leveraging on the hope of a day when precision medicine will turn weeks to years for a select few. We are far too advanced to not deliver the "precision" along with the "therapy"—ALK inhibitors in a well-defined subset of NSCLC as a prime example.
2. Professional societies and scientific journals must raise their standards and avoid giving prominence to marginal outcomes, while continuing to report them, since they are equally if not more important than successes. These organizations must also insist on transparency, the sharing of all published data in a timely and enforceable manner, and clear, straightforward descriptions of benefit in terms that are meaningful to patients. Actual gains of benefit must be emphasized and not hazard ratios or other measures that ascribe "significance" to gains that are often only weeks in duration and that no patient—not even one who has toiled as a statistician—would consider "significant" with respect to her or his own life expectancy.
3. The value of the cooperative groups must be acknowledged, and such groups must receive robust support. In return, they must be truly innovative, conducting cutting-edge trials that are lean in numbers of patients enrolled as they strive for *truly significant* outcomes. With pharmaceutical companies as the source of most cancer therapeutics, cooperative groups will need to make a special effort to look at other sources for novel agents and strategies.
4. The me-too mentality that settles for incremental improvement or a slice of another drug's existing market share must be addressed. Although there were legitimate reasons for encouraging the biopharmaceutical industry to develop many cancer therapeutics—beginning in 1971 with President Nixon's "War on Cancer"—we now seem to be at an inflection point in biomedicine where truly transformative therapies are within reach if we can execute more efficiently. Rather than criticizing the industry or railing against the high cost of new drugs, we must focus instead on providing greater incentives for developing clinically meaningful improvements. A small but important first step would be to establish an *independent* entity charged with the mission of producing uniform measures of the benefits of each FDA-approved drug using unbiased patient-oriented metrics such as quality-adjusted life-years.
5. Once a standardized measure of clinically meaningful improvement is established, we can have the more difficult conversation regarding the viability of our current rate of health care expenditures and what we can do to address this emerging crisis. In response to Memorial Sloan Kettering's public rejection of the cost of Zaltrap, Sanofi S. A. cut the price in half.[112] Pharmaceutical companies deserve to charge premium prices for therapies offering premium benefits, but marginal benefits should not be rewarded. Patients and their families must be included in this conversation to help determine the proper trade-off between cost and benefit for the system.
6. Finally, we must make every effort to attract more philanthropic and altruistic investment capital, and we must leverage our federal funds optimally. These dollars can and should be used for truly independent research not otherwise being conducted by pharmaceutical companies, research that may offer little or no immediate return on investment but which can yield enormous benefit years from now. We must stop talking about "out of the box" thinking and start truly investing in such thinking. As with the proteasome, yesterday's "irrelevant" can become the foundation for tomorrow's blockbuster.[113] Yet human nature and, in turn, granting agencies all too often are motivated to support that which is the current hot topic. We have spent a decade favoring grants that involved "targeted therapies." We need to avoid that mistake in the era of "checkpoint inhibitors." The portfolios of cooperative groups and those of all publicly funded research must be truly different and not simply another version of a pharmaceutical company.

Rapidly rising drug costs have had a major impact on cancer drug development and patients with cancer, with both positive and negative outcomes. However, this trend is clearly unsustainable and must be addressed by reengineering our collective cancer ecosystem to achieve better outcomes for society. The stakes could not be higher.

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