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Systematic review of combinations of targeted or immunotherapy in advanced solid tumors

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ABSTRACT

With rapid advances in our understanding of cancer, there is an expanding number of potential novel combination therapies, including novel–novel combinations. Identifying which combinations are appropriate and in which subpopulations are among the most difficult questions in medical research. We conducted a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-guided systematic review of trials of novel–novel combination therapies involving immunotherapies or molecular targeted therapies in advanced solid tumors. A MEDLINE search was conducted using a modified Cochrane Highly Sensitive Search Strategy for published clinical trials between July 1, 2017, and June 30, 2020, in the top-ranked medical and oncology journals. Trials were evaluated according to a criterion adapted from previously published Food and Drug Administration guidance and other key considerations in designing trials of combinations. This included the presence of a strong biological rationale, the use of a new established or emerging predictive biomarker prospectively incorporated into the clinical trial design, appropriate comparator arms of monotherapy or supportive external data sources and a primary endpoint demonstrating a clinically meaningful benefit. Of 32 identified trials, there were 11 (34%) trials of the novel–novel combination of anti-programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) and anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) therapy, and 10 (31%) trials of anti-PD-1/PD-L1 and anti-vascular endothelial growth factor (VEGF) combination therapy. 20 (62.5%) trials were phase II trials, while 12 (37.5%) were phase III trials. Most (72%) trials lacked significant preclinical evidence supporting the development of the combination in the given indication. A majority of trials (69%) were conducted in biomarker unselected populations or used pre-existing biomarkers within the given indication for patient selection. Most studies (66%) were considered to have appropriate comparator arms or had supportive external data sources such as prior studies of monotherapy. All studies were evaluated as selecting a clinically meaningful primary endpoint. In conclusion, designing trials to evaluate novel–novel combination therapies presents numerous challenges to demonstrate efficacy in a comprehensive manner. A greater understanding of biological rationale for combinations and incorporating predictive biomarkers may improve effective evaluation of combination therapies. Innovative statistical methods and increasing use of external data to support combination approaches are potential strategies that may improve the efficiency of trial design. Designing trials to evaluate novel–novel combination therapies presents numerous challenges to demonstrate efficacy in a comprehensive manner. A greater understanding of biological rationale for combinations and incorporating predictive biomarkers may improve effective evaluation of combination therapies. Innovative statistical methods and increasing use of external data to support combination approaches are potential strategies that may improve the efficiency of trial design.

INTRODUCTION

With rapid advances in our understanding of cancer genomics and immunobiology, an expanding number of novel therapies are being evaluated in clinical trials.[1] As a consequence, there is an exponentially increasing number of mathematically possible drug combinations,[2] including novel–novel combinations, in which two or more drugs are investigational and are not yet approved standards of care. Concordantly, there has been an increase in the number of clinical trials evaluating combination therapies.[3] The use of combination therapies to improve efficacy has traditionally been a central tenet of medical oncology ever since the initial use of combination chemotherapy regimens in hematological malignancies and breast cancer.[4] The underlying rationale is anchored in the synergistic or additive effects of drugs with differing and potentially complementary mechanisms of action to increase the likelihood of response, forestall or overcome resistance and minimize overlapping toxicities. However, patient-to-patient variability and

the independent action of drugs may also confer benefit for combination therapies without additive or synergistic interactions.[5]

Multiarm, 'pick-the-winner' or factorial trial designs may often be used to evaluate more than one novel treatment individually and in combination in a single trial.[6] However, it may be impractical to conduct such trials due to finite resources, particularly with an increasing number of novel therapies and potential combinations. Identifying which combinations are appropriate in which patient subpopulations are among the most difficult questions in medical research. Garnering regulatory approval requires demonstrating that each component of a combination contributes to its benefit. This creates numerous challenges for clinicians, industry and regulatory bodies alike in designing, conducting and interpreting trials of novel–novel combination therapies. Therefore, the rational, efficient and effective evaluation of novel–novel drug combinations is crucial. Regulatory agencies, such as the US Food and Drug Administration (FDA), have recognized these challenges and have released formal guidance for trial sponsors.[7] Nevertheless, a fine balance between the level of evidence required to obtain regulatory approval of a novel–novel combination versus the practicality of conducting such trials is needed. Furthermore, as the drug development landscape in oncology continues to evolve, such as the advent of immunotherapeutic strategies, capabilities to adapt clinical trial design remain crucial.[8]

We sought to conduct a focused systematic review of clinical trials of novel–novel combination therapies involving immunotherapies or molecular targeted therapies in advanced solid tumors in order to identify opportunities to improve paradigms for the drug development pathway and clinical trial evaluation of the efficacy of rational combination therapies. Selected studies were evaluated and assessed according to a set of criteria adapted from the aforementioned FDA guidance and other key considerations in designing trials of novel–novel combination therapies. This included the underlying biological rationale for the combination, the incorporation of an established or emerging predictive biomarker, and the clinical trial design in terms of comparator arms and the primary endpoint.

METHODS

Search strategy

The search strategy was conducted in MEDLINE according to a modified Cochrane Highly Sensitive Search Strategy to identify published clinical trials that evaluated novel combination therapies in advanced solid tumors. In order to maintain contemporary relevance and focus on the most innovative/promising agents, our search covered the time period from July 1, 2017, to June 30, 2020, and was restricted to articles published in eight selected high-tier peer-reviewed journals (*New England Journal of Medicine*, *Lancet*, *Journal of the American Medical Association*, *Lancet Oncology*, *Journal of Clinical Oncology*, *Cancer Discovery*, *JAMA Oncology*, and *Annals of Oncology*). These journals were selected as the top-ranked general medical or general oncology journals by impact factor that publish oncology clinical trials according to the Journal Citation Reports 2019.

Study selection

A priori inclusion criteria were established. To be eligible for inclusion, studies had to be primary research articles reporting the outcomes of a phase II or III clinical trial evaluating novel–novel combination therapy with programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) or cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) immune checkpoint targeting agents or molecularly targeted agents. Novel–novel combination therapy was defined as two or more investigational drugs, of which none were approved or recommended by treatment guidelines for the given indication. Exclusion criteria included pediatric studies (subjects<18 years of age), observational studies, meta-analyses, publications using pooled data from two or more trials, dose finding or phase I trials, early stage or locally advanced solid tumor studies, and hematological studies. In cases of updated analyses after initial study publication, studies were included in this analysis only if prespecified additional analysis for mature data of primary endpoints was being reported. Board-certified or equivalent oncologists (ACT and MK) reviewed the articles for final eligibility, and disagreement was resolved by discussion and consensus.

Data extraction

Data extracted for each study included (1) study name/clinical trial ID; (2) journal; (3) authors; (4) trial sponsor; (5) tumor type and study population (newly diagnosed vs recurrent); (6) drugs studied; (7) treatment arms; (8) trial phase; (9) treatment regimens; (10) Common Terminology Criteria for Adverse Events version used; (11) biomarker selection criteria; (12) trial endpoints; (13) response data including objective response rate (ORR); (14) survival data including progression-free survival (PFS) and overall survival (OS); (15) adverse event data, including number of total and severe adverse events and mortality; (16) FDA approval for the combination therapy as of September 2020.

Study evaluation and statistical analysis

The trial design of each study was evaluated according to a set of criteria adapted from the criteria outlined by the FDA in their guidance on the development of novel combination therapies.[7] As this review consisted only of studies involving patients with advanced cancer, it was accepted that all studies fulfilled the first FDA criteria, in that studies were evaluating a combination treatment for a serious disease or condition. Further general criteria in the FDA guidance included (1) a strong biological rationale for use of the combination and (2) the combination may provide a significant therapeutic advance over

available therapy and is superior to the individual agents. In addition, factors which contribute to the efficiency of trial design and subsequent clinical impact, such as the use of external data sources and clinically meaningful primary endpoints, were also evaluated.

Trial designs were assessed according to the following criteria:

1. A strong biological rationale, defined as any published in vitro or in vivo preclinical data demonstrating activity specifically for the combination therapy with class-specific agents over the individual agents alone in the given indication. The presence of a biological rationale was considered 'limited' if published preclinical data were conducted only in a single experimental model system.
2. Use of a new established or emerging predictive biomarker prospectively incorporated into the clinical trial design to define eligible patients for the combination therapy and for which there are no approved or recommended therapeutic options for the given biomarker.
3. Appropriate comparator arms where applicable, allowing for an evaluation of the efficacy and safety of the individual agents alone, or supportive external data sources such as prior studies of monotherapy.
4. Primary endpoint which demonstrates a clinically meaningful benefit in the given indication and according to the phase of trial, such as ORR, PFS and/or OS.

RESULTS

Study selection and characteristics

We identified 160 potentially eligible studies. After full-text review and applying the selection criteria, 32 studies were included in the final analysis (figure 1). The characteristics of the studies are listed in table 1. Studies were broadly classified based on the drug–target combination for further in-depth analysis according to the evaluation criteria (see online supplemental appendix for additional results).

Inhibition of PD-1/PD-L1 and CTLA-4 combination therapy

There were 11 trials of the novel–novel combination of anti-PD-1/PD-L1 and anti-CTLA-4 therapy, as shown in figure 2, table 2 and online supplemental appendix, including six (55%) phase II and five (45%) phase III trials. There were four studies conducted in non-small cell lung cancer (NSCLC), with a range of other tumor types in the remaining studies (figure 2).

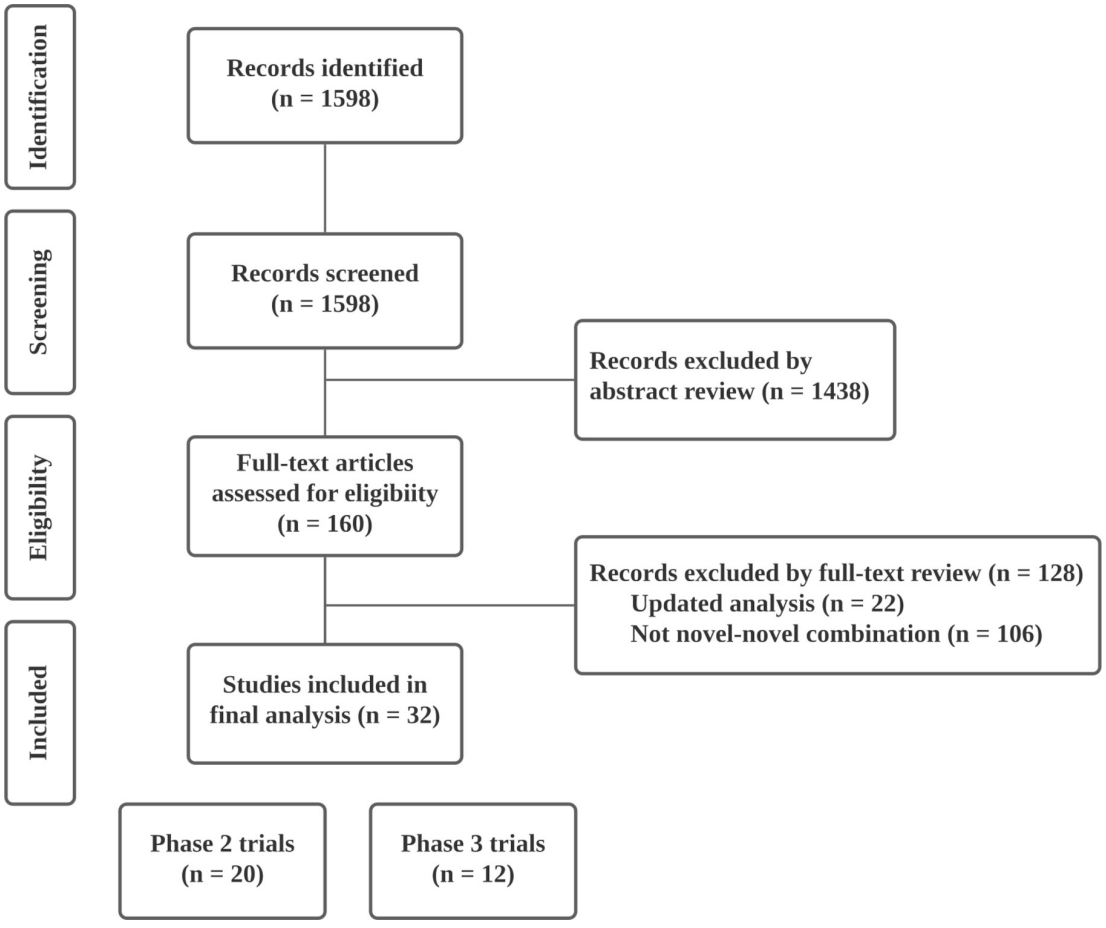

Figure 1 Selection of studies evaluating a novel–novel combination therapy with a targeted therapy and/or immune checkpoint inhibitor.

Table 1 Study characteristics

Characteristics (n=32)	n (%)
Trial phase	
II	20 (62.5)
III	12 (37.5)
Trial sponsor	
Academic	10 (31)
Industry	22 (69)
Tumor type	
Breast	1 (3)
Colorectal	4 (13)
Endometrial	1 (3)
HCC	1 (3)
HNSCC	1 (3)
Melanoma	1 (3)
Mesothelioma	1 (3)
Multiple, including basket	2 (6)
NSCLC	5 (16)
Ovarian	2 (6)
Pancreatic	1 (3)
RCC	7 (22)
Salivary	1 (3)
Sarcoma	3 (9)
Thyroid	1 (3)
Journal	
Annals of Oncology	4 (13)
Cancer Discovery	0 (0)
JAMA	0 (0)
JAMA Oncology	7 (22)
Journal of Clinical Oncology	5 (16)
Lancet	1 (3)
Lancet Oncology	8 (25)
New England Journal of Medicine	7 (22)
Combination therapy	
Immunotherapy	13 (41)
Targeted therapy	8 (25)
Both immunotherapy and targeted therapy	11 (34)
Drug targets	
PD-1/PD-L1+CTLA-4	11 (34)
PD-1/PD-L1+VEGF	10 (31)
BRAF+MEK (±EGFR)	4 (13)
HER2	2 (6)
Other*	5 (16)
Biomarker selection	
Selected	15 (47)
Unselected	17 (53)
Primary endpoint	
Phase II trials (n=36)	
ORR	15 (75)
PFS	3 (15)
OS	1 (5)
DCR	1 (5)
Phase III trials (n=12)	
PFS	2 (17)
OS	3 (25)
PFS and OS	6 (50)

*Chemotherapy+VEGF, chemotherapy+PARP, PD-1+HPV16 vaccine, PD-1+oncolytic virus, PD-L1+MEK.
CTLA-4, cytotoxic T lymphocyte-associated antigen-4; DCR, disease control rate; EGFR, epidermal growth factor receptor; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; JAMA, *The Journal of the American Medical Association*; MEK, mitogen-activated protein kinase kinase; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death 1
; PD-L1, programmed death ligand 1
; PFS, progression-free survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

Rationale for combinations

We first assessed for the presence of a strong biological rationale for the combination approach, according to preclinical data supporting superior efficacy of the combination compared with the individual agents alone, in the given indication. The combination of nivolumab and ipilimumab was first approved in unresectable or metastatic melanoma in 2015, while there is currently no approved indication for the combination of durvalumab and tremelimumab. Preclinical models in melanoma demonstrated the enhanced antitumor activity for combination checkpoint blockade,[9] and development of the combination was also supported by synergistic activity observed in murine colorectal and ovarian tumor models.[10 11] Anti-CTLA-4 therapy impacts the lymphoid compartment, resulting in an increase in the number as well as breadth of specificity of tumor antigen reactive T cells, whereas anti-PD-1 impacts the immunosuppression within the tumor microenvironment. Clinical activity was subsequently seen in a phase I trial of nivolumab and ipilimumab in patients with advanced melanoma.[12] As a result, trials of combination checkpoint blockade were evaluated in numerous other cancers. Of the 11 trials investigating inhibition of PD-1/PD-L1 and CTLA-4 combination therapy included in this review, there was a distinct absence of a strong biological rationale in most studied indications, with limited *in vitro* or *in vivo* data supporting the combination, although in many cases

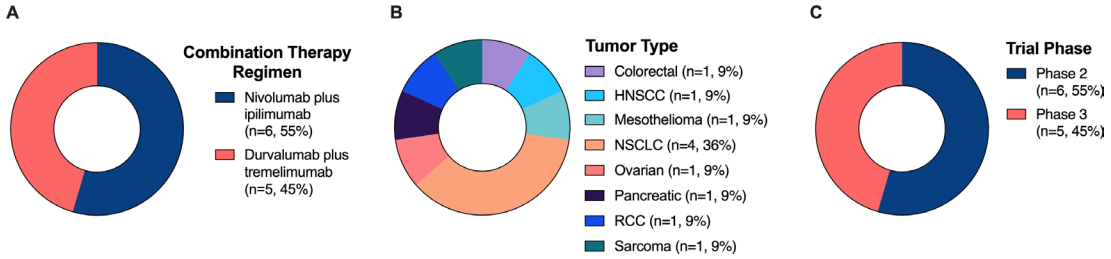

Figure 2 Characteristics of combination anti-PD-1/PD-L1 and anti-CTLA-4 therapy trials. (A) Combination therapy regimen, (B) tumor type, and (C) trial phase. HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

there were preliminary signs of efficacy in early-phase trials, including phase I trials, emphasizing the need for better preclinical models to select rational combination immunotherapy approaches.[13]

Utility of biomarkers

Next, we assessed the incorporation of a newly established or emerging predictive biomarker into the trial design that may suggest efficacy of the combination superior to monotherapy. Of the 11 trials, 6 (55%) were conducted in unselected patient populations. Four (44%) trials selected patients based on PD-L1 status, a previously established but somewhat controversial biomarker to select patients for anti-PD-1/PD-L1 monotherapy. Only one (9%) trial incorporated a new established or emerging biomarker, with the CheckMate 227 trial including a coprimary endpoint of PFS in patients with high tumor mutation burden (TMB) for nivolumab plus ipilimumab versus chemotherapy.[14]

Comparator arms

The use of appropriate comparator arms that would allow for the comparison of the efficacy and safety of the individual agents alone versus the combination was also critically examined. This was evaluated in the context of the presence or absence of supportive external data sources, such as prior studies of monotherapy. Of the phase III trials, one trial was conducted in first-line renal cell carcinoma (RCC), with the remaining trials conducted in NSCLC. CheckMate 214 evaluated nivolumab plus ipilimumab versus sunitinib as first-line therapy in advanced RCC.[15] There was prior monotherapy data for ipilimumab in a phase II trial that allowed pretreated and treatment naïve patients.[16] Nivolumab monotherapy, already approved in the treatment resistant setting,[17] had also been evaluated in treatment-naïve patients in a multicohort phase Ib expansion study.[18] CheckMate 227 was an open-label phase III randomized trial in untreated advanced NSCLC.[14 19] The trial was designed to test multiple nivolumab-based regimens in different patient populations. Nivolumab monotherapy had been previously evaluated in treatment-naïve advanced NSCLC in the phase III CheckMate 026 study in patients with PD-L1 expression of 5% or more,[20] while ipilimumab monotherapy had been evaluated in a previous phase II trial.[21] Durvalumab plus tremelimumab was evaluated in two phase III trials for NSCLC, with the MYSTIC trial[22] as first-line therapy and the ARCTIC trial[23] as third-line or later line therapy. Durvalumab monotherapy had been investigated in the treatment-refractory setting in NSCLC,[24] but neither durvalumab or tremelimumab monotherapy had been previously evaluated in the first-line setting.

Overall, the phase II and III trials of combination anti-PD-1/PD-L1 and anti-CTLA-4 therapy were appropriately designed with comparator arms of either individual agent alone and where there were no prior studies in the given indication.

Primary endpoints

The primary endpoints of the selected studies were also evaluated. In general, the phase II studies used ORR or DCR, while the phase III studies used PFS and/or OS. The primary endpoints were assessed overall as appropriate and clinically meaningful in all studies.

Inhibition of PD-1/PD-L1 and VEGF combination therapy

There were 10 trials of the novel–novel combination of anti-PD-1/PD-L1 and anti-vascular endothelial growth factor (VEGF) therapy, as shown in figure 3, online supplemental table 1 and online supplemental appendix.

Rationale for combinations

The combination of antiangiogenic therapy and immune checkpoint inhibitor therapy is based on evidence demonstrating that aberrant angiogenesis is a hallmark of many solid tumors, resulting in immune evasion.[25] Therefore, normalization of abnormal tumor vasculature with antiangiogenic therapy may improve immune effector cell function by decreasing hypoxia, acidosis and nutrient deprivation and may increase the infiltration of immune effector cells into the tumor microenvironment in order to enhance the efficacy of immunotherapy. VEGF also has pleotropic immunosuppressive effects including impairment of dendritic cell function, as well as mobilization of immunosuppressive cells such as tumor associated macrophages, regulatory T cells, and myeloid-derived suppressor cells.[26] Consequently, this has led to a proliferation of studies of novel–novel combinations of therapeutics from these two classes. Improved efficacy with combination inhibition of VEGF and immune checkpoint blockade has been shown in animal models for melanoma,[27] colorectal cancer,[28] breast cancer and

Table 2 Combination anti-PD-1/PD-L1 and anti-CTLA-4 therapy trials

Study name	Year, lead author	Tumor type	Line of therapy	Combination regimen	Patients (total n)	Biomarker selection	Primary endpoint	Trial design	Primary endpoint met	FDA-approved therapy	Strong biological rationale	New biomarker	Comparator arms of monotherapy	Clinically meaningful primary endpoint
Phase II trials														
Alliance A091401	2018, D'Angelo	Sarcoma	2+	Nivolumab plus ipilimumab	96	Unselected	ORR (N and N+I)–non-comparative	N or N+I (1:1)	Yes	No	No	No	Yes	Yes
CONDOR	2019, Siu	HNSCC	2+	Durvalumab plus tremelimumab	267	PD-L1	ORR (D+T)–non-comparative	PD-L1<25%, D+T or D or T (2:1:1)	Yes	No	No	No	Yes	Yes
IFCT-1501 MAPS2	2019, Scherpereel	Mesothelioma	2+	Nivolumab plus ipilimumab	125	Unselected	DCR at 12 weeks (N and N+I)–non-comparative	N or N+I (1:1)	Yes	No	No	No	Yes	Yes
NCT02558894	2019, O'Reilly	Pancreatic	2	Durvalumab plus tremelimumab	65	Unselected	ORR (D+T and D)–lead-in safety study, with expansion pending efficacy signal, non-comparative	D+T or D (1:1)	No	No	No	No	Yes	Yes
CO.26	2020, Chen	Colorectal	3+	Durvalumab plus tremelimumab	180	Unselected	OS (D+T vs BSC)	D+T or BSC (2:1)	Yes	No	Limited	No	No	Yes
NRG GY003	2020, Zamarin	Ovarian	2+	Nivolumab plus ipilimumab	100	Unselected	ORR at 6 months (N vs N+I)	N or N+I (1:1)	Yes	No	Limited	No	Yes	Yes
Phase III trials														
CheckMate 214	2018, Motzer	RCC	1	Nivolumab plus ipilimumab	1096	Unselected	Coprimary: OS, ORR and PFS (in intermediate or poor prognostic risk)	N+I or sunitinib (1:1)	Yes	Yes	No	No	Yes	Yes
CheckMate 227	2018, Hellmann	NSCLC	1	Nivolumab plus ipilimumab	1739	TMB	Coprimary: PFS (N+I vs chemo in TMB high)	PD-L1≥1%, N+I or N or chemo (1:1:1)	No	Yes	No	Yes	Yes	Yes
CheckMate 227	2019, Hellmann	NSCLC	1	Nivolumab plus ipilimumab	1739	PD-L1	Coprimary: OS (N+I vs chemo in PD-L1≥1%)	PD-L1<1%, N+I or N+chemo or chemo (1:1:1)	Yes	Yes	No	No	Yes	Yes
MYSTIC	2020, Rizvi	NSCLC	1	Durvalumab plus tremelimumab	1118	PD-L1	Coprimary: OS (D vs chemo in PD-L1≥25%), PFS and OS (D+T vs chemo in PD-L1≥25%)	D or D+T or chemo (1:1:1)	No	No	No	No	Yes	Yes
ARCTIC	2020, Planchard	NSCLC	3+	Durvalumab plus tremelimumab	595	PD-L1	Coprimary: PFS and OS (D+T vs SOC in PD-L1<25%)	Study A: PD-L1≥25%, D or SOC (1:1); Study B: PD-L1<25%, D+T or SOC or D or T (3:2:2:1)	No	No	No	No	Yes	Yes

BSC, best supportive care; Chemo, chemotherapy; D, durvalumab; DCR, disease control rate; HNSCC, head and neck squamous cell carcinoma; I, ipilimumab; N, nivolumab; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression free survival; RCC, renal cell carcinoma; SOC, standard of care; T, tremelimumab; TMB, tumor mutation burden.

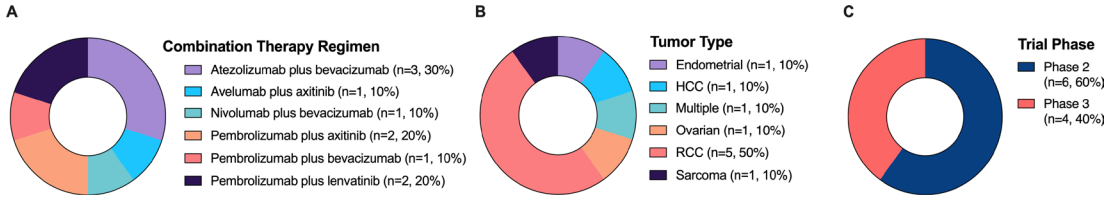

Figure 3 Characteristics of combination anti-PD-1/PD-L1 and anti-VEGF therapy trials. (A) Combination therapy regimen, (B) tumor type, and (C) trial phase. HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

pancreatic neuroendocrine tumors.[29] Specifically, lenvatinib plus anti-PD-1 therapy has also been evaluated in murine hepatocellular, colorectal and melanoma models.[30 31] However, preclinical data demonstrating the efficacy of other specific drug combinations are sparse. For example, the combination of axitinib plus avelumab in RCC had not been published in preclinical models, and the rationale for the combination as first-line therapy was based on the toxicity profile for axitinib, with lower hepatotoxicity compared with sunitinib.[32] There were also no preclinical data published for the remaining combination therapies in the given studied indications.

Utility of biomarkers

Of the 10 trials evaluating combination anti-PD-1/PD-L1 and anti-VEGF therapy, a majority (80%) were conducted in biomarker unselected populations of patients. The two (20%) trials, which included biomarker selection criteria, selected patients on the basis of PD-L1 IHC for avelumab[33] and atezolizumab,[34] respectively, in advanced RCC. PD-L1 IHC had not been previously established as a biomarker for patient selection for anti-PD-1/PD-L1 therapy in advanced RCC and therefore represented a new predictive biomarker in this patient population. No robust biomarkers for anti-VEGF therapy have been identified, and consequently, no trial attempted to select a biomarker for this class of agents.

Comparator arms

Overall, the phase II trials of combination anti-PD-1/PD-L1 and VEGF therapy were appropriately designed with comparator arms of either individual agent alone and where there were no prior studies in the given indication. Two phase III trials in patients with treatment-naïve metastatic RCC involved axitinib combinations. Axitinib monotherapy is approved in the second-line setting[35] but had not been previously evaluated as first-line therapy.

Primary endpoints

The primary endpoint in five of the six phase II trials was ORR, with the remaining trial of pembrolizumab plus axitinib in metastatic sarcoma using PFS rate at 3 months as the primary endpoint. Coprimary endpoints of PFS and OS were used in the four phase III trials of combination anti-PD-1/PD-L1 and anti-VEGF therapy. Overall, these endpoints were considered appropriate and clinically meaningful. It should be borne in mind that in tumors of the central nervous system, both pseudoprogression and pseudoresponse have been identified as limiting characteristics of immune checkpoint inhibitors and antiangiogenic inhibitors, respectively, and in certain extracranial settings, concern regarding post-treatment peritumoral inflammatory changes ('pseudoprogression') following checkpoint inhibition has been described. These could limit the validity of ORR as an endpoint in such studies.

Inhibition of BRAF and MEK combination therapy

There were four trials of the novel–novel combination of BRAF and mitogen-activated protein kinase kinase (MEK) inhibitor therapy, as shown in online supplemental table 2 and online supplemental appendix. In addition, the BEACON CRC trial evaluated epidermal growth factor receptor (EGFR) inhibitor therapy in combination with BRAF and MEK inhibition.[36]

Rationale for combinations

In *BRAF*-mutated melanoma, the combination of BRAF and MEK-pathway inhibition had initially established clinical efficacy and tolerability compared with BRAF-inhibitor monotherapy with two combinations (dabrafenib plus trametinib, and vemurafenib plus cobimetinib).[37 38] BRAF and MEK inhibitor combinations were originally developed based on preclinical data demonstrating that the combination could improve efficacy and delay the emergence of resistance.[39 40] Reactivation of the MAPK pathway was a commonly reported mechanism of resistance to BRAF-inhibitor monotherapy.[41 42] The combination of encorafenib and binimetinib was subsequently evaluated due to the increased potency of encorafenib compared with dabrafenib and vemurafenib, related to a greater dissociation half-life and improved pharmacodynamics.[43] Furthermore, the combination with binimetinib, which ameliorated the toxicity of encorafenib monotherapy, allowed for high doses of encorafenib in the combination treatment.[43]

The rationale for the inhibition of BRAF, MEK and EGFR in *BRAF* V600E mutated colorectal cancer was developed after extensive preclinical investigations characterizing these pathways. Rapid feedback activation through EGFR after BRAF inhibition alone explained the poor efficacy of BRAF monotherapy and led to the development of BRAF plus EGFR inhibitor combinations.[44 45] Subsequently, the combination of BRAF and MEK inhibition to improve efficacy compared with BRAF plus EGFR inhibition was also demonstrated preclinically.[46 47]

Utility of biomarkers

All four combination trials of BRAF plus MEK inhibition selected patients based on the presence of a *BRAF* mutation. For advanced melanoma, there were already approved therapies for patients harboring *BRAF* mutations. In the remaining tumor types, however, the combination therapies represented a new genotype-directed therapeutic option.

Comparator arms and primary endpoints

COLUMBUS was a three-arm, randomized phase III study evaluating combination encorafenib (450 mg daily dose) plus binimetinib versus encorafenib monotherapy (300 mg daily dose) versus vemurafenib monotherapy.[48] Binimetinib monotherapy had previously been investigated in a phase II study for patients with NRAS or BRAF-mutated melanoma.[49] BEACON CRC (Binimetinib, Encorafenib, and Cetuximab Combined to Treat BRAF-Mutant Colorectal Cancer) was also a three-arm, randomized phase III study, with study arms consisting of triplet therapy (encorafenib, binimetinib and cetuximab), doublet therapy (encorafenib and cetuximab) or investigator's choice of cetuximab plus irinotecan or cetuximab plus FOLFIRI (control group).[36] There had been no prior trials of encorafenib, binimetinib or cetuximab monotherapy in patients with advanced *BRAF* V600E mutated colorectal cancer. Cetuximab monotherapy had previously been studied in unselected patients with metastatic colorectal cancer.[50] Retrospective analyses, however, suggested responses to cetuximab may be lower in patients with BRAF mutations.[51] Additionally, vemurafenib monotherapy had been investigated in *BRAF* V600E mutated colorectal cancer in a small phase II trial and a basket trial.[52 53] There was no meaningful clinical activity for vemurafenib monotherapy, with only one response out of 31 patients across the two trials. The primary endpoints in COLUMBUS and BEACON CRC were both considered clinically meaningful.

Inhibition of HER2 combination therapy

There were two studies reporting the novel–novel combination of human epidermal growth factor receptor 2 (HER2) inhibitor therapy with trastuzumab and pertuzumab, as shown in online supplemental table 3 and online supplemental appendix. Both studies were reports from the MyPathway basket trial for patients with colorectal cancer[54] and salivary gland cancers,[55] respectively.

Rationale for combinations

In colorectal cancer, pre-clinical data from HER2-amplified colorectal tumor grafts or xenografts, had demonstrated limited activity of single agent HER2 targeted therapy with trastuzumab, pertuzumab or lapatinib.[56 57] Anti-tumor activity however, was increased with combination HER2 targeting regimens, although with trastuzumab plus lapatinib or pertuzumab plus lapatinib. The complementary mechanisms of action of trastuzumab and pertuzumab, and demonstrated efficacy in breast cancer,[58] provided a strong rationale for this combination in HER2-amplified colorectal cancer.

Utility of biomarkers

As HER2 targeted therapies had not been approved in either tumor type, both studies were assessed as incorporating a new established or emerging biomarker.

Comparator arms and primary endpoints

As a phase IIa multiple basket trial of various targeted therapies in advanced solid tumors, ORR was considered an appropriate and clinically meaningful endpoint for the MyPathway trial. Understandably, as a basket trial, comparator arms of either trastuzumab or pertuzumab monotherapy were not included in this trial.

Other combination therapies

There were five trials evaluating other novel–novel combination therapies, including chemotherapy plus VEGF inhibitor therapy, chemotherapy plus poly(ADP-ribose) polymerase (PARP) inhibitor therapy, anti-PD-1 plus HPV16 vaccine therapy, anti-PD-1 plus an oncolytic virus therapy, and anti-PD-L1 plus MEK inhibitor therapy (online supplemental appendix and online supplemental table 4).

COTEZO IMblaze 370 was a three-arm randomized phase III study of atezolizumab plus cobimetinib versus atezolizumab monotherapy versus regorafenib in patients with previously treated metastatic colorectal cancer.[59] In the initial phase I trial of cobimetinib monotherapy, there were 41 patients with metastatic colorectal cancer, but no responses were seen.[60] The combination of anti-PD-L1 and MEK inhibitor in colorectal cancer was developed on the basis of preclinical data, suggesting MEK inhibition could affect the immune contexture in the tumor microenvironment.[61] Cobimetinib had been shown to increase T-cell infiltration into tumors and downregulate immunosuppressive cytokines and receptors.[62] Combination therapy of cobimetininb with anti-PD-L1 inhibition also resulted in synergistic and durable tumor regression in mice models.[62]

BROCADE was a three-arm phase II trial for patients with *BRCA1/2*-mutated recurrent or metastatic breast cancer.[63] Patients were randomized to receive veliparib plus carboplatin/paclitaxel or veliparib plus temozolomide or carboplatin/paclitaxel. The primary endpoint was PFS comparing both veliparib containing arms with chemotherapy alone. Veliparib plus temozolomide was considered the novel–novel combination for this review. Veliparib monotherapy had been evaluated in a single-arm phase II trial for patients with germline *BRCA1/2* associated metastatic breast cancer,[64] while temozolomide monotherapy had previously shown a lack of activity in an unselected population of patients with metastatic breast cancer.[65] The rationale for the combination of temozolomide and veliparib was from preclinical breast cancer models which demonstrated synergistic activity for the combination.[66 67] At the time the study was developed,

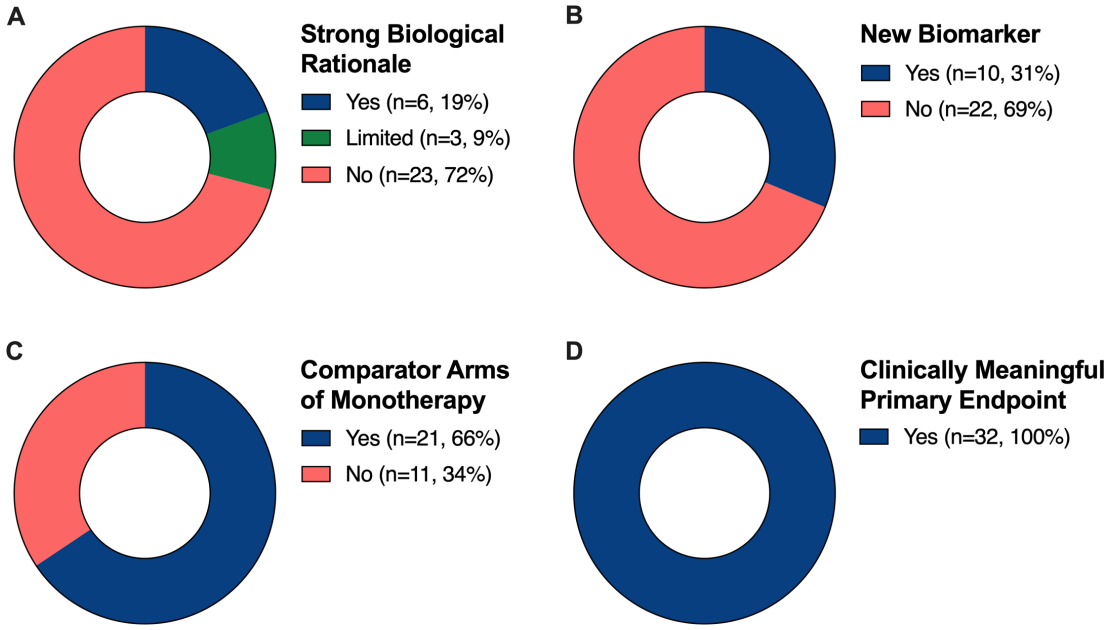

Figure 4 Overall evaluation of novel–novel combination therapies of immune checkpoint inhibitors or molecular targeted agents in solid tumor oncology. (A) Strong biological rationale, (B) new biomarker, (C) comparator arms of monotherapy, and (D) clinically meaningful primary endpoint.

there were no targeted therapies approved for patients *BRCA1/2*-mutated breast cancers.[68]

Overall evaluation of novel–novel combination therapies in oncology

The overall assessment and evaluation of trial designs of novel–novel combination therapies according to the four criteria are shown in figure 4.

Discussion

With an expanding number of novel therapies in clinical development and possible drug combinations, the fundamental challenge remains to evaluate rational combinations efficiently and effectively. In particular, a mechanistic understanding of the contribution of each drug to the treatment effect is needed, both from a scientific and regulatory perspective.[69] Based on a systematic review of the top general medical and oncology journals over the past 3 years, we identified 32 recently published trials evaluating novel–novel combinations and evaluated each trial according to criteria adapted from FDA guidance on the development of novel combination therapies (box 1).

First, we assessed the strength of the biological rationale according to the presence of published preclinical data. Most trials (72%) lacked significant preclinical evidence supporting the development of the combination in the given indication. This was particularly evident in studies evaluating combination immune checkpoint blockade, for which there were only two studies with limited preclinical data in colorectal and ovarian cancers. This could, in part, be attributed to difficulties in developing preclinical animal models for immunotherapy, due to the inability of immunocompetent animal models to fully recapitulate the human immune system.[70] Phase I studies were also excluded from our analysis, for which preclinical data may be especially relevant in the initial decision to evaluate a combination. Notably, however, significant clinical efficacy in tumor types such as NSCLC[14 19] and RCC[15] has been seen, despite the lack of supportive preclinical data. For some of these tumors (such as RCC), evidence of single agent activity or early efficacy in phase I trials served as the rationale for subsequent combination phase II and III studies. Coupled with the initial outcomes of trials in melanoma,[12] this has resulted in a rapid increase in the number of combination immunotherapy trials.[3] Nevertheless, the value of numerous trials with overlap and duplication in the combination partner targets, being conducted in unselected patients can be questioned,[3] particularly in cancers for which single-agent immunotherapy has no activity. This observation highlights the importance of a greater understanding of tumor-specific immunity and the need to develop more effective biomarkers.[71] Given the expanding number of potential combinations, rational selection of combinations based on mechanistic evidence and robust biological rationale is crucial.[72] Additionally, for many trials in our review, preclinical data supporting the combination may have been demonstrated in other tumor types outside the given trial's studied indication. Particularly for targeted therapies, there can be significant diversity across tumor types in the actionability of oncogenic driver mutations.[73] *BRAF* V600E mutations are a prominent example, with a spectrum of activity for combination BRAF and MEK inhibition across histologies.[74] This diversity is also exemplified in colorectal cancer, with the role for combined BRAF plus EGFR inhibition demonstrated elegantly in preclinical studies.[44]

Box 1 What is specifically learned about combinations of novel–novel agents?

Summary: We searched MEDLINE according to a modified Cochrane Highly Sensitive Search Strategy to identify published clinical trials that evaluated novel combination therapies in advanced solid tumors. Our search covered the period from July 1, 2017, to June 30, 2020. We restricted our search to articles published in eight selected peer-reviewed journals (*New England Journal of Medicine*, *Lancet*, *Journal of the American Medical Association*, *Lancet Oncology*, *Journal of Clinical Oncology*, *Cancer Discovery*, *JAMA Oncology* and *Annals of Oncology*). We identified 160 potentially eligible studies. After full-text review and applying the selection criteria, 32 studies were included in the final analysis (figure 1). Studies were broadly classified based on the drug–target combination for further in-depth analysis. Below is a summary of the key messages and recommendation.

A. Key Messages

1. Combinations are the future of clinical trials and this is so in most diseases.
2. Identifying which combinations are appropriate and in which patient subpopulations are among the most difficult questions in medical research.
3. In 72% of the analyzed studies, there was no significant preclinical evidence supporting the development of the specific combination in the given indication. This was especially true in studies with combination immune checkpoint blockade. This, in part, may be due to difficulties in developing immunocompetent animal models to fully recapitulate the human immune system.
4. In 69% of the analyzed studies, trial populations were unselected and did not use pre-existing predictive biomarkers for the given indication for patient selection.
5. Sixty-six per cent of the trials analyzed had appropriate comparator arms or had supportive external data sources such as monotherapy prior studies.
6. A greater understanding of the biological rationale for the combination and incorporating novel biomarkers can improve the practical evaluation of novel–novel combination therapies. However, biomarker-driven clinical trials using combination therapies present additional challenges and require careful consideration of the biomarkers' performance and clinical utility.
7. Actionability of oncogenic driver mutations and utility of a specific biomarker in one cancer type does not predict similar outcomes in other cancers, for example, EGFR in NSCLC versus CRC, TMB in NSCLC versus gliomas. Therefore, preclinical and clinical rationales for biomarker-driven combination therapies in one cancer cannot justify a combination trial in another histology.
8. There were no prior activity data for monotherapy in specific tumor cohorts in many basket trials (eg, MyPathway and ROAR).
9. Garnering regulatory approval requires demonstrating that each component of a combination contributes to its benefit. Such demonstrations may entail factorial designs and require interacting closely with regulators.
10. Partial factorial designs in adaptive clinical trials are likely to be the best and most efficient solutions for the future, especially in the context of precision medicine where biomarker-defined subpopulations are becoming the norm.

B. Recommendations

1. Avoid duplication in partner targets in unselected patients, particularly in cancers for which single-agent immunotherapy has no activity.
2. In the design of a combination, consider whether other monotherapy arms are required when trial designs are conceived.
3. Consider if randomized arms of monotherapy are ethical; for example, if based on the mechanism of action, no clinical activity of monotherapy is expected.
4. Consider use of milestone survival or response endpoints to more efficiently generate early evidence.
5. Consider the incorporation of real-world evidence and novel hybrid designs, including in regulatory decision making.
6. Consider using (historical) data on single-agent efficacy, ideally to be obtained from multiple datasets and for all agents within the combination.
7. Consider introducing experimental therapies, including novel–novel combinations, into the trial at any time, allowing for rational combinations based on new biological or clinical insights.
8. Consider innovative but sound statistical methods, including use of historical or external data sources to support combination approaches.

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TMB, tumor mutational burden.

We then evaluated the use of a newly established or emerging predictive biomarker incorporated into the clinical trial design. Similarly, we found that a majority of trials (69%) were conducted in biomarker unselected populations or used pre-existing biomarkers within the given indication for patient selection. No studies included separate novel predictive biomarkers for both novel agents. Biomarker-driven clinical trial designs and analysis plans present additional challenges and require careful consideration of the biomarkers' performance and clinical utility.[75] However, the use of biomarker-selected patients has the potential to both improve patient care and accelerate drug development with greater efficiency.[76] CheckMate 227,[14] which incorporated association of TMB with OS as a second coprimary endpoint after an amendment prior to the initial analysis, demonstrated the flexibility of a large phase III trial to adapt to the emerging science. The biomarker was also investigated as a subset of the overall trial population—an important consideration in prospective biomarker-driven clinical trial design. Ultimately, the role for TMB as a predictive biomarker in NSCLC remains unclear.[77] Furthermore, despite tissue agnostic approval for TMB of ≥10 as a biomarker for pembrolizumab,[78] there remains controversy over its use with numerous biological and practical considerations across tumor types.[79 80] This illustrates the difficulties in identifying predictive biomarkers, which may lag behind the development of novel therapeutics.[81] Dynamic biomarkers, which may change over time as tumors evolve, and the cost of developing biomarkers further complicate the development process. Nevertheless, particularly for immunotherapies, different agents may have pleiotropic effects on a variety of different cells and compartments where they are operational. There may also be heterogeneity in the relative contribution of

the various elements among patients. Therefore, without relevant biomarker selection-driven trial design, clinical efficacy may not be gleaned with an all-comers approach.

Trial design with appropriate comparator arms of monotherapy was also assessed for each trial. Most studies (66%) were considered to have appropriate comparator arms or had supportive external data sources such as prior studies of monotherapy. Noticeably, in basket trials, such as MyPathway[54 55] and ROAR (Rare Oncology Agnostic Research),[82] there were no data for monotherapy in certain tumor cohorts. However, basket trials in rare tumor types or uncommon molecular subsets clearly face practical challenges in terms of statistical design and patient recruitment. This emphasizes the need for a comprehensive understanding of tumor biology to identify optimal combinations.[83] There is also increasing use and acceptance of real-world evidence in regulatory decision making.[84] Historical data on single-agent efficacy would ideally come from multiple datasets and for all agents within the combination.[85] There may also be situations in which randomized arms of monotherapy may be unethical, for example, if no clinical activity of monotherapy is expected based on the mechanism of action. This heightens the importance of careful consideration to determine whether additional arms of monotherapy are required when trial designs are conceived.

Finally, all studies were evaluated as selecting a primary endpoint, which demonstrated a clinically meaningful benefit. Nonetheless, there can be complexities in determining the validity of surrogate endpoints particularly for early-phase combination immunotherapy trials. Milestone survival or response endpoints are increasingly used[86] to more efficiently generate early evidence. KEYNOTE-146[87] for example, had a primary endpoint of ORR at 24 weeks, and ultimately was the basis of FDA approval for the combination of pembrolizumab plus lenvatinib in endometrial cancer.[88] This trial also provides important insights into the use of historical data to evaluate the treatment effect of lenvatinib and pembrolizumab monotherapy.[89 90] Additional exploratory post hoc analyses using propensity score approaches were also conducted by the FDA to evaluate the contribution of each agent.[88] Importantly though, confirmatory randomized trials evaluating the combination are still ongoing.

Collectively, our review has identified that improvements in the effective evaluation of novel–novel combination therapies are clearly needed. Many of these findings may also be applicable to other combination therapies, including a new combination of two previously approved agents or the addition of a new agent to an existing approved therapy. In box 1, we provide a series of recommendations on the efficient design of future clinical trials evaluating novel combination therapies. Novel adaptive trial designs represent one approach that may enhance the efficiency of trials. GBM AGILE, a phase II/III adaptive platform trial (NCT03970447), is an example which incorporates statistical innovations such as Bayesian Adaptive design in a seamless registration trial.[91] Candidate biomarkers may be identified and validated under this single platform master protocol. Furthermore, experimental therapies, including novel–novel combinations, may be introduced into the trial at any time, allowing for rational combinations based on advances in our biological understanding of tumors. Pharmaceutical platforms are also increasingly using multiarm randomized trials, for example, MORPHEUS (NCT03193190, NCT03281369, NCT03280563, NCT03424005, and NCT03337698), with multiple combination therapy arms compared against a single standard-of-care control arm, and allow for the introduction of novel–novel combinations at any time.[92] Additionally, seamless phase I/II trials are becoming more commonly used[93] and highlight that many of the considerations we have outlined previously may become increasingly important in the strategic design of early-phase studies as well. In particular, this includes the introduction of experimental rational combinations based on emerging biological or clinical insights—to establish appropriate dosing and characterize safety.

There are several limitations to our review, including the restricted time period (July 2017–June 2020) and journal selection, which may have introduced inherent publication bias into the studies included in our review. However, there were still 6/32 (19%) trials, which did not meet the primary endpoint included, and our evaluation criteria were not dependent on the trial's primary outcome. In selecting only published trials, which was required to assess our evaluation criteria, contemporary trials such as the aforementioned adaptive platform trials will have been excluded. Broader evaluation of ongoing and unpublished trials is therefore also warranted, although outside the scope of this study. The included trials also represent the data known at the time of initial publication, not necessarily the data known at the time of trial design, and may therefore not completely reveal the historical sequence of events at the time of study conception. Ultimately though, there also needs to be inherent flexibility to adapt to rapidly evolving clinical paradigms. Lastly, there is significant heterogeneity of the included trials, particularly with regard to tumor types, trial design and mechanism of action of drug combinations. Nevertheless, the primary focus of this review was to identify guiding principles to improve trial efficiency in evaluating novel–novel drug combinations. Our analysis provided key insights into the published literature with recommendations (box 1) to improve paradigms for drug development and future trial design.

CONCLUSIONS

Designing trials to evaluate novel–novel combination therapies presents numerous challenges to demonstrate efficacy in a comprehensive manner. Critically, a greater understanding of the biological rationale for the combination and incorporating novel predictive biomarkers may further improve the effective evaluation of novel–novel combination therapies. Innovative statistical methods and increasing the use of historical or external data sources to support combination

approaches are potential strategies that may improve the efficiency of trial design.

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