

MINI-REVIEW

Changing the drug development and therapeutic paradigm with biologic drug combinations and bispecifics: How to choose between these two approaches?

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Abstract

Biologics are increasingly being co-developed in combination or as novel constructs like bispecific antibodies (BsAbs) with the goal of targeting multiple, non-redundant mechanisms of action. Rational design of combinations and dual-targeting approaches that consider disease complexities have the potential to improve efficacy and safety, to increase duration of clinical benefit, and to minimize clinical resistance mechanisms. Here we summarize examples of BsAbs and biologic combinations that have been approved by health authorities and present drug development considerations when deciding between these two strategies. These include an understanding of target biology, nonclinical safety risks, dose optimization strategies, the regulatory framework, pharmacokinetic, immunogenicity, and bioanalytical assay considerations. The disease biology, target dynamics, and pharmacology objectives were identified as important factors in early drug development to decide between a BsAb versus a combination. Nonclinical safety assessment and dose optimization strategies can also pose challenges for BsAb versus combinations. High unmet medical needs and lack of treatment options are often the common denominators for deciding to develop a BsAb or a combination. Future development of biologic triple combinations and BsAbs combinations with other biologics will further increase drug development complexities and hold promise for more effective treatment options for patients.

INTRODUCTION

Bispecific antibodies (BsAbs) and biologic combinations are becoming increasingly used to treat complex diseases, to achieve higher levels of patient response, and to combat resistance mechanisms. The first BsAb (catumaxomab) and biologic combination (bevacizumab and interferon

alpha-2A) were approved in 2009 for oncology indications (Table 1). Since then, at least three additional BsAbs and eight additional biologic combinations were granted health authority approval (Table 1).

Catumaxomab was the first T cell directed BsAb targeting the tumor antigen EpCAM and CD3 on T cells, and while removed from the market for cited commercial

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TABLE 1 Examples of bispecifics and biologic combinations granted health authority approval

Brand name	International Nonproprietary Name (INN)	Initial approval year	Indication ^a	Drug targets	Drug type
Bispecifics					
Removab [®]	Catumaxomab	2009(EMA) ^b	Malignant ascites	EpCAM-directed CD3 T cell-engager	Rat/mouse chimeric IgG2
Blinicyto [®]	Blinatumomab	2014 (US)	B-cell precursor acute lymphocytic leukemia (ALL)	CD-19-directed CD3 T cell-engager	BiTE [®] (scFv)
Hemlibra [®]	Emicizumab-kxwh	2017 (US)	Reduce bleeding with hemophilia A with or without factor VIII inhibitors	Factor IXa Factor X	Humanized IgG4
Rybrevant [®]	Amivantamab-vmjw	2021 (US)	NSCLC EGFR exon 20 insertion mutation positive	EGFR MET receptor	Low fucose human IgG1
Biologic Combinations					
Avastin [®] Roferon-A [®]	Bevacizumab Interferon alpha-2A	2009 (US)	RCC	VEGF Interferon receptor	Humanized IgG1 Protein
Perjeta [®] Herceptin	Pertuzumab Trastuzumab	2012 (US) ^c	HER2-positive metastatic breast cancer ^d	HER2 HER2	Humanized IgG1 Humanized IgG1
Opdivo [®] Yervoy [®]	Nivolumab Ipilimumab	2015 (US)	Advanced MEL ^e	PD-1 CTLA4	Human IgG4 Human IgG1
Ryzodeg [®]	Insulin degludec Insulin aspart	2015 (US)	Diabetes	Insulin receptor Insulin receptor	Peptide Peptide
Soliqua [®]	Insulin glargine Lixisenatide	2016 (US)	Type 2 diabetes	Insulin receptor GLP1 receptor	Peptide Peptide
Avastin [®] Tecentriq [®]	Bevacizumab Atezolizumab	2018 (US)	NSCLC ^f	VEGF PD-L1	Humanized IgG1 Humanized IgG1
Keytruda [®] Herceptin [®]	Pembrolizumab Trastuzumab	2021 (US)	HER2-positive gastric cancer ^g	PD-1 HER2	Humanized IgG4 Humanized IgG1
Not available	Bamlanivimab Etesevimab	2021 (US) ^h	Mild/moderate COVID-19	Distinct but overlapping epitopes on the spike protein receptor binding domain of SARS-CoV-2	Human IgG1 Human IgG1
Regen-Cov [®]	Casirivimab Imdevimab	2021 (US) ^h	Mild/moderate COVID-19	Non-overlapping epitopes on the spike protein receptor binding domain of SARS-CoV-2	Human IgG1 Human IgG1

Abbreviations: EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; MEL, melanoma; MET, mesenchymal-epithelial transition; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

^aSee US prescribing information for detailed indications and usage.

^bNo longer marketed (<https://en.wikipedia.org/wiki/Catumaxomab>).

^cPhesgo[®] approved in 2020 (pertuzumab/trastuzumab subcutaneous formulation with hyaluronidase).

^dCombination with docetaxel without prior anti-HER2 therapy and combination with chemotherapy; combination with chemotherapy in neoadjuvant or adjuvant treatment.

^eNivolumab/ipilimumab combination regimens approvals followed in renal cell carcinoma (RCC), microsatellite instability-high or mismatch repair deficient colorectal cancer, hepatic cell carcinoma (HCC), non-small cell lung cancer (NSCLC) with and without chemotherapy, and mesothelioma.

^fCombination with paclitaxel and carboplatin in NSCLC and combination approval in HCC.

^gCombination with fluoropyrimidine and platinum-containing chemotherapy.

^hEmergency use authorization.

Question	Advantage to bispecifics	Advantage to combinations
Disease area		
Clinical proof of biology with single agents?		✓
Challenges with target drugability?	✓	
High unmet medical need?	✓	✓
Target Biology		
Targets locating on the same cell?	✓	
Targets located on different cells?	✓	✓
Kinetics of target binding, occupancy, turnover, and epitopes understood?	✓	✓
Nonclinical safety		
Safety related to pathway synergism? ^a		✓
On-target, off-tissue related safety events? ^b	✓	✓
Prior monotherapy animal safety established?		✓
Clinical pharmacology		
Spatial proximity important for pharmacology?	✓	
Target-mediated pharmacokinetics?	✓	
Additive and/or synergistic pharmacology?	✓	✓
Clinical safety and efficacy		
Narrow therapeutic index of both target modulations? ^c		✓
One pathway dominates efficacy?	✓	
Standard of care not established?	✓	✓
Chemistry, manufacturing, and controls (CMC)		
Prone to protein aggregation?		✓
Consolidated release testing and characterization?	✓	
Manufacturing costs high?	✓	

TABLE 2 Checklist of questions when deciding to develop biologic combinations or bispecific antibodies

^aIn cases where simultaneous engagement of both targets results in synergistic toxicity, development of a combination product allows mitigation strategies such as sequential administration or dose modification of one of the therapeutics.

^b“On-target, off-tissue” refers to a target that is overexpressed in a tissue other than the intended tissue (i.e., tumor). Combinations or bispecific antibodies (BsAbs) each could have an advantage with combinations through adjusting the dose ratio and BsAbs by redirecting binding away from the off-tissue target.

^c“Narrow therapeutic index” here represents a situation where careful dose titration is needed for each target modulation, where combinations could offer greater flexibility in maximizing the therapeutic index.

reasons, it established proof of concept (POC) for T cell directing agents.¹ In 2014, blinatumomab, a CD19xCD3 BsAb T cell engager (BiTE[®]), was approved to treat relapse, refractory B-cell acute lymphoblastic leukemia (ALL). More recently, BsAb approvals were obtained in hematology for emicizumab and in oncology for amivantamab. Emicizumab acts as a BsAb glue connecting factor FIXa and FX to activate clot formation in patients with congenital factor VIII deficiency.² Amivantamab targets both epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) receptor on tumor cells and was granted accelerated approval recently

to treat EGFR exon 20 insertion mutation positive non-small cell lung cancer (NSCLC).³

Biologic combinations are approved for targeting generally different but complimentary mechanisms of action. These include insulin and glucagon-like peptide 1 (GLP1) (Supplemental Reference [Sup Ref] 1), long and rapid-acting insulins (Sup Ref 2), nivolumab (anti-programmed cell death protein 1 [PD-1]) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA4]) immune checkpoint inhibitors (Sup Ref 3), bevacizumab (vascular endothelial growth factor inhibitor) and interferon alpha-2A (immune stimulator)

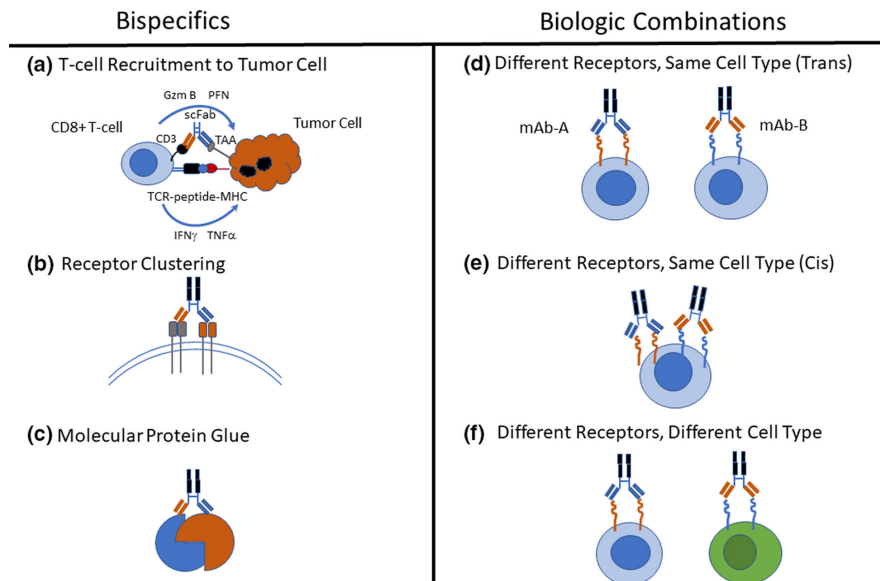


FIGURE 1 Different mechanistic advantages for bispecifics and biologic combinations. Bispecifics can re-direct T cells to tumor cells (a), facilitate receptor clustering (b), or form the molecular glue bridging enzymes together (c). Biologic combinations can target different receptors on the same cell type binding in a trans configuration (d) or binding to the same cell type in a cis configuration (e). Alternatively, biologic combinations could target different cell types (f). GzmB, granzyme B; IFN γ , interferon γ ; mAb-A, monoclonal antibody A; mAb-B; monoclonal antibody B; MHC, major histocompatibility complex; PFN, perforin; scFab, single-chain Fab; TAA, tumor-associated antigen; TCR, T-cell receptor; TNF α , tumor necrosis factor α .

(Sup Ref 4), atezolizumab (anti-programmed death ligand 1 [PD-L1]) and bevacizumab combinations (Sup Ref 5), and pembrolizumab (anti-PD1) and trastuzumab (anti-human epidermal growth factor receptor 2 [HER2]) (Sup Ref 6). Pertuzumab and trastuzumab are the first biologic combination that target the same receptor (HER2), but through different epitopes and approved as a combination treatment for patients with metastatic HER2-positive tumors.⁴ Recently, two separate mAb combinations (casirivimab and imdevimab) and (bamlanivimab and etesevimab) were authorized for emergency use to treat mild to moderate COVID-19 infection.⁵ These mAb combinations target unique epitopes on the spike protein receptor binding domain, preventing viral attachment to host cells.⁵

The decision to develop a BsAb or a combination depends on several factors such as disease biology, knowledge of the targets, single agent POC, nonclinical safety, the desired clinical profiles, and manufacturing considerations (Table 2). BsAbs have a unique advantage in allowing for new pharmacology that is not accessible to mAbs either as single agents or in combination. Examples of BsAb advantages include: (1) redirecting potential of T effector cells (via CD3) or NK cells (via CD16) to tumor cells, (2) facilitating receptor clustering and synapse formation to signal downstream events such as cellular activation and cytotoxicity, and (3) bridging distinct proteins together for therapeutic effect (i.e., to initiate clot formation) (Figure 1). While BsAbs and

biologic combinations can each target distinct receptors on the same or different cell types, the advantage goes to biologic combinations for staged dose optimization, allowing independent control over each mechanism to dial in the needed efficacy and dial out unwanted safety (Figure 1).

This mini-review summarizes considerations for early design strategies during lead optimization, nonclinical experiences with T cell directing agents, dose optimization examples in the clinic, and regulatory considerations.

BIOLOGY, BIOPHYSICS, AND PHARMACOLOGY DRIVEN RESEARCH AND DEVELOPMENT (R&D) STRATEGY: COMBINATIONS VERSUS BISPECIFICS

Monoclonal antibodies (mAbs) are bivalent and monospecific, binding the same epitope on one target. In contrast, most BsAbs can be bivalent or monovalent and bispecific, binding two different epitopes located on distinct targets or cells (Sup Ref 7). The technical difficulties in molecular design, screening optimization, formulation, and manufacturing are generally more challenging for a BsAb than for a mAb. Despite these challenges, many BsAbs are currently at different development stages for human malignancies and other disease areas. Previous reviews have summarized the types and formats of these BsAbs

as well as their respective targets and binding epitopes, covering a range of targets in oncology, hematology, and immunology.^{6,7}

BsAbs and mAb combinations often offer distinct advantages (Table 2). The fundamental question regarding the R&D strategy for BsAbs versus mAb combinations is “When to consider a BsAb given the potential dosing challenges to optimize dosing and binding stoichiometries to each of the targets compared with a combination approach of two mAbs for which varying dose-ratios can be explored to achieve the optimal therapeutic benefit?” To answer this question, probing into the “design thinking” of a BsAb versus mAb combination at project inception is critical. In general, the following should be considered:

- Therapeutic indications and mechanism of actions (MOAs)
- Knowledge of each target's biology and dynamics
- Protein design strategy of a BsAb based on the pharmacology, e.g., asymmetric binding domains (2+1 or 1+1), symmetric binding domains (2+2 or 1+1); use of a fusion protein versus single-chain variable fragment (scFv) to maximize the therapeutic window through improved efficacy and reduced toxicities.

Additional considerations include understanding the desirable molecular size and pharmacokinetics (PK) with consideration for tissue distribution and target-mediated drug disposition (TMDD), ensuring effective target engagement (TE) as it relates to receptor occupancy (RO) and circulating target levels, and demonstrating pharmacodynamics (PD) utilizing downstream biomarkers to obtain the desirable pharmacology and ultimately efficacy. It is important when designing the molecule to ensure low immunogenic potential and to maintain appropriate stability while enabling the needed flexibility for activity using the appropriate construct/linker technology. Manufacturing may also factor into the design strategy with different production formats and ease of production for a given format (e.g., designed and manufactured through genetic recombination, chemical conjugation, or hybrid hybridomas [quadromas]).⁷

If the thorough “mental exercise” results in a clear differentiation and potential therapeutic advantage for a BsAb compared with a mAb combination approach, the subsequent molecule generation, lead identification, and candidate selection often require a stepwise comparison of the BsAb versus the combination of the respective mAbs in various fit-for-purpose *in vitro* and *in vivo* studies. Depending on the BsAb formats and MOAs, utilizing control BsAbs with null binding arms can be critical in assessing individual TE versus dual TE, and the associated functions (Sup Ref 8). More sophisticated and extensive *in vivo* biodistribution and functional (PK/TE/PD) studies

using advanced techniques such as imaging⁸ have been shown to enhance the understanding of the MOA(s) of a BsAb and to enable smarter design of a construct including the selection of binding affinities and epitopes of each arm based on experimental data⁹ (Sup Ref 9) and quantitative modeling & simulation approaches (Sup Ref 10, 11).¹⁰ The learnings are valuable from preclinical animal models (particularly the determination of how both arms of the BsAb construct impact tissue distribution), *in vivo* TE and RO, and combined PD outcomes compared with a mAb combination approach for translational medicine considerations and early clinical development.

Despite the challenges in the clinic for a number of re-directing T cell BsAbs, including cytokine release syndrome, loss of tumor targets, upregulation of the immune system and immune escape,⁷ the true value of developing a BsAb instead of mAb combinations lies in a series of unique characteristics displayed under specific therapeutic concepts and hypotheses that have been tested in preclinical and clinical settings. These include bridging and effector cell redirection, avidity and affinity-driven pharmacology, and safety advantages. In addition, BsAbs open the door for additional combination strategies of a BsAb with another mAb for a triplet design (e.g., CD3 or CD28 T cell engagers with checkpoint inhibitors¹¹ or another BsAb [e.g., CD3+CD28 T cell engagers]) which provides co-stimulatory signals for complete T cell activation and more sustained T cell response¹² bringing in new treatment options and potential for unmet medical needs.

NONCLINICAL SAFETY ASSESSMENT OF T CELL REDIRECTORS TO SUPPORT CLINICAL INVESTIGATION

While BsAbs are not considered in the same realm as biotherapeutic combinations, they do create novel challenges for the nonclinical safety assessment strategies. Specifically focusing on CD3-redirecting T cell therapies for oncology, these molecules are designed to bind to the CD3 subunit of the T cell receptor (TCR) on the surface of T cells and to a specific tumor-associated antigen (TAA) expressed on the tumor cell surface. Once the TAAxCD3 engages both targets, an immunological synapse between the tumor and T cell forms, activates the T cell, and “redirects” the cytolytic activity against the tumor.⁹

When developing CD3-engaging BsAb therapies, several molecular properties should be considered during the nonclinical safety assessment to support entry into clinical development. Although numerous CD3-engaging molecular formats are being investigated, all of which may have their own unique challenges, there are certain properties of

the molecule that will determine the appropriate nonclinical safety strategies (Sup Ref 12, 13).¹³ The first must-do-assessment is whether the TAA- and CD3-targeting arms of the molecule both bind to the nonclinical species and result in the expected pharmacological activities. When one or both of the binding domains do not cross-react with any nonclinical species, there will be a lack of *in vivo* pharmacological activity and the nonclinical safety assessment may be limited to *in vitro*-only approaches (Sup Ref 14, 15).¹⁴ Several additional variables also influence the potency, selectivity, pharmacokinetics, biodistribution, and safety of CD3 T cell engagers. These include, but are not limited to, the specific CD3 epitope, size and format of the molecule, density (i.e., copy number per cell) of the TAA, affinity/valency to CD3 (i.e., on/off rate), affinity/valency to the TAA (i.e., on/off rate), distance of TAA epitope from the cellular membrane, and distance between the T cell and the tumor cell.¹³

If the molecule is pharmacologically active in relevant nonclinical species, typically non-human primates, *in vivo* safety studies will need to be conducted. Administration of CD3-redirecting molecules in a pharmacologically relevant species results in a spectrum of changes in clinical signs and symptoms. These changes include emesis, diarrhea, inappetence, decreased activity, and transiently increased body temperature, which are often associated with acute phase responses (i.e., increase in C-reactive protein, increase in globulin and fibrinogen, and decreased albumin), acute and transient cytokine release, and transient decrease in lymphocyte counts (redistribution/margination into the tissues). Approaches often used to mitigate the acute phase response and cytokine release include prolonged infusion times and step-up dosing or dose-fractionation (i.e., intra-animal dose escalation) regimens.¹⁴

Solid tumor indications represent the next hurdle for CD3-engaging BsAbs. One of the main reasons is that TAAs for solid tumors are often expressed on normal tissues at some level unlike hematologic malignancies where TAA expression tends to be lineage restricted. Due to the highly potent nature of these molecules, there is potential to drive on-target/off-tumor toxicities. In order to take full advantage of the clinical promise of CD3-engaging therapies in solid tumors, new approaches and/or technologies need to be developed to minimize these liabilities.

SELECTION AND OPTIMIZATION OF DOSING REGIMENS FOR COMBINATIONS AND BISPECIFICS

Dose selection and optimization are vital components in drug development and regulatory approvals, especially for BsAbs and combinations that can have complicated MOAs and require demonstration of each pharmacodynamic component for efficacy.

Combination dose selection historically follows three steps: (1) start with the prior dosing regimens of each mAb in the respective indications, (2) evaluate various dose ratios of both mAbs in phase I studies and demonstrate contribution of each drug to efficacy, and (3) select the doses for the optimal dose ratio based on the totality of clinical PK, efficacy, and safety data. Nivolumab and ipilimumab represent a dual therapy for approved indications in advanced melanoma¹⁵ (Sup Ref 16) and first-line NSCLC indications¹⁶ (Sup Ref 17, 18), and infliximab and adalimumab have been studied in inflammatory bowel disease (Sup Ref 19–21). The paradigm of dosing to the maximum tolerated dose (MTD) for oncology drug products, including biologic combinations, often does not result in the optimal dose, requiring post-marketing commitments for additional dose optimization. The FDA recently initiated Project Optimus, an initiative to provide guidance on dose optimization in oncology, due to the recognized lack of dose ranging randomized trials (Sup Ref 22 and 23).¹⁷ In contrast, phase II randomized, dose ranging trials have been more widely practiced for dose selection in non-oncology drug development.

An example of dose optimization after the pivotal study for a combination comes from the nivolumab and ipilimumab combination. Nivolumab body weight-based dosing given every 2 weeks (Q2W) was used for the pivotal CheckMate743 study (NCT02899299) (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W). Scientific rationale, population pharmacokinetics (PPK), and exposure-response (E-R) analyses combined with subgroup analysis of clinical data (Sup Ref 3, 24 and 25) supported a comparable benefit:risk of nivolumab 360 mg Q3W + ipilimumab and nivolumab 3 mg/kg Q2W + ipilimumab, and approval of this alternative dosing regimen in patients with untreated unresectable mesothelioma (Sup Ref 25).

Dose selection for combinations that are needed in a global health emergency take alternative approaches. The mAb combinations (casirivimab and imdevimab) and (bamlanivimab and etesevimab) were recently approved under emergency use to treat SARS-CoV-2 infection (Sup Ref 26).^{5,18} Dose selection and confirmation was conducted in a combined phase I/II/III study for casirivimab and imdevimab with two doses for each patient in the phase I part with the higher doses selected for each mAb in the randomized phase II/III part.¹⁸ For bamlanivimab and etesevimab, dose selection of each mAb was conducted in separate phase I trials enrolling healthy volunteer with the higher doses selected mainly using safety data and administered in the randomized phase II/III trials in patients. Rapid dose selection for concomitant COVID-19 treatment, without a dose-ranging randomized study, was primarily driven by the urgent unmet public

health need, neutralizing nature of both mAbs against the virus, and clinical safety demonstration.

BsAb dose selection generally follows the scientific principles and regulatory guidance for mAbs, including the first-in-human starting dose and dose selection (Sup Ref 27 and 28).¹⁹ BsAb dose optimization should consider the projected in vivo concentration ranges and optimal binding kinetics for both arms to engage with their respective target(s). Depending on the MOA/format of a BsAb, the clinical development goal is to find the dosing regimen that can maximize the therapeutic index (TI), which can pose challenges particularly if one arm has a greater impact on the overall TI. For example, selection of the dosing schedule for blinatumomab was based on the rapid terminal elimination half-life of ~2.1 h, clinical efficacy indicated by completed response (CR) and CR with partial hematological recovery, and clinical safety by cytokine-related adverse events (Sup Ref 29). As BsAbs enter subcutaneous administration rather than the conventional IV infusion route,²⁰ new challenges and opportunities will arise for drug development of these agents.

CLINICAL PHARMACOLOGY CONSIDERATIONS FOR SUPPORTING REGULATORY SUBMISSION: COMBINATIONS VERSUS BISPECIFICS

During drug development, the clinical pharmacology program characterizes PK, PD, and dose–exposure–response relationships for investigational products to support dose selection for clinical trials and ultimately for the approved drug label. The well-established drug development paradigm used for mAbs involves stepwise data-gathering

to support demonstrating the product's safety and efficacy and is applicable to BsAbs. A comparison between the bispecific-targeting product and the respective monospecific-targeting products could be informative to the benefit:risk of BsAbs.¹⁹ Certain unique considerations may be necessary because of their novel structure(s), function(s), and MOAs.¹⁹ To develop a combination drug, the basic guiding principles are (1) each component contributes to the claimed effects and (2) the dosage of components in the combination is safe and effective.²¹ For a combination of two previously approved monotherapies, any alterations of PK, PD, or dose–exposure–response relationships when used in combination is a subject for evaluation of the clinical pharmacology program. To identify an appropriate combination dosing regimen, thoughtful evaluations of a range of differing dose-ratios of active components are important before or in phase III studies. When the proposed combination treatments contain any investigational products, clinical pharmacology characterizations for each investigational product remain essential in supporting the combination regimen (Figure 2). In rare cases where the individual components cannot be evaluated separately in clinical studies (e.g., combo-therapies for viral infections), nonclinical data can serve to illustrate the contribution of each component and the advantage of co-administering multiple components.²²

The bioanalytical strategy for determining the exposure of functionally active BsAbs may depend on the MOAs.²³ For instance, when simultaneous engagement of both targets is essential, a method that detects the drug form with both target-binding domains free is often necessary. When binding to only one of the targets can contribute to the therapeutic effects, determining the active drug concentration may require more than one method.¹⁹ For mAb combination products, a comprehensive bioanalytical

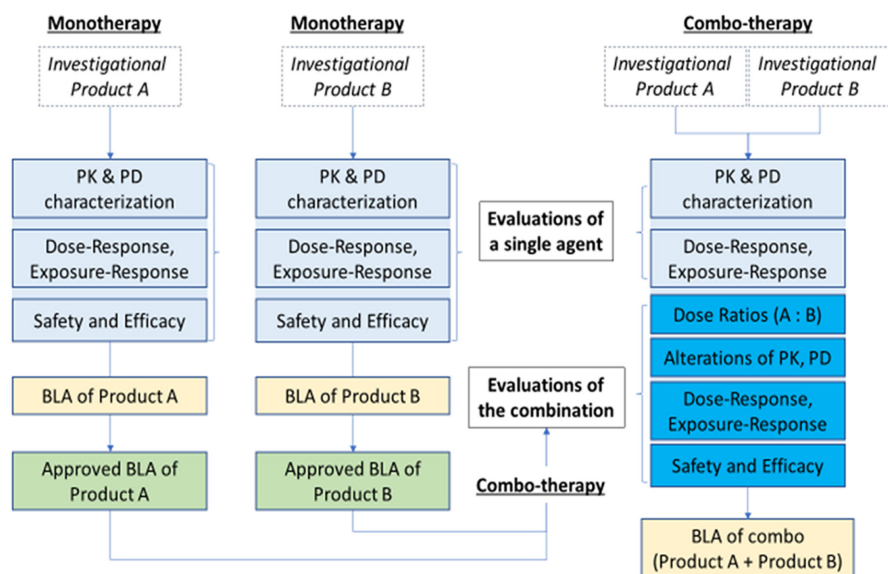


FIGURE 2 Clinical pharmacology framework to support regulatory submission of monotherapy and combination therapy of investigational products A and B. Light blue boxes represent evaluations of a single agent and darker blue boxes represent evaluations of the combination. BLA, biologics license application; PD, pharmacodynamics; PK, pharmacokinetics.

strategy is critical because bioanalytical methods used to analyze samples from monotherapy studies (containing a single drug) may not be suitable for study samples that are collected from combination studies and contain multiple drugs as in the case of trastuzumab in combination with pertuzumab.²⁴

The assessment of clinical impact of immunogenicity is a standard component of the clinical pharmacology evaluation because the immunogenicity effect on systemic exposure, if any, generally precedes its effect on clinical efficacy. BsAbs have the potential to induce antidrug antibodies (ADAs) that interfere with the functionality of one or both domains. Thus, assessing the nature of ADAs with respect to the domain-specificity is important. The immunogenicity profile for each component of the combination biologics may differ when administered alone compared to when administered in combination (Sup Ref 30). Therefore, immunogenicity assessments should be implemented in clinical programs of combination biologics regardless of whether the individual components have been previously approved.

SUMMARY

Biologic drug combinations and BsAb antibodies are becoming more common drug development approaches to treat high unmet medical needs not only for oncology indications, but also for metabolic, hematological, and immunological diseases. Biologic combinations have a lower threshold to develop, especially if the individual components of the combination have demonstrated POC and are approved by health authorities. The investment in a BsAb approach is favored when the underlying pharmacology demonstrates a clear efficacy or safety advantage over a combination approach, including facilitating cell–cell and protein–protein bridging or receptor clustering for a new or enhanced pharmacology.

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CONFLICTS OF INTEREST

SZ owns shares in Adagene due to employment. RP owns shares in Genentech due to employment. LH and JS own

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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