

Cortellis

European Commission approves first two drugs under PRIME program

August 2018 saw the European approval of the first two drugs under the PRiority MEdicines (PRIME) program – Novartis’s Kymriah (tisagenlecleucel) and Kite Pharma/Gilead’s Yescarta (axicabtagene ciloleucel). Both are groundbreaking chimeric antigen receptor (CAR) T-cell therapies that harness the immune system to target hematological malignancies.

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The PRIME designation

The PRIME program was introduced by the European Medicines Authority (EMA) in March 2016. Its aim is to smooth the regulatory pathway and provide faster patient access to drugs providing significant advantage over existing therapies, or for serious conditions where there are currently no treatments available. While companies of any size can benefit from the scheme, the designation is especially targeted toward small and medium enterprises and academic institutions, to help compensate for any lack of experience in the regulatory arena, compared with large companies. For larger companies, application is based on preliminary evidence of clinical benefit, while smaller companies and academic institutions can apply for the designation earlier in the development process, on the basis of promising preclinical data and clinical tolerability¹.

Candidates selected for PRIME gain access to specific guidance and support in development planning and regulatory approach. Successful applicants gain early access to a rapporteur from the EMA’s Committee for Medicinal Products for Human Use (CHMP) or from the Committee on Advanced Therapies (CAT). An initial kick-off meeting is conducted with the rapporteur and a multidisciplinary group of experts from relevant EMA scientific committees and working parties. A dedicated contact within the EMA is assigned, and scientific advice is provided at key milestones. PRIME therapies would also expect to gain Accelerated Assessment status, although this is not guaranteed¹.

The first drugs approved

Since the scheme was introduced, more than 40 products have been granted PRIME designation². In August 2018, two years after the start of the program, the first two therapies with PRIME designation were granted marketing approval by the European Commission (EC) – Yescarta and Kymriah, which are both CAR T-cell therapies targeting the B-cell cancer marker CD19. Yescarta is indicated for two types of non-Hodgkin lymphoma (NHL), while Kymriah is for B-cell precursor acute lymphoblastic leukemia (B-cell ALL) and one type of NHL^{3,4}.

CAR T-cell therapy is a novel treatment approach, personalized to an individual patient’s cancer. The therapy involves removing a patient’s own T cells, engineering them to express a receptor that binds to a cancer marker (such as CD19), and then re-infusing them back into the patient to recognize and bind the tumor

antigen, triggering T-cell-mediated destruction of the cancer cells⁵. To date, the majority of clinical experience with CAR-T therapies has been in the field of blood cancers². Yescarta and Kymriah represent the first two therapies in this class to be approved, both in the E.U. and in the U.S.^{6,7}

The companies: the old and the new

The two owners of the drugs come from opposite ends of the pharma industry spectrum. Kite Pharma, registered in California in 2010, is a relative newcomer to the pharma scene⁸. Gilead Sciences, seeing the early promise of Kite's cell therapies, acquired the company for an impressive \$11.9 billion in October 2017⁹. Kite specializes in cancer immunotherapy, particularly in the fields of CAR-T and T-cell receptor products. Kite's pipeline currently lists four drugs in clinical development, including Yescarta; three CAR-T therapies aimed at blood cancers, and one T-cell receptor product targeted at solid tumors. Yescarta is the company's first launched drug¹⁰. As a company new to the later stages of drug development and regulation, the potential benefits of PRIME designation can easily be appreciated, allowing access to specific guidance and support in terms of trial design, which is particularly critical with a completely new and innovative type of therapy, necessitating particular regulatory and scientific scrutiny.

In contrast, Swiss company Novartis is one of the world's five largest pharmaceutical companies, with approximately 235 preclinical and clinical drugs currently in development, according to Cortellis². The company was created in 1996, through the merger of Ciba-Geigy and Sandoz, and can trace its lineage back more than 250 years¹¹. As such one would expect Novartis to have vast experience in effective clinical trial design and navigating regulatory landscapes. In this case the novelty of the therapy makes the PRIME designation and the extra input of the EMA and its rapporteurs desirable, even for such a large and established company.

Clinical experience with Yescarta and Kymriah

Yescarta

Kite's Yescarta has been approved in the E.U. for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy³. PRIME designation is held for refractory DLBCL, and also for mantle cell lymphoma (MCL)^{12,13}.

The standard first-line treatment for DLBCL is chemotherapy plus Rituxan (rituximab), or potentially high-dose chemotherapy plus an autologous stem cell transplant in eligible patients. Despite the high rate of response to these treatment options, a significant portion of patients do not respond, are not clinically eligible, or relapse after transplant, and thus aggressive NHL remains a major unmet medical need¹⁴. DLBCL is the most common form of lymphoma with a prevalence of approximately 56,000 patients of whom approximately 25,000 and 19,000 patients would be eligible for second- and third-line CAR T-cell treatment, respectively¹⁵.

In June 2016, the company was granted access to PRIME for Yescarta for the treatment of patients with refractory DLBCL¹². Designation was based on preliminary clinical data from the phase I/II trial ZUMA-1. Subsequently, the Marketing Authorization Application (MAA) was based on data from this trial, and from NCI-sponsored phase I trial NCI 09-C-0082, as well as findings from other clinical studies^{3,16}.

Trial NCI 09-C-0082 is an open-label, non-randomized trial enrolling 43 adult patients with DLBCL, PMBCL and MCL, which is expected to complete in December 2020¹⁷. Preliminary data have been reported for the whole patient population: The objective response rate was 74%, with a complete response rate of 54% and a partial response rate of 21%. Response was maintained in 49% of patients, with a median duration of response of 35 months. Complete remission was ongoing in 42% of patients for more than one year¹⁶.

ZUMA-1 is a single-arm, open-label, multicenter, non-randomized trial, enrolling 200 adult patients with refractory aggressive NHL, including DLBCL, PMBCL and transformed follicular lymphoma. As of July 2018, the trial was still recruiting participants, and expected to complete in March 2032¹⁸. Patients receive an initial chemotherapy conditioning regimen, followed by a single infusion of personalized anti-CD19 CAR-T cells. In data reported from 101 patients, 72% responded to therapy, with 51% achieving a complete response³. The one-year survival rate was 60%, and the median overall survival had not been reached. Long-term follow up of the trial, reporting minimum one-year follow up data indicated 42% of the patients continued to respond to therapy, including 40% with complete remission¹⁶.

Including ZUMA-1, there are currently several clinical trials ongoing, and another planned, in patients with various lymphomas. In MCL, the second indication for which YESCARTA has PRIME designation, the phase II ZUMA-2 trial is ongoing¹⁹.

Kymriah

Kymriah from Novartis has been approved by the EC for the treatment of patients aged up to 25 years with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse, and for adults with relapsed or refractory DLBCL after two or more lines of systemic therapy⁴. Kymriah has PRIME designation for the pediatric B-cell ALL indication²⁰.

Currently, patients diagnosed with ALL are treated initially with chemotherapy, and optionally with stem cell transplant. ALL is the most common malignancy in children, representing approximately 25% of all pediatric cancers. The treatment options for patients with relapsed and refractory ALL are limited, and the survival chances for children with relapsed and refractory ALL are 16 to 30%²¹.

Kymriah's acceptance into the PRIME program, and the subsequent approval of its MAA for pediatric B-cell ALL was based on results from the ELIANA trial – an ongoing, open-label, phase II trial with no comparator, in patients aged 3 to 30 years. The trial is expected to complete in November 2022²². Overall remission was achieved by 81% of patients, and at six months, 80% of responders were still in remission, and overall survival was 90%⁴.

Several clinical trials are ongoing or planned with Kymriah, including trials for relapsed/refractory follicular lymphoma and relapsed/refractory chronic lymphocytic leukemia¹⁹, for which regulatory filings are planned for 2020 and 2021, respectively²³.

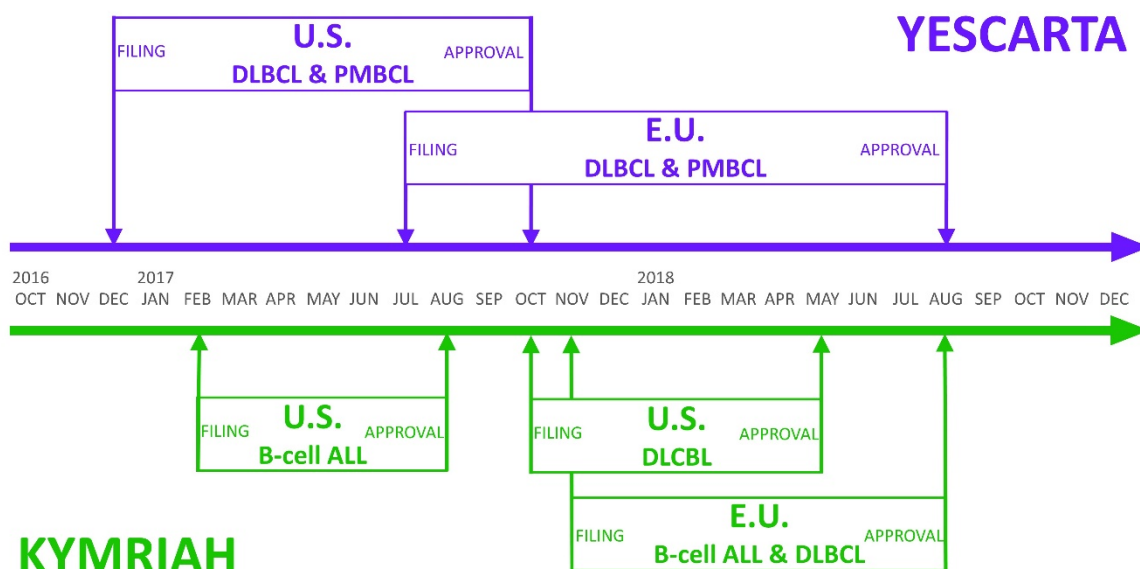
Toxicity concerns

While the response rates for both drugs are promising, concerns exist regarding potentially life-threatening side effects, primarily cytokine-release syndrome (CRS) and neurological toxicities (NTs). In the U.S., both drugs have black-box warnings highlighting the risk of CRS and NTs, and are only available through restricted risk evaluation and mitigation strategy (REMS) programs^{24,25}. Both Yescarta and Kymriah have been marked for additional monitoring by the EMA, and will be monitored more intensely than other medicines. The EMA's CAT and CHMP consider it is necessary to address the issues of safety by conducting a non-interventional post-authorization safety study (PASS) with regular follow up until December 2038^{16,20}.

The regulatory timeline to approval

The two therapies were the first CAR T-cell therapies to be approved anywhere in the world, with U.S. approvals granted for Kymriah and Yescarta in August and October 2017, respectively. Both drugs had been granted Breakthrough designation from the FDA, which is similar to PRIME in that it is aimed at drugs targeting unmet medical needs²⁶. Kymriah additionally received Fast Track status from the FDA. For Kymriah, Breakthrough designation was granted in April 2016; the drug was filed for approval in February 2017 and approved in August 2017, 209 days after filing. Yescarta received Breakthrough designation in December 2015 and was filed for approval in March 2017. Approval was granted in October 2017, 201 days after filing^{27,28}.

In Europe, Novartis received scientific advice and protocol assistance for Kymriah from the EMA, before submitting its MAA in November 2017. Approval of Kymriah was granted 294 days later in August 2018. Similarly, Kite received scientific advice for Yescarta before filing in July 2017; the drug was approved in August 2018, 390 days after filing^{27,28}.



THE TIMELINES OF U.S. AND E.U. APPROVAL FOR YESCARTA AND KYMRIAH

Figure 1: Timelines of U.S. and E.U. approval for Yescarta and Kymriah. Source: Cortellis Regulatory Intelligence, Clarivate Analytics.

Reversion of accelerated to standard assessment

Although the EMA outlines in its information relating to PRIME that drugs receiving PRIME designation are eligible for accelerated assessment, neither Yescarta nor Kymriah received this. Both drugs were reverted to standard assessment, in December 2017 and May 2018, respectively^{16,20}. For Yescarta, the CAT stated that the evaluation of the MAA dossier was no longer compatible with an accelerated assessment timetable due to the adoption of a substantial list of questions, including major objections, and the requirement for a good clinical practice (GCP) inspection¹⁶. Kymriah’s assessment timetable was also reverted due to the identification of major objections that precluded accelerated assessment²⁰.

Reimbursement issues

Within 10 days of EC marketing approval, the UK’s National Institute for Health and Care Excellence (NICE), approved reimbursement for Kymriah under the National Health Service (NHS) England for children and young adults with B-cell ALL (the PRIME indication)²⁹. This was followed by NICE rejection of reimbursement for the adult DLBCL indication, citing a lack of evidence of cost-effectiveness. EC approval for adult DLBCL was based on the JULIET trial, which, like the ELIANA pediatric trial, was an open-label single-arm trial with no comparator. NICE argued that, because there were no direct data comparing the treatment with standard chemotherapy, the benefits were unclear, and although the company offered an undisclosed discount on the

price tag of GBP 282,000, it was deemed to still be too expensive. Although reimbursement has not been granted in the adult DLBCL setting, NICE stated that further discussions were welcomed, thus an agreement may yet be reached³⁰.

Reimbursement for Yescarta was also initially rejected in August 2018 by NICE for both DLBCL and PMBCL, again stating that cost-effectiveness had not been ascertained due to a lack of direct comparison with salvage chemotherapy³¹. However, Gilead subsequently came to a commercial agreement with the NHS England which will allow reimbursement of the drug via NHS England's Cancer Drugs Fund³².

Conclusion

It is very early days for the PRIME designation, and thus difficult to assess the future overall benefit and success of the scheme. PRIME designation was introduced for medicines that show significant advantages over existing treatments or meet an unmet medical need – criteria that both Yescarta and Kymriah fulfill. Part of the stated aim of the PRIME designation is to “optimise development plans and speed up evaluation”¹. In this case, however, although the developers of both drugs received regulatory advice and support during development, when it came to the point of regulatory assessment for these first two drugs to be approved under the PRIME program, neither received the accelerated assessment they would have expected. In addition, although the trial designs were accepted for European regulatory approval, they were not initially considered sufficient for granting reimbursement in the UK.

At this early juncture, it is difficult to say whether the PRIME designation is meeting its objective of providing faster access for patients to new medicines. Certainly, in the US, the time taken between filing and approval was considerably less – 209 versus 294 days for Kymriah, and 390 versus 201 days for Yescarta. However, this is generally the case and it could be argued that the approval process for Kymriah has been accelerated given the complex nature of the drug and considering the median 383 days review time for EMA-approved drugs³³.

It is possible that one of the overall benefits of the PRIME program will be to equalize the opportunities between the very large well-established pharmaceutical companies and the smaller, less-experienced commercial entities and academics. It will be very interesting to follow the progress of the other drugs currently partaking in the PRIME program.

Editor's note

This article was written in collaboration with Charlotte Jago (Clarivate Analytics, London), H el ene Rousseau (Clarivate Analytics, Paris) and Chaitali Talreja (Clarivate Analytics, Mumbai).

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