POSC321

Estimating long-term survivorship rates for previously untreated intermediate or poor risk advanced renal cell carcinoma patients treated with nivolumab plus ipilimumab: Analyses from the CheckMate 214 Trial

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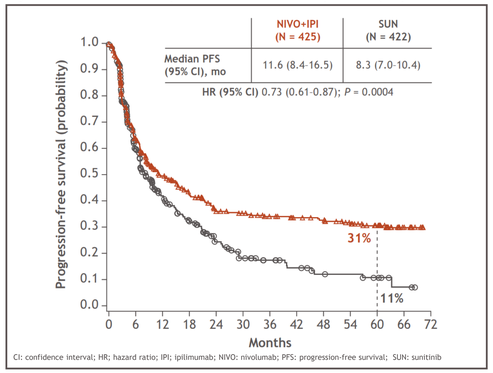
Background

- Immuno-oncologic combination of nivolumab plus ipilimumab (NIVO+IPI) is one of the most recent standard-of-care options for the first-line treatment of intermediate/poor (I/P)-risk advanced renal cell carcinoma (aRCC) [1]
- Regulatory approval of this combination was gained from data generated from CheckMate 214.[2] Key results, at a minimum follow-up of 60 months, showed that:
  - NIVO+IPI showed superior overall survival (OS; hazard ratio [HR]: 0.68 [95% confidence interval {CI}, 0.58-0.81]) and a significantly higher proportion of patients achieving an objective response (42% vs. 27%, respectively, $P < 0.001$) compared with sunitinib (SUN) in the I/P-risk patient population[3]
  - For progression-free survival (PFS) assessed per independent radiology review committee (IRRC), NIVO+IPI demonstrated delayed separation of the curves after approximately 6 months (HR: 0.73 [95% CI, 0.61-0.87])[3]
  - PFS data for NIVO+IPI exhibited a survival plateau above 30% from year 2 in the I/P population, whereas the PFS data for SUN showed gradually declining-survival curves with no demonstrable plateau[3] (Figure 1)
- Given the mechanism of action of immune checkpoint inhibitors and the heterogeneity in trend and durability of survival among patients, standard parametric distributions may not adequately capture the changes in the hazards over time[4]
- Mixture cure models (MCMs) have been used for many years by statisticians and epidemiologists to estimate the proportion of cancer patients who could be long-term survivors (LTS) [6,7]
  - These models explore survival heterogeneity by estimating the proportion of "cured" patients whose mortality rate follows an identical trend to that of the general population, after accounting for characteristics such as age, sex, and geographical distribution
  - Since the cure concept is explored from a statistical point of view in these models, rather than a clinical standpoint, the estimated rates are commonly referred to as "statistical cure" rates
  - Therefore, to avoid confusion with "clinical cure," estimated statistical cure rates are referred to as LTS rates in this poster
  - In the absence of mature OS data, PFS data can be used in MCMs to determine the proportion of LTS in trial populations[8]
  - LTS rates estimated from PFS data are more conservative but more consistent with the notion of clinical cure than those estimated from the OS data since they rely on the assumption that only progression-free patients can be cured

Figure 1. CheckMate 214 Kaplan-Meier curves for PFS per IRRC (I/P patients)



CI: confidence interval; HR: hazard ratio; IPI; ipilimumab; NIVO: nivolumab; PFS: progression-free survival; SUN: sunitinib

Objective

- To estimate the proportion of patients who are progression-free LTS based on analysis of PFS data for NIVO+IPI in previously untreated, I/P-risk aRCC from CheckMate 214 trial [Clinical Trials.gov identifier: NCT02231749]

Methods

- MCMs were fitted to PFS data from two successive database locks (DBL) with 48 and 60 months minimum of follow-up data. In the model, all patients were subject to risk of non-disease-related mortality, but only non-LTS were subject to risk of progression and additional disease-related mortality
- In an MCM, the structural form of the survival function of a population with a latent group of LTS can be expressed as:

$$S(t) = S^*(t)[\pi + (1 - \pi)S_u(t)], \text{ in which}$$

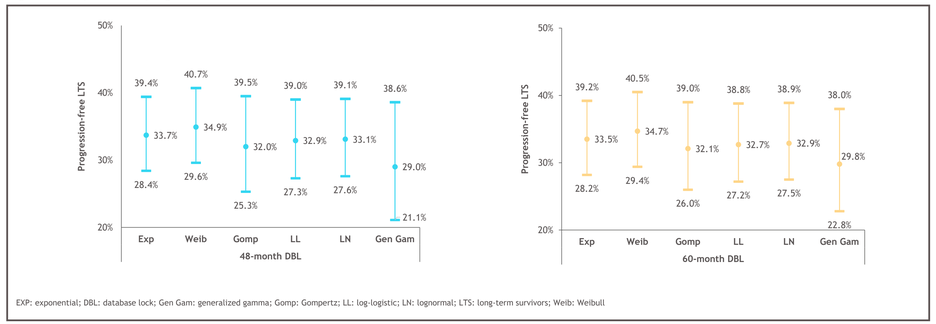
  - $S(t)$ is survival at time t for the overall population
  - $S^*(t)$ is background survival at time t (i.e., 1 – background mortality)
  - π is probability of being statistically "cured" (i.e., proportion of LTS)
  - $S_u(t)$ is disease-specific survival of the statistically "uncured" subpopulation. In our case, because MCM is employed on PFS data, $S_u(t)$ indicates survival up to progression or death, whichever occurs sooner, for the uncured subpopulation.

- UK Office of National Statistics life tables were used to inform the baseline hazard in the MCMs (i.e. the background survival $S^*(t)$)
  - Based on baseline age and gender information, conditional background survival probabilities are determined for all patients across their lifetimes
  - These are then averaged to produce a cohort-level background survival distribution representative of LTS
- To model disease-specific mortality (for the statistically "uncured" fraction), standard parametric distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalized gamma) were tested and best fits for PFS were selected based NICE Decision Support Unit Technical Support Documents[4,5]
- In addition to the LTS rates estimated from the time of randomization for the overall population, Bayes' Rule was employed to indirectly derive LTS rates among 5-year survivors
- Mean lifetime PFS times were also estimated for all candidate models

Results

- Estimated LTS rates ranged between 29.0%-34.9% in the 48-month DBL and between 29.8%-34.7% in the 60-month DBL [3] (Figure 2)
- When compared to landmark observed PFS rate at 60 months (30.8% [26.0, 36.5%]), model predictions from the 48-month DBL had a deviation between -0.3% and 1.9%
- Based on the extrapolations from MCMs, mean lifetime PFS times ranged from 7.8-8.7 years in the 48-month DBL and 7.9-8.7 in the 60-month DBL. The shortest mean survival times were generated from the generalized gamma model whereas the longest mean survival times were generated from the Weibull model in both DBLs
- In the 60-month DBL, the generalized gamma MCM provided the best statistical fit but had the widest 95% CI and the most conservative LTS rates (29.8% [95% CI, 22.8%-38.0%]), whereas the exponential MCM generated the best visual fit to both observed survival and hazard trends, with the narrowest 95% CI around the second-highest LTS rates (33.5% [95% CI, 28.2%-39.2%])
  - Hazard plots for all models are presented in Figure 3 and survival curves for the two selected distributions are in Figure 4a and 4b
- 5-year conditional LTS rates were above 90% across all models (99.7% for the exponential MCM and 90.7% for the generalized gamma MCM)

Figure 2. Proportion of progression free LTS and corresponding 95% CIs for NIVO+IPI estimated from MCMs for 48- and 60-month DBLs



EXP: exponential; DBL: database lock; Gen Gam: generalized gamma; Gomp: Gompertz; LL: log-logistic; LN: lognormal; LTS: long-term survivors; Weib: Weibull

Figure 3. Modeled hazard rates vs observed hazard rates for 60-month DBL

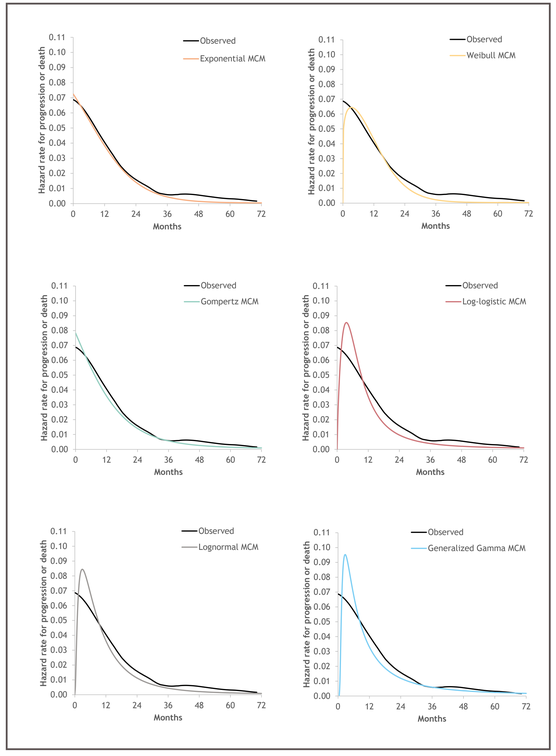
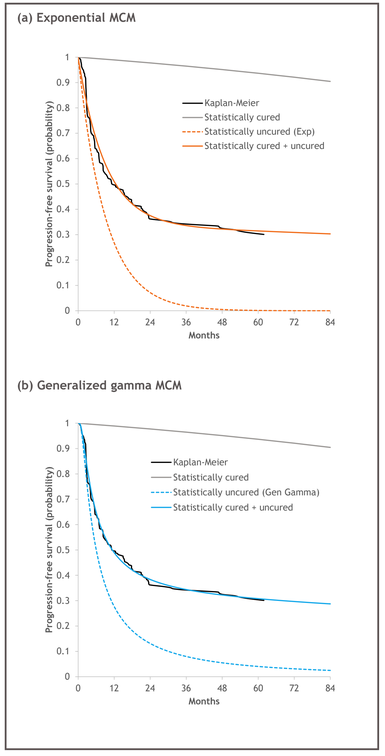


Figure 4. Survival trends (observed and predicted by selected MCMs) from 60-month DBL



Discussion

- The existence and the strength of the PFS plateau for NIVO+IPI patients in the trial was accurately captured by MCMs
- Estimated LTS rates were consistent across models and both DBLs, showing approximately one-third of I/P-risk patients with aRCC treated with NIVO+IPI were progression-free LTS with minimal risk of progression or excess risk of death due to the disease
- These results are supportive of previously reported analysis of conditional survival for NIVO+IPI among I/P risk patients from CheckMate 214, which showed that the probability of remaining progression free for an additional 2 years with NIVO+IPI increased from time zero to year 3 from 36% to 90%[3]
- The consistency between the 48-month and 60-month DBLs highlights that the earlier data cut is sufficiently long enough to produce reliable LTS rates
- This analysis was limited to NIVO+IPI patients and PFS data only
  - Given the mechanism of action for SUN, there is not a clinical expectation of durable PFS benefit as seen in immuno-oncologic combinations, and therefore, applying MCMs was not deemed appropriate
  - The OS data from CheckMate 214 has yet to demonstrate a plateauing effect for NIVO+IPI, and therefore, was not considered in this analysis but will be an area for further research as the data continue to mature

Conclusions

- The estimates of LTS, if confirmed by longer-term follow-up for NIVO+IPI, would represent a paradigm shift in the first-line treatment of I/P-risk patients with aRCC

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