The Breakthrough Therapy Designation

Implications and Strategic Business Considerations

The breakthrough therapy designation has generated substantial interest since its creation one year ago, as this new pathway represents the most comprehensive set of clinical development benefits available for a pipeline agent. However, the breakthrough therapy pathway may also lead to potential commercial downsides and regulatory risk. Most notably, the limited dataset from the breakthrough clinical program may be insufficient to garner favorable pricing and reimbursement, particularly in Europe. In addition, the abridged clinical trials may not be considered satisfactory for regulatory approval in ex-U.S. markets. Taken together with several other commercial considerations, it is critical for manufacturers to develop a comprehensive understanding of these advantages and disadvantages prior to pursuing the breakthrough therapy pathway.

A Novel Pathway Breaks Through The FDA

In late 2012, the breakthrough therapy designation joined the ranks of fast track, priority review, and accelerated approval as a pathway to expedite clinical development of new agents. This pathway was formed as a result of the Food and Drug Administration Safety and Innovation Act (FDASIA) and was largely borne out of pressure from patient advocacy groups and cancer societies to more quickly gain access to highly promising agents. To date, this designation has been granted 27 times for a variety of oncologic and non-oncologic indications (Appendix Table 1).

The breakthrough therapy designation is intended for agents that have demonstrated substantial benefit over the existing standard of care for serious or life threatening conditions with high unmet need. The designation may be based on initial clinical data or potentially even preclinical research. The key benefits of

this breakthrough status are centered on clinical development and regulatory processes, and are in large part an amalgamation of the benefits provided with accelerated approval, fast track, and priority review (Figure 1). Given these benefits, it may appear straightforward to pursue a breakthrough designation. However, this may not always be the appropriate strategic decision, and therefore a more careful evaluation of the potential advantages and disadvantages of this new regulatory pathway should be considered.

Faster Than Fast Track

Two key considerations when evaluating whether to pursue the breakthrough pathway are the impact on clinical development timeline and the potential development risk. By consolidating the core benefits of fast track, accelerated approval, and priority review into one new pathway, the breakthrough therapy designation more effectively addresses both key considerations, compared to any other individual pathway.

The most evident benefit of the breakthrough therapy designation is the decreased time to FDA approval. A drug that receives a breakthrough designation early in clinical development may progress quickly to a pivotal trial or even to an FDA submission for approval. For example, the Janssen/Pharmacyclics drug, ibrutinib, catapulted directly from its Phase I/II clinical trial in chronic lymphocytic leukemia directly to an NDA submission for approval

FIGURE 1

The breakthrough therapy designation consolidates many aspects of the accelerated approval, fast track, and priority review status

	ACCELERATED APPROVAL	FAST TRACK DESIGNATION	PRIORITY REVIEW	BREAKTHROUGH DESIGNATION
KEY ADVANTAGES	• Conditional approval granted based on surrogate end point	• Often eligible for accelerated approval and priority review • Earlier and more frequent communication with the FDA —Option for rolling NDA / BLA submission	• Shortened 6 month review following NDA / BLA submission	• May result in conditional approval based on surrogate endpoint • Earlier and more frequent communication with the FDA • Shortened review following NDA / BLA submission
DRUG ELIGIBILITY	• Intent to treat a serious or life threatening disease	• Intent to treat a serious or life threatening disease	• Demonstrates significant advancement compared to existing therapies • Agent may or may not be indicated for a serious disease	Intent to treat a serious or life threatening disease Demonstrates substantial superiority over standard of care

(Figure 2). As stated by Peter F. Lebowitz, the Global Oncology Head at Janssen, "as part of [the] breakthrough therapy designation pathway, we have been able to accelerate the ibrutinib development program for the benefit of patients." Of note, ibrutinib has received breakthrough status for three indications: mantle cell lymphoma, CLL/SLL, and Waldenström's macroglobulenemia.

for a clinical program. Similar to the fast track pathway, the breakthrough designation creates opportunities for frequent and detailed communication with the FDA. This increased access to the FDA facilitates greater alignment on a drug's clinical trial design (i.e., endpoints, comparator arms, patient inclusion criteria, etc.). Consequently, it should result in a smoother, more expedited NDA/BLA process.

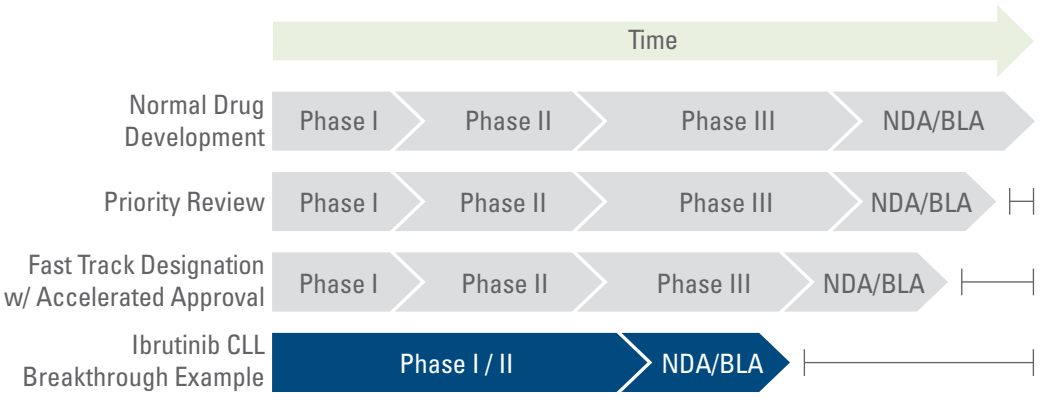


FIGURE 2

The breakthrough designation represents the fastest to market pathway for a novel agent, and may result in decreasing the time to market by several years

The breakthrough therapy designation also provides value for later-stage agents which may still benefit from shorter development programs. One such example is Vertex's combination therapy of Kalydeco and VX-809 for cystic fibrosis (CF). After receiving the breakthrough designation in Phase II, Vertex aligned with the FDA on a shortened Phase III program comprised of 6-month efficacy endpoints. This represents a significant time savings compared to traditional Phase III CF trials, which typically measure efficacy endpoints at one year or later. In so doing, Vertex is leveraging the breakthrough designation to submit its NDA in 2014, up to two years earlier than would have otherwise been achieved.

In addition to a shorter development timeline, breakthrough status provides benefits that may reduce regulatory risk

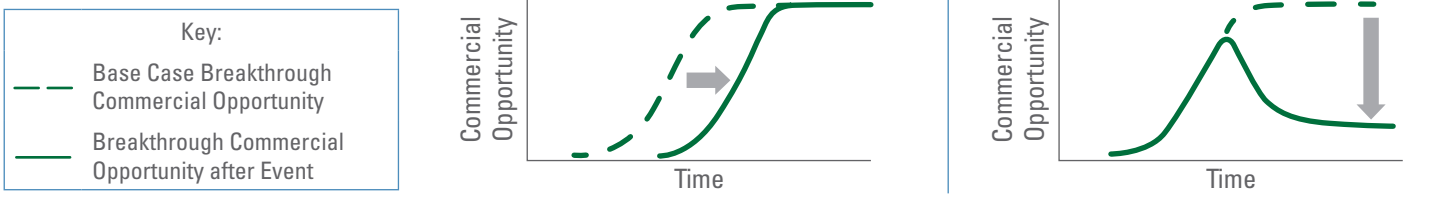
In summation, the breakthrough therapy designation has the potential to offer significant benefits stemming from increased likelihood of regulatory success and decreased clinical development time required for approval.

Deliberating The Dangers Of Breakthrough Designation

Despite the advantages associated with breakthrough status, several potential risks are inherent to this new pathway (Figure 3). While the type and degree of impact varies, each risk represents a potential downside that should be carefully considered prior to pursuing this new designation.

FIGURE 3

Various risks associated with the breakthrough therapy designation may dampen the commercial opportunity associated with a novel agent



One such risk relates to the commercialization potential of a breakthrough therapy outside the U.S. There is currently no equivalent pathway with the EMA or other ex-U.S. regulatory agencies. As a result, the abridged breakthrough therapy clinical trials may be inapplicable for approval ex-U.S., limiting access to other markets. To avoid such a situation, an entirely separate clinical development program may be required to garner regulatory approval in ex-U.S. countries.

In addition to approval concerns, the abbreviated breakthrough therapy pathway may be insufficient for favorable payer coverage both in the U.S. and ex-U.S. Countries such as Germany, France, and the UK increasingly rely on robust comparative effectiveness data to determine pricing and/or reimbursement. In addition, U.S. payers are moving toward value-based decision-making when determining reimbursement. It is plausible that the relevant government bodies and payers will require more substantial data (e.g. HEOR data, patient reported outcomes, etc.) than the surrogate clinical outcomes allowable via the break-through pathway. Once again, the end result may be that the breakthrough product is either excluded from select markets entirely, or that the drug may face significant pricing and reimbursement hurdles. To circumvent this risk, additional larger and longer clinical trials may be necessary.

More broadly, the breakthrough therapy pathway may expose a novel product to other risks. For example, a serious adverse event (SAE) may disproportionately impact the ability to gain regulatory approval via the breakthrough pathway. If an unexpected SAE surfaces, the abridged trial design may be insufficient to demonstrate that the event is unrelated to the drug. Consequently, to better understand the underlying cause of the SAE, the FDA may require new and larger trials, without which the commercialization potential of the drug would likely significantly decline. In this case, embarking on the new trials will extend the overall timeline and cost of clinical development beyond what would have been required if breakthrough status were not originally pursued.

Finally, the breakthrough pathway may create commercial risk once a product receives regulatory approval. For example, physicians may note that their empirical observations with the breakthrough drug do not match the efficacy data demonstrated in clinical trials, resulting in concerns that the findings in the abbreviated studies may have been uncharacteristically favorable. Therefore, physicians may be reluctant to widely prescribe the drug. If instead a more traditional clinical development program had been pursued, there may be less inclination to question the efficacy of the new product.

Breaking Down The Implications For Breakthrough Status

The breakthrough therapy designation provides the most comprehensive set of benefits related to clinical development timeline and regulatory risk. Drugs receiving breakthrough status may not only can be marketed more quickly, but can do so with smaller and less expensive trials. In addition, the frequent communication with the FDA reduces the regulatory risk upon submission of an NDA/BLA.

However, the decision to pursue a breakthrough designation should be given great consideration. There exist multiple scenarios in which the breakthrough designation could be suboptimal for a novel drug program. As a result, it will be important to conduct a robust risk-benefit analysis of pursuing a breakthrough designation.

The most critical consideration relates to pricing and reimbursement in both ex-U.S. and U.S. markets. In ex-U.S. markets, particularly those in Europe, garnering favorable pricing and reimbursement for new drugs is becoming increasingly challenging. In such an environment, it is imperative to understand what will be required to achieve success in these markets. If additional clinical trials are necessary ex-U.S., in certain cases it may be prudent to forgo a breakthrough therapy path in the U.S. in lieu of a more rigorous global trial.

Moreover, the decision to pursue breakthrough status may become increasingly complex as value-based decision-making becomes more prominent in the U.S. Over time, stricter decision-making may spread even to novel agents that would be designated for the breakthrough pathway. In such an instance, the abbreviated breakthrough therapy clinical program may be insufficient for commercial success and further studies may be required to garner payer support.

In addition to the pricing and reimbursement risks, companies should seek to understand the impact of the regulatory risks in ex-U.S. markets. In particular, evaluations should focus on determining the tradeoff between the additional clinical efforts required for regulatory approval versus the impact on overall commercial opportunity associated with being excluded from ex-U.S. markets. Taken together with the risks related to SAEs and less positive empirical observations, it is critical to have a comprehensive understanding of the potential downsides associated with pursuing a breakthrough designation. Performing a comprehensive risk-benefit analysis will ensure that the optimal development strategy for the novel therapy is pursued, enabling sponsors to move forward with confidence in the selected development pathway.

DRUG	COMPANY	PHASE AT TIME OF DESIGNATION	INDICATION
Ibrutinib	Janssen/Pharmacyclics	II/III	Mantle cell lymphoma (MCL)
Ibrutinib	Janssen/Pharmacyclics	Ib/II	CLL / SLL
Ibrutinib	Janssen/Pharmacyclics	II/III	Waldenström's macroglobulenemia
Kalydeco (ivacaftor)	Vertex	II	Cystic fibrosis
Kalydeco + VX-809	Vertex	II	Cystic fibrosis
LDK-378	Novartis	II	Metastatic non-small cell lung cancer
SD-101	ScioDerm	II	Epidermolysis bullosa
Daclatasvir + asunaprevir + BMS-791325	Bristol-Myers Squibb	II	Hepatitis C
Palbociclib + letrozole	Pfizer	II	Breast cancer
Lambrolizumab (MK-3475)	Merck	Ib	Advanced melanoma
Drisapersen	GlaxoSmithKline	II	Duchenne muscular dystrophy
Serelaxin (RLX-030)	Novartis	III	Acute heart failure
Sebelipase alfa	Synageva BioPharma	II/III	LAL deficiency
Gazvya (obinutzumab)	Biogen/Genentech - Roche	III	Chronic lymphocytic leukemia (CLL)
Daratumumab	Genmab/Johnson & Johnson	I/II	Multiple myeloma
Volasertib	Boehringer Ingelheim	II	Acute myeloid leukemia (AML)
Entinostat	Syndax Pharmaceuticals	II	Metastatic breast cancer
Firdapse (amifampridine phosphate)	Catalyst Pharmaceutical Partners	III	Lambert–Eaton myasthenic syndrome (LEMS)
BYM338 (bimagrumab)	Novartis/MorphoSys	II	Sporadic inclusion body myositis
Investigational 3-DAA with and without ribavirin	Abbvie	II	Hepatitis C
Asfotase alfa	Alexion Pharmaceuticals	II	Hypophosphatasia (HPP)
Sofosbuvir + Ledipasvir	Gilead	II	Hepatitis C
Ofatumumab	Genmab/GlaxoSmithKline	III	Chronic lymphocytic leukemia (CLL)
Alectinib	Roche	I	Non-small cell lung cancer (NSCLC)
MK-5172 + MK-8742	Merck	IIb	Hepatitis C
ALXN1101	Alexion Pharmaceuticals	III	Molybdenum cofactor deficiency (MoCD)
Betrixaban (andexanet alfa)	Portola Pharmaceuticals	III	Venous thromboembolism prophylaxis

APPENDIX TABLE 1: Agents that received the breathrough therapy designation, as of November 2013

ClearView Healthcare Partners is a boutique consulting firm providing superior strategic consulting services to companies and investors seeking to drive growth and value creation within the life science sector of the healthcare industry.

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