Determination of the starting dose in the first-in-human clinical trials with monoclonal antibodies: a systematic review of papers published between 1990 and 2013

Abstract: A systematic review was performed to evaluate how the maximum recommended starting dose (MRSD) was determined in first-in-human (FIH) studies with monoclonal antibodies (mAbs). Factors associated with the choice of each MRSD determination method were also identified. PubMed was searched for FIH studies with mAbs published in English between January 1, 1990 and December 31, 2013, and the following information was extracted: MRSD determination method, publication year, therapeutic area, antibody type, safety factor, safety assessment results after the first dose, and number of dose escalation steps. Seventy-nine FIH studies with mAbs were identified, 49 of which clearly reported the MRSD determination method. The no observed adverse effects level (NOAEL)-based approach was the most frequently used method, whereas the model-based approach was the least commonly used method (34.7% vs 16.3%). The minimal anticipated biological effect level (MABEL)- or minimum effective dose (MED)-based approach was used more frequently in 2011–2013 than in 1990–2007 (31.6% vs 6.3%, P=0.036), reflecting a slow, but steady acceptance of the European Medicines Agency’s guidance on mitigating risks for FIH clinical trials (2007). The median safety factor was much lower for the MABEL- or MED-based approach than for the other MRSD determination methods (10 vs 32.2–53). The number of dose escalation steps was not significantly different among the different MRSD determination methods. The MABEL-based approach appears to be safer and as efficient as the other MRSD determination methods for achieving the objectives of FIH studies with mAbs faster.

Keywords: MRSD determination method, starting dose in first-in-human study, first-in-human study with monoclonal antibody, MRSD, safety factor

Introduction

Determining the safe starting dose for humans is one of the most important steps before any new biopharmaceutical product under development can enter clinical testing for the first time. Ideally, the starting dose should be low not to cause any harm in humans, while it is expected to be not too low for efficacy, thereby reducing the number of patients exposed to ineffective doses in the first-in-human (FIH) clinical trials. The regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have published guidance documents to select the maximum recommended starting dose (MRSD) in the FIH study. The FDA guidance has been used in many FIH studies with new chemical entities of low-molecular weight, although it is also applicable to the FIH studies with biological agents. The emphasis in the FDA guidance is placed on the no observed adverse effects level (NOAEL) assessed in...
To achieve these objectives, we performed a systematic review of the papers that reported the results of FIH studies with mAbs from 1990 to 2013.

Materials and methods

Literature search and selection of the FIH studies

To construct a database for the FIH studies with mAbs, we searched PubMed using the combination of the following terms: clinical trial, phase I or phase 1, first-in-human or first-in-man, first-time-in-human or first-time-in-man, starting dose or initial dose, and mAb. The literature search was complemented by an additional manual search of the references from the published papers and reviews focusing on mAbs. Eligible studies had to meet all of the following inclusion criteria: 1) the full text was available or there was at least a clear indication of how the MRSD was determined in the abstract or proceedings, 2) the text was written in English, and 3) the studies were published between January 1, 1990 and December 31, 2013.

Classification of MRSD determination methods and data extraction

If papers explicitly stated that the MRSD was determined based on a NOAEL, MABEL, minimum effective dose (MED), or pharmacologically active dose (PAD), they were classified as the respective dose- or level-based. Although a paper did not clearly indicate the MRSD determination method, it was also classified as NOAEL-, MABEL-, MED-, or PAD-based if the paper presented other information or supplemental data that enabled us to identify which method was used. For example, if a paper emphasized that no toxicity was found in the preclinical animal model up to a certain dose, which was used as the basis for determining the MRSD in humans, the method was NOAEL-based. Similarly, if the MRSD was determined from a dose identified in preclinical models that produced any or minimal pharmacological effect, the paper was classified as PAD- or MED-based, respectively. However, if animal pharmacokinetic (PK) data were the basis of MRSD determination or if a PK model was used to estimate the human PK parameters, which eventually resulted in the MRSD, the method was PK model-based. If the information about the receptor occupancy or other biomarkers was used to determine the MRSD, the method was pharmacodynamic (PD) model-based. If a PK–PD modeling approach was used to determine the MABEL, however, the paper was classified as MABEL-based. Because there were some similarities among MRSD determination methods, they were further grouped as follows: 1) MABEL- or MED-based

preclinical toxicology studies. The NOAEL is then converted into the human equivalence dose by applying an appropriate scaling factors to adjust for body surface area among different species. In contrast, the EMA guidance stresses the minimal anticipated biological effect level (MABEL) approach, in which all in vitro and in vivo information will be taken into consideration. The NOAEL- or the MABEL-derived human equivalence dose can be reduced further by applying the safety factor, a number by which the calculated human equivalence dose is divided to increase the assurance that the first dose will not cause toxicity in humans.

Since the 1980s, monoclonal antibodies (mAbs) have been actively incorporated into clinical medicine as a beneficial therapeutic option, particularly in oncology and immunology. However, protein-based drugs such as mAbs can have more uncertain safety profiles than those of chemistry-based drugs before an FIH study is conducted. For example, a severe life-threatening cytokine storm was developed in all the subjects who received the active drug in FIH study with TGN1412, a superagonist mAb against CD28, although a conservatively low starting dose was administered derived from the NOAEL (ie, a large safety factor of 160). This tragic incident highlighted the importance of and difficulties in selecting the safest maximum starting dose in FIH studies with mAbs. After the incident in the FIH study of TGN1412, several publications have proposed various ways to determine MRSD for FIH studies with biological agents. Many of these follow-up publications emphasized that MRSD for the FIH study with novel biological agents should be chosen after taking into account multiple points, for example, different endpoints, interspecies scaling, and safety factors. In support of this notion, a recent review found that the preclinical animal models and key toxicity parameters used to determine the starting dose for FIH studies with molecularly targeted agents in cancer patients were variable and heterogeneous. To the best of our knowledge, however, no investigation has reported how MRSD was determined in FIH studies with mAbs and which factors were associated with the choice of MRSD determination methods. Furthermore, the consequences of various MRSD determination methods have not been assessed, particularly in terms of safety and efficiency in achieving the objectives of FIH clinical trials. On the basis of this understanding, the objectives of the present study were 1) to evaluate MRSD determination methods employed in FIH studies with mAbs, 2) to identify factors associated with choosing one method over the others, and 3) to compare the safety and efficiency of each MRSD determination method. To achieve these objectives, we performed a systematic
Any differences were discussed until an agreement was reached.

Statistical analysis
Safety factor and MRSD determination method were summarized using descriptive statistics. The Fisher’s exact test was performed to analyze whether MRSD determination method was significantly affected by the publication year, therapeutic area, and the type of mAbs. To test whether the median safety factor and the mean number of dose escalation steps were significantly different by MRSD determination method, the Kruskal–Wallis and the analysis of variance tests were performed, respectively. The SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC, USA) was used for the statistical analysis, and a two-tailed P-value ≤0.05 was considered statistically significant.

Results
Study identification
The literature search identified 140 candidate FIH studies with mAbs, 61 of which were excluded because they did not meet the selection criteria: full text unavailable (n=58) or not in English (n=1); published before January 1, 1990 or after December 31, 2013 (n=2). Hence, a total of 79 FIH studies were included in the final study database (Table S1). Overall, the majority of FIH studies with mAbs were performed in oncology (n=41, 51.9%), followed by immunology (n=14, 17.7%) and infection (n=10, 12.7%). The number of FIH studies with fully human antibodies and humanized antibodies has drastically increased since the early 2000s, whereas the number of FIH studies with murine or chimeric antibodies remained steadily low during the entire period (Figure 1).

MRSD determination method
Of 79 FIH studies with mAbs included in the study database, 49 studies (62.0%) clearly indicated how the MRSD was determined. The MRSD was determined based on a dose associated with the minimal pharmacological effect or by a model-based approach. We also collected the information about the factors that could have been associated with the choice of MRSD determination method: publication year, therapeutic area (ie, oncology, immunology, infection, and others), and antibody type (ie, murine, chimeric, humanized, fully human, and others). Because the MABEL-based approach was officially first introduced in the EMA guidance in 2007, partly prompted by the TGN1412 incident,3 we categorized the publication year into three periods: before 2007 (ie, 1990–2007) and two 3-year periods after 2007 (ie, 2008–2010 and 2011–2013) to investigate the impact of the EMA guidance.

Furthermore, we extracted or derived the safety factor using the information available in the paper. In addition, we collected the safety result after the first dose and the number of dose escalation steps to evaluate the consequence of each MRSD determination method.

Two authors (HYS and HL) independently reviewed the papers and performed data extraction. The extracted data were then cross-checked for concurrence, and any differences were discussed until an agreement was reached.
determined, whereas the remaining 30 studies (38.0%) did not report the MRSD determination method (Figure 2). Of the 49 studies that reported the MRSD determination method, more than one-third used the NOAEL-based approach ($n=17, 34.7\%$), followed by the PAD-based approach ($n=13, 26.5\%$) and the MABEL- or MED-based approach ($n=11, 22.4\%$). The model-based approach was the least common method ($n=8, 16.3\%$).

Factors associated with the choice of MRSD determination method

The more recent the publications were the more frequently they reported which method was used to determine the MRSD. Almost 90% of the studies published from 2011 to 2013 clearly indicated which method was used to determine the MRSD, whereas only half of the studies published before 2007 did (Table 1). The MABEL- or MED-based approach was used more frequently in 2011–2013 than in 1990–2007 (31.6% vs 6.3%, Table 1). Notably, the MABEL-based approach was not used until 2005 (Table S1; Figure 3). In contrast, the proportions of the other MRSD determination methods, particularly the model-based approach, did not appear to change much over the entire period of 1990–2013. Collectively, MRSD determination method varied significantly by publication year ($P=0.036$, Table 1), whereas therapeutic area or antibody type was not significantly associated with the choice of MRSD determination method ($P=0.995$ and 0.982, respectively, Table 1).

Safety factor and consequence of MRSD determination method

The median safety factor was numerically much lower for the MABEL- or MED-based approach than for the other approaches, although this difference failed to reach statistical significance (10 vs 32.2–53, $P=0.416$, Table 2). Fourteen studies (17.7%) indicated that the first dose was safe, in which the MRSD was determined by the NOAEL-based ($n=6$) and the MABEL- or MED-based approaches ($n=6$). Only one study reported the first dose was not safe, in which the NOAEL was the basis for MRSD determination. The mean number of dose escalation steps was comparable among the different MRSD determination methods ($P=0.177$, Figure 4).

Discussion

We have found that the NOAEL-based approach was still the most commonly used MRSD determination method for FIH studies with mAbs, while the model-based approach was used far less frequently. Our results showed that more than one-third of the FIH studies employed the NOAEL-based approach, which was double the number of studies using the model-based approach (34.7% vs 16.3%, Figure 2). This trend was rather disappointing, given that the usefulness of the model-based approach has been repeatedly emphasized in determining the MRSD.$^{10–13}$ For example, a PK–PD model derived from cynomolgus monkeys enabled choosing 0.01 mg/kg as the MRSD for the FIH study with TRC105, an antibody with antiangiogenic effect to solid tumors. On the basis of the PK–PD model, the MRSD would successfully result in concentrations above the dissociation constant for the antibody, leading to a pharmacologic effect in humans.$^{14}$ However, the infrequent use of the model-based approach to determine the MRSD can be attributed to the fact that animal data may not be available in sufficient detail to construct a model at the time of the FIH studies with mAbs.$^{2,11,15}$ Furthermore, concerns about interspecies differences in bioavailability and metabolism could be another factor that has prevented the model-based approach from being applied more frequently in FIH studies with mAbs.$^{16}$

Our results also showed that publication year was significantly associated with the choice of MRSD determination method, which was demonstrated in two ways. First, the proportion of FIH studies not reporting the MRSD determination method fell sharply to 10.5% in 2011–2013.
Starting dose in first-in-human trials with monoclonal antibodies

Table 1: Publication year, therapeutic area, and antibody type by MRSD determination method

| Factor           | NOAEL-based approach | MABEL- or MED-based approach | PAD-based approach | Model-based approach* | Not reported | Total | P-value* |
|------------------|----------------------|------------------------------|-------------------|-----------------------|-------------|-------|---------|
| Publication year |                      |                              |                   |                       |             |       | <0.05   |
| 1990–2007        | 4 (12.5%)            | 2 (6.2%)                     | 7 (21.9%)         | 3 (9.4%)              | 16 (50.0%)  | 32 (40.5%) |         |
| 2008–2010        | 8 (28.6%)            | 3 (10.7%)                    | 2 (7.1%)          | 3 (10.7%)             | 12 (42.9%)  | 28 (35.4%) |         |
| 2011–2013        | 5 (26.3%)            | 6 (31.6%)                    | 4 (21.1%)         | 2 (10.5%)             | 2 (10.5%)   | 19 (24.1%) |         |
| Therapeutic area |                      |                              |                   |                       |             |       | 0.995   |
| Oncology         | 9 (21.9%)            | 4 (9.8%)                     | 8 (19.5%)         | 5 (12.2%)             | 15 (36.6%)  | 41 (51.9%) |         |
| Immunology       | 3 (21.4%)            | 3 (21.4%)                    | 1 (7.1%)          | 1 (7.1%)              | 6 (43.0%)   | 14 (17.7%) |         |
| Infection        | 2 (20.0%)            | 1 (10.0%)                    | 2 (20.0%)         | 1 (10.0%)             | 4 (40.0%)   | 10 (12.7%) |         |
| Others           | 3 (21.4%)            | 3 (21.4%)                    | 2 (14.3%)         | 1 (7.1%)              | 5 (35.8%)   | 14 (17.7%) |         |
| Antibody type    |                      |                              |                   |                       |             |       | 0.982   |
| Murine           | 0 (0.0%)             | 1 (25.0%)                    | 1 (25.0%)         | 1 (25.0%)             | 1 (25.0%)   | 4 (5.1%)   |         |
| Chimeric         | 1 (10.0%)            | 1 (10.0%)                    | 2 (20.0%)         | 1 (10.0%)             | 5 (50.0%)   | 10 (12.7%) |         |
| Humanized        | 6 (21.4%)            | 4 (14.3%)                    | 4 (14.3%)         | 2 (7.1%)              | 12 (43.0%)  | 28 (35.4%) |         |
| Fully human      | 9 (25.7%)            | 5 (14.3%)                    | 6 (17.2%)         | 4 (11.4%)             | 11 (31.4%)  | 35 (44.3%) |         |
| Others           | 1 (50.0%)            | 0 (0.0%)                     | 0 (0.0%)          | 0 (0.0%)              | 1 (50.0%)   | 2 (2.5%)   |         |
| Total            | 17 (21.5%)           | 11 (13.9%)                   | 13 (16.5%)        | 8 (10.1%)             | 30 (38.0%)  | 79 (100%)  |         |

Notes: The row percent is shown except for the total, in which the column percent is displayed. *The model-based methods included the PK model-based, PD model-based, and PK–PD model-based approaches. †P-values from Fisher’s exact test.

Abbreviations: MABEL, minimal anticipated biological effect level; MED, minimum effective dose; MRSD, maximum recommended starting dose; NOAEL, no observed adverse effects level; PAD, pharmacologically active dose; PD, pharmacodynamic; PK, pharmacokinetic.

from 42.9% in 2008–2010 and 50.0% in 1990–2007 (Table 1, Figure 3). It is encouraging that more FIH studies started reporting the MRSD determination method because this not only indicates increased transparency, but also it may allow for evaluating whether a certain type of MRSD determination method was useful or not in a particular study setting. Second, the MABEL- or MED-based approaches were more frequently used in 2011–2013 (31.6%) than in 1990–2007 (6.2%) and 2008–2010 (10.7%, Table 1). In particular, the first MABEL-based FIH study with mAbs was published in 2005, followed by another in 2007 and six during 2010–2013 (Table S1). This sharp increase during the latest period certainly reflects the impact of the tragic TGN1412 incident and the EMA guidance that followed the incident, which strongly recommended the use of the MABEL-based approach to determine MRSD.8,17 This trend is expected to continue in
the future given the heightened concern about the potential safety issues of biological agents including mAbs. However, the MABEL-based approach requires extensive knowledge regarding the pharmacological mechanisms and their integration, preferably via PK–PD modeling. Therefore, smaller safety factors indicated greater confidence for human safety at the time of FIH studies. The MABEL-based approach always results in a smaller human equivalence dose than the other MRSD determination methods, particularly the NOAEL-based approach. Therefore, the safety factor tends to be smaller with the MABEL-based approach than with the other methods, as shown in our results.

Although the MABEL-based approach came up with an MRSD lower than those derived by the other approaches, the average number of dose escalation steps was similar (Figure 4). Fewer dose escalation steps indicated more efficient FIH studies. Therefore, the MABEL-based approach did not appear to be inferior to the other MRSD determination methods. Furthermore, more than half (6/11=54.5%) of the papers that employed the MABEL-based approach explicitly indicated that the first dose was safe, which was almost 20% points higher than that with the NOAEL-based approach (6/17=35.3%). Of course, this interpretation needs caution because >80% of the papers did not explicitly mention about the safety results after the first dose.

The major limitation of the present study was the possibility of misclassifying MRSD determination method, particularly between the model- and MABEL-based approaches. Because the EMA guidance suggests that all information available from PK/PD data…wherever possible…should be integrated in a PK/PD modeling approach for the determination of the MABEL (emphasis added)

some FIH studies classified as using the model-based approach had, in fact, used the MABEL-based approach. However, this possible misclassification was very unlikely to influence our final conclusion because only a small number of FIH studies (n=8, 10.1%, Table 2) were classified as model-based. Another limitation was that the MRSD determination method was not identifiable in 30 (=38%) FIH studies with mAbs because the authors did not report which method was used. Although our study database was constructed by a thorough literature search, further studies are warranted to circumvent this type of publication bias.

Conclusion
We anticipate that the MABEL-based approach will be more frequently used in FIH studies with mAbs in the future,
while the NOAEL-based approach is still likely to be the most commonly used method. The MABEL-based approach appears to be safer and as efficient as the other MRSD determination methods for achieving the objectives of FIH clinical trials faster. To the best of our knowledge, this is the first report showing the rapid acceptance of the MABEL-based approach in FIH studies with mAbs, reinforcing the impact of the EMA guidance. Our study can also illuminate the trends of the choice of MRSD determination methods, which may contribute to a safer design and conduct of FIH studies with mAbs in humans.

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Disclosure
The authors report no conflicts of interest in this work.

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# Supplementary material

## Table S1 Study characteristics

| Reference                | Year | Biologicals | Therapeutic area | Target of action | Type of action | Antibody type | MRSD determination method | Preclinical model | Safety factor* |
|--------------------------|------|-------------|------------------|------------------|----------------|-----------------|--------------------------|------------------|---------------|
| Drobskyi et al\(^1\)     | 1991 | MSL-109 (sevirumab) | Transplantation (related infection) | CMV | Antagonist | Fully human | NOAEL-based | Non-human primate | 3.2 |
| Klein et al\(^2\)        | 1992 | B-E8 | Oncology (multiple myeloma) | IL6 | Antagonist | Murine | PAD-based | In vitro | NR |
| Maloney et al\(^3\)      | 1994 | IDEC-C288 (rituximab) | Oncology (non-Hodgkin lymphoma) | CD20 | Antagonist | Chimeric | NR | Non-rodent | |
| Handgretinger et al\(^4\) | 1995 | ch14.18 | Oncology (metastatic melanoma) | GD2 | Agonist | Chimeric | NR | NR | |
| Brooks et al\(^5\)       | 1995 | 42/6 Antibody | Oncology (advanced cancer) | Transferrin receptor | Antagonist | Murine | NR | Rodent | |
| Everett et al\(^6\)      | 1996 | RSH219 | Infection (respiratory syncytial virus) | F protein | Antagonist | Humanized | NR | |
| Vincenti et al\(^7\)     | 1997 | Anti-tac (dacilzumab) | Transplantation (graft vs host disease) | IL2R-alpha | Antagonist | Humanized | NR | NR | |
| Zaane et al\(^8\)        | 1998 | CNTO-328 (siltuximab) | Oncology (multiple myeloma) | IL6 | Antagonist | Chimeric | NR | NR | |
| Bowen et al\(^9\)        | 1998 | Hu23F2G (rovelizumab) | Immunology (multiple sclerosis) | CD11/CD18 | Antagonist | Humanized | NR | NR | |
| Harder et al\(^10\)      | 1999 | YM337 | Coagulative vascular disorder | Glycoprotein Ib/Illa | Antagonist | Humanized | Model-based | Non-human primate | 6.5 |
| Gottlieb et al\(^11\)    | 2000 | huI 124 (efalizumab) | Immunology (psoriasis) | CD11a | Antagonist | Humanized | NR | NR | |
| Crombet et al\(^12\)    | 2001 | ior egfr3 | Oncology (brain tumor) | EGFR | Antagonist | Murine | Model-based | NR | |
| Gordon et al\(^13\)     | 2001 | rhuMAb (bevacizumab) | Oncology (advanced cancer) | VEGF | Antagonist | Humanized | NR | NR | |
| Verbon et al\(^14\)     | 2001 | ICI4 | Infection (sepsis) | CD14 | Antagonist | Chimeric | NR | Non-rodent | |
| Chow et al\(^15\)       | 2002 | SB 249417 | Coagulative vascular disorder | Factor IX | Antagonist | Humanized | PAD-based | Non-rodent | 32.2 |
| Posey et al\(^16\)      | 2003 | IMC-1C11 | Oncology (colorectal cancer) | VEGFR2 | Antagonist | Chimeric | PAD-based | Rodent | |
| Kaufman et al\(^17\)    | 2004 | Anti-IL-12p40 | Immunology (psoriasis) | p40 of IL12, IL23 | Antagonist | Fully human | NOAEL-based | Non-rodent | 161 |
| Bekker et al\(^18\)     | 2004 | AMG 162 (denosumab) | Osteoporosis | RANKL | Antagonist | Fully human | NR | NR | |
| Agus et al\(^19\)       | 2005 | 2C4 (pertuzumab) | Oncology (advanced solid tumor) | HER2 | Antagonist | Humanized | Model-based | Non-human primate | 300 |
| Dowling et al\(^20\)    | 2005 | ccrStx2 | Infection (Shiga toxin-producing Escherichia coli) | Stx2 | Antagonist | Chimeric | PAD-based | Rodent | NR |
| Pacey et al\(^21\)      | 2005 | HGS-ETR2 (laxatumumab) | Oncology (advanced solid tumor) | TRAIL-R2 | Agonist | Fully human | PAD-based | Rodent | 2 |
| Subramanian et al\(^22\) | 2005 | Pam | Infection (anthrax) | Protective antigen | Fully human | PAD-based | Non-rodent | NR | |
| Ribas et al\(^23\)      | 2005 | CP-675,206 (tremelimumab) | Oncology (solid tumor) | CTLA4 | Antagonist | Fully human | MABEL-based | Rodent and non-rodent | |
| Reilly et al\(^24\)     | 2005 | T1-2 (tefizumab) | Infection (Staphylococcus aureus) | Clumping factor A | Antagonist | Humanized | NR | NR | |
| Suntharalingam et al\(^25\) | 2006 | TGN1412 | Immunology | CD28 | Agonist | Humanized | NOAEL-based | Non-human primate | 160 |
| Ng et al\(^26\)         | 2006 | TRXl | Immunology (autoimmune disease) | CD4 | Antagonist | Humanized | PAD-based | Non-rodent | |
| Lacy et al\(^27\)       | 2006 | CP-751,871 (figitumumab) | Oncology (multiple myeloma) | IGFlR | Antagonist | Fully human | NR | NR | |
| Tabrizi and Roskos\(^28\) | 2007 | Anti-Muc18 antibody | Oncology (malignant melanoma) | Mucl8 | Antagonist | Murine | MABEL-based | Non-human primate | |
| Tolcher et al\(^29\)    | 2007 | HGS-ETR1 (mapatumumab) | Oncology (advanced solid tumor) | TRAIL-R1, DR4 | Agonist | Fully human | NOAEL-based | Non-rodent | 1,290 |
| Vonderheide et al\(^30\) | 2007 | CP-870,893 | Oncology (advanced solid tumor) | CD40 | Agonist | Humanized | NR | NR | |
| Scott et al\(^31\)      | 2007 | ch806, 111 In-ch806 | Oncology | EGFR | Antagonist | Chimeric | NR | NR | |
| Mullamitha et al\(^32\) | 2007 | CNTO 95 | Oncology (solid tumor) | αv integrins | Antagonist | Fully human | NR | Rodent | |
| Furie et al\(^33\)      | 2008 | Belimumab | Immunology (systemic lupus erythematosus) | B lymphocyte stimulator | Antagonist | Fully human | NOAEL-based | |
| Hagenbeek et al\(^34\)  | 2008 | Ofsatamab | Oncology (follicular lymphoma) | CD20 | Antagonist | Fully human | PAD-based | Rodent | |
| Bouman-Thio et al\(^35\) | 2008 | CNTO 528 | Erythropoiesis | Erythropoietin receptor | Agonist | Fully human | NR | Rodent and non-rodent | |
| Year | Reference | Field | Target | Dose | Phase | Efficacy | Species | Route | Toxicity |
|------|-----------|-------|--------|------|-------|----------|---------|-------|----------|
| 2008 | Bargou et al. | AMG 103 (blinatumomab) | Oncology (non-Hodgkin lymphoma) | CD19, CD3ε | Agonist | Bi-specific | NR | NR | NR |
| 2008 | Szol et al. | BMS-663513 | Oncology (advanced melanoma) | CD137 | Agonist | Fully human | NR | NR | NR |
| 2008 | Mendelson et al. | CVX-045 | Oncology (advanced solid tumor) | Thrombospondin | Antagonist | Fully human | NR | NR | NR |
| 2008 | Taylor et al. | CDA-1 | Infection (Clostridium difficile) | C. difficile toxin A | Antagonist | Humanized | NR | Rodent | NR |
| 2008 | Weisman et al. | BSYX-AMD (pagibaximab) | Infection (Staphylococcus) | Lipoteichoic acid | Antagonist | Chimeric | MED-based | Rodent (rat) | NR |
| 2009 | Lazar et al. | KBPA 101 | Infection (Pseudomonas aeruginosa) | LPS | Antagonist | Fully human | NOAEL-based | Rodent (mouse) | 10 |
| 2009 | Lachmann et al. | ACZ885 (canakinumab) | Immunology (cryopyrin-associated periodic syndrome) | IL1-beta | Antagonist | Fully human | Model-based | NR | NR |
| 2009 | Herbst et al. | AMG 386 | Oncology (advanced solid tumor) | Antigenoprotein | Antagonist | NR | NOAEL-based | Rodent | NR |
| 2009 | Tolcher et al. | AMG 479 (ganitumab) | Oncology | IGFR1 | Antagonist | Fully human | NOAEL-based | Rodent and non-rodent | 10 |
| 2009 | Lum et al. | U3-1287 | Oncology (advanced solid tumor) | HER3 | Antagonist | Fully human | Model-based | Rodent and non-rodent | NR |
| 2009 | White et al. | MEDI-528 | Immunology (asthma) | IL9 | Antagonist | Humanized | NR | NR | NR |
| 2010 | Gordon et al. | AMG 102 | Oncology (advanced solid tumor) | HGFSF | Antagonist | Fully human | NOAEL-based | Non-human primate | 100 |
| 2010 | Herbst et al. | AMG 655 (conatumumab) | Oncology (advanced solid tumor) | DR5 | Agonist | Fully human | PAD-based | Non-human primate | 322 |
| 2010 | Camidge et al. | PRO95780 | Oncology (advanced tumor) | DR5 | Agonist | Fully human | MED-based | NR | 10 |
| 2010 | Spratlin et al. | IMC-I 121B (ramucirumab) | Oncology (advanced solid tumor) | VEGFR2 | Antagonist | Fully human | Model-based | Non-human primate | 53 |
| 2010 | Beigel et al. | MGAWIN1 | Infection (West Nile Virus) | Envelope | Antagonist | Humanized | NOAEL-based | Rodent (rat) | 33 |
| 2010 | Burris et al. | RAVI2 | Oncology (gastrointestinal cancer) | RAAAG12 | Agonist | Chimeric | NOAEL-based | Non-rodent | 10 |
| 2010 | Verhamme et al. | TB-402 | Coagulative vascular disorder | Factor VII | Agonist | Fully human | MABEL-based | Rodent and non-rodent | 10 |
| 2010 | Krop et al. | T-DM1 | Oncology (metastatic breast cancer) | HER2 | Antagonist | Humanized | NOAEL-based | Non-rodent | 12 |
| 2010 | Hussein et al. | Dacetuzumab | Oncology (multiple myeloma) | CD40 | Partial agonist | Humanized | NR | NR | NR |
| 2010 | Kuenen et al. | IMC-I 118 (nectumumab) | Oncology (advanced solid tumor) | EGFR | Antagonist | Fully human | NR | NR | NR |
| 2010 | Brahmer et al. | MDX-1106 | Oncology (solid tumor) | PD-1 | Agonist | Fully human | NR | NR | NR |
| 2010 | Genovese et al. | LY2439821 | Immunology (rheumatoid arthritis) | IL17 | Antagonist | Humanized | NR | NR | NR |
| 2010 | Adler et al. | FG-3019 | Diabetic kidney disease | CTGF | Antagonist | Fully human | NR | NR | NR |
| 2010 | Busse et al. | MEDI-563 | Immunology (asthma) | ILSR-alpha | Antagonist | Humanized | NR | NR | NR |
| 2011 | Riddle et al. | MDX-1303 | Infection (antrax) | B. anthracis protective antigen | Antagonist | Fully human | Model-based | Non-human primate | 53 |
| 2011 | Xu et al. | CTNTO 136 (sirukumab) | Immunology (rheumatoid arthritis) | IL6 | Agonist | Fully human | MED-based | Non-human primates | 53 |
| 2011 | Martinsson- | TB-403 | Oncology (solid tumor) | PIGF | Antagonist | Humanized | MABEL-based | Rodent (mouse) | 10 |
| 2011 | Niskanen et al. | RG7160 (GA201) | Oncology (solid tumor) | EGFR | Antagonist | Humanized | NOAEL-based | Non-Rodent | >30 |
| 2011 | Paz-Ares et al. | AMG 785 | Osteoporosis | Sclerostin | Antagonist | Humanized | NOAEL-based | Rodent | NR |
| 2011 | Burmester et al. | CAM-3001 (mavrilumab) | Immunology (rheumatoid arthritis) | GM-CSFR-alpha | Antagonist | Fully human | NR | NR | NR |
| 2011 | Rosen et al. | TRC105 | Oncology (angiogenesis) | CD105 | Agonist | Chimeric | Model-based | Non-human primate | NR |
| 2012 | Morris et al. | AGS-PSCA | Oncology (prostate cancer) | PSA | Antagonist | Fully human | PAD-based | Rodent | NR |
| 2012 | Curtin et al. | GNAb1C1 | Immunology (multiple sclerosis) | MSR-V-env protein | Antagonist | Humanized | MABEL-based | In vitro | 2.3 |
| 2012 | Stein et al. | REGN727 | Hypercholesterolemia | PCSK9 | Antagonist | Fully human | PAD-based | Non-rodent | NR |
| 2012 | Zonder et al. | Anti-CS1 (elotuzumab) | Oncology (multiple myeloma) | CS1 | Antagonist | Humanized | PAD-based | Rodent | NR |
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