PCN421

STABILITY OF LIFETIME OVERALL SURVIVAL ESTIMATES OF NIVOLUMAB+IPILIMUMAB IN FIRST-LINE ADVANCED/METASTATIC INTERMEDIATE- OR POOR-RISK RENAL CELL CARCINOMA

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Background

- Renal cell carcinoma (RCC) forms in cells in the lining of small tubules in the kidney that filter blood. RCC is the most common type of kidney cancer, accounting for 80-90% of all kidney malignancies.[1]
- RCC often lacks early warning signs; thus, up to 30% of cases are diagnosed at an advanced or metastatic stage.[2] Despite available therapies, life expectancy for patients with advanced or metastatic RCC is short, with a 5-year survival rate of only 10-15%.[3]
- Nivolumab plus ipilimumab was the first immuno-oncology combination therapy to show a significant overall survival (OS) benefit compared to the standard of care, sunitinib, in previously untreated RCC patients (1L RCC) with intermediate and poor risk in the phase 3 CheckMate 214 randomized controlled trial (NCT02231749).[4]
  - At the interim OS analysis in 2017 (minimum follow-up: 18 months), the independent data monitoring committee unanimously recommended that the study be stopped early as the study met the pre-specified boundary for OS.
- More recently published OS data with a minimum of 30 months[5] and 37 months follow-up[6] have demonstrated the significant OS benefit for nivolumab plus ipilimumab versus sunitinib is sustained; these data represent the longest follow-up for any phase 3 study of an immuno-oncology therapy in 1L RCC.
- Submissions to health technology authorities require extrapolation of survival data beyond the trial period to estimate lifetime survival benefits; however, a level of uncertainty exists when using relatively immature data.
- Therefore, confirmation of extrapolation methods and survival outcomes using more mature data, once available, is necessary.

Objective

- This study assesses the stability of lifetime OS extrapolations for nivolumab plus ipilimumab based on the 18-month, 30-month and 37-month DBLs of CheckMate 214.

Methods

- The mean survival, landmark survival, and the OS hazard ratio (HR) of the 18-month, 24-month, 30-month and 37-month DBL were compared to assess the stability of OS efficacy estimates for nivolumab plus ipilimumab as observed in the trial.
- Parametric functions (traditional distributions and cubic splines) were used to extrapolate OS to a lifetime time horizon based on previously published 18-, 30- and 37-month DBLs of CheckMate 214. As patient-level data for the 24-month DBL was not available, this DBL was not considered for further analysis.
- Selection of the best performing model was based on NICE DSU guidance (TSD-14)[7]:
  - The proportional hazards assumption was investigated using both qualitative assessment (parallelism of log-cumulative hazards plots and Schoenfeld residuals visualization) and quantitative assessment (chi-square test).
    - If the proportional hazards assumption was not rejected, a single dependent model was fitted to both arms of the trial data, incorporating an adjustment factor for treatment effect.
    - If the proportional hazard assumption was rejected, independent distributions were separately fitted to survival data of both trial arms.
  - An initial selection of extrapolation models was based on statistical fit of the models to the trial data, based on Akaike's information criterion (AIC) and the Bayesian information criterion (BIC).
  - The models were further evaluated by visual inspection of the survival curves, smoothed hazard functions and a comparison of median survival and landmark survival estimates with the KM curve. External validation could not be performed due to the limited external evidence available.
  - Parametric survival extrapolations were adjusted to account for background mortality, using British life tables.[8]
- Functional form of the extrapolations, landmark OS rates, restricted mean OS (RMS) and lifetime mean OS were compared across DBLs to assess stability of lifetime OS estimates based on 18-month data.
- Table 1 gives an overview of the settings that were used in the OS extrapolation.

Table 1. Survival extrapolation settings

Setting applied to survival extrapolations	Base case value
Time horizon	40 years (lifetime horizon)
Discounting for effects	3.5% (NICE DSU guidelines)
Patient characteristics (age, gender)	Baseline age: 61 years Baseline male proportion: 73% Based on the CheckMate 214 RCT
Selection of best performing model for OS	Based on NICE DSU guidance (TSD-14)
Background mortality	Applied to parametric survival extrapolations using British life tables

DSU: decision support unit; NICE: The National Institute for Health and Care Excellence; OS: overall survival; RCT: randomized controlled trial; TSD: technical support document

Results

Comparison of trial data

- Across all DBLs, nivolumab plus ipilimumab maintained statistically superior OS versus sunitinib (Table 2).

The HR for nivolumab plus ipilimumab versus sunitinib was unchanged from a minimum of 24 months follow-up to 37 months follow-up (HR: 0.66; p<0.0001).

- Median OS for nivolumab plus ipilimumab still was not reached at a minimum follow-up of 37 months.

Table 2. OS efficacy across CheckMate 214 DBLs

DBL date (minimum follow-up)	Median OS (95% CI)	Landmark survival at DBL follow-up	OS HR versus sunitinib
August 2017 (18 months)	NR (95% CI: 28.2-NE)[4]	75%[4]	0.63 (99.8% CI: 0.44-0.89; p<0.001)[4]
March 2018 (24 months)	NR (95% CI: 32.5-NE)[9]	66%[9]	0.66 (95% CI: 0.54-0.81; p<0.0001)[9]
August 2018 (30 months)	NR (95% CI: 35.6-NE)[5]	60%[5]	0.66 (95% CI: 0.54-0.80; p<0.0001)[5]
April 2019 (37 months)	NR (95% CI: 35.6-NE)[6]	53%[6]	0.66 (95% CI: 0.54-0.79; p<0.0001)[6]

CI: confidence interval; DBL: database lock; HR: hazard ratio; NE: not estimable; NR: not reached; OS: overall survival

Selection of the best fitting model for the 18-, 30- and 37-month DBL

- Patient-level data were used to extrapolate OS beyond the follow-up period. As the proportional hazards assumption was not violated in the 18-month, 30-month and 37-month DBLs, a single dependent model, including a treatment effect (HR), was fitted on both the nivolumab plus ipilimumab and the sunitinib arm from CheckMate 214 on all DBLs.
- Standard parametric models and splines were explored for OS. Table 3 reports AIC and BIC values for each model for all DBLs.
- A **dependent log-normal model** was selected for the 18-month DBL, as it achieved the lowest BIC score based on the statistical fit criteria and visual inspection (Table 3). The 30-month and 37-month DBLs confirmed the choice of a **dependent log-normal model**, based on the statistical fit criteria, the visual inspection of survival curves and the smoothed hazard rates.

Table 3. Goodness of fit – 18-month DBL, 30-month DBL and 37-month DBLs

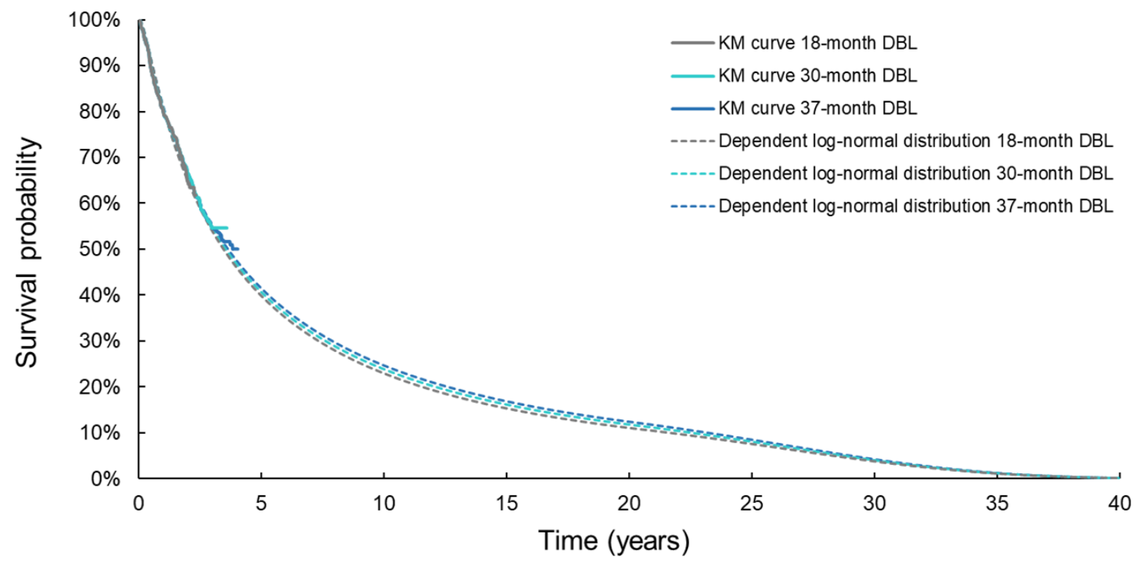
18-month DBL			30-month DBL			37-month DBL		
Distribution	**AIC**	**BIC**	**Distribution**	**AIC**	**BIC**	**Distribution**	**AIC**	**BIC**
Log-normal*	**3144.1**	**3158.3**	**Log-normal***	**6772.9**	**6787.1**	**Log-normal***	**7439.4**	**7453.6**
Spline 1k-probit	3143.6	3162.5	Spline 1k-odds	6773.4	6792.4	Spline 1k-hazard	7439.2	7458.2
Spline 1k-odds	3144.6	3163.6	Spline 1k-hazard	6773.9	6792.9	Spline 1k-odds	7439.4	7458.4
Gen. gamma	3146.0	3165.0	Spline 1k-probit	6774.5	6793.5	Spline 1k-probit	7440.6	7459.5
Spline 1k-hazard	3146.1	3165.0	Gen. gamma	6774.8	6793.8	Gen. gamma	7441.2	7460.1
Log-logistic	3149.1	3163.3	Spline 2k-odds	6774.8	6798.5	Spline 2k-odds	7440.8	7464.5
Spline 2k-probit	3145.2	3168.9	Spline 2k-hazard	6775.5	6799.2	Spline 2k-hazard	7440.8	7464.5
Spline 2k-odds	3145.9	3169.6	Spline 2k-probit	6776.5	6800.2	Spline 2k-probit	7442.5	7466.2
Spline 2k-hazard	3148.0	3171.7	Log-logistic	6781.3	6795.5	Log-logistic	7449.2	7463.4
Gamma	3154.8	3169.0	Gompertz	6792.3	6806.6	Gompertz	7458.3	7472.6
Exponential	3157.7	3167.2	Exponential	6795.3	6804.8	Exponential	7468.2	7477.7
Weibull	3156.1	3170.4	Gamma	6796.8	6811.0	Weibull	7469.4	7483.6
Gompertz	3159.7	3174.0	Weibull	6797.3	6811.5	Gamma	7470.2	7484.4

1k: 1-knot; 2k: 2-knots; AIC: Akaike's information criterion; BIC: Bayesian information criterion; DBL: database lock; Gen. gamma: generalized gamma
* The highlighted top row indicates the best-fitting curve based on BIC

Comparison of extrapolated models across the 18-, 30- and 37-month DBLs

- The best fitting distribution, a dependent log-normal, indicated a long-term survival plateau.
- Figure 1 gives an overview of the models over a time horizon of 40 years. The figure shows that the extrapolations of all DBLs are very similar, confirming the robustness of the earlier 18-month DBL.

Figure 1. KM-curves and parametric fittings of the 18-, 30- and 37-month DBLs over a 40-year time horizon



DBL: database lock; KM curve: Kaplan-Meier curve

Comparison of landmark OS across the 18-, 30-, and 37-month DBLs

- Table 4 shows a comparison of landmark survival estimates between the KM curves (denoted as "observed") and the parametric functions (denoted as "predicted") across DBLs.
- The results show that the estimated parametric curves of the three DBLs are very capable of reflecting KM landmark survival. Differences between the two curves are very small for all DBLs and the largest discrepancy between predicted and observed survival can be seen at the 4-year landmark timepoint, where the extrapolation based on the 37-month DBL underpredicts observed survival with 2.64 percentage points (p.p.).
- The difference between the 37-month DBL observed survival at 4 years (50.13%) and the 18-month DBL predicted survival at 4 years (45.96%) indicates that the 18-month DBL estimates slightly underpredicted OS for nivolumab plus ipilimumab.
- Predicted landmark estimates between DBLs are very similar, with differences at all landmark timepoints being below 2 p.p., confirming the robustness of the 18-month DBL predictions.

Table 4. Landmark survival estimates 18-, 30- and 37-month DBLs

Database lock	KM curve and extrapolation	Landmark survival (% of patients alive at time x)								
		1 year	2 years	3 years	4 years	5 years	10 years	20 years	30 years	40 years
18-month DBL	**Observed**	80.08%	64.76%	NR	NR	NR	NR	NR	NR	NR
	Predicted	80.55%	64.80%	53.92%	45.96%	39.88%	22.99%	11.10%	3.82%	0.18%
	Predicted - Observed	+0.47 p.p.	+0.04 p.p.	NE	NE	NE	NE	NE	NE	NE
30-month DBL	**Observed**	80.08%	66.42%	54.57%	NR	NR	NR	NR	NR	NR
	Predicted	80.59%	65.17%	54.51%	46.70%	40.71%	23.91%	11.85%	4.09%	0.20%
	Predicted - Observed	+0.51 p.p.	-1.25 p.p.	-0.06 p.p.	NE	NE	NE	NE	NE	NE
37-month DBL	**Observed**	80.08%	66.42%	54.72%	50.13%	NR	NR	NR	NR	NR
	Predicted	80.87%	65.73%	55.22%	47.49%	41.54%	24.73%	12.47%	4.30%	0.21%
	Predicted - Observed	+0.79 p.p.	-0.69 p.p.	+0.50 p.p.	-2.64 p.p.	NE	NE	NE	NE	NE

DBL: database lock; KM curve: Kaplan-Meier curve; NE: not estimable; NR: not reported; OS: overall survival; p.p.: percentage points
Key: Within +/- 1 p.p.; Over- or under-predicts by more than +/- 1 p.p.

Comparison of RMS for the 18-, 30- and 37-month DBLs

- The results of the RMS comparison at 12, 24, 36 and 48 months for the 18-, 30- and 37-month DBLs are shown in Table 5.
- The extrapolated RMS (denoted as "predicted RMS") based on the 37-month DBL is strongly aligned to the observed KM data (denoted as "observed RMS") at all timepoints ranging from 12 to 48 months. Deviations were no larger than 0.12 months, less than four days, at a four-year time horizon.
- Differences between DBLs were small, and predictions based on the different DBLs were similar. However, the estimates do highlight the conservativeness of the 18-month DBL. A clear example of this is that at an RMS timepoint of 48 months, the 18-month DBL underestimated RMS with almost 0.5 months when compared to the 37-month DBL observed RMS: 32.53 months versus 33.04 months, respectively.

Table 5. Comparison of RMS between parametric models and the observed trial data at several timepoints

RMS timepoint	18-month DBL			30-month DBL			37-month DBL		
	Observed RMS	Predicted RMS	Predicted RMS – Observed RMS	Observed RMS	Predicted RMS	Predicted RMS – Observed RMS	Observed RMS	Predicted RMS	Predicted RMS – Observed RMS
12 months	10.77	10.88	+0.11	10.77	10.87	+0.10	10.77	10.89	+0.12
24 months	19.61	19.54	-0.07	19.61	19.56	-0.05	19.61	19.62	+0.02
36 months	NR	26.58	NE	26.77	26.66	-0.11	26.77	26.80	+0.02
48 months	NR	32.53	NE	NR	32.69	NE	33.04	32.92	-0.12

DBL: database lock; NE: not estimable; NR: not reported; RMS: restricted mean survival
Key: Within +/- 0.10 months; Over- or under-predicts by more than +/- 0.10 months

Comparison of mean lifetime OS across the 18-, 30- and 37-month DBLs

- An overview of the undiscounted and discounted mean lifetime OS for nivolumab plus ipilimumab is given in Table 6.
- As no lifetime OS observations are available, comparison between predicted and observed mean lifetime survival is not possible. However, both the discounted and undiscounted results show that the estimated mean lifetime survival increases by DBL, as was also shown in Figure 1.

Table 6. Mean OS across the 18-, 30- and 37-month DBLs

Minimum follow-up	Mean OS, without discounting	Mean OS, with discounting
18-month DBL	7.13 years	5.44 years
30-month DBL	7.34 years	5.57 years
37-month DBL	7.53 years	5.69 years

DBL: database lock; OS: overall survival

Discussion

- Thirteen models were tested to explore the extrapolation of efficacy data from Checkmate 214, including cubic spline models.
- For all DBLs, the log-normal distribution provided the best fit to the observed data.
- Landmark survival, restricted mean survival and lifetime mean survival comparisons indicate that the 18-month DBL estimates are robust.
- As the more mature 37-month DBL shows a slight increase in survival, submissions made based on the previous 18-month DBL included conservative OS estimates for nivolumab plus ipilimumab. When looking at survival over a lifetime period, these conservative estimates underestimate mean lifetime survival with 4.8 months (undiscounted) when compared to the mature 37-month DBL.
- Due to the limited external evidence available to validate extrapolations, only the (statistical) fit of the models to the CheckMate 214 trial data was used to guide model selection. No nivolumab plus ipilimumab clinical data are available that have a longer study follow-up than the CheckMate 214 trial.

Conclusions

- The new DBLs confirm the robustness of the 18-month DBL analyses, including the choice of a log-normal distribution for extrapolation, indicating a long-term survival plateau.
- Though differences between DBLs are relatively small, this study shows that the 18-month DBL estimates of the CheckMate 214 trial can be considered conservative.
- Nivolumab plus ipilimumab is the first immuno-oncology combination that has shown significant and stable long-term OS benefit in 1L RCC compared with standard of care (sunitinib).

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Acknowledgments

- Bristol-Myers Squibb (Princeton, NJ) and ONO Pharmaceutical Company Ltd. (Osaka, Japan).
- This study was supported by Bristol-Myers Squibb.
- All authors contributed to and approved the presentation.

Presented at ISPOR Europe 2019; November 2–6, 2019; Copenhagen, Denmark

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