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REVIEW – CLINICAL ONCOLOGY

A systematic review of head-to-head trials of approved monoclonal antibodies used in cancer: an overview of the clinical trials agenda

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Abstract

Background Since 1997, several monoclonal antibodies (mAbs) targeting the same receptor or its ligand have been approved for use in oncology. However, no studies have summarized head-to-head trials of these mAbs.

Methods Systematic search of the biomedical literature and ClinicalTrials.gov for randomized studies comparing mAbs targeting the same receptor or its ligand that have been completed and published, completed and unpublished, or ongoing. We extracted trial characteristics including phase, indication, enrollment or target enrollment, randomization, primary endpoint and sponsor.

Results Twenty-two approved cancer mAbs had at least one other approved mAb targeting the same receptor or its ligand, totaling 41 different oncology indications. These include 5 anti-CD20 mAbs, 5 anti-PD1/PDL1 mAbs, 4 anti-HER2 mAbs, 3 anti-EGFR mAbs, 3 anti-VEGF mAbs and 2 anti-IL6/IL6R mAbs. Seventeen were completed and published and 14 were unpublished or ongoing trials. The completed and published trials enrolled 11,373 patients and tested 13 mAbs (13/22, 59%). Additionally, 13 (76%) contained drugs manufactured by the same company and 13 (76%) reached conclusions felt to be favorable to the sponsor. Of the 14 ongoing/completed unpublished trials, there is a total target enrollment of 3404 patients with 9 mAbs tested. Of these, 86% (12/14) are testing mAbs manufactured by the same company and 71% (10/14) are sponsored by the company that made the drug being tested.

Conclusions Most trials test drugs manufactured or sponsored by the same company. An overview of clinical trials agenda may lead to more uniform testing, helping clinicians make better evidence-informed prescribing decisions.

Keywords Head-to-head trial · Monoclonal antibodies · Immunotherapy

Key points

Question What head-to-head trials have been or are being performed for mAbs with the same target receptor or its ligand in oncology?

Findings We found 17 completed and published and 14 completed and unpublished or ongoing trials of head-to-head mAbs targeting the same receptor or its ligand. Most combinations of the 22 approved mAbs and 150 possible head-to-head trials have not been tested, and most studies test drugs manufactured by the same company.

Meaning For cancer mAbs with the same target, to maximize informed decision making, the overarching trials agenda should be examined.

Jia Luo and Go Nishikawa are contributed equally to this work.

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Introduction

Since the US Food and Drug Administration's (FDA) approval of anti-CD20 monoclonal antibody (mAb) rituximab in 1997 for relapsed/refractory low-grade non-Hodgkin lymphoma, several mAbs have been approved for use in various cancers. Approvals have been granted for mAbs targeting growth factor receptors (ErbB family EGFR and HER-2, and VEGF), and recently immune modulating mAbs targeting T cell activation signals (PD-1/PDL-1 and CTLA-4). The FDA has approved multiple mAbs targeting the same protein that have individually shown durable clinical benefit, allowing oncologists flexibility in choosing therapy for patients.

Despite the approval of multiple Abs with the same target, most randomized clinical trials have tested therapies against placebo. Performing head-to-head randomized controlled trials for mAbs would be desirable to directly compare relative benefits and side effects of these interventions (Song et al. 2009; Song et al. 2003). For this reason, we sought to summarize all completed and upcoming trials of head-to-head mAbs targeting the same protein. Specifically, we aimed to describe which mAbs have been directly compared, how the trials were conducted, the outcomes, and a descriptive summary of the overall clinical trials agenda.

Methods

We sought to identify all head-to-head trials comparing two mAbs with the same target that have been performed or are actively being tested in oncology.

Search and inclusion criteria

To identify candidate mAbs, we searched the US FDA Drugs website (Drugs@FDA) beginning in 1997, when rituximab was first approved, for all monoclonal antibodies approved for a cancer indication on 1/28/18 (US Food and Drug Administration 2018). We collected the generic name, brand name, manufacturer, type of antibody (animal, human, humanized or chimeric), first approval year, and FDA approved indication. We then included groups of mAbs that targeted the same receptor or its ligand. We searched for and read the most recent FDA drug label at Drugs@FDA and noted the approved indications for that drug under "Indications and Usage."

To identify all published head-to-head trials of mAbs targeting the same protein, we performed MEDLINE and Google Scholar searches between 3/4/2018 and 3/22/2018. We performed the search in the following four ways. First, for each mAb, we found the most recent FDA drug label per above and identified all randomized head-to-head trials. Next, using MEDLINE, we searched names (generic, and letter and number name e.g. MYL 1401O) of all combinations of pairs of mAbs and filtered by clinical trials, and a second search of the mAbs and "randomized." We also used Google Scholar, searching for the drug names and "phase 3" and a second search using "randomized."

To identify all unpublished and ongoing trials comparing mAbs head-to-head, we searched ClinicalTrials.gov (NIH US National Library of Medicine 2018). For each of the queries, we used a combination of two mAbs and "randomized". We scanned each of the trials that met our criteria which included trials categorized as "recruiting," "terminated," "active, not recruiting," and "completed".

We first scanned titles, then abstracts and papers. We excluded trials that used experimental drugs, and those that did not test drugs head-to-head. We included trials where there were at least two arms comparing mAbs of the same target head-to-head. A consort diagram is located in the Supplement.

Data collection

For each published randomized trial, we collected names of the mAbs, trial name, phase and design, disease indication, number of patients enrolled, randomization scheme, blinding, treatment arms, primary endpoint, sponsor, NCT (from ClinicalTrials.gov) and PMID (from MEDLINE).

We classified the conclusion of a trial as favorable to the sponsor if the mAb manufactured by the sponsor showed the statistically superior primary endpoint. For noninferiority trials, we classified the trial as favorable if the sponsor's drug was non-inferior to the control arm. For trials where the sponsor tested their own drugs head-to-head, we classified the result as favorable if the newer drug had the more favorable primary endpoint result.

For the ongoing head-to-head trials, we collected the following information: names of the mAbs, phase, indication, target enrollment, status of the trial and completion date, treatment arms, primary endpoint, sponsors and collaborators, and NCT. Two authors extracted the data and discrepancies were discussed among all three authors to reach an agreement.

Data analysis

Descriptive statistics were used when appropriate. Tables were made in Microsoft Excel 2017. Figures were made in Adobe Illustrator CC 2017. To identify the number of possible combinations to search, we calculated the number of potential comparisons of pairs of mAbs with the same target as follows: $C(n, k) = P(n, k)/k! = n!/(n–k)!$, where n = total

number of mAbs with the same target and $k=2$. This study of head-to-head trials did not involve human subjects and did not require IRB approval. Our study was conducted between January 28, 2018 and May 7, 2018.

Results

Characteristics of included antibodies

We found 34 mAbs approved for treating cancer from 1997 to 2017.

Of these, 22/34 (65%) had at least one other approved mAb targeting the same receptor or its ligand (Table 1). There were five approved anti-CD20 mAbs and anti-PD1/PDL1 mAbs. We identified four approved anti-HER2, three anti-EGFR, three anti-VEGF and two anti-IL6/IL6R mAbs. Among these, eight are human antibodies (8/22, 36%), nine humanized antibodies (9/22, 41%), four chimeric antibodies (4/22, 18%) and one mouse antibody (1/22, 5%).

Defining a "unique indication" as both the cancer type and, if specified, line of treatment per the FDA drug label, we found each mAb is approved for between 1 and 10 indications in cancer. In sum, 11 unique indications exist for the anti-PD1/PDL1 mAbs, 6 for the anti-CD20 mAbs, 6 for the anti-HER2 mAbs, 8 for the anti-EGFR mAbs, 9 for the anti-VEGF mAbs and 1 for the anti-IL6/IL6R mAbs.

Using the combinatorics calculation described in the methods, when we account for the number of unique indications for each type of mAb, the maximum number of potential head-to-head trials is 55 for anti-PD1/PDL1 mAbs, 36 for anti-VEGF, 28 for anti-EGFR, 15 for anti-CD20, 15 for anti-HER2 and 1 anti-IL6 head-to-head trials. We found 1 anti-PD1/PDL1 [0 completed and published (C), 1 ongoing or completed and unpublished (O)], 1 anti-VEGF (1 C, 0 O), 1 anti-EGFR (1 C, 0 O), 19 anti-CD20 (10 C, 9 O), 13 anti-HER2 (5 C, 8 O), and 0 anti-IL6/IL6R trials. In short, out of a maximum possible number of head-to-head trials of 150, we found that 31 (21%) were completed or ongoing.

Characteristics of included trials

We searched a total of 14,818 papers and excluded 14,801 as shown in our CONSORT diagram (Supplementary Table 1). We found a total of 17 completed and published randomized head-to-head trials of a total of 13 (13/22, 59%) FDA approved cancer mAbs with the same target (Table 2). These trials were published between 2002 and 2018. The most common journals were JCO (6/17, 35%) and Lancet Haematology or Oncology (5/17, 29%). Anti-CD20 mAbs had 10 head-to-head trials (10/17, 59%), anti-HER2 mAbs had 5 trials (5/17, 29%), and EGFR mAbs and anti-VEGF mAbs had 1 trial each (1/17, 6%). The most commonly tested mAb was rituximab in 10 trials (10/17, 59%) (Fig. 1). Other common drugs included rituximab and hyaluronidase (5/17, 29%), trastuzumab (5/17, 29%) and ado-trastuzumab emtansine (4/17, 24%) (Fig. 1).

In total, 11,373 patients were randomized in these trials. The most common mAb patients were randomized to was rituximab (3174/11,373, 28%), followed by obinutuzumab (1640/11,373, 14%) and rituximab and hyaluronidase (1498/11,373, 13%). The median sample size was 500, ranging from 143 to 1418. Most of the trials were phase III (13/17, 76%), and the rest were two phase IB and phase II trials (2/17, 12%) (Table 2). Eight trials tested statistical hypotheses related to drug superiority (8/17, 47%), five noninferiority (5/17, 29%), two equivalence (2/17, 12%), one was a crossover trial (1/17, 6%) and one did not have a formal statistical hypothesis (1/17, 6%).

The most common indications were breast cancer (5/17, 29%) and DLBCL (4/17, 23%). The most common primary endpoint was progression free survival, used in five trials (5/17, 29%). Other common primary endpoints included ORR (4/17, 23%) and CR (either CR or pathological CR, 4/17, 23%). Out of the 17 trials, 13 (76%) were head-to-head trials of mAbs manufactured by the same company and 13 had a conclusion that favored its sponsor (13/17, 76%) (Supplementary Table 3, Fig. 1).

Regarding ongoing studies, we searched a total of 174 studies and found 14 randomized head-to-head trials that met our criteria (Supplementary Table 2). The most common drug tested was trastuzumab in seven trials (7/14, 50%), then rituximab in six trials (6/14, 43%) (Fig. 2). Trastuzumab and ado-trastuzumab emtansine was the most commonly tested head-to-head pair, noted in six trials (6/14, 43%), followed by rituximab and obinutuzumab in four trials (4/14, 29%). There were no head-to-head trials in the anti-EGFR or anti-VEGF or anti-IL6/IL6R groups.

Regarding the status of the trials, nine were recruiting (9/14, 64%), four terminated (4/14, 29%) and one completed (1/14, 7%). Most trials were phase II or III (12/14, 86%), and the rest were phase 1 or phase 1/2 (2/14, 14%). The target enrollment ranged from 32 to 1846, with a median of 409. Overall if all of these trials met their target, they would include 3404 patients. A network diagram of these trials shows that they are manufactured by 4 companies. 12/14 (86%) of these trials test two mAbs manufactured by the same company (Fig. 2, Supplementary Table 3). The most common indication was breast cancer in seven trials (7/14, 50%). The most common primary endpoint was PFS (6/14, 43%), followed by DFS (3/14, 21%). Only one of the trials (1/14, 7%) had OS as a primary endpoint. Of these studies, ten trials (10/14, 71%) were sponsored by, or included as a collaborator, the company that made the mAb being tested.

Table 1 All FDA approved cancer monoclonal antibodies with the same target or its ligand

Monoclonal antibody (mAb) and manufacturer	Type	First approval	FDA approved cancer indications
Anti-CD20 mAbs			
Rituximab (Rituxan, Genentech/Roche)	Chimeric	1997	Relapsed/refractory FL, FL with chemo, FL maintenance, DLBCL, treated CLL and untreated CLL
Y90 ibritumomab tiuxetan (Zevalin, Spectrum; formerly IDEC)	Mouse	2002	Relapsed/refractory FL, untreated FL
Ofatumumab (Arzerra, Novartis)	Human	2009	Untreated CLL, relapsed CLL, recurrent CLL, refractory CLL
Obinutuzumab (Gazyva, Genentech/Roche)	Humanized	2013	Untreated CLL, relapsed/refractory FL after rituximab, untreated FL
Rituximab and hyaluronidase (Rituxan Hycela, Genentech/Roche)	Chimeric	2017	Relapsed/refractory FL, FL with chemo, FL maintenance, DLBCL, treated CLL and untreated CLL
Anti-HER2 mAbs			
Trastuzumab (Herceptin, Genentech/Roche)	Humanized	1998	Adjuvant breast (±chemo), metastatic breast (±chemo), metastatic gastric
Pertuzumab (Perjeta, Roche)	Humanized	2012	Untreated metastatic breast with trastuzumab, neoadjuvant breast, adjuvant breast
Ado-trastuzumab emtansine (TDM1) (Kadcyla, Genentech/Roche)	Humanized	2013	Metastatic breast after trastuzumab
Trastuzumab-dkst (Ogivri, Mylan)	Humanized	2017	Adjuvant breast (±chemo), metastatic breast (±chemo), metastatic gastric
Anti-EGFR mAbs			
Cetuximab (Erbitux, Lilly)	Chimeric	2004	HNSCC, metastatic HNSCC (±chemo), metastatic CRC (±chemo)
Panitumumab (Vectibix, Amgen)	Human	2006	Metastatic CRC (with or after chemo)
Necitumumab (Portrazza, Lilly)	Human	2015	Squamous NSCLC
Anti-VEGF mAbs			
Bevacizumab (Avastin, Genentech/Roche)	Humanized	2004	Metastatic CRC, NSCLC w chemo, GBM, metastatic RCC, metastatic cervical, recurrent ovarian/peritoneal/fallopian tube
Ramucirumab (Cyramza, Lilly)	Human	2014	Gastric (±chemo), metastatic NSCLC after chemo, metastatic CRC
Bevacizumab-awwb (Mvasi, Amgen)	Humanized	2017	Metastatic CRC (first line or after bevacizumab progression), NSCLC with chemo, GBM, metastatic RCC, metastatic cervical
Anti-IL6/IL6R mAbs			
Tocilizumab (Actemra, Genentech/Roche)	Humanized	2010	Cytokine release syndrome
Siltuximab (Sylvant, Janssen)	Chimeric	2014	Multicentric Castleman disease
Anti-PD1/PDL1 mAbs			
Nivolumab (Opdivo, BMS)	Human	2014	Metastatic melanoma (±ipilimumab), adjuvant melanoma, metastatic NSCLC, advanced RCC, HL, metastatic HNSCC, metastatic bladder, MSI-H or dMMR CRC, HCC
Pembrolizumab (Keytruda, Merck)	Human	2015	Metastatic melanoma, metastatic NSCLC, metastatic HNSCC, refractory HL
Atezolizumab (Tecentriq, Genentech/Roche)	Humanized	2016	Metastatic bladder, metastatic NSCLC
Avelumab (Bavencio, Pfizer)	Human	2017	Metastatic merkel cell carcinoma
Durvalumab (Imfinzi, AstraZeneca)	Human	2017	Metastatic bladder

NSCLC non small cell lung cancer, *RCC* renal cell, *HL* hodgkin lymphoma, *HNSCC* head and neck squamous cell cancer, *MSI-H* microsatellite instability-high, *dMMR* mismatch repair deficient, *CRC* colorectal cancer, *HCC* hepatocellular carcinoma, *FL* follicular lymphoma, *DLBCL* diffuse large B-cell lymphoma, *CLL* chronic lymphocytic leukemia, *GBM* glioblastoma multiforme

Table 2 Summary of published head-to-head trials of FDA approved cancer monoclonal antibodies

mAb 1	mAb 2	Trial	Phase, Design	Indication	*n* and randomization	Blinding	Arms	Primary endpoint	Sponsor	Conclusion favoring sponsor	NCT	PMID
Anti-CD 20 mAbs												
Y90 ibritumomab tiuxetan (Y90 IT) (Zevalin, Spectrum; formerly IDEC)	Rituximab (Rituxan, Genentech/Roche)	JCO 2002 20:2453–63	Phase III	Relapsed/refractory low grade FL or transformed NHL	143, 1:1	Open label	Y90 IT vs R	ORR	IDEC*	Yes	None	12011122 (Witzig et al. 2002)
Obinutuzumab (Gazyva, Genentech/Roche)	Rituximab	CLL11; NEJM 2014;370:1101–10	Phase III	Untreated CLL	787, 1:2:2	Open label	Chlorambucil (C) vs G-C vs R–C	PFS	Genentech/Roche	Yes	NCT01010061	24401022 (Goede et al. 2014)
Obinutuzumab	Rituximab	GOYA; JCO 2017 35:3529–37	Phase III	Untreated advanced stage DLBCL	1418, 1:1	Open label	Obinituzumab-CHOP (G-CHOP) vs rituximab-CHOP (R-CHOP)	PFS	Genentech/Roche	No	NCT01287741	28796588 (Vitolo et al. 2017)
Obinutuzumab	Rituximab	GALLIUM; NEJM 2017;377:1331–44	Phase III	Untreated indolent NHL	1202, 1:1	Open label	G-CHOP/G-CVP vs R-CHOP/R-CVP	PFS	Genentech/Roche	Yes	NCT01332968	28976863 (Marcus et al. 2017)
Ofatumumab (Arzerra, Novartis)	Rituximab	ORCHARRD; JCO 2016 35:544–551	Phase III	Relapsed/refractory DLBCL	447, 1:1	Open label	Ofatumumab-DHAP vs R-DHAP	PFS	GSK, Genmab, Novartis	No	NCT01014208	28029326 (van Imhoff et al. 2017)
Rituximab and hyaluronidase (sQ R) (Rituxan Hycela, Genentech/Roche)	Rituximab	JCO 2014 32:1782–91	Phase IB, noninferiority	Maintenance FL	154, 1:1	Open label	sQ R vs R	Serum trough concentration	Genentech/Roche	Yes	NCT00930514	24821885 (Salar et al. 2014)
Rituximab and hyaluronidase	Rituximab	SAWYER; Lancet Haem 2016 3:e128–38	Phase IB, noninferiority	Untreated CLL	176, 1:1	Open label	sQ R-flu-Cy vs R-flu-Cy	Serum concentration cycle 5	Genentech/Roche	Yes	NCT01292603	26947201 (Assouline et al. 2016)
Rituximab and hyaluronidase	Rituximab	SABRINA; Lancet Haem 2017 4:e272–282	Phase III, noninferiority	Untreated FL	410, 1:1	Open label	sQ R-CHOP/sQ R-CVP vs R-CHOP/R-CVP	ORR at end of induction	Genentech/Roche	Yes	NCT01200758	28476440 (Davies et al. 2017)
Rituximab and hyaluronidase	Rituximab	MabEASE; Haematologica 2017 102:1913–1922	Phase III, "no formal statistical hypothesis"	Untreated DLBCL	572, 2:1	Open label	sQ R-CHOP vs R-CHOP	CR	Genentech/Roche	Yes	NCT01649856	28935843 (Lugtenburg et al. 2017)
Rituximab and hyaluronidase	Rituximab	PrefMab; Ann Onc 2017 28:836–842	Phase III, crossover	Untreated DLBCL	743, 1:1	Open label	(R -> sQ R -> R)-CHOP/CVP/B vs (R -> sQ R)-CHOP/CVP/B	Patient preference survey	Genentech/Roche	Yes	NCT01724021	28031173 (Rummel et al. 2017)

Table 2 (continued)

mAb 1	mAb 2	Trial	Phase, Design	Indication	*n* and randomization	Blinding	Arms	Primary endpoint	Sponsor	Conclusion favoring sponsor	NCT	PMID
Anti-HER2 mAbs												
Pertuzumab (Perjeta, Genentech/Roche)	Trastuzumab (Herceptin, Genentech/Roche)	NeoSphere; Lancet Onc 2012 13:25–32	Phase II	HER2 + treatment naïve breast cancer	417, 1:1:1:1	Open label	Trastuzumab + docetaxel vs pertuzumab + trastuzumab + docetaxel vs pertuzumab + trastuzumab vs pertuzumab + docetaxel	PathCR	Genentech/Roche	No	NCT00545688	22153890 (Gianni et al. 2012)
Ado-trastuzumab emtansine (TDM1) (Kadcyla, Genentech/Roche)	Trastuzumab	MARIANNE; JCO 2017 35:141–148	Phase III, noninferiority	HER2 + advanced breast cancer	1095, 1:1:1	Open label	Trastuzumab + taxane vs TDM1 vs TDM1 + trastuzumab	PFS	Genentech/Roche	Yes	NCT01120184	28056202 (Perez et al. 2017)
Ado-trastuzumab emtansine	Trastuzumab	ADAPT; JCO 2017 35:3046–54	Phase II	HER2 + HR + early breast cancer	375, 1:1	Open label	TDM1 ± endocrine therapy vs trastuzumab + endocrine therapy	PathCR	Genentech/Roche	Yes	NCT01817452	28682681 (Harbeck et al. 2017)
Ado-trastuzumab emtansine	Trastuzumab	KRISTINE; Lancet Onc 2018 19:115–26	Phase III	HER2 + stage II–III breast cancer	444, 1:1	Open label	TDM1 pertuzumab vs docetaxel, carboplatin, trastuzumab, pertuzumab	PathCR	Genentech/Roche	No	NCT02131064	29175149 (Hurvitz et al. 2018)
Trastusumab-dkst (Ogviri, Mylan)	Trastuzumab	HERiTAge; JAMA 2017 317:37–47	Phase III, equivalence	Metastatic breast	500, 1:1	Open label	Trastuzumab-dkst + taxane vs trastuzumab + taxane	ORR at week 24	Mylan	Yes	NCT02472964	27918780 (Rugo et al. 2017)
Anti-EGFR mAbs												
Panitumumab (Vectibix, Amgen)	Cetuximab (Erbitux, Lilly)	ASPECCT; Lancet Oncol 2014; 15:569–79	Phase III, noninferiority	Chemo refractory WT KRAS metastatic colorectal cancer	1010, 1:1	Open label	Panitumumab vs cetuximab	OS	Amgen	Yes	NCT01001377	24739896 (Price et al. 2014)
Anti-VEGF mAbs												
Bevacizumab-awwb (ABP 215) (Mvasi, Amgen)	Bevacizumab (Avastin, Genentech/Roche)	JTO 2017 P2.03a-025 (abstract only)	Phase III, equivalence	Non-squamous NSCLC	642, 1:1	Open label	ABP 215, carbo-taxel vs bevacizumab, carbo-taxel	ORR	Amgen	Yes	NCT01966003	None

*At the publication of this trial, both Y90 ibritumomab tiuxetan and rituximab were manufactured by IDEC pharmaceuticals

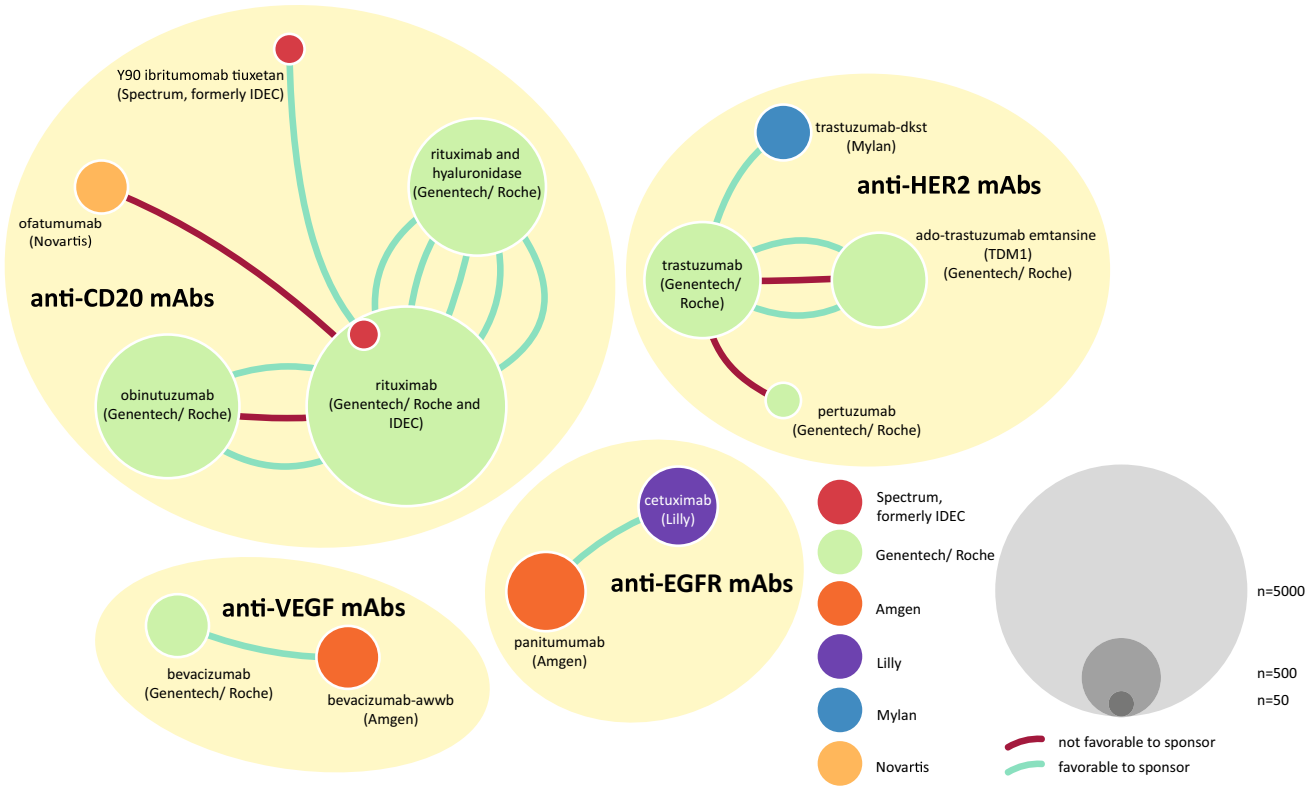

Fig. 1 Network diagram of completed and published head to head trials of mAbs of the same target or its ligand. We identified 17 of these trials. The area of each node represents the approximate total number of patients who received the drug in these studies. Nodes are color coded by manufacturer. Each line connecting two circles represents one head to head trial, and the color designates whether the result favors the sponsor, as defined in the methods

Discussion

There are a limited number of head-to-head trials comparing approved oncology mAbs

We found few head-to-head trials of monoclonal antibodies that are FDA approved in oncology. In the published literature, we found 17 completed and published head-to-head trials of these drugs, though more combinations were possible (Table 2). All of the trials were industry sponsored by one of the mAb manufacturers, and the majority of these trials were comparing two mAbs manufactured by the same sponsor (13/17, 76%) (Fig. 1, Supplementary Table 3). A search through trials in the ClinicalTrials.gov database of recently completed and ongoing trials yielded 14 randomized head-to-head trials and 12/14 (86%) of these compared mAbs manufactured by the same sponsor (Supplementary Table 3, Fig. 1). In sum, these 21 studies in total test 15 of the 22 (68%) mAbs in cancer that have multiple approvals with the same target. Interestingly there are no published and only 1 ongoing head-to-head trial of approved anti-PD1/PD-L1 mAbs, despite the popularity of these drugs. This finding is similar to studies that show a lack of head-to-head comparisons in other fields of medicine (Flacco et al. 2015; Estellat and Ravaud 2012; Buesching et al. 2012). While we do not believe that all potential head-to-head trials ought to be performed, it is notable that a minority of comparisons have been or are being attempted.

Out of a total of 150 combinations of head-to-head trials that could be performed due to unique approved FDA indications, we found that only 21% (31/150) have been or are being undertaken. While not all of these trials should be performed given the cost of testing every possible combination, the published literature is predominantly represented by mAbs made by the sponsor, with results favoring the sponsor. Of the 17 completed trials, the majority (13/17, 76%) reach results that favor the sponsor (Fig. 1, Table 1).

Inefficiencies may exist in the research agenda testing mAbs

These results suggest that despite the fact that there are many randomized trials of mAbs in oncology, there may be inefficiencies in selecting the clinical trials being performed (Ioannidis 2016), similar to what has been previously shown in the literature for different anti-cancer drugs (Carlisle et al.

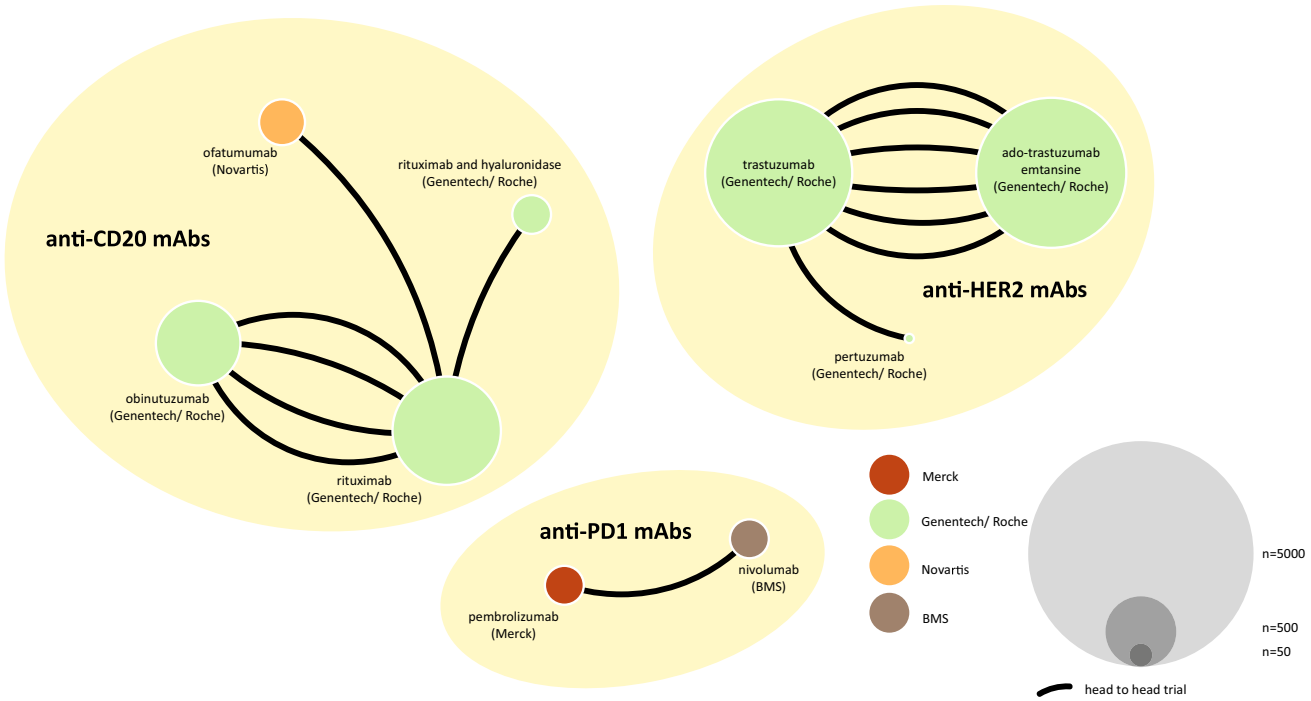

Fig. 2 Network diagram of ongoing and completed but not published head to head trials of mAbs of the same target or its ligand. We identified 14 of these trials. The area of each node represents the approximate number of patients who received or will receive the drug in these studies (target enrollment divided by the number of arms). Nodes are color coded by manufacturer. Each line connecting two nodes represents one head to head trial

2016; Mattina et al. 2017). Our review indicates that there are additional inefficiencies when looking at the sum total of head-to-head trials in cancer.

Per the National Academy of Medicine's (formerly Institute of Medicine) Initial National Priorities for Comparative Effectiveness Research, "Once an intervention has been shown to be effective against a placebo, head-to-head trials address the critical question 'What works best for whom?'" (Institute of Medicine 2009). In our study, we found that in the mAb space, important head-to-head trials may not be conducted. This is particularly interesting when contrasting this agenda against a recent study that found over 1000 trials testing the new immune modulating mAbs in different combinations. Thus, although there are many trials of checkpoint inhibitors, few seek to ascertain if one antibody is superior to the other, or offer different side effect profiles. Given that antibodies are biological molecules, prone to idiosyncratic differences, this omission is notable.

Limitations

There are several limitations to our work. First, it is possible we did not identify all head-to-head trials of mAbs targeting the same receptor or its ligand. However, we systematically performed multiple MEDLINE and Google Scholar searches and looked on ClinicalTrials.gov for additional studies in accordance with standardized systematic review reporting criteria.

Second, some of the FDA approved drugs, especially those in the PD1/PDL1 family, were only recently approved in oncology–thus, limiting the amount of time during which comparisons could be attempted. However, a recent study found over 1000 ongoing trials of anti-PD1/PDL1 mAbs with other agents with target enrollment of thousands of patients (Tang et al. 2018), suggesting that even though early in the lifecycle of this class of mAbs, there is potential for ongoing comparisons.

Third, our study only examined mAbs targeting the same receptor or its ligand. We are missing head-to-head comparisons between mAbs and other targeted agents. However, even when focused on mAbs themselves, we have identified notable patterns. Future research may consider examination of broader collections of agents.

Conclusion

Our study found that mAbs used in cancer targeting the same receptor or ligand are often not tested in head-to-head randomized trials; and if they were completed and published, 76% (13/17) reach conclusions that favored the sponsoring company. Consideration of the overarching clinical trials agenda of mAbs may lead to more rational clinical trial portfolios.

Compliance with ethical standards

Conflict of interest Dr Prasad reports receiving royalties from his book *Ending Medical Reversal*; that his work is funded by the Laura and John Arnold Foundation; that he has received honoraria for Grand Rounds/lectures from several universities, medical centers, and professional societies and payments for contributions to Medscape. Drs. Luo and Nishikawa have no conflict of interest.

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