Approval of CD19-Directed CAR T cells : FDA licensure of new cell-based gene therapy products with a challenging safety profile

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The FDA has approved 2 CD19-directed CAR T cell products for 3 indications in < 1 year

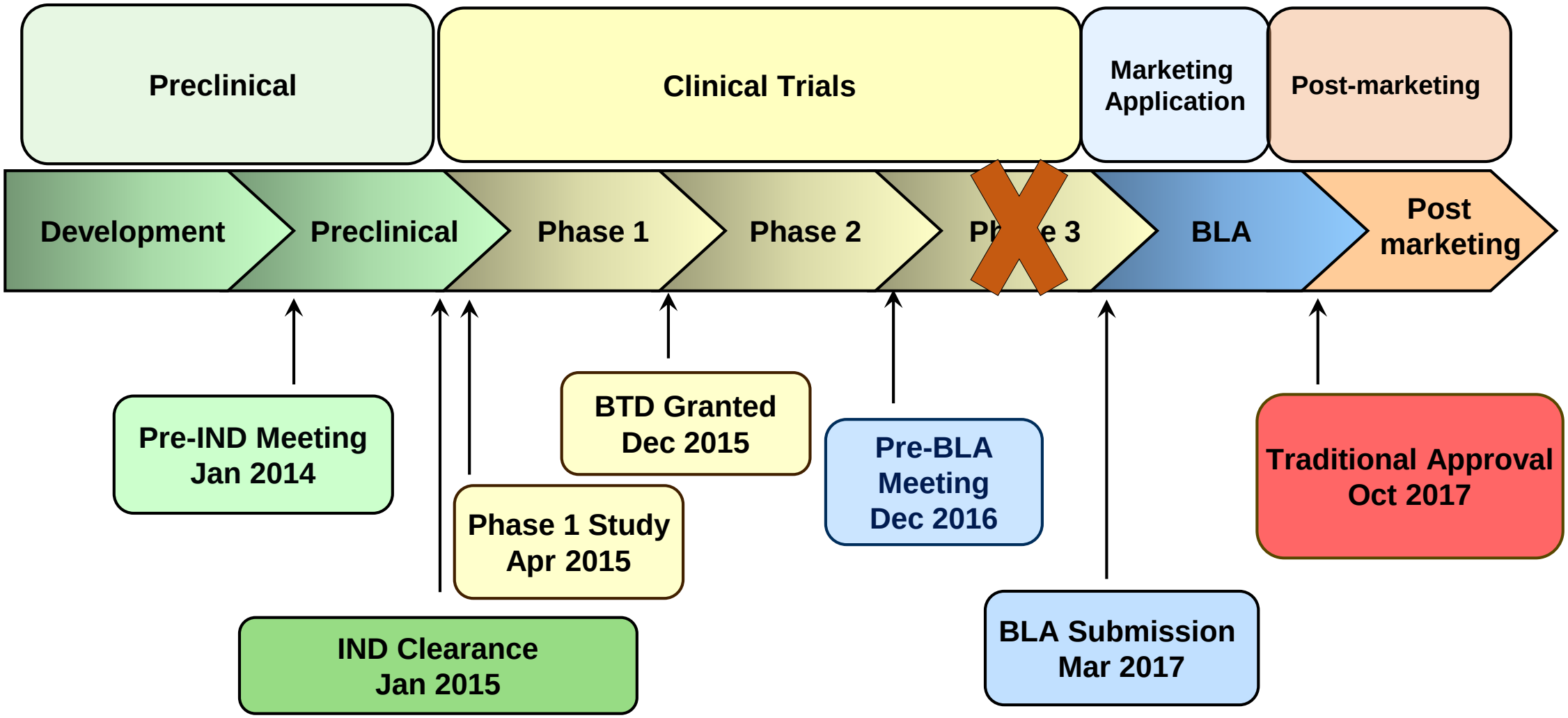
Novartis Kymriah for Acute Lymphoblastic Leukemia

Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

Kite Yescarta and Kymriah for B-cell Non-Hodgkin Lymphoma

Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, (*primary mediastinal large B-cell lymphoma-Yescarta only*), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Product Development of Axicabtagene Ciloleucel



Duration of Clinical Trials and FDA Review

Product	Kymriah	Yescarta	Kymriah
Pivotal study	ELIANA	Zuma-1	Novartis
Disease	Childhood ALL	Adult DLBCL	Adult DLBCL
Pivotal study Duration (months)	20	24	25
BLA Review Process Duration (months)	7	7	6

Overview of the Phase 2 Pivotal trials

Product	Kymriah	Yescarta	Kymriah
Pivotal Study	ELIANA	Zuma-1	Novartis
Indication	Childhood ALL	Adult DLBCL	Adult DLBCL
Pts Enrolled	88	111	160
Pts Withdrawn w/o Treatment	20	10	49
Pts in Efficacy Set	**63**	**101**	**68**
% Enrolled Pts in Efficacy Set	72%	91%	66%

Expected Outcomes for Key Endpoints with Standard of Care Therapy

	r/r Acute Lymphoblastic Leukemia	r/r Large B cell Lymphoma
Objective Response Rate	(CR+CRi) <20%	(CR+PR) <20%
High-Grade Response Rate	MRD-neg response <15%	CR < 15%
Duration of Response	Median OS < 1 year	Median OS < 1 year

Observed Results for Key Endpoints in CAR T cell -treated Subjects

	Kymriah – ALL	Yescarta- LBL	Kymriah- LBL
Objective Response Rate	83% CR/CRi*	72% CR + PR*	50% CR + PR*
Criteria for high grade response	83% MRD-response	51% CR	32% CR
Duration of Response for CRs	Not reached (7.5, NE**)	Not reached (8.2, NE**)	Not reached (10.0, NE**)

* 95% Lower Confidence Limit of response exceeds 20%

** Not estimable

Based on the high objective response rate (ORR) with prolonged benefit each product was granted traditional approval despite the absence of long-term follow-up data and a significant incidence of severe treatment-related adverse events

Incidence of Cytokine Release Syndrome (CRS) and neurotoxicity in the Pivotal Trials

	Kymriah- ALL (n=68)	Yescarta- LCL (n=108)	Kymriah- LCL (n=106)
	% Occurrence (% ≥ Grade 3)		
CRS	79% (49%)	94% (13%)	74% (23)
% treated with tocilizumab	50%	45%	15%
Deaths at least partially attributed to CRS	2	4	4
Neurotoxicity	72% (21%)	87% (31%)	58% (18%)
Deaths attributable to neurotoxocity	0	0	0

Measures adopted in earlier Phase 1-2 studies to reduce risk

1. CRS and neurotoxicity were identified early as critical dose limiting toxicities in determining a maximal tolerated CAR T cell dose.
2. Eligibility criteria were modified to delay or withhold CAR T cell treatment from subjects with major organ dysfunction or ongoing inflammation which appears to enhance vulnerability to CRS
3. Grading systems for CRS were formalized and linked to stepwise algorithmic guidelines for managing pressor, steroid, and anti-cytokine therapies
4. Tocilizumab was identified as an effective agent for treatment of severe or life-threatening CRS and with active FDA assistance was approved for that indication

Creation of Risk Evaluation and Mitigation Strategies (REMS) on Approval

REMS are designed to reduce the occurrence or severity of a particular serious adverse event. They help support a drug's safe use as described in the product's FDA-approved prescribing information.

The goals of the REMS created for these products are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

1) Ensuring that hospitals and their associated clinics that dispense product are specially certified and have on-site, immediate access to tocilizumab.

2) Ensuring those who prescribe, dispense, or administer product are aware of how to manage the risks of CRS and neurological toxicities.

Post-Marketing Requirement for Long-Term Follow-up

- CAR T cell products produced using retroviral and lentiviral vectors have the potential risk of inducing malignant transformation by:
  - Generation of replication-competent virus through recombination events
  - Incidental insertional mutagenesis in normal T cells or other cell types.

- The Applicant is responsible for long-term follow-up for 15 years to assess the potential prevalence of these events.

Other Challenges to the safe and effective use of CAR T cell products

Problems in Dosing a “living drug”

- The dosing and pharmacokinetics of conventional pharmaceuticals can be predictably controlled.
- By contrast, the yield of CAR T cells manufactured and their propensity to expand and persist in vivo varies substantially from patient to patient and product to product.
- Based on the safety and efficacy observed in Phase 1 and 2 studies, Novartis and Kite have developed quite different dosing recommendations.
  - Kymriah dose for adults with NHL is 60 to 600 x 10^6 cells flat dose if weight is >50kg
  - Yescarta dose for NHL is 2×10^6 cells/kg
- Advances that improve the reproducibility of CAR T cells expansion and persistence are needed if we are to optimize efficacy and safety.

Manufacturing Delays and Failures

- Manufacturing failure affected up to 10% of enrolled subjects in the 3 Pivotal studies. Affected subjects all died during the delay or were dropped from the protocol.
- An additional 1-10% of subjects in these Pivotal trials died or were dropped because of progressive disease while awaiting manufacture.
- Over 80% of subjects in some protocols required bridging chemotherapy to contain disease while awaiting manufacture.

Impact of Manufacturing Delays and failure on Clinical Trials

- The 3 pivotal studies excluded significant numbers of subjects because of manufacturing issues. By agreeing to assess efficacy on a per protocol population, efficacy was demonstrated.
- Phase 3 trials, using Intention-to-treat (ITT) criteria for assessment, will be needed in the future to assess whether CAR T cells are superior to other therapies in early treatment of refractory disease. In the ITT setting adverse consequences of manufacturing delays or failures can negatively impact study outcome.
- The selective use of ad hoc bridging chemotherapy in the CAR T cell arm of phase 3 trials can make clinical responses difficult to interpret.

Impacts of problems in manufacture of approved product on clinical practice

- Unexpected manufacturing delays and failures adversely affect patient care for the reasons discussed earlier.

- Whenever the yield or specifications of an approved CAR T cell product falls outside the approved limits, the FDA has been reviewing the product and clinical indication under a single patient IND before approving administration.

Repeated administration of approved CAR T cell products

CAR T cell products have been approved so far based only on a single product administration. Repeat administration for late relapse, and to restore CAR T cell activity after loss of B cell aplasia are reasonable approaches for preventing and treating recurrence, but there is as yet no systematic data addressing its risks and benefits.

Conclusions

- CD19-directed CAR T cells are the first cell-based immunotherapy products to be approved by the FDA
- The rapid success in gaining approvals for patients with disease refractory to other modalities is a testimony to their efficacy
- With increasing clinical experience and further technical advances with product development it is likely that the safety profile of these agents will continue to improve with time.
- The prospects are also good that efficacious products directed against target antigens on other hematologic and non-hematologic malignancies will be developed and approved.