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Validation of Overall Survival (OS) Extrapolations Using 5-Year Follow-up Data from the KEYNOTE-177 MSI-H/dMMR Metastatic Colorectal Cancer (mCRC) Study

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Background

- Pembrolizumab is the current standard of care in management of patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) mCRC[1,2]
- The second interim analysis (IA2) (February 2020) of the phase 3 randomized open-label KEYNOTE-177 (NCT02563002) study showed that when compared to chemotherapy, first-line (1L) pembrolizumab resulted in a better progression-free survival (PFS) with reduced mortality[3]
- To establish timely access to innovative therapies, health technology assessments are often informed by survival data with limited follow-up[4]
- As of July 2023, the 5-year follow-up data from the KEYNOTE-177 trial is available and the lifetime survival benefits estimated using statistical extrapolation methods based on IA2 data could be validated against it[5]

Objective

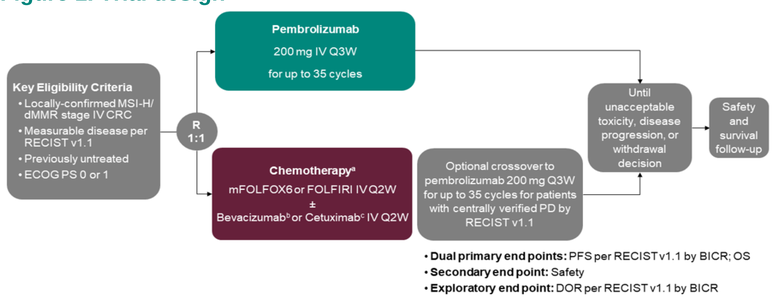
- To retrospectively validate survival extrapolations based on the second intermediate analysis (IA2) with additional 5-year follow-up data from the phase 3 KEYNOTE-177 study

Method

Trial information

- In KEYNOTE-177, 307 MSI-H/dMMR mCRC patients were randomized 1:1 to receive 1L pembrolizumab for up to 2 years or standard of care (SoC, defined as a combination of mFOLFOX6 or FOLFIRI Q2W ± bevacizumab or cetuximab) (Figure 1)[3]
- Primary endpoints were Overall Survival (OS) and PFS. The secondary end point was safety[3]

Figure 1. Trial design



Key: *CRC, colorectal cancer; DOR, duration of response; MSI-H, microsatellite instability-high; OS, overall survival; PD, progressed disease; PFS, progression-free survival; Q#W, once every # weeks*

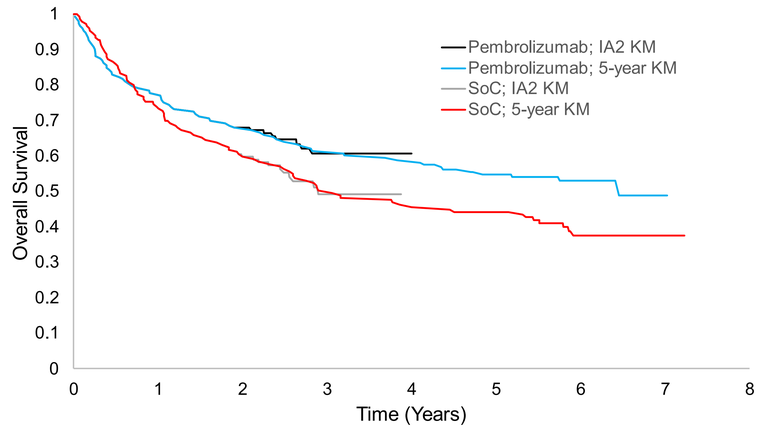
Note:
a. Chosen by investigator before randomization b. Bevacizumab 5mg/kg IV day 1 c. Cetuximab 400 mg/m² IV over 2 hours, then 250 mg/m² IV over 1 hour once per week

IA2 data versus 5-year follow-up data

- The extrapolations based on IA2 data were compared with the 5-year follow up Kaplan–Meier (KM) data using landmark survival times and restricted mean survival time (RMST)[3,5]
- RMST analysis was conducted at the mid-point between the maximum actual follow up of IA2 and 5-year datacuts, which was approximately 66 months. An analysis was not conducted at the maximum follow-up time since the KM curve is highly uncertain at this point due to the small number of patients at risk[6,7]
- All analyses presented are unadjusted for crossover
  - Among the 154 patients randomized to the SoC arm, 93 (60.4%) crossed over to pembrolizumab or received another anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy

Presented at ISPOR 2024, Atlanta, GA, USA; May 5-8, 2024

Figure 2. IA2 and 5-year KM data plots for pembrolizumab and SoC



Key*: IA2, second interim analysis; KM, Kaplan-Meier; SoC, standard of care*

Results

- The OS data from IA2 was originally extrapolated by fitting piecewise parametric survival distributions, using KM data until 12 months. Extrapolated outcomes were compared to the 5-year follow-up OS KM data
  - The exponential distribution was considered conservative but clinically plausible and was used in the base case extrapolations
  - The Weibull distribution was explored in scenario analysis
- The IA2 OS extrapolated using the exponential distribution underpredicted the 7-year survival rate by 10.7% in the pembrolizumab arm and 14.1% in the SoC arm (Table 1 and Table 2). At earlier time points, extrapolations more closely matched the observed KM data
  - The Weibull distribution also underpredicted the observed data, but to a lesser extent

Table 1. OS KM and extrapolated data comparison for pembrolizumab

Year	Piecewise Exponential	Piecewise Weibull	5-year - KM	% Difference Exponential vs. KM	% Difference Weibull vs. KM
1	77.8%	77.8%	77.8%	0.0%	0.0%
2	69.1%	67.8%	68.0%	1.2%	-0.2%
3	61.5%	62.1%	61.4%	0.0%	0.6%
5	48.6%	53.7%	54.8%	-6.3%	-1.1%
7	38.3%	47.4%	48.9%	-10.7%	-1.6%

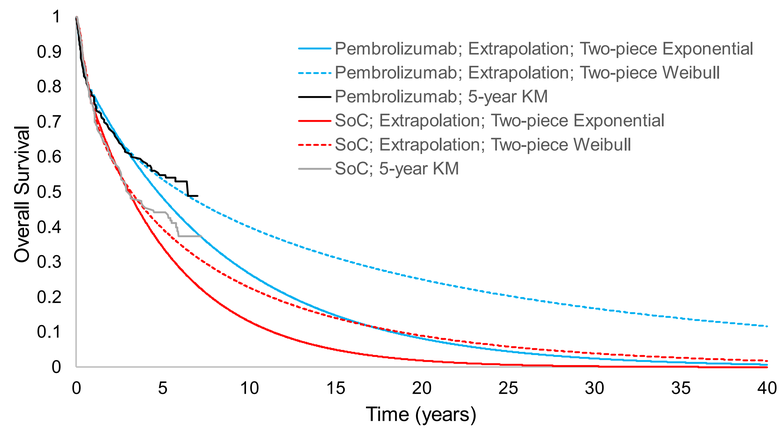
Key*: KM, Kaplan-Meier; OS, overall survival*

Table 2. OS KM and extrapolated data comparison for SoC

Year	Piecewise Exponential	Piecewise Weibull	5 year - KM	% Difference Exponential vs. KM	% Difference Weibull vs. KM
1	74.0%	74.0%	74.0%	0.0%	0.0%
2	61.1%	59.9%	59.8%	1.4%	0.1%
3	50.5%	51.4%	50.3%	0.2%	1.2%
5	34.5%	39.7%	44.2%	-9.7%	-4.5%
7	23.4%	31.4%	37.5%	-14.1%	-6.1%

Key*: KM, Kaplan-Meier; OS, overall survival; SoC, standard of care*

Figure 3. IA2 long-term extrapolations and 5-year follow-up KM data plots



Key*: IA2, second interim analysis; KM, Kaplan-Meier; OS, overall survival*

- Using an RMST analysis at 66 months, piecewise exponential curves underpredicted OS for pembrolizumab and SoC by 1.0 months and 1.5 months, respectively, when compared to the observed 5-year KM data
- Using the more optomistic piecewise Weibull curves resulted in an underprediction for pembrolizumab and SoC of only 0.2 months and 0.6 months, respectively

Conclusion

- The 5-year follow-up data demonstrates that the base case extrapolations informed by IA2 for both pembrolizumab and SoC were conservative. The authors of the original economic evaluation note that this was intended to mitigate uncertainty of immature survival outcomes
- For SoC, the observed survival outcomes are heavily influenced by the impact of crossover as 60.4% of patients went on to receive PD-(L)1 targeted therapies
- The base case piecewise exponential distribution similarly underpredicted OS for both pembrolizumab and SoC. This would suggest that the impact on cost-effectiveness analysis results would be minimal
- This validation study suggests that the piecewise Weibull distribution better predicts short and intermediate-term survival outcomes for both pembrolizumab and SoC. However, in the long-term the Weibull distribution predicts clinically implausible results with patients surviving more than 40 years
- Real-world evidence and/or more flexible statistical models could provide a better fit to the observed data while providing clinically plausible long-term extrapolations
- Where long-term survival predictions remain too optomistic after general population mortality adjustment, real-world evidence may also provide more appropriate sources of background mortality to effectively predict long-term all-cause mortality for metastatic colorectal cancer patients

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