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Editor's Corner

Probabilities of success for antibody therapeutics

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Probabilities of success (POS) play a key role in determining the distribution of resources by both investors and the pharmaceutical industry. Resources such as time, money and personnel are more likely to be directed toward programs in categories with acceptable rates of success. What is considered acceptable may, of course, vary between companies and other decision-makers. With the increased focus on development of antibody therapeutics, it is important for stakeholders to understand the utility, and limitations, of POS values such as cumulative approval success rates and clinical phase transition probabilities. A key point is that cumulative approval success rates are derived from data for only those candidates with known fates (either approved or terminated), but clinical phase transition probability calculations include data on the status of all candidates.

POS values for various cohorts of monoclonal antibody (mAb) therapeutics have been reported previously.[1-6] For mAb POS, a key consideration is the source of the protein sequence. Data for humanized and human mAbs must be analyzed separately because, overall, these molecules display improved safety and efficacy profiles compared to murine and chimeric versions. Humanized mAbs comprise the 'canonical' cohort because a large number (>150) of these candidates have entered clinical study over the last two decades (1988–2008), and 12 have been approved (Table 1). However, ultimate fates (approval or termination) are known for only about half, and the cumulative approval success rate for the entire cohort of humanized mAbs will only be an estimate until the fates of all the molecules have been decided. The current cumulative approval success rate estimate for humanized mAbs is 17%.[2]

It is important to note that time plays an essential role in POS calculations. In general, clinical study and regulatory review periods for therapeutics are lengthy, and mAbs are not exceptional in this regard. The mean (median) for the combination of the clinical and US Food and Drug Administration (FDA) approval phases for 23 mAbs (Table 1) is currently 8 (7) years. This has important implications for POS calculations for mAb cohorts that include high percentages of candidates that have entered clinical study within the past seven or eight years. Candidates that have entered clinical study since 2001 have not had sufficient time, on average, for approval, but might have been terminated for a variety of reasons. This suggests that there is a downward bias in cumulative success rates for cohorts that include candidates that recently entered clinical study. Indeed, the cumulative success rate for humanized mAbs changes dramatically when the cohort is divided into two groups: candidates that entered clinical study during 1988–1996 (n = 30; eight approved) and 1997–2008 (n = 125; two approved). Ultimate fates are known for 87% of the older candidates, and the cumulative success rate for the cohort is 31%. However, ultimate fates are known for only 33% of the newer candidates, and because many have not been in clinical study long enough to accumulate the data needed for approval, the cumulative success rate is 5%. This value will rise to 9% if the two humanized mAbs in FDA review (Table 1) are approved.

Clinical phase transition probabilities are another important measure of the success of a cohort such as humanized mAbs. Whereas cumulative approval success rates include data only for candidates that are either approved or terminated, clinical phase transition probabilities take the status of all candidates into account. It is critical to understand the relationship between the two parameters in order to interpret POS values appropriately. The mathematical product of the phase transition probabilities will exactly equal the cumulative success rate only when the fates of all the candidates are known. In practice, the two values will converge as the percentage with known fates goes to 100%. When the fates of fewer than 50% are known, then the values can be quite different. One reason for this phenomenon is that candidates that will ultimately be discontinued remain, technically, at Phase 2 for long periods while the company decides whether to advance these perhaps marginal candidates into expensive Phase 3 studies, or attempts to partner or out-license the projects. In these cases, the candidates contribute in a positive way to the Phase 1 to Phase 2 transition probability, and inflate the mathematical product, but are not yet included in the cumulative success rate calculation because they have not been officially terminated.

A comparison of phase transition probabilities for humanized mAbs with the cumulative approval success rates provides a good example of the phenomenon. The values for candidates that entered clinical study during the three periods 1988–2008, 1988–1996 and 1997–2008 are quite similar: Phase 1 to 2 transition probabilities were 83, 90 and 80%, respectively; Phase 2 to 3 transition probabilities were 48, 50 and 46%, respectively; Phase 3 to FDA review transition probabilities were 75, 73

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Table 1 **Therapeutic monoclonal antibodies in FDA review or approved**

Generic name	Trade name	Type	Indication under consideration or first approved	FDA approval year
Raxibacumab	Pending	Human IgG1	Anthrax infection	Pending
Tocilizumab	Actemra*	Humanized IgG1	Rheumatoid arthritis	Pending
Ustekinumab	Stelara*	Human IgG1	Psoriasis	Pending
Motavizumab	Numax*	Humanized IgG1	Prevention of respiratory syncytial virus infection	Pending
Canakinumab	Pending	Human IgG1	Muckle-Wells syndrome	Pending
Denosumab	Pending	Human IgG2	Bone loss	Pending
Ofatumumab	Arzerra*	Human IgG1	Chronic lymphocytic leukemia	Pending
Golimumab	Simponi	Human IgG1	Rheumatoid and psoriatic arthritis, ankylosing spondylitis	2009
Certolizumab pegol	Cimzia	Humanized Fab	Crohn disease	2008
Eculizumab	Soliris	Humanized IgG2/4	Paroxysmal nocturnal hemoglobinuria	2007
Panitumumab	Vectibix	Human IgG2	Colorectal cancer	2006
Ranibizumab	Lucentis	Humanized IgG1 Fab	Macular degeneration	2006
Natalizumab	Tysabri	Humanized IgG4	Multiple sclerosis	2004
Bevacizumab	Avastin	Humanized IgG1	Colorectal cancer	2004
Cetuximab	Erbitux	Chimeric IgG1	Colorectal cancer	2004
Efalizumab	Raptiva	Humanized IgG1	Psoriasis	2003#
Tositumomab-I131	Bexxar	Murine IgG2a	Non-Hodgkin lymphoma	2003
Omalizumab	Xolair	Humanized IgG1	Asthma	2003
Adalimumab	Humira	Human IgG1	Rheumatoid arthritis	2002
Ibritumomab tiuxetan	Zevalin	Murine IgG1	Non-Hodgkin lymphoma	2002
Alemtuzumab	Campath-1H	Humanized IgG1	Chronic myeloid leukemia	2001
Gemtuzumab ozogamicin	Mylotarg	Humanized IgG4	Acute myeloid leukemia	2000
Trastuzumab	Herceptin	Humanized IgG1	Breast cancer	1998
Infliximab	Remicade	Chimeric IgG1	Crohn disease	1998
Palivizumab	Synagis	Humanized IgG1	Prevention of respiratory syncytial virus infection	1998
Basiliximab	Simulect	Chimeric IgG1	Prevention of kidney transplant rejection	1998
Daclizumab	Zenapax	Humanized IgG1	Prevention of kidney transplant rejection	1997
Rituximab	Rituxan	Chimeric IgG1	Non-Hodgkin's lymphoma	1997
Abciximab	Reopro	Chimeric IgG1 Fab	Prevention of blood clots in angioplasty	1994
Muromonab-CD3	Orthoclone	Murine IgG2a	Reversal of kidney	1986

Note: Information current as of May 15, 2009. *Proposed trade name; #Voluntarily withdrawn from US market in April 2009. FDA, US Food and Drug Administration. Source: Tufts Center for the Study of Drug Development

and 80%, respectively; and the review to approval transition probability was 100% for all three cohorts. The mathematical products of the phase transition probabilities for the three cohorts are similar: 30, 33 and 29%, respectively, despite the fact that the current cumulative approval success rates vary (17, 31 and 5%, respectively). This suggests that, so far, the newer candidates are proceeding through clinical studies at a pace that is similar to the older candidates. However, the cohort of candidates that entered clinical study recently (n = 125) is much larger compared to the cohort of candidates that entered clinical study during 1988–1996 (n = 30), and many are in early clinical studies. It remains to be seen whether a similar proportion of the newer candidates will ultimately be approved.

POS for human mAbs are affected by the same factors. Analysis of this cohort is additionally affected by the time-frame of clinical entry because of technological advances in production methods. Early attempts to produce human mAbs from hybridomas were largely unsuccessful, so human mAbs did not start entering clinical study in large numbers until after transgenic mice and display technologies were developed. As a consequence, the majority of candidates are in clinical studies, and thus far, only three human mAbs, adalimumab, panitumumab and golimumab, have been approved in the US. However, five additional human mAbs (Table 1) are undergoing review by FDA (as of May 2009). Approval of these candidates would dramatically affect the cumulative success rate of the cohort.

Additional complexity arises when POS values from various sources are compared. Such comparisons should be done cautiously because factors such as variations in methodology, time-frame, and cohort inclusion criteria can have dramatic effects on the calculated results. End users, including investors and strategic planners, should carefully consider whether a distinction between a cumulative approval success rate and the mathematical product of phase

transition probabilities has been made, and whether sufficient information about the cohort and methodology has been provided so that the POS values presented can be clearly understood.

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