

PLANNING FOR UNCERTAINTY

FUTURE TREATMENT DYNAMICS IN NHL & IMPLICATIONS FOR STRATEGIC PLANNING

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New promising agents, Roche’s follow-on to Rituximab, and quickly evolving biomarker data are expected to set off a cascade of events significantly altering the treatment paradigm within NHL. Hematologists-Oncologists will be faced with key and previously unasked, as well as unnecessary, questions of how and whether to incorporate multiple targeted agents into their treatment algorithm. Evaluation of a similar past situation in multiple myeloma offers some initial lessons. This paper will address the critical implications on development and new product planning in NHL.

EARLY COMMERCIAL INSIGHT CRUCIAL TO PREPARE FOR PARADIGM CHANGE

NO OBVIOUS PATH TO BLOCKBUSTER NHL INDICATIONS

COST OF ENTRY SKYROCKETING, PLANNING/RISK MANAGEMENT CRITICAL

Since the introduction of Rituximab in the late 1990s, anti-CD20 directed antibody therapy has been the cornerstone of NHL treatment. Within that period, drug development in NHL has had two clear foci: (1) Develop new agents against novel targets (e.g., CD22, CD80, etc.) and (2) Build a better anti-CD20 mAb through antibody engineering. The former has generated minimal success, translating into the continued dominance of the anti-CD20 approach. While the latter has yielded some new drugs (see Figure 1), these agents have not formidably challenged the hegemony of Rituximab in front-line FL¹ and DLBCL² settings.

RITUXIMAB: UNCHALLENGED IN NHL

As a result, questions surrounding the treatment paradigm within NHL have largely focused on peripheral issues – optimizing the chemotherapy

Anti-CD20 mAbs			
Product	Company	Characteristics	Status
Arzerra	Genmab/GSK	<ul style="list-style-type: none"> Fully human Distinct epitope 	<ul style="list-style-type: none"> Approved CLL Failed in NHL
Bexxar	GSK	<ul style="list-style-type: none"> I-131 labeled 	<ul style="list-style-type: none"> Approved NHL
GA101	Roche	<ul style="list-style-type: none"> Humanized Glyco-engineered 	<ul style="list-style-type: none"> Phase III
Veltuzumab	Immunomedics	<ul style="list-style-type: none"> Humanized Subcutaneous 	<ul style="list-style-type: none"> Phase I/II
Ocrelizumab	Roche/Biogen	<ul style="list-style-type: none"> Humanized Modified Fc 	<ul style="list-style-type: none"> Discontinued
AME-133V	AME/Eli Lilly	<ul style="list-style-type: none"> Humanized Modified Fc 	<ul style="list-style-type: none"> Stalled

Figure 1: CD20 mAb Development in NHL

regimens to combine with Rituximab or identifying new therapies for niche populations or later line settings. Within most of NHL, however, Hematologists-Oncologists have not faced questions of whether or how to incorporate potentially rival targeted agents into the treatment algorithm. This situation may change in the very near future. New targeted agents, the

emergence of biosimilars (and Roche’s pursuit of GA-101 as a result), Personalized Medicine tools and a better understanding of CD20 resistance will alter the treatment paradigm (see Figure 2). Drug developers in NHL will need to fully understand the various potential scenarios that may emerge, and incorporate these learnings into their own clinical and commercial strategic plans.

We suggest that an understanding of how Hematologists-Oncologists addressed the issue in Multiple Myeloma will help clarify the potential impact for NHL, as well as underscore how potentially complex NHL may become.

MULTIPLE MYELOMA CASE STUDY

During the last decade, Hematologists-Oncologists were faced with how to incorporate new therapies (i.e., lenalidomide and bortezomib) into the treatment algorithm for multiple myeloma, specifically whether these agents should be used in combination for first-line settings or whether they should be used sequentially. This issue turned into a fierce debate with each side vocally defending their position in articles, conferences, and editorials over an extended period of time. Though neither side could declare a total victory, combination therapy has become the predominant choice. Combination therapy largely “won out” as the improvements in efficacy (defined by response rates) trumped concerns over the loss of follow-up options. Past multiple myeloma treatments (i.e., steroids and chemotherapies) had relatively poor efficacy with only modest response rates, making the improvement shown by combination therapy all the more impressive. This has had significant impacts on multiple myeloma drug development ranging from the immediate (e.g., raising the hurdle for new drugs being used in front-line

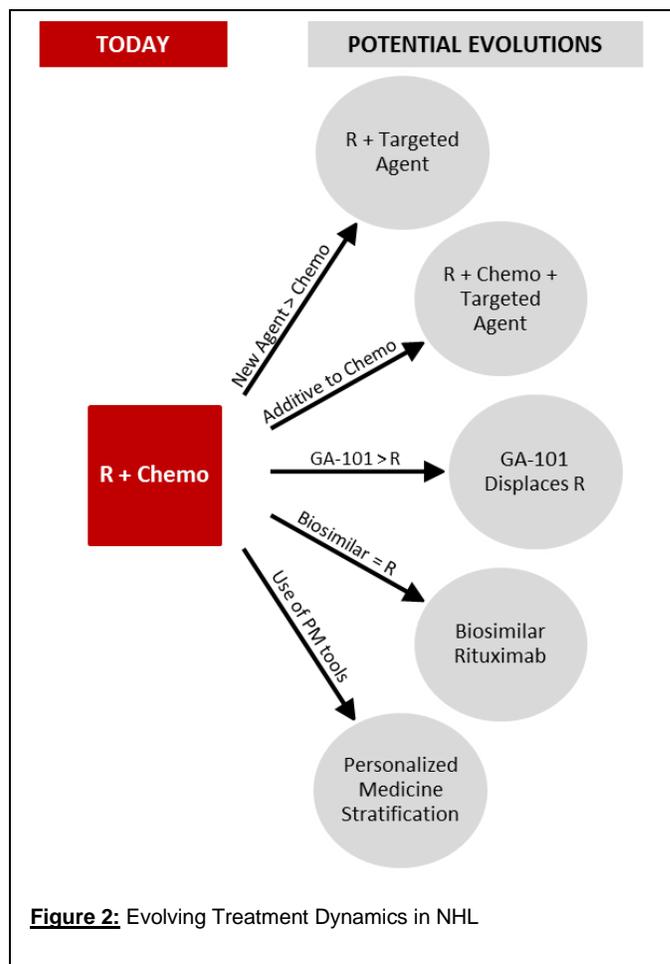


Figure 2: Evolving Treatment Dynamics in NHL

settings) to the indirect (e.g., defining patient populations in later line settings, characterizing resistance to lenalidomide or bortezomib, etc.)

The situation in NHL is likely to be even more complex given the diverse nature of NHL and the level of competition (both in terms of number of companies and agents in development).

EARLY COMMERCIAL INSIGHT

In order to address the uncertainty surrounding the treatment paradigm and the significantly different outcomes (shown in Figure 2), more extensive scenario planning will be a critical component of new product strategy development.

This will require a thorough understanding of the potential scenarios, specifically addressing:

- What will be the critical event(s) or inflection point(s) which might initiate a specific scenario? What research and/or competitive intelligence should be utilized to identify these events?
- What are the direct and indirect impacts of these scenarios on your own drug development?
- How does this change timing, risk, and investment in your own drug?
- Are certain scenarios dominant?

IMPLICATIONS FOR NEW PRODUCT PLANNING

The number of scenarios outlined above may prove daunting and more multi-faceted than most scenario planning. However, we have found that developing a pragmatic framework is of critical importance for both making decisions and communicating these decisions internally.

To that point, development and commercial plans (and specifically trade-offs in priorities and/or investment) should be assessed not only against the status quo or the *presumed* base case evolution of the market, but also against these potential futures.

“ *Companies who devise early strategic plans will be better prepared to deal with the upcoming changes* ”

NO OBVIOUS PATH TO BLOCKBUSTER INDICATIONS

There are multiple entry points into NHL, with the end goal being a front-line indication in the larger, more profitable indications (e.g., DLBCL, FL): later line positioning in one of these indications versus a quick to market strategy in a smaller niche indication (e.g., CLL, MCL). However, unless a product has a significant reason to believe for use in a niche indication, going directly into the larger indications may make more sense. Shortcuts to a front-line indication are limited, and will require some bets to be made. One potential path to front-line includes the use of Personalized Medicine tools to further stratify patients and identify sub-groups that do not respond well to the current SOC – for example – the non-GCB DLBCL subtype, which responds poorly to R-CHOP therapy in front-line. With the high response rates in FL and the potential for cures in DLBCL, sub-segmentation and stratification may become increasingly necessary.

PLANNING AND RISK MANAGEMENT

As a result of the changing environment in NHL, clinical development is likely to become riskier and more expensive. Additional trials to demonstrate efficacy both as a single agent and in combination with the SOC will become standard practice, and trial endpoints will become more stringent, requiring significant survival benefits over the SOC. Importantly, with the emergence of new agents, and the likely improvement in survival, pivotal trial duration will increase. Longer trial duration, coupled with higher clinical hurdles, highlights the importance of appropriate risk management and careful planning to ensure proper trial design and execution.

A LOOK TO THE FUTURE

As new therapies are approved, KOLs and payers will be faced with new treatment dilemmas in NHL, and new product planning will need to adapt accordingly to ensure clinical and commercial success. Clinical pathways, designed to standardize treatment algorithms, optimize treatment and reduce costs, are likely to become increasingly important as additional therapies are approved in NHL. Pathways are already in place for some of the most common cancers,

including breast, lung and colon cancers, and a number of pathway providers are expected to release lymphoma pathways in the short-term. Consequently, now more than ever, clinical and commercial planning will be required to navigate through the changing dynamics and address the crucial questions that are emerging.

¹ Follicular Lymphoma

² Diffuse Large B-Cell Lymphoma

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