www.pei.de

\\ Use of RWD in gene-therapy approvals \\ axicabtagene ciloleucel (Yescarta)

PD Dr. Benjamin Hofner
Head of Section Biostatistics

Disclaimer:

The following slides represent my personal views and do not necessarily reflect the views of the Paul-Ehrlich-Institut or any other European agency.

www.pei.de

\\ Use of historic controls in gene-therapy approvals \\ axicabtagene ciloleucel (Yescarta)

PD Dr. Benjamin Hofner
Head of Section Biostatistics

Disclaimer:

The following slides represent my personal views and do not necessarily reflect the views of the Paul-Ehrlich-Institut or any other European agency.

Sources

- European Public Assessment Report (EPAR) for YESCARTA (EMA/481168/2018)

- Papadouli, Mueller-Berghaus, Beuneu et al. "*The European Medicines Agency review of axicabtagene ciloleucel (Yescarta) for the treatment of diffuse large B-cell lymphoma (DLBCL)*", Submitted to The Oncologist.

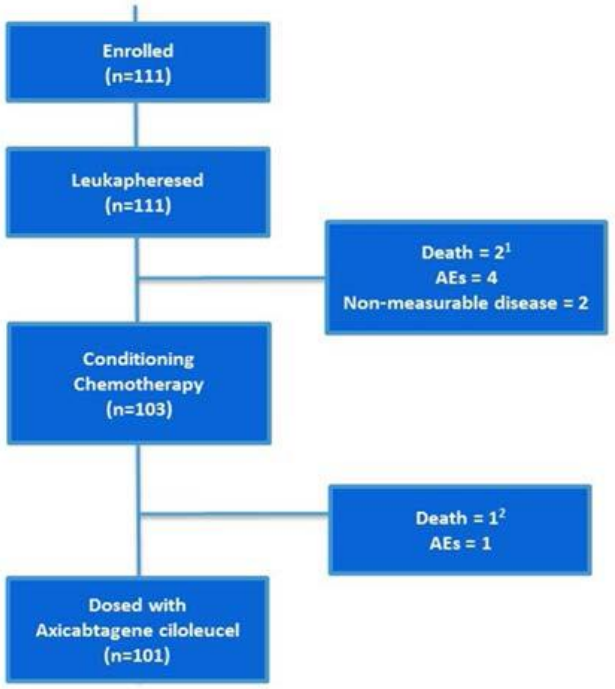
Background

- Axicabtagene-ciloleucel (axi-cel)
  - CAR-T cell therapy for treatment of DLBCL (diffuse large B-cell lymphoma) after two or more lines of systemic therapy
- Treatment
  - Leukapheresis to collect patient's own T-cells (> autologous treatment)
  - Ex vivo genetic modification of the T-cells to target B cell specific antigen (CD19)
  - Infusion of CAR-T cells after lymphodepleting chemotherapy
- Procedure
  - Initially accelerated procedure, reverted to standard TT after first round
  - Two rounds of questions (LoQ, LoOI)
  - CAT/CHMP adopted a positive opinion in June 2018

Pivotal study

- ZUMA-1
  - Prospective, single-arm Phase 2 trial
  - Enrolled patients: N = 111
  - Patients treated with axi-cel: N = 101
  - Median time from leukapheresis to infusion was 24 days (range: 16 to 73 days)
  - Pre-specified historic control rate (ORR):

    H_0: ORR ≤ 20%
    H_1: ORR > 20%



[1] Both deaths due to progressive disease
[2] Death due to tumor lysis syndrome, deemed related to conditioning chemotherapy

Supportive study

- SCHOLAR-1
  - Retrospective historic control
  - Based on 4 studies
    - 2 randomized clinical trials (follow up data after progression)
    - 2 institutional databases from academia
    - Partially unclear follow-up routines
  - Key eligibility criteria:
    - chemo-refractory aggressive B-cell Non-Hodgkin-Lymphoma (DLBCL, TFL, PMBCL)
    - no history of allogeneic SCT
  - Sample size was “variable”:
    - Enrolled: N = 861
    - Scholar-1 evaluable set: N = 636
    - RR-evaluable set: N = 523
    - Survival-evaluable set: N = 603
    - RR/survival-evaluable set: N = 513

Discussions during assessment

- Choice of analysis set
  - Company focused on mITT (all treated patients)
  - ➢ CAT/CHMP has a strong **preference for ITT** (all enrolled patients) as only this allows a suitable comparison to control

- Choice of relevant endpoints
  - Primary endpoint: ORR
    - Considered as indicator of tumour response but no patient relevant outcome
    - Company focused on local investigator assessment
    - ➢ CAT/CHMP focused on **central review** for better standardization
  - Important secondary endpoints:
    - CR rate, DoR, OS
    - ➢ CAT/CHMP laid strong focus on **CR rate and OS** (supported by ongoing response)
  - General discussion on outstanding effects, magnitude of bias, …
    - Results need to be outstanding in SATs

Discussions during assessment

- Choice of relevant historic control
  - Checking comparability of patient populations and sensitivity of results crucial
    - ➢ **Patient-level data** was requested by CAT/CHMP to allow a better understanding
  - Same / similar follow up routine
    - visit schedules, standardized definition of endpoints, …
  - Data sources (registries, EHRs, RCTs, …)
    - Company presented a mixture of data sources
    - ➢ CAT/CHMP mainly focused on the two **RCTs**
  - Changes in response to standard of care over time
    - Difficult to assess based on limited data

Main results

	ZUMA-1 All leukapheresed (ITT, N = 111)		SCHOLAR-1*
	12-month analysis	**24-month analysis**	
ORR (%) [95% CI]	66 (56, 75)	68 (58, 76)	26 (21, 31)
CR (%)	47	50	7
12 month OS (%) [95% CI]	59.3 (49.6, 67.8)	59.5 (49.7, 67.9)	28
24 month OS (%) [95% CI]	N/A	47.7 (38.2, 56.7)	20

* Combined results of all 4 data sources with varying analysis sets

- Refinement of control ORR (pre-specified as 20%) based on SCHOLAR-1
  - RR in SCHOLAR-1 was 26% (95% CI: 21%, 31%)
  - ORR results (66% at 12 months) considered outstanding
- High CR rate and high survival rates are considered outstanding

General issues

- When are SATs (complemented with RWD/historic controls) acceptable?
  - Exceptional circumstances only
  - RCTs remain the gold standard for very good reasons
- How can historic controls become more accessible to reviewers?
  - Transparent selection criteria of data sources and/or subsets of patients
  - Pre-specification of criteria and statistical methods
  - Discussed and agreed with CAT/CHMP in advance
- Which endpoints are preferable in a pragmatic trial / SAT with RWD?
  - ORR
  - + DOR?
  - + OS?
  - + …
  - Not PFS