LymphomaHub

HL

# KEYNOTE-087: 2-year follow up of pembrolizumab in R/R classic Hodgkin lymphoma

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For many years scientists have been perusing the idea of harnessing the power of the immune system to fight malignant tumours. Recently, immunotherapy has drawn a lot of attention due to expanding knowledge and technological advances. Immune checkpoint inhibitors are currently being developed and rapidly adopted in treatment regimens of different cancer types. Pembrolizumab, an inhibitor of programmed death 1 (PD-1) has been approved by the US Food and Drug Administration (FDA) (read the Lymphoma Hub article here) and European Medicines Agency (summarised on the Lymphoma Hub here) for the treatment of patients with refractory or relapsed classic Hodgkin lymphoma (R/R cHL) based on efficacy and safety demonstrated in the KEYNOTE-013 (NCT01953692) and KEYNOTE-087 (NCT02453594) clinical studies. However, at the time of approval, only limited follow-up data was available and therefore the durability of response and treatment-related adverse effects are unknown.

KEYNOTE-087, a multi-centre, single-arm, non-randomised phase II study of pembrolizumab in patients with R/R cHL previously reported overall response rate (ORR) of 69.0% and a complete response (CR) rate of 22.4% after a median follow-up of 10.1 months.[1] More recently, Robert Chen from City of Hope National Medical Center, Duarte, CA, USA, and colleagues, published the results of two years follow up of this study in Blood.[2]

## Methods

- Patients ≥ 18 years of age were enrolled in three cohorts based on cHL progression:
- Cohort 1 - after (autologous stem cell transplantation) ASCT and subsequent (brentuximab vedotin) BV
- Cohort 2 - after salvage chemotherapy and BV, ineligible for ASCT
- Cohort 3 - after ASCT without subsequent BV
- Treatment consisted of pembrolizumab 200mg intravenously every three weeks for up to two years or until disease progression/ substantial toxicity
- Patients with CR could stop treatment after receiving treatment for at least 24 weeks
- The response was monitored using computed tomography (every 12 weeks) and positron emission tomography (at weeks 12 and 24, and as clinically indicated)

## Results (at the data cut off on 21 March 2018)

- The median age of 210 patients enrolled in the study was 35 years (18–76)
- 18.6% of patients have completed the treatment and 2.4% are continuing
- 79% of patients discontinued treatment, with disease progression (41%) the most common cause of discontinuation, followed by CR (13.3%) and adverse events (AE) (8.6%)

- The median follow-up was 27.6 months (1.0–9)
- Overall responses are presented in Table 1 with the median time to response (TTR) of 2.8 months (2.1–5) which was similar between cohorts
- 84.5% of patients achieved CR after ≥ 6 months on treatment and 63.8% after ≥ 12 months

**Table 1.** Response by cohort based on a blinded independent central review.

| | All patients (N= 210) | | Cohort 1 after ASCT/BV (n= 69) | | Cohort 2 after BV ineligible for ASCT (n= 81) | | Cohort 3 no BV after ASCT (n= 60) | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | 95% CI | n (%) | 95% CI | n (%) | 95% CI | n (%) | 95% CI |
| ORR | 71.9 | 65.3-77.9 | 76.8 | 65.1-86.1 | 66.7 | 55.3-76.8 | 73.3 | 60.3-83.9 |
| CR* | 27.6 | 21.7-34.2 | 26.1 | 16.3-38.1 | 25.9 | 16.8-36.9 | 31.7 | 20.3-45.0 |
| PR | 44.3 | 37.5-51.3 | 50.7 | 38.4-63.0 | 40.7 | 29.9-52.2 | 41.7 | 29.1-55.1 |
| SD | 11.0 | 7.1-16.0 | 13.0 | 6.1-23.3 | 8.6 | 3.5-17.0 | 11.7 | 4.8-22.6 |
| PD | 15.2 | 10.7-20.8 | 7.2 | 2.4-16.1 | 22.2 | 13.7-32.8 | 15.0 | 7.1-26.6 |
| Not assessed | 1.9 | 0.5-4.8 | 2.9 | 0.4-10.1 | 2.5 | 0.3-8.6 | 0 | NA |

*, a residual mass was permitted if patients had negative results of positron emission tomography; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease

- The median duration of response (DOR) was 22.1 months in cohort 1, 11.1 months in cohort 2, and 24.4 months in cohort 3
- Median progression-free survival (PFS) in all patients was 13.7 months (95% CI, 11.1–0), with 16.4 months, 11.1 months and 19.4 months in cohorts 1, 2, and 3 accordingly
- Median PFS was not reached in patients with CR
- Median OS was not reached in any cohort

- ORR for the eight evaluable patients who received a second course of pembrolizumab was 75%

**Safety**

- Treatment-related AEs appeared in 72.9% patients, mostly grade 1–2 (60.9%) (Table 2)
- Grade 3 AEs occurred in 11% of patients, with neutropenia and diarrhea most common
- Two patients had grade 4 treatment-related AEs (one had increased lipase and one myocarditis)
- No treatment-related deaths were recorded
- The median time to onset of the first immune-related AE was 85 days (1–787 days)

**Table 2.** Adverse events (AEs) occurring in ≥ 5% of patients.

| AE | Grade 1-2 | Grade 3 | Any grade |
|---|---|---|---|
| **Treatment-related AEs (%)** | | | |

| | | | |
|---|---|---|---|
| **Hypothyroidism** | 14.3 | 0 | 14.3 |
| **Pyrexia** | 10.9 | 0.5 | 11.4 |
| **Rash** | 11.0 | 0 | 11.0 |
| **Fatigue** | 10.5 | 0.5 | 11.0 |
| **Headache** | 7.6 | 0 | 7.6 |
| **Diarrhea** | 7.1 | 1.4 | 8.6 |
| **Nausea** | 7.1 | 0 | 7.1 |
| **Cough** | 6.2 | 0.5 | 6.7 |
| **Pruritus** | 6.2 | 0 | 6.2 |
| **Arthralgia** | 5.2 | 0.5 | 5.7 |
| **Infusion-related reaction** | 5.2 | 0 | 5.2 |
| **Neutropenia** | 2.9 | 2.4 | 5.2 |
| **Immune-mediated AEs and infusion-related reactions (%)** | | | |
| **Hypothyroidism** | 15.7 | 0 | 15.7 |
| **Infusion-related reaction** | 5.2 | 0 | 5.2 |
| **Pneumonitis** | 4.8 | 0 | 4.8 |

## Conclusion

The data from the trial has demonstrated that pembrolizumab improves outcomes for patients with R/R cHL that has progressed after, or are unsuitable for, ASCT. After longer follow-up pembrolizumab continued to show durable responses in all three cohorts of patients. The safety profile was manageable and consistent with previous reports, with no new treatment-related events or toxicities.

**References**

1. Chen R *et al*., Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol. 2017 Jul 1;35(19):2125-2132. DOI: 10.1200/JCO.2016.72.1316

2. Chen R *et al*., Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019 Oct 3;134(14):1144-1153. DOI: 10.1182/blood.2019000324

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