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Mechanisms of therapeutic anti-tumor monoclonal antibodies

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Abstract

Monoclonal antibodies (mAb) are a major component of cancer therapy. In this review, we summarize the different therapeutic mAbs that have been successfully developed against various tumor-expressed antigens and examine our current understanding of their different mechanisms of anti-tumor action. These mechanisms of action (MOA) largely center on the stimulation of different innate immune effector processes, which appear to be principally responsible for the efficacy of most unconjugated mAb therapies against cancer. This is evident in studies of mAbs targeting antigens for hematologic cancers, with emerging data also demonstrating the critical nature of innate immune-mediated mechanisms in the efficacy of anti-HER2 mAbs against solid HER2+ cancers. While HER2-targeted mAbs were originally described as inhibitors of HER2-mediated signaling, multiple studies have since demonstrated these mAbs function largely through their engagement with Fc receptors to activate innate immune effector functions as well as complement activity. Next generation mAbs are capitalizing on these MOAs through improvements to enhance Fc-activity, although regulation of these mechanisms may vary in different tumor microenvironments. Additionally, novel antibody-drug conjugates (ADC) have emerged as an important means to activate different MOAs. Although many unknowns remain, an improved understanding of these immunologic MOAs will be essential for the future of mAb therapy and cancer immunotherapy.

Keywords

Monoclonal antibody; targeted therapy; cancer treatment; HER2; Trastuzumab; Antibody Dependent Phagocytosis

The idea of using antibodies as anti-cancer therapeutics has a long history dating back over fifty years when serologic techniques allowed assessments of cancer cells and foretold the possible use of antibodies as therapeutics for cancer. Since that time, there has been a revolution in the development of monoclonal antibodies (mAbs), which now

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comprise a major pharmaceutical therapeutic market. While mAbs have a variety of uses, significant efforts have been directed towards anti-tumor therapeutics, which began in 1997 with the development and approval of Rituximab. This mAb remains a standard-of-care (SOC) therapy for B-cell Non-Hodgkins' Leukemia (NHL) and is now the basis for the development of two biosimilar mAbs (1). Therapeutic anti-tumor mAbs selectively target cell surface antigens in cancer. These antigens can represent proteins that are overexpressed or selectively expressed in cancer, and proteins that are mutated or post-translationally modified in a manner that is different in cancer cells than non-transformed cells. The functional effect of a mAb is related to a cancer antigen profile and the specific ability of the mAb to be internalized, activate Fcγ-receptors (FCGR) on innate immune cells, trigger the activation of complement, or block receptor-mediated oncogenic signaling. These therapeutic outcomes depend strongly on the isotype and the specific nature of the mAb (i.e., specific binding site, avidity of target binding, and particular conformation), as well as the nature of the target antigen. The long history of iterative clinical development of anti-tumor mAbs has demonstrated the importance of all of these factors, including the significance of appropriate monitoring of the pharmacokinetic and pharmacodynamics properties of mAbs in early clinical trials (2,3). An important consideration is the distribution of mAb target protein expression in non-malignant tissues, which has important implications for off-target toxicities. For instance, the respective expression of EGFR in epidermal tissue and HER2 in cardiac tissue generate a degree of toxicity using mAb against these targets, which is a critical concern in the development of anti-tumor mAbs and ADCs (4–6). These consideration thus stated, the purpose of this review is to summarize the types of mAbs that have been successfully developed against cancer expressed antigens and review our current understanding of their different mechanisms of anti-tumor action, with a particular emphasis on emerging studies of HER2-specific mAbs.

Current FDA approved monoclonal antibodies:

As a means of cancer therapy, mAbs in an idealized setting promise a potentially high degree of specificity and efficacy with a minimal degree of off-target toxicity. In cancers where mAbs have achieved considerable efficacy, such as in HER2+ breast cancer (BC), they have become the frontline standard-of-care, largely outperforming HER2-specifc small molecule inhibitors (such as Lapatinib and Neratinib) and have offered excellent response profiles with modest toxicities (7). However, only a small number of cancers have been successfully treated with mAbs, many of which are hematologic malignancies. Since the first approval of Rituximab in 1997 for NHL, >30 anti-tumor mAbs have received FDA approval for the treatment of cancer (Table 1), with many more being tested in clinical trials. To meet FDA approval, mAbs usually need to demonstrate an improvement of overall survival (OS) or a surrogate marker, such as progression free survival (PFS), in comparison to the current standard-of-care in phase III clinical trials. This high bar ensures that approved mAbs confer a significant clinical benefit for the intended population. Among the FDA approved tumor-targeting mAbs, it is notable that the majority of mAbs receiving approval in solid tumors have targeted either HER2 or EGFR (8 of 12), both members of the ERBB family. Additionally, a large class of these approved mAbs target more restricted immune markers (such as CD20 or CD52) of hematologic cancers, predominantly lymphomas and

myelomas. Initially, the approvals of mAbs were for ‘naked’ non-conjugated mAbs against these targets (such as Rituximab in 1997 and Trastuzumab in 1998), which spawned the development of conjugated versions that generally incorporated a cytotoxic agent onto the mAb through a chemical linker. In general, non-conjugated mAbs can invoke several different mechanisms of action (MOA), while conjugated mAbs typically rely on the direct cytotoxic action of their payloads, ingested through endocytosis of receptor bound conjugated mAbs.

Different mechanisms of action for non-conjugated mAbs:

Typically, direct antibody binding (for example to pathogens) causes immediate steric disruption, thereby suppressing pathogen entry into cells. This property is the most frequently sought after in the development of therapeutic antibodies to elicit blockade of specific signaling molecules. Binding of mAbs to specific receptors can also allow for their internalization through different processes, suggestive of a conserved regulatory mechanism. In anti-cancer therapies, this ability to block interactions and internalize receptors has provided a means to inhibit oncogenic cellular signaling.

In addition to this function, the majority of antibodies possess a conserved Fc (named from earlier studies, fragment crystallizable) domain that allows for their direct engagement with Fcγ-receptors (FCGR) on different types of immune cells (Figure 1A). This enables mAbs to directly trigger different immune responses, which are mediated by a difference in binding ratios to activating and inhibitory FCGRs (A:I ratio), which vary by antibody isotype (8). A major function of activating FCGR engagement allows for phagocytic engulfment of antibody-bound pathogens or cells. This process allows for target cell clearance and elimination, termed Antibody-Dependent-Cellular-Phagocytosis (ADCP). FCGR engagement and signaling activity also provokes cellular stimulation of different classes of immune cells (such as DCs, macrophages, or neutrophils), which can further alter adaptive immune responses through antigen presentation, cytokine production, and chemotaxis. Additionally, the Fc portion of bound antibodies can also stimulate other innate immune cells, such as Natural Killer (NK) cells, to directly lyse sufficiently opsonized targets, termed Antibody-Dependent-Cellular-Cytotoxicity (ADCC). The activation of FCGR is complex and is governed by the expression of different activating and inhibitory FCGRs on the surface of a given cell, as well as a collection of other signaling molecules (such as CD47-SIRPα in phagocytosis), which further govern cell signaling upon Fc-FCGR engagement. These dynamic signaling complexes directly modulate cellular activities (such as phagocytosis or degranulation), as well as indirectly affecting immunity through alterations of cellular activation and cytokine/chemokine secretion (9,10).

Finally, the Fc portions of mAbs can also trigger the activation of serum proteins, such as the complement family (Figure 1A) (11,12). When the Fc domains bind soluble C1q, they can facilitate the assembly of C1q hexamers. Once assembled, these complexes stimulate a proteolytic cascade that leads to the activation of complement, which produces a series of anaphylotoxins that can opsonize cells as well as stimulate or inhibit the activity of various C3a-receptor and C5a-receptor expressing immune cells. Moreover, this can result in the assembly of the Membrane-Attack-Complex (MAC), which allows for direct cellular target

destruction (12). As with FCGR signaling, the activation of complement is highly regulated at the cell surface by a series of complement receptors, allowing for dynamic control of this process. In summary, the engagement of both FCGR and complement, while complex, can result in direct cellular destruction as well as the modulation of local and systemic immune responses, demonstrating the potency of mAbs as a critical arm of adaptive immunity and its potential as an anti-tumor therapeutic strategy (Figure 1B–C).

Given the importance of these functions, many efforts have been made to molecularly engineer the Fc region to optimize effector functions and antibody half-life. These interactions can be modulated through the introduction of point mutations, inserting/deleting amino acids, modifying glycan composition, or exchanging Fc domains. More detailed reviews on mAb Fc modifications has been discussed elsewhere (13,14). One important example of Fc-modified mAb that recently passed a large clinical trial is Margetuximab (15), which contains several optimization mutations and exhibits improved FCGR3A engagement and ADCC activity compared to the parental antibody Trastuzumab (16). Alternatively, strategies to increase hexamerization of mAbs to improve complement activation are being developed for clinical use (17)

Mechanisms of action for conjugated mAbs:

One of the fastest growing uses of mAb in cancer is through their conjugation to different cytotoxic payloads, termed antibody-drug conjugates (ADCs) (18,19). In this approach, a cytotoxic drug is conjugated to the heavy or light chain domain of a mAb through different types of chemical linkers. The ability of mAbs to internalize allows for a more specific delivery of the cytotoxic agent to tumor cells while simultaneously reducing systemic toxicity. This method is also exploited using alternatives to cytotoxic molecules, such as innate immune-stimulatory molecules, such as Toll-like receptor agonists, that allow for the activation of anti-tumor immunity (20). For conjugated approaches, the intended mechanism of actions straightforward: to enhance the delivery of a conjugated drug to the tumor. However, there are many parameters that affect the efficacy of this strategy, including the type of linker, the type of conjugated payload, the ratio of payload to mAb, the distribution of the antigen target, the ability of the mAb to bind and internalize, and the stability and biodistribution profile of the ADC. While complex, there have been great strides in the optimization of specific ADCs with a generally simpler MOA, which has resulted in their comprising a majority of recent FDA mAb approvals (7 of 12 since 2017, see Table 1). As such, ADCs may allow for a more direct means of eliciting therapeutic responses against different cancers.

Unconjugated therapeutic monoclonal antibodies in hematologic cancers:

In 1997, Rituximab became the first FDA approved mAb targeting cancer after demonstrating therapeutic activity in combination with chemotherapy against B-cell lymphomas. This mAb targets CD20, encoded by the MS4A1 gene (21), which was one of the first described markers of B-cells (22). CD20 is a highly restricted cell surface antigen with abundant, stable, and highly characterized expression in B-cells (23). The majority of studies to date support a major role for Fc-mediated myeloid cell activities as the dominant

mediators of Rituximab efficacy, while other studies suggest that interruption of cell signaling and complement activity may also contribute substantially to efficacy (12,22,24–27). Clinical studies have demonstrated a synergy with different types of chemotherapy, typically cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), which may be due to sensitization of cell signaling interruption or enhanced immunogenicity (28). The reasons for potential synergy between different chemotherapies and Rituximab are not well studied; thus, it is unclear what MOAs are dominant in the clinical use of Rituximab, which is usually used in conjunction with chemotherapy.

Since the development of Rituximab, five other CD20-targeting mAbs (three murine mAbs and two 'humanized' mAbs) received FDA approval for the treatment of CD20+ B-cell cancers (Table 1). These mAbs differed in their binding sites, which altered the impact on CD20 signaling and growth, along with their ability to engage with FCGRs and activate complement (22,24,29,30). Despite these differences, Rituximab has remained a clinical mainstay of treatment, suggesting that slight alterations to these MOAs may not be sufficient to achieve significant differences in clinical outcomes for most patients. However, resistance to CD20-targeting mAbs can occur, which is thought to be potentially mediated by altering CD20 expression, upregulation of complement regulator genes, or elevated expression of suppressors of phagocytosis (27,30,31). In this last instance, the use of a CD47 blocking mAb has demonstrated early clinical indications of success in reversing resistance (32), potentially suggesting this strategy to enhance the phagocytosis MOA as a critical one in mitigating Rituximab-resistance in B-cell leukemias.

After the success of CD20-targeting mAbs, studies on other hematologic markers yielded FDA approval for mAbs targeting other immune cell antigens, including: CD52 (Alemtuzumab), CD38 (Daratumumab and Isatuximab), SLAMF7 (Elotuzumab), CCR4 (Mogamulizumab) and CD19 (Tafasitamab). Critically, these mAbs all contain human IgG1 isotypes (high A:I binding ratio), with multiple studies demonstrating their collective ability to elicit ADCC, ADCP, and some degree of CDC (3,12,33–35). While it is unclear which of these mechanisms mediate their impact, there is emerging consensus that the Fc portion of these mAbs is indispensable for their therapeutic activity, consistent with previous studies of CD20-targeting mAbs. As such, there is strong reason to believe that these mAbs may be similarly enhanced through strategies to potentiate Fc-based immune mechanisms.

Conjugated therapeutic monoclonal antibodies in hematologic cancers:

Early successes and failures of different 'naked' mAbs against hematologic antigens suggested the obvious potential of the conjugation of different cytotoxic agents to mAbs. This would provide a direct means to enhance tumor elimination and therapeutic efficacy, especially in comparison to systemic chemotherapies. The first successful use of this approach utilized radio-labeling (131I and 90Y-labeling) of both high and low A:I isotype CD20-targeting mAbs (Ibritumomab tiuxetan and tositumomab, respectively), which both demonstrated improved response rates and PFS in patients with NHL in 2002–2003. Notably, their comparable efficacy suggests their impact is due to their emission of beta particles to enhance tumor killing and not due to ADCP/ADCC mechanisms (36,37).

Aside from radiolabeling, efforts to directly conjugate cytotoxic agents to mAbs resulted in additional approvals for mAbs targeting CD30, CD33, CD22, BCMA and CD79b in the past decade. These antigens are highly restricted to different lymphoid and myeloid cell types, allowing a high degree of specificity of their different cytotoxic payloads, comprised of DNA toxins, microtubule inhibitors, and exotoxins (38–40). While many of these ADCs are used in isolation, Polatuzumab vedotin is used in combination with chemotherapy and Rituximab for the treatment of large B-cell lymphomas (40–42). This combinatorial approach demonstrates the potential of combining ADCs with unconjugated mAbs against different targets within a singular cancer to improve clinical outcomes and minimize toxicities.

Since the approval of Rituximab in 1997, there has been great progress in developing mAbs for the treatment of different hematologic cancers. These efforts have resulted in at least 16 (to date) different mAb drugs to treat a variety of myeloid and lymphoid carcinomas. Lacking complex stromal and extracellular matrix components, these cancers appear to be more sensitive to mAb-based depletion, whether through FCGR-interactions and complement activation or utilizing conjugated immunotoxins. The advent of agents to improve FCGR effector function suggests that blocking these types of innate immune checkpoints (e.g., blocking CD47-SIRPα interactions to improve phagocytosis) may enhance the activity of unconjugated mAbs (32), although it is unclear if there is a biological ceiling on the efficacy of this approach. Moreover, the interaction between unconjugated mAbs and chemotherapy, as well as the potential for combination usage of different unconjugated and/or conjugated mAbs, remains largely unexplored. The recent approval of multiple ADCs for different cancer antigens (e.g., CD79b, BCMA, and CD38) suggests the strong clinical potential for ADCs in the treatment of these malignancies. As such, the forefront of new treatments for hematologic cancers will more than likely consist of the development of new ADCs, as well as refined usage of unconjugated mAbs.

Monoclonal antibodies targeting ERBB family proteins in solid cancer:

In addition to their use against hematological tumor antigens, mAbs have also been extensively explored to target antigens in solid tumors (3). Notably, the majority of FDA approved mAbs target two members of the ERBB family, HER2 and EGFR (Table 1). Both EGFR and HER2 are cell surface membrane-spanning Type-I receptors that are highly expressed on different solid cancers and enable a broad repertoire of oncogenic signaling upon homo and hetero-dimerization (43). Ongoing clinical trials are also currently exploring therapeutic mAbs targeting HER3, a heterodimerization binding partner for both EGFR and HER2 (44). The combination of their elevated cell surface expression and their critical role in maintaining oncogenic signaling is thought to make these receptors ideal mAb-targets. While the goal of initial efforts to develop mAbs against these targets was to block their signaling, subsequent studies have revealed that the mAbs against HER2 have largely immunologic MOAs. In the following sections, we will discuss the latest preclinical and clinical developments on HER2 and EGFR mAbs therapy and the lessons learned from those studies, which is important for future mAbs developments of other solid tumor targets.

HER2-specific unconjugated mAbs:

In 1998, Trastuzumab became the first mAb approved for treatment of a solid cancer for use in HER2+ breast cancer (BC) and later in HER2+ gastric cancer. HER2 is amplified in 15–20% of breast cancers, which initially associated with poor prognosis and higher rates of recurrence (45). The use of Trastuzumab in combination with chemotherapy demonstrated impressive survival gains and quickly became the standard-of-care therapy for HER2+ BC (46,47). Initially, this mAb was thought to suppress HER2 signaling (48,49), with multiple studies have confirming the inhibition of downstream PI3K/Akt signaling pathway, resulting in the upregulation of p27 and inhibition of cellular proliferation (50–53). However, the parallel development of HER2-selective tyrosine-kinase inhibitors (TKIs, such as lapatinib, neratinib, and tucatinib) have proven to be far superior at suppressing HER2-mediated signaling (52,54–57). But despite being a weaker inhibitor of HER2 signaling, Trastuzumab has exhibited greater clinical efficacy in comparison to TKIs, becoming the backbone of therapy for HER2+ BC for more than 20 years (48,58–60). Clinically, this difference in efficacy suggests that the immunological engagement of antibody therapy, largely absent in TKIs, is likely critical for successful therapeutic outcome.

Indeed, pre-clinical and clinical studies have revealed that the anti-tumor effect of anti-HER2 mAbs depends on engagement with immune cells (61–63). Early studies using xenografts first demonstrated the requirement of FCGR host expression for Trastuzumab's activity in vivo (64,65). Subsequent studies using a novel murinized version of Trastuzumab (4D5) in both syngeneic and HER2+ transgenic mouse models, demonstrated that the Trastuzumab principal therapeutic MOA occurs through ADCP by macrophages (54). These studies also found this effect was enhanced by the blockade of CD47, similar to findings observed with Rituxumab, suggesting that this strategy may overcome Trastuzumab resistance (54,66). These findings presaged the FDA approval in 2020 of Margetuximab, a HER2 mAb with an altered Fc domain that increases FCGR3A binding and activity (16). Its approval in metastatic HER2+ patients who had received two prior lines of HER2-specific therapies, highlights the importance and clinical need to improve the efficacy of FCGR engagement as dominant MOA in HER2 mAb therapies (15).

Aside from highlighting the importance of Fc activity, several studies have suggested that Trastuzumab may also be capable of activating HER2-specific adaptive immunity (67–70). This activation reportedly occurs through HER2 antibody-complexes that are engulfed by FCGR+ dendritic cells and macrophages (61,71–75). This phagocytic process is thought to trigger HMGB1-MyD88 and Type-I interferon signaling pathways, which are critical for the generation of adaptive anti-tumor T-cell responses (61,73,76–79). However, studies using a fully murine Trastuzumab mAb in an endogenous HER2+ transgenic model failed to demonstrate a significant stimulation of HER2-specific immune responses (54), which may relate to the lack of immunogenicity present in the treatment of an endogenous tumor with fully murine Trastuzumab. However, since its approval, Trastuzumab has been used in conjunction with immunogenic taxane-based chemotherapy as the standard-of-care regimen for HER2+ cancer. Taxane-based chemotherapy has been documented to induce immunogenic tumor cell death and augment phagocytosis (80), which can increase tumor antigen presentation to T-cells (9,81). Intriguingly, clinical studies have

documented that lymphocytic infiltrates are positively correlated with clinical response rates and their transcriptional signatures predict lower recurrence in Trastuzumab treated patients (78,82,83). Collectively, these studies suggest that immunogenic chemotherapy could potentially stimulate adaptive immunity, which is likely enhanced by Trastuzumab-mediated ADCP, although further studies will be required to understand the relationship between HER2-targeted mAbs in combination with chemotherapy.

Building upon the efficacy with Trastuzumab plus chemotherapy treatment, clinical studies demonstrated that the addition of another HER2 mAb (Pertuzumab) to this regimen significantly improved the outcomes of both metastatic HER2+ BC (84) and early-stage HER2+ BC (85), resulting in Pertuzumab FDA approval in 2012. Pertuzumab has the ability to block HER2 oncogenic signaling through its binding to domain II of HER2, which sterically inhibits HER2 heterodimerization with other ERBB family proteins (86). However, despite this ability to inhibit heterodimerization, Pertuzumab has demonstrated minimal efficacy as a monotherapy in pre-clinical and clinical studies (87,88). One possible explanation for this lack of efficacy is HER2 homodimerization (mediated by HER2Δ16 or HER2-p95), which allows for constitutive signaling while minimizing the requirement for ligand-driven heterodimerization (89–91). Nevertheless, pre-clinical and clinical studies have firmly documented the synergistic effects on tumor growth suppression by the combination of Pertuzumab and Trastuzumab, suggesting that emergent immune-mediated mechanisms may be responsible (88,92,93). Pertuzumab is a humanized IgG1 mAb capable of strongly activating innate responses such as ADCC, ADCP, and CDC (88,94–96). However, evidence that connects these immunologic mechanisms to Pertuzumab's therapeutic synergy with Trastuzumab have been lacking. One intriguing hypothesis is the combination of these HER2 mAbs may allow for a more potent activation of complement, as has been suggested from in vitro studies (95), as well as with combinations of EGFR mAbs (97). This may allow for future strategies to exploit the activation of complement, which could be achieved by targeting complement regulators CD46, CD55, and CD59, which are often amplified in solid cancers (95,98). Intriguingly, these genes have been described as amplified in gastric cancers (99–102), where the addition of Pertuzumab did not enhance Trastuzumab treatment responses against HER2+ gastric carcinomas (7,103). But it is unknown how the activation of complement may impact other aspects of local immunity, such as modulation of cytokine secretion, DC maturation, and T-cell activation (104–106). Given the success of this dual HER2 targeting mAb combination with chemotherapy (Figure 1B–C), understanding the interplay between these therapies may be essential in the future success of mAb in other solid cancers.

HER2-specific conjugated mAbs:

The efficacy and ability to selectively target HER2+ tumors made HER2-specific mAbs an early candidate for cytotoxic conjugation. These efforts have resulted in two approved HER2-targeted ADCs in patients, Ado-Trastuzumab emtansine (T-DM1) and fam-trastuzumab deruxtecan (T-Dxd) in 2013 and 2020. These ADCs have been conjugated with cytotoxics (a microtubule inhibitor and a topoisomerase inhibitor, respectively) and approved as second-line therapies for patients who have developed resistance or progressed on Trastuzumab-based regimens (107) (108). Recently, TDM-1 was found to be superior

to Trastuzumab in preventing recurrence in patients with early-stage HER2+ BC (109), while preclinical studies have demonstrated a T-Dxd impact against T-DM1 resistant HER2+ BC (110). However, multiple clinical studies have thus far failed to document notable improvements in survival, progression, or safety by using T-DM1 in place of Trastuzumab plus chemotherapy as front-line treatment in both early and advanced HER2+ BC (111–113). These findings suggest that improvements in the chemotherapeutic MOA (achieved by HER2-ADC targeting) are unlikely to shift the efficacy achieved by current treatment combinations. However, a plethora of additional conjugations to HER2 mAbs, many of which contain novel immune-stimulating agents, may allow for enhancements of additional therapeutic mechanisms. While early in development, if these agents could alter local anti-tumor immunity in substantial ways, they could offer the means to promote HER2-specific adaptive immunity that could translate into meaningful clinical therapeutic improvements.

EGFR-specific unconjugated mAbs:

Like HER2, EGFR is another member of the ERBB family responsible for the activation of multiple oncogenic signaling pathways. As a result, it is often overexpressed, dysregulated, or mutated in many cancers, including: colorectal carcinoma (CRC), head-and-neck squamous cell carcinoma (HNSCC), squamous non-small-cell-lung cancer (NSCLC) and Triple-Negative BC (TNBC) (114). This widespread tumor overexpression made EGFR an early mAb target, resulting in the approval of Cetuximab in 2004 for its use in metastatic CRC and HNSCC in combination with chemotherapy (115). However, retrospective analyses determined that efficacy occurred only in KRAS wild-type (non-mutated) cancers (116). And while Cetuximab has also demonstrated utility with radiotherapy in HNSCC, it has not been approved in many other EGFR expressing cancers (117). Two additional EGFR-targeting mAbs, Panitumumab and Necitumumab, subsequently gained FDA approval in metastatic CRC patients (Panitumumab) and NSCLC patients (Nectumumab) (118,119). While these mAbs all target different binding sites, they also differ in their isotype and degree of humanization. Cetuximab and Nectumimab are IgG1 mAbs (a high A:I isotype), while Pantumimab is an IgG2 (low A:I isotype) mAb. Given these differences, it is unsurprising that Cetuximab has demonstrated an enhanced ADCC and CDC capacity in multiple cancers, compared to Pantumimab (120–123). This may explain why Panitumumab has been less clinically effective than Cetuximab in both billary cancers and HNSCC (124,125). But despite these differences, both therapies appear relatively equivalent in CRC (126–128). Additionally, common resistance mechanisms to these therapies are often intrinsic, caused by mutations in KRAS, BRAF, and NRAS. These occur in about 50% of CRC, and are utilized as exclusion criteria for EGFR mAb treatment (129,130). The equivalent efficacy, side effect profile, and signaling-based resistance mechanisms of EGFR mAbs collectively suggest that EGFR signaling blockade is the dominant MOA for anti-EGFR mAbs. However, it is unknown if improvements of Fc activities of EGFR mAbs could offer enhanced therapeutic efficacy against CRC or other EGFR-expressing cancers. Additionally, strategies to enhance systemic adaptive anti-tumor immune responses of Cetuximab through combination with immunotherapy may be beneficial (121,131), which are also being investigated with other EGFR mAbs (132).

Other mAbs for non-ERBB family targets in solid cancers:

While initial approvals of mAbs in solid cancers have been against ERBB antigens, pre-clinical studies have evaluated a variety of different tumor targets (Table 1). This growing interest has now led to several FDA approvals for unconjugated and conjugated mAbs against multiple highly expressed antigens in solid cancers. The first such mAb to gain continual usage occurred in 2015, with the FDA approval of Dinutuximab for second-line treatment of children with high-risk neuroblastoma (133,134). This chimeric mAb targets GD2, a glycolipid found on cells of the neuroectoderm (135). An improved humanized version (Naxitamab) was later approved in 2020, with both allowing for Fc-mediated activation of ADCC, ADCP, and CDC activity (135–140). Notably, these mAbs were developed after extensive pre-clinical and clinical validation and utilized as part of an immunotherapeutic strategy, in combination with GM-CSF and chemotherapy. Recently, two other ADCs have been approved for solid cancers, Enfortumab vedotin for urothelial carcinoma and Sacituzumab govitecan for TNBC. These cytotoxic ADCs target two different tumor-associated antigens, Nectin-4 and TROP-2, respectively. Nectin-4 is a cell adhesion member of the Nectin family and is overexpressed in many cancers, including urothelial bladder cancer (141). TROP-2 is a transmembrane glycoprotein first identified in the trophoblast, with roles in growth, invasion, and spread. It is also highly expressed in many cancers, including Triple-Negative Breast Cancer (142,143). In both indications, these ADCs were approved as secondary therapies, but Enfortumab vedotin was also approved as a frontline therapy for urothelial carcinoma in combination with pembrolizumab (anti-PD1 mAb) as a first-line treatment for cisplatin ineligible patients (141,142,144,145). While both have direct anti-tumor effects through their cytotoxic payloads, this type of immunotherapeutic synergy suggests that ADCs targeting tumor-associated antigens may offer a viable therapeutic path as secondary therapies for resistant cancers, or in combination with immune-modulating agents as frontline therapies.

Conclusion and Future Directions:

The advent and development of mAbs directly targeting cancers has fundamentally altered the landscape of targeted therapy in oncology, having become a frontline standard-of-care for many hematologic and some solid cancers. In combination with chemotherapy, these mAbs have generated success against advanced-stage cancers, which previously had poor outcomes. This is due to the induction of multiple, mostly immunologic MOAs, which collectively serve to engage innate immune cells and stimulate anti-tumor immunity, likely in combination with chemotherapy. These same MOAs appear to be present in mAbs against hematologic cancers (e.g. Rituximab), as well as in other solid cancers (e.g. HER2 mAbs). In cases where these immunologic MOAs are not strongly induced (potentially with EGFR mAbs), responses have been more muted. As such, the selection of new mAbs should likely prioritize the ability to elicit robust immune stimulation, in addition to ensuring adequate binding affinity, bio-distribution, and tumor penetrance. Additionally, these responses are likely to vary by tissue type in the regulation of these MOAs, potentially evidenced by a lack of Pertuzumab additive efficacy in HER2+ gastric carcinomas. This also may explain why greater mAb efficacy has been observed against hematologic cancers, which have less stromal influence. Strategies to enhance these MOAs, such as CD47 blockade to enhance

ADCP (54) or reducing mAbs fucosylation to enhance Fc activity (146), have demonstrated promising clinical signals and suggest the potential for these types of approaches. Moreover, the use of ADCs and novel conjugations may also serve to enable existing MOAs or elicit novel MOAs (e.g., cytotoxicity and immune stimulation) against different cancers. This may be particularly pertinent given the success of PD-1/PD-L1 immune checkpoint blockade mAbs, which have demonstrated the potential to enable adaptive anti-tumor immunity. Given their ability to elicit innate anti-tumor immunity, it may only be a matter of time before the full potential of anti-tumor mAbs are realized, as a means to cooperatively marshal both innate and adaptive immune responses against cancer.

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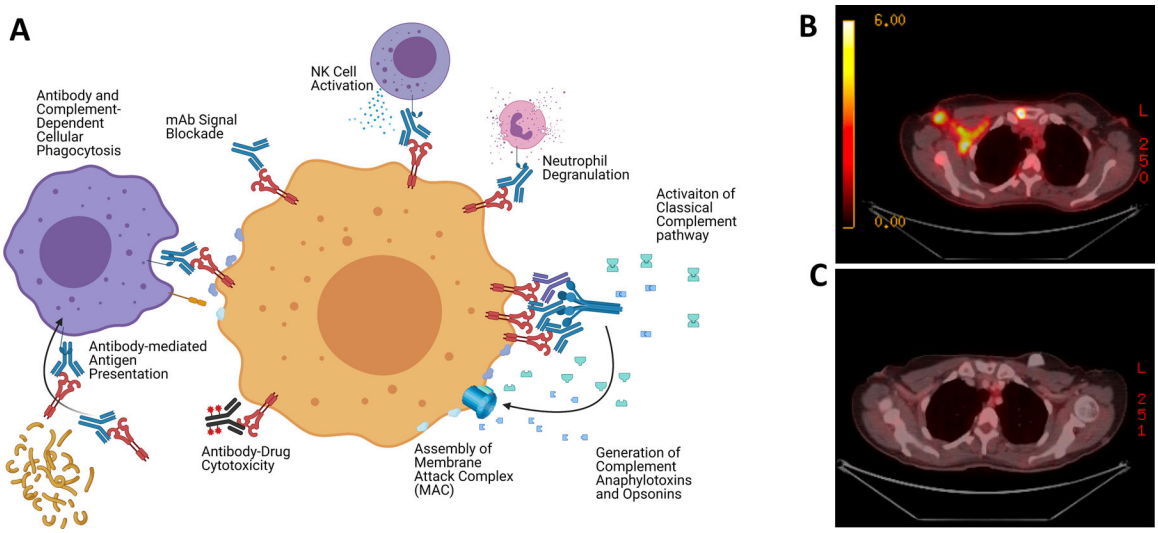

Figure 1. Immunologic mechanisms and potential of HER2 targeted mAb therapies.

A) Diagram illustrating the potential MOAs involved in anti-tumor mAb directed therapies. B) A PET scan demonstrating FDG avid sites of disease in a patient initially diagnosed with metastatic HER2 positive breast cancer who had a complete response, or C) following induction docetaxel combined with trastuzumab and pertuzumab.

Table 1.

List of FDA-approved monoclonal antibodies targeting tumor antigens

Antigen category	Antibody (INN)	Antibody (Trade name)	Target antigen	IgG Type	Year of FDA approval	Tumor disease	Major Mechanism of Action
Hematological cancer	Rituximab	Rituxan	CD20	Chimeric IgG1	1997	Non-Hodgkin's lymphoma; chronic lymphocytic leukemia;	ADCP, ADCC, CDC
	Ofatumumab	Arzerra	CD20	Human IgG1	2009	Chronic lymphocytic leukemia	ADCP, ADCC, CDC
	Ibritumomab tiuxetan	Zevalin	CD20	Murine IgG1 / radioisotope conjugate	2002	Non-Hodgkin's lymphoma	radionucleotide delivery
	Tositumomab-I131	Bexxar	CD20	Murine IgG2a / radioisotope conjugate	2003 *	Non-Hodgkin's lymphoma	radionucleotide delivery
	Obinutuzumab	Gazyvaro	CD20	Humanized IgG1	2013	Chronic lymphocytic leukemia	ADCC, ADCP
	Alemtuzumab	Campath	CD52	Humanized IgG1	2001 *;2014	B-cell chronic lymphocytic leukemia	ADCP, ADCC, CDC
	Tafasitamab	Monjuvi	CD19	Humanized IgG1	2020	Diffuse large B-cell lymphoma	ADCP, ADCC, CDC
	Loncastuximab tesirine	Zynlonta	CD19	Humanized IgG1	2021	Diffuse large B-cell lymphoma	cytotoxic drug delivery
	Polatuzumab vedotin	Polivy	CD79b	Humanized IgG1 ADC	2019	Diffuse large B-cell lymphoma	cytotoxic drug delivery
	Daratumumab	Darzalex	CD38	Human IgG1/ κ	2015	Multiple Myeloma	CDC, ADCC, ADCP, neutralization
	Isatuximab	Sarclisa	CD38	Chimeric IgG1	2020	Multiple Myeloma	ADCP, ADCC, CDC
	Mogamuizumab	Poteligeo	CCR4	Humanized IgG1	2018	Cutaneous T cell lymphoma	ADCP, ADCC, CDC
	Gemtuzumab ozogamicin	Mylotarg	CD33	Humanized IgG4 / toxin conjugate	2000 *; 2017	Acute myeloic leukemia (AML)	cytotoxic drug delivery
	Inotuzumab ozogamicin	BESPONSA	CD22	Humanized IgG4 as ADC	2017	B-cell precursor acute lymphoblastic leukemia	cytotoxic drug delivery
	Moxetumomab pasudotox	Lumoxiti	CD22	Murine IgG1 dsFv immunotoxin	2018	Hairy cell leukemia	cytotoxic drug delivery
	Belantamab mafodotin	BLENREP	BCMA	Humanized IgG1 ADC	2020	Multiple Myeloma	cytotoxic drug delivery
	Brentuximab vedotin	Adcetris	CD30	Chimeric IgG1 as ADC	2011	Hodgkin lymphoma (HL), systemic anaplastic large	cytotoxic drug delivery

Antigen category	Antibody (INN)	Antibody (Trade name)	Target antigen	IgG Type	Year of FDA approval	Tumor disease	Major Mechanism of Action
						cell lymphoma (ALCL)	
	Elotuzumab	Elotuzumab	SLAMF7	Humanized IgG1	2015	Multiple Myeloma	ADCP, ADCC, CDC
Solid cancer (ErbB family)	Trastuzumab	Herceptin	HER2	Humanized IgG1	1998	Breast cancer; metastatic gastric or gastroesophageal junction adenocarcinoma	ADCP, CDC **
	Ado-Trastuzumab emtansine	Kadcyla	HER2	Humanized IgG1 as ADC	2013	Breast cancer	cytotoxic drug delivery
	[fam]-trastuzumab deruxtecan	Enhertu	HER2	Humanized IgG1 ADC	2019	Breast cancer	cytotoxic drug delivery
	Pertuzumab	Perjeta	HER2	Humanized IgG1	2012	Breast cancer	signal blockade, ADCP, CDC **
	Margetuximab	MARGENZA	HER2	Chimeric IgG1	2020	Breast cancer	ADCP, ADCC
	Cetuximab	Erbitux	EGFR	Chimeric IgG1	2004	Head and neck cancer; colorectal cancer	signal blockade, ADCC, CDC
	Panitumumab	Vectibix	EGFR	Human IgG2	2006	Metastatic colorectal carcinoma	signal blockade
	Necitumumab	Portrazza	EGFR	Human IgG1	2015	Carcinoma, non-small-cell lung	signal blockade, ADCC
Solid cancer (other targets)	Dinutuximab	Unituxin	GD2	Chimeric IgG1	2015	Neuroblastoma	ADCC, ADCP, CDC
	Naxitamab	DANYELZA	GD2	Humanized IgG1	2020	Neuroblastoma	ADCC, ADCP, CDC
	Enfortumab vedotin	Padcev	Nectin-4	Human IgG1 ADC	2019	Urothelial cancer	cytotoxic drug delivery
	Sacituzumab govitecan	Trodelvy	TROP-2	Humanized IgG1 ADC	2020	Breast cancer	cytotoxic drug delivery
	Arcitumomab	CEA-scan	CEA	Murine Fab fragment	1996	colorectal cancer	Detection (non-therapeutic)
	Satumomab	OncoScint	TAG-72	Murine MAb	1992	colorectal and ovarian cancers	Detection (non-therapeutic)
	Capromab	ProstaScint	PSMA	Murine MAb	1996	prostate adenocarcinoma	Detection (non-therapeutic)

Footnotes:

* indicates a mAb that was withdrawn from the market after initial FDA approval

** major mechanism of action when Trastuzumab and Pertuzumab are used in combination

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https://www.antibodysociety.org/resources/approved-antibodies/.

https://www.accessdata.fda.gov/scripts/cder/daf/