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Evaluation of the contribution of randomised cancer clinical trials evaluating agents without documented single-agent activity

Jared Foster ,[1] Boris Freidlin,[1] E L Korn,[1] Malcolm Smith[2]

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[1]Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland, USA
[2]Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland, USA

Correspondence to
Dr Jared Foster;
jared.foster@nih.gov

ABSTRACT

Background With the development of targeted agents, the approach to combination cancer therapy has evolved to focus on identifying ways in which pathway inhibition by one agent may enhance the activity of other agents. In theory, this implies that under this new paradigm, agents are no longer required to show single-agent activity, as the pathway inhibited by the targeted agent may only have a therapeutic effect when given with other agents. This raises the question of the extent to which anticancer agents without single-agent activity can contribute to effective combination regimens.

Patients and methods We reviewed outcomes of randomised phase 2 combination trials sponsored by the National Cancer Institute Cancer Therapy Evaluation Program that were activated in 2008 to 2017 and noted the single-agent activity of the experimental agents.

Results Fifty-three trials were identified, and 50 had available results: 7 (14%), 15 (30%) and 28 (56%) had experimental agents with single-agent activity classified as active, inactive and indeterminate, respectively. Thirteen per cent (95% CI=1.7% to 40.5%) of trials evaluating inactive agents and 11.6% (95% CI=3.9% to 25.1%) of trials evaluating agents without known single-agent activity (pooled inactive and indeterminate) were positive, compared with 42.9% (95% CI=9.9% to 81.6%) for agents with single-agent activity.

Conclusions Incorporating agents without documented single-agent activity into treatment regimens is unlikely to produce meaningful improvements in activity unless there is compelling biological rationale. This finding has important implications for the prioritisation of anticancer agents for combination testing, and for the allocation of clinical trial resources.

Key questions

What is already known about this subject?

► With the development of targeted agents, the approach to combination therapy has evolved to focus on identifying ways in which pathway inhibition by an agent may enhance the activity of other components of a treatment regimen. Agents without single-agent activity would previously have been discarded, but this new paradigm removed the requirement for single-agent activity, as the pathway inhibited by the targeted agent may only have a therapeutic effect when given with other agents. Removing this requirement for single-agent activity has dramatically expanded the number of potential combinations evaluable in cancer patients, as agents can now be selected for evaluation in a combination regimen based on a plausible mechanism of action, and on some level of preclinical supportive data that the mechanism is relevant.

What does this study add?

► We examined the outcomes of randomised phase 2 trials sponsored by the NCI Cancer Therapy Evaluation Program (CTEP) to better understand the extent to which anticancer agents without single agent activity can contribute to effective combination therapy regimens. The results of this review may help inform future prioritisation of anticancer agents for combination testing, and the allocation of clinical trial resources.

How might this impact on clinical practice?

► Our results suggest that this approach has a very low yield in the absence of compelling biological rationale, and that the level of evidence currently used to select agents lacking single-agent activity for combination testing is inadequate.

INTRODUCTION

Determining which combinations of anticancer agents to evaluate in specific patient populations was reasonably straightforward through most of the second half of the 20th century, and was based on rules from the 1950s developed for treating children with acute lymphoblastic leukaemia, with supportive evidence coming from studies of mouse models of leukaemia.[1 2] The basic principle was that combinations of active agents were likely to be more effective than the same agents used alone, and that sufficient numbers of active agents used in combination could potentially result in curative therapy. Potential explanations of the benefit of treatment regimens that combine active agents

include increased anticancer cell kill, circumvention of development of resistance to the single agents that make up the regimen, greater efficacy against heterogeneous tumours with different resistance mechanisms and synergistic interactions between agents used in the regimen.[3] Furthermore, combinations of active agents can also address between-patient tumour heterogeneity when different patients are sensitive to different agents of the combination.

With the development of targeted agents that potently inhibit signalling pathways, the approach to combination therapy has evolved to focus on identifying ways in which pathway inhibition by an agent may enhance the activity of other components of a treatment regimen. Whereas previously agents without single-agent activity would have been discarded, this new paradigm removed the requirement for single-agent activity, as the pathway inhibited by the targeted agent may only have a therapeutic effect when given with other agents. Without a requirement for single-agent activity, the number of potential combinations evaluable in cancer patients has expanded dramatically, as agents can now be selected for evaluation in a combination regimen based on a plausible mechanism of action, and on some level of preclinical supportive data that the mechanism is relevant. In most settings, isolating the contribution of the new agent to the combination requires a randomised trial. Typically, an 'add-on' design is used, where patients are randomised between two arms, with the control arm receiving the standard regimen and the combination arm receiving the new agent in addition to the standard regimen.

The question of the extent to which anticancer agents without single-agent activity can contribute to effective combination therapy regimens is an empirical one. To investigate this question, we identified randomised phase 2 trials sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and categorised the trials into those for which the experimental agent had single-agent activity, minimal or no single-agent activity or unknown single-agent activity. The outcomes of these phase 2 trials were then examined.

METHODS

The CTEP trials database was searched for randomised comparative phase II trials involving more than one agent (including radiation) that were activated on or after 1 January 2008 and were permanently closed to accrual by 31 December 2017. This search was limited to add-on trials. Because the focus was on clinical trials evaluating agents tested in combination with systemic therapies, trials in which the experimental regimen involved the addition of surgery or radiation to the control-arm regimen were excluded, as were trials in which the experimental agent was being evaluated as a radiosensitizer. Because the result of adding anti-angiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway to chemotherapy regimens has been well-delineated for multiple cancer types as modestly prolonging time to event in the advanced disease setting but not in the adjuvant setting,[4] trials adding agents with VEGF targets were excluded. Trials involving immunotherapy agents were also excluded given the distinctive mechanism of action of these agents and the possibility that the rules for identifying beneficial combinations involving the addition of immunotherapy agents may differ from those of agents acting directly on cancer cells. In addition, trials in which patients were required to have previously progressed on the experimental agent (or another similar agent) were excluded. Trials which achieved less than 30% of the target accrual (unless this was because an interim stopping bound was crossed) were also excluded. For trials with more than two arms and multiple additive comparisons, each additive comparison was treated as a separate trial. To find trial publications, Internet searches were performed using the CTEP trial ID, NCI's National Clinical Trials Network (NCTN) number, trial title and a combination of the principal investigator's surname, agents in the trial and cancer histology.

For each trial, all published/publicly available single-agent trial data (including data that were not available at the time the trial protocol was written) were used to classify the level of single-agent response activity of the experimental agent for the specific histology of interest. As summarised in table 1, experimental agents were classified as active for a particular histology if the corresponding observed response rate (pooled across all relevant trials) was greater than 5%, and those for which the observed response rate was at most 5% were classified as inactive. Experimental agents received the classification 'indeterminate' activity if at most one response was observed among 13 or fewer patients, or exactly one response was observed among 14 to 19 patients. Single-agent activity assessments were completed prior to viewing the results of the trials in this review. After it was

Table 1 Single-agent activity classification guidelines

	Conclusion about activity based on number of responses		
Number of evaluable patients	Active	Inactive	Not enough data
n<14	≥2	--	≤1
n≥14 and n<20	≥2	0	1
n>20	>5%	≤5%	--

discovered that some experimental agents that met criteria for single-agent activity were used in combination at dose intensities 50% less than their single-agent dose per unit time, these agents were reclassified as having indeterminate single-agent activity.

Once single-agent activity was assessed for the experimental agent in each trial, the trial publications were reviewed, and results were classified as 'positive', 'negative' or 'unknown' based on the following criteria. If at least 80% of the target accrual was achieved (and the trial was not stopped early due to futility or efficacy), the trial was classified as positive or negative based on the published primary analysis (assuming this was the per-protocol primary analysis). Likewise, if a trial was stopped early as a result of a preplanned interim efficacy or futility analysis, the results were classified as positive or negative, respectively. If a trial achieved less than 80% of the target accrual (and an early stopping rule was not triggered), we used the published primary analysis (as well as the point estimate and SE, when necessary) to (separately) test the protocol-defined null and alternative hypotheses using one-sided errors set at the protocol-defined type I and type II errors, respectively. If the observed result was significantly better than the null, the trial was classified as positive. If the observed result was significantly worse than the alternative (and did not differ significantly from the null), the trial was classified as negative. Finally, the trial was classified as unknown if the observed result was not found to differ significantly from either the null or alternative.

The sample proportion of positive trials (and the corresponding 95% CI) was computed using only trials that were classified as positive or negative. These estimates were obtained separately for the subgroups of trials whose experimental agents were classified as active, inactive and indeterminate. In addition, though power was limited, the proportion of positive trials was compared among the trial subgroups using Fisher's exact test with one-sided type I error of 0.05: the active experimental agent subgroup was compared with the inactive-agent subgroup alone and to the pooled inactive and indeterminate-activity agent subgroups.

RESULTS

Sixty-seven eligible protocols representing 73 randomised trials were identified (figure 1). Three trials were excluded because results were not published (or otherwise publicly available), and an additional 20 trials were excluded because they enrolled <30% of their planned accrual for reasons unrelated to efficacy/futility (including 13 trials with zero accrual), leaving 50 trials analysed in this review. Among these 50 trials, 7 (14%), 15 (30%) and 28 (56%) had experimental agents that were classified as active, inactive and indeterminate activity, respectively.

Five of 43 (11.6%) randomised trials evaluating experimental agents not known to have single-agent activity were considered positive based on their protocol-defined criteria for success: 2 of 15 (13.3%) trials of inactive experimental agents and 3 of 28 (10.7%) trials with indeterminate activity. These two subgroups of trials are considered together because a common reason for not evaluating single-agent activity is the belief that the experimental agent in question is likely to be ineffective as a single-agent and needs to be studied in combination. Details for the five trials evaluating experimental agents with either no (8457 and S1406) or indeterminate (E2511, GOG-0186I and N064B) single-agent activity that met protocol-defined criteria for 'positive' are provided in table 2. Additional details of these five trials are provided below:

- Trial 8457 evaluated the addition of bortezomib to fulvestrant for women with oestrogen receptor (ER)-positive metastatic breast cancer resistant to aromatase inhibitors.[5] There was no difference in median progression-free survival (PFS) between the experimental and control arms (2.7 months each), but the HR for PFS significantly favoured the combination arm (HR=0.73 with p=0.06, one-sided log-rank test) as the result of a modest separation of the curves at later time points. Although the study met protocol-defined criteria for 'positive', the impact of the addition of bortezomib appeared small and there has been no subsequent definitive clinical trial of bortezomib pursued for the study's patient population.
- The S1406 study evaluated the addition of vemurafenib to irinotecan and cetuximab for patients with BRAF-mutant colorectal cancer.[6] For patients receiving vemurafenib, the median PFS was more than doubled (4.4 vs 2.0 months, HR=0.42 with p<0.001, one-sided log-rank test) and the objective response rate was higher (16% vs 4%). This study is discussed further below.
- Trial E2511 evaluated the addition of veliparib to cisplatin and etoposide for newly diagnosed patients with extensive-stage small cell lung cancer.[7] The two arms showed a small difference in median PFS favouring the veliparib arm (6.1 vs 5.5 months, stratified HR=0.63 with p=0.01, one-sided stratified log-rank test).
- Trial GOG-0186I evaluated fosbretabulin (combretastatin A4-phosphate) in combination with bevacizumab for patients with ovarian cancer, and extended median PFS from 4.8 months for single-agent bevacizumab to 7.3 months for the combination (HR=0.69 with p=0.05).[8] However, a subsequent phase 2 to phase 3 trial evaluating fosbretabulin in combination with bevacizumab and chemotherapy failed when the company terminated the study due to the lack of a meaningful improvement in PFS.[9]
- Trial N064B evaluated the addition of panitumumab to erlotinib and gemcitabine for patients with advanced pancreatic cancer.[10] Median overall survival was significantly improved (8.3 vs 4.2 months, HR=0.82 with p=0.18), but with an extension in median PFS of only 1.6 months (3.6 months vs 2.0 months) and increased toxicity among patients receiving dual epidermal

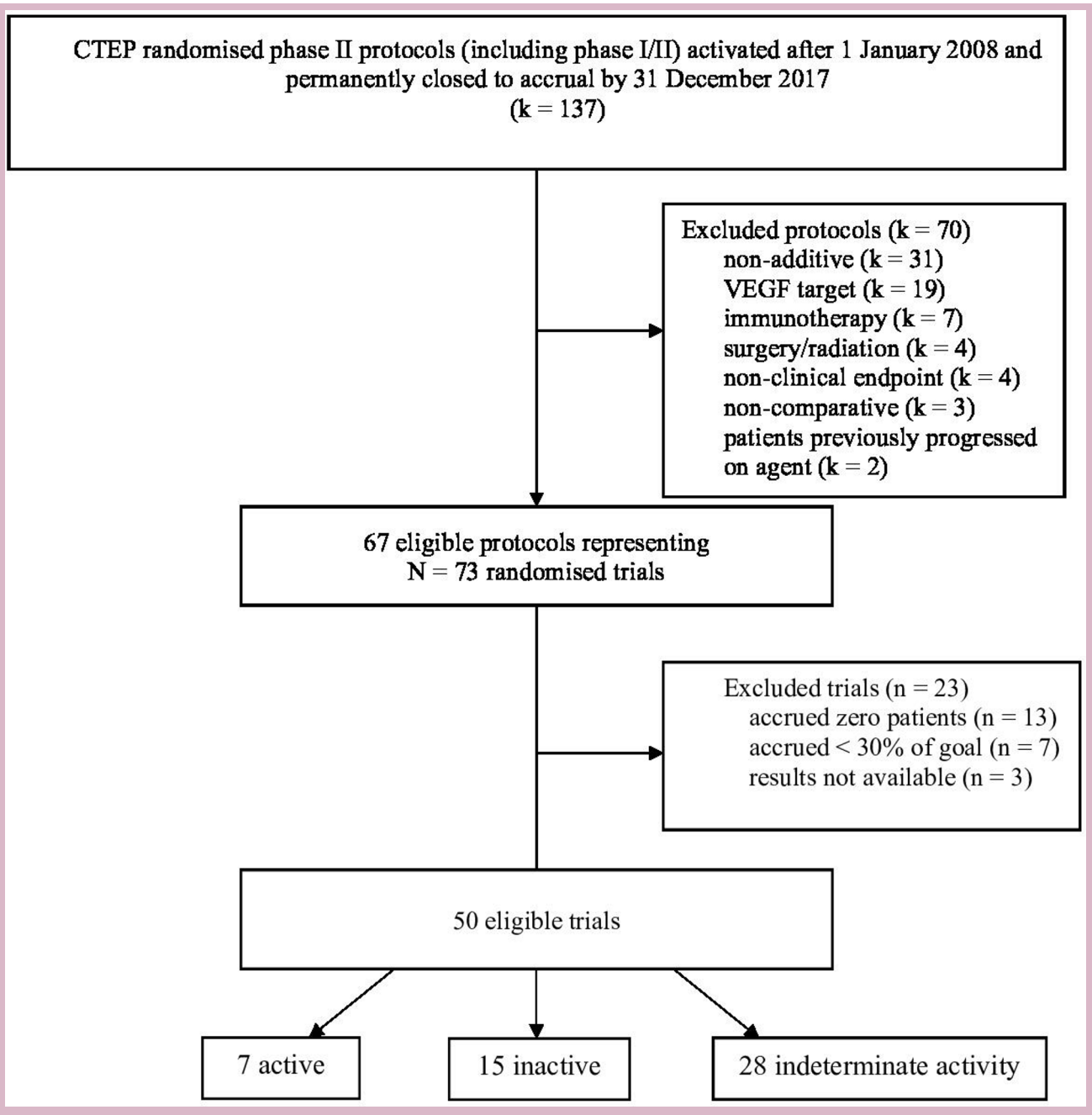

Figure 1 Flow diagram of trial selection. ('Active/inactive/indeterminate' in the last row refers to the single-agent activity of the experimental agent.) CTEP, Cancer Therapy Evaluation Program; VEGF, vascular endothelial growth factor.

growth factor receptor (EGFR) blockade. The authors concluded that further studies of EGFR inhibitors administered concurrently with cytotoxic agents were unlikely to result in a meaningful improvement in the outcome of patients with metastatic pancreatic cancer and were therefore not recommended.

There were seven randomised trials with experimental agents that had single-agent activity (table 3). Among these were three positive trials, E1412, E2211 and E2408[11–13] (see online supplemental table 1 for details). The single-agent response rates for the agents studied ranged from approximately 10% for rapalogs for ovarian cancer to 50% for bortezomib for follicular lymphoma.[14 15] The single-agent response activity for capecitabine was high (75%), but was based on only four patients.[16]

The percentage of positive trials among trials evaluating inactive agents was 13.3% (95% CI=1.7% to 40.5%), and that for trials evaluating agents without known single-agent activity (pooled inactive and indeterminate activity single agents) was 11.6% (CI=3.9% to 25.1%) (table 4). This is contrasted with 42.9% (95% CI=9.9% to 81.6%) positive trials among trials evaluating active agents. The comparison of positive trial rates between active and inactive agents did not meet criteria for statistical significance (p=0.16),

Table 2 Clinical trials of experimental agents without confirmed single-agent activity that met protocol-defined criteria for success

Clinical Trial #	NCT #	Tumour type	Exptl agent	Single-agent activity (N/IND)	Stnd arm agent(s)	N (exptl)	N (stnd)	Primary endpoint	Exptl outcome	Stnd outcome	P value	Exptl ORR	Stnd ORR	Reference #
8457	NCT01142401	ER(+) breast cancer	Bortezomib	No	Fulvestrant	59	59	PFS	Median 2.7 months	Median 2.7 months	0.06	NA	NA	[5]
S1406	NCT02164916	BRAF mutant colorectal cancer	Vemurafenib	No	Cetuximab + irinotecan	49	50	PFS	Median 4.4 months	Median 2.0 months	<0.001	0.16	0.04	[6]
E2511	NCT01642251	Extensive-stage small cell lung cancer	Veliparib	IND	Cisplatin + etoposide	64	64	PFS	Median 6.1 months	Median 5.5 months	0.023	0.72	0.66	[7]
GOG-0186I	NCT01305213	Ovarian	Fosbretabulin Tromethamine	IND	Bevacizumab	53	51	PFS	Median 7.3 months	Median 4.8 months	0.05	0.357	0.282	[8]
N064B	NCT00550836	Pancreatic cancer	Panitumumab	IND	Erlotinib + gemcitabine	46	46	OS	Median 8.3 months	Median 4.2 months	0.18	0.065	0.087	[10]

ER, oestrogen receptor; Exptl, experimental; IND, indeterminate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Stnd, standard.

Table 3 Clinical trials of experimental agents with confirmed single-agent activity

Clinical Trial #	NCT #	Tumour type	Exptl agent	Stnd arm agent(s)	N (exptl)	N (stnd)	Primary endpoint	Exptl outcome	Stnd outcome	P value	Positive study Y/N (per protocol)	Exptl # eval for response	Exptl # responders	Exptl ORR	Stnd # eval for Response	Stnd # responders	Stnd ORR	Reference #
E1412	NCT01856192	Diffuse large B cell lymphoma	Lenalidomide	Rituximab + chemotherapy	145	135	PFS	Median not reached	NA	0.03	Y	NA	NA	0.97	NA	NA	0.92	[11]
E2211	NCT01824875	Pancreatic neuroendocrine tumours	Capecitabine	Temozolomide	72	72	PFS	Median 22.7 months	Median 14.4 months	0.01	Y	NA	NA	0.33	NA	NA	0.28	[12]
E2408	NCT01216683	Follicular lymphoma	Bortezomib	Rituximab + bendamustine	85	137	CR	74%	58%	0.016	Y	NA	NA	0.74	NA	NA	0.58	[13]
E2408	NCT01216683	Follicular lymphoma	Lenalidomide	Rituximab	112	60	1 year DFS	45%	72%	0.99	N	NA	NA	NA	NA	NA	NA	[41]
9012	NCT01576172	Metastatic castration-resistant prostate cancer	Veliparib	Abiraterone + prednisone	79	74	PSA response	72%	63%	0.27	N	76	55	0.724	72	46	0.639	[42]
CALGB-50904	NCT01286272	Follicular lymphoma	Bortezomib	Ofatumumab + bendamustine	62	66	CR	60%	62%	0.68	N	62	37	0.597	66	41	0.621	[43]
GOG-0186G	NCT00886691	Ovarian	Everolimus	Bevacizumab	75	75	PFS	Median 5.9 months	Median 4.5 months	0.39	N	63	14	0.222	58	7	0.121	[44]

CR, Complete Response; DFS, Disease Free Survival; Exptl, experimental; ORR, objective response rate; PFS, progression-free survival; PSA, Prostate-Specific Antigen; Stnd, standard.

Table 4 Trial outcomes by single-agent activity level

Single-agent activity	Trial result		Proportion of positive trials (95% CI)	P value*
	Negative	Positive		
Active	4	3	0.43 (0.10 to 0.82)	–
Inactive	13	2	0.13 (0.02 to 0.40)	0.16
Indeterminate	25	3	0.11 (0.02 to 0.28)	–
Inactive/indeterminate	38	5	0.12 (0.04 to 0.25)	0.07

*One-sided Fisher's exact test comparing proportion of positive trials to that among active agents.

nor did the comparison of such rates between active and no-known-activity agents (p=0.07), but, as noted earlier, there is limited power for these comparisons.

DISCUSSION

Our key finding is that incorporating agents without documented single-agent activity into treatment regimens is unlikely to produce meaningful improvements in clinical activity. Only 5 of 43 (11.6%) trials evaluating experimental agents without documented single-agent activity were considered positive based on their protocol-defined criteria for success. When considering the percentage of 'positive' studies among the 43 trials using agents without documented single-agent activity, it is relevant to note that the average type 1 error rate among these 43 trials was 0.11. Hence a finding of 10% to 15% positive trials aligns with the expected rate for false-positive results. Furthermore, it appears that only one of these five positive trials, S1406, identified potential true therapeutic advances. This means a single trial among 43 trials of agents without documented single-agent activity represents a potential true treatment advance.

The addition of an agent without single-agent activity to another treatment can be hypothesised to increase efficacy through several mechanisms (eg, synergy, prevention of resistance, overcoming existing resistance). As noted above, the most clear-cut example of a positive clinical trial for an agent without single-agent activity is S1406, which evaluated the addition of vemurafenib to irinotecan and cetuximab for BRAF-mutant metastatic colorectal cancer. The study was convincingly positive, with a HR for PFS of 0.042 (p<0.001). The inactivity of BRAF inhibitors for BRAF-mutated colorectal cancer illustrates the importance of cellular context in defining the activity of some targeted agents.[17] Multiple research teams identified the role of EGFR-pathway signalling in the resistance of colorectal cancer to vemurafenib,[18–20] and hence the mechanistic rationale for concurrent BRAF-EGFR inhibition for overcoming an existing resistance mechanism was compelling: a known genomic alteration (BRAF) associated with sensitivity to a kinase inhibitor in other diseases plus a clearly defined resistance pathway in colorectal cancer resulting from EGFR-pathway signalling. A subsequent phase 3 trial in colorectal cancer confirmed clinical benefit for combining BRAF inhibition (using encorafenib and binimetinib) with EGFR inhibition with cetuximab.[21] This example provides proof of concept that it is possible for an agent without single-agent activity to meaningfully contribute when used in combination if the biological rationale for the combination is truly understood and if excessive toxicity doesn't intervene.

A complementary line of research that informs the question of the role of anticancer agents lacking single-agent activity is the evaluation of the contribution of components of known effective regimens. Palmer and Sorger evaluated Food and Drug Administration (FDA)-approved drug combinations and found that patient-to-patient variability and independent drug action were able to explain the superiority of many FDA-approved drug combinations in the absence of drug synergy or additivity.[22] In a second report from these authors examining the contributions of individual agents to a curative regimen (R-CHOP), they found that effectiveness of the regimen was adequately explained by assuming independently active drugs with non-overlapping mechanisms of resistance, and that there was no need to assume synergistic interactions between the regimen's components. Both of these reports are consistent with our finding that agents lacking single-agent activity are unlikely to add in a meaningful way to standard treatment regimens.

There are agents such as bevacizumab that slow tumour growth through an anti-angiogenic mechanism, and they were not included in this analysis because the activity of this class of agents when added to standard-of-care regimens has been evaluated in phase 3 trials for multiple tumour types and has been described.[4] As single agents, objective response rates tend to be low, with notable exceptions for cancers such as renal cell carcinoma, ovarian cancer and alveolar soft part sarcoma. For patients with advanced disease, this class of agents can prolong progression-free survival by a modest amount for multiple tumour types, and in some cases overall survival may be extended as well. However, this class of agents is not effective when added to standard regimens in the adjuvant (curative) setting. The cyclin-dependent kinase (CDK)4/6 inhibitors may be similar to the anti-angiogenic agents in primarily working through slowing tumour growth, although they work through a different mechanism of action. These agents have been shown to prolong PFS when added to endocrine therapy for patients with advanced ER(+), human epidermal growth factor receptor 2 (HER2)(-) breast cancer, but early results suggest that their role in

potentially curative treatments (ie, adjuvant therapy) may be limited.[23] Their single-agent activity was not extensively studied, but for abemaciclib objective responses were observed.[24]

Kimmelman and colleagues applied a complementary approach to analyse the benefit, burden and impact of combination trials, and their findings are comparable to those that we report.[25] They examined 323 published post-approval trials exploring combinations involving anticancer agents first licensed 2005 to 2007 inclusive (termed index agents). Over 70% of the trials evaluated a combination for an indication for which the index agent was not approved by FDA. Among the combinations evaluated, the only ones that resulted in either subsequent FDA approvals or a National Comprehensive Cancer Network guideline recommendation were those for which the index agent had single-agent activity for the relevant patient population. Importantly, the authors noted that for those trials randomising between a combination arm and a comparator, patients receiving the combination experienced comparable overall survival rates but higher rates of grade 3 to grade 4 severe adverse events and deaths.

Our results also complement those of Gyawali and Prasad who examined 18 FDA-approved combination therapies that incorporated a drug with negligible single-agent activity.[26] Seven of the 18 combinations included a VEGF-targeted agent. Median prolongation in PFS (or time to progression) was only 2.3 months, and only 9 of 18 approved combinations were associated with improved overall survival (median increase 1.6 months). These analyses indicate that, even in the 'best case' scenario of a combination that achieves regulatory approval, clinical benefit is generally minimal.

The challenge of enhanced toxicity associated with combinations, such that dose reductions of component agents is required, was an issue for combinations involving the poly (ADP-ribose) polymerase (PARP) inhibitor veliparib with cytotoxic chemotherapy agents/regimens (8788, 9026, E2511 and S1513). While veliparib is tolerated at 400 mg two times per day (total daily dose of 800 mg) on a continuous dosing schedule as a single agent and shows activity in breast cancer gene (BRCA)-mutant patients at this dose,[27–29] the clinical trials that we evaluated that combined veliparib with cytotoxic agents (8788, 9026, E2511 and S1513) used veliparib at a dose per unit time reduced by 75% to more than 90% compared with its single-agent dose per unit time.[7 30–32] The issue of enhanced toxicity also applies to novel-novel combinations, as exemplified by studies in which phosphoinositide 3-kinase (PI3K) pathway and mitogen-activated protein (MAP) kinase pathway inhibitors are combined. Identifying tolerable doses for these combinations has been difficult due to high levels of toxicity at doses below the recommended doses of the agents used alone,[33–36] and clinical development of these combinations has not progressed despite promising mechanistic and preclinical rationale.

The paradigm of using documentation of pathway inhibition rather than objective response rate as a threshold for testing agents in combination is similar to the approach proposed in 2007 for cancer vaccines and related biologics.[37] This proposal from the Cancer Vaccine Clinical Trial Working Group was based on concerns that conventional phase 2 trials with objective response endpoints were not adequate for capturing the clinical potential of immunotherapy treatments, and that clinical trials designed to identify relevant biological activities of the vaccine/agent were needed to better credential candidate therapeutics for further evaluation. The paper was written in the early years of clinical development of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) targeted therapies,[38] and the initial reports of objective responses to programmed cell death protein 1 (PD1)-targeted antibodies[39] and to T-cell engaging antibodies appeared shortly thereafter.[40] These subsequent reports re-established objective response rate as the gold-standard for an agent's potential as a clinically effective immunotherapeutic agent.

In closing, the concept that targeted agents lacking single-agent activity may be able to potentiate in clinically meaningful ways the activity of other agents by inhibiting relevant signalling pathways has become widespread among cancer researchers. Our results suggest that applying this concept in clinical trials has a low yield in the absence of compelling biological rationale, and that the level of evidence currently used to select agents lacking single-agent activity for combination testing is inadequate. This finding has important implications for the prioritisation of anticancer agents for combination testing and for the allocation of clinical trial resources towards more promising lines of clinical investigation.

Contributors JF: conception and design of this review; acquisition, analysis and interpretation of data; drafting, revising and final approval of the manuscript. BF: conception and design of this review; acquisition and interpretation of data; drafting, revising and final approval of the manuscript. ELK: conception and design of this review; acquisition and interpretation of data; drafting, revising and final approval of the manuscript. MS: conception and design of this review; interpretation of data; drafting, revising and final approval of the manuscript. JF, BF, ELK and MS agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ORCID iD

Jared Foster http://orcid.org/0000-0002-2931-4850

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