Use of historical data to support gene-therapy approval: example from Kymriah

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Disclaimer

The views expressed in this presentations are those of the speakers and are not necessarily those of the MHRA, EMA or Expert Working Group.

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References

European Assessment Report (EPAR) for Kymriah (EMA/485563/2018)

Pending publication

The European Medicines Agency review of Kymriah for the treatment of acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL)

Report on CAR T-cell therapy Registries Workshop 9 February 2018 (EMA/204454/2018)

Background and proposed indications

Kymriah is chimeric antigen receptors (CAR) T-cells medicines for advanced blood cancer:

- **Childhood leukaemia**
- **Adult lymphoma**

Company submitted multicentre, single-arm, open-label studies:

- **Study B2202**
- **Study C2201**

Supported by historical studies :SCHOLAR-1, the pooled CORAL extension studies, and the PIX301 study

Comparisons of outcomes across studies using matched adjusted indirect approach

Adult lymphoma (Study C2201)

- Based on historical data, a threshold of 20% was used to determine efficacy

Primary endpoint (Overall response rate : CR + PR):

- All infused patients: ORR = 53.1% (n = 43/81); p<0.0001;
- 39.5% (32/81 patients) achieved a CR

The interpretation of the study results was hampered by a number of issues:

- Selection bias, lead time bias, population enrichment, estimand, and limited safety data
  - Enrolment of patients before product become available (**waiting time for infusing ~= 52 weeks**)
  - **30% of patients discontinued** from the study prior to infusion (reasons: death, investigator choice, manufacturing issues)

Estimate of treatment effect based on **all enrolled patients** was deemed more appropriate for decision-making

Adult lymphoma: Historical comparisons results

All Infused patients

Comparison	ORR Difference (95% CI)	CR Difference (95% CI)	OS Hazard ratio (95% CI)
C2201 vs SCHOLAR-1	20.5% (8.9%, 32.0%)**	30.8% (19.9%, 41.8%)**	0.681 (0.48, 0.96)*
C2201 vs Pooled CORAL extensions	12.2% (0.6%, 23.7%)*	12.2% (1.1%, 23.3%)*	0.412 (0.31, 0.54)**

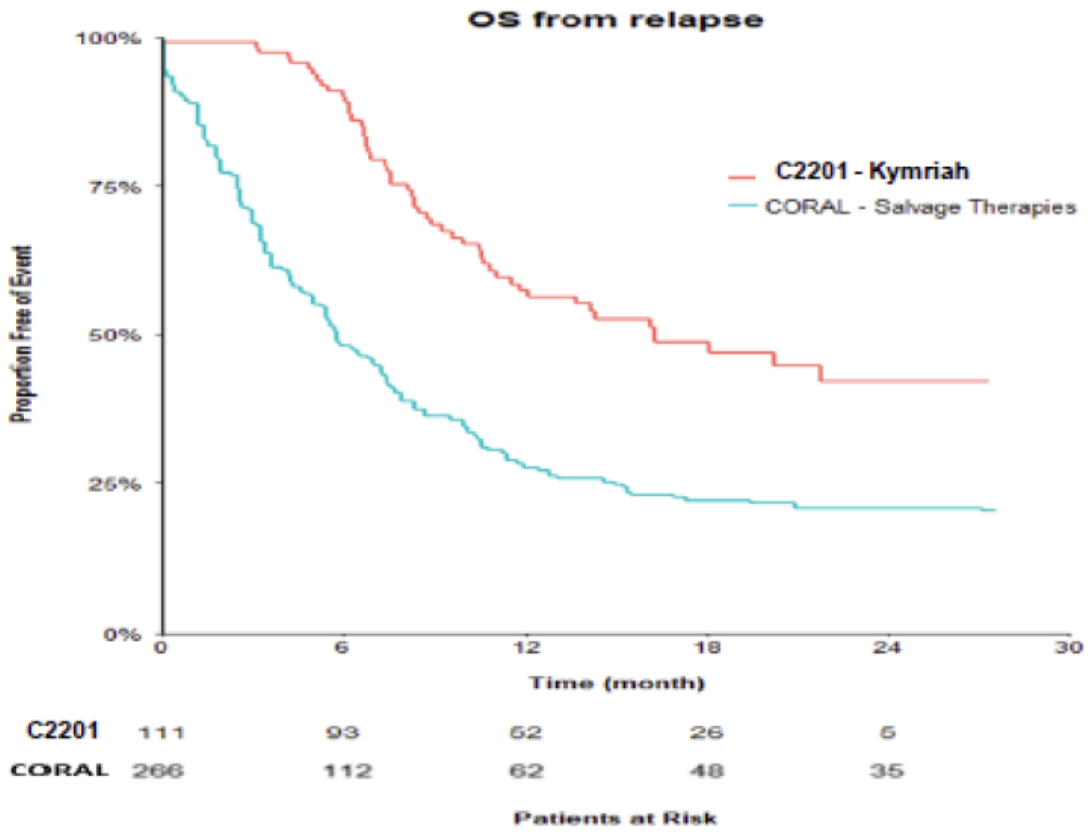
* P-value < 0.05. ** P-value < 0.01. 1. OS from treatment. 2. OS from last relapse.

All Enrolled patients

Comparison	ORR Difference (95% CI)	CR Difference (95% CI)	OS Hazard ratio (95% CI)
C2201 vs SCHOLAR-1	6.1% (-3.6%, 15.8%)	19.2% (10.3%, 28.1%)**	0.781 (0.59, 1.04)
C2201 vs Pooled CORAL extensions	-5.0% (-14.7%, 4.8%)	-1.7% (-10.7%, 7.2%)	0.532 (0.42, 0.68)**

* P-value < 0.05. ** P-value < 0.01. 1. OS from enrollment in Study C2201. 2. OS from last relapse.

Event Free Survival



CORAL curve was truncated at the maximum follow-up for C2201

Key challenges with historical comparisons

- **Target population:**

SCHOLAR-1 was an international, multicohort retrospective non-Hodgkin lymphoma research study, evaluating responses and OS rates in patients with refractory NHL, including DLBCL, transformed follicular lymphoma (TFL) and primary mediastinal B cell lymphoma (PMBCL).

CORAL Extension studies included patients with relapsed DLBCL who were then randomised to receive either R-ICE or R-DHAP followed by autologous SCT (±rituximab)

- **Confounding adjustment only possible for known but not unknown factors**
- **Individual level patient data required but often only aggregated data are available**
- **Information about other relevant treatment often missing**
- **Outcome assessment criteria not always clearly defined**

Approval of Kymriah

On 28 June 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Kymriah, intended for the treatment of acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL). As Kymriah is an advanced therapy medicinal product, the CHMP positive opinion is based on a assessment by the Committee for Advanced Therapies.

Kymriah: regulatory tools and measures applied pre- and post-authorisation
• In patients with relapsed/refractory DLBCL by June 2022
Qualification of patient registry
Workshop on patient registries for CAR-T cell therapies

Use of historical data: Regulatory expectations

High level of evidence is required for drug approval.

The role and added value of historical data in certain disease settings is recognised**.**
But the strength of evidence from historical studies to support **MAA** will depend on:

- Disease setting: unmet need, orphan condition, life threatening
- Data quality: consistency, accuracy, completeness and representativeness
- Heterogeneity between datasets
- Heterogeneity in methods used for analysing datasets

Collection of **RWD** using disease registries post MA enable generation of meaningful safety and efficacy data on the new treatment in a real world setting**. But a high level of co-ordination, collaboration, and adherence to recommendations to assure data quality are required to optimise and facilitate the use of these data.**

MHRA provides opportunities for innovators to seek advice

Thank You

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