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Assessing the Impact of PD-L1 and BRAF Biomarkers on Long-Term Survivorship Rates Among Treatment-Naive Advanced Melanoma Patients Receiving Immune Checkpoint Inhibitors

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Background

- Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape in advanced melanoma; however, many patients do not achieve durable clinical benefit.[1]
- Cure rates estimated from mixture cure models (MCMs) fitted to overall survival (OS) and progression-free survival (PFS) in the CheckMate-067 trial were 16–26% (ipilimumab), 38–46% (nivolumab), and 49–54% (nivolumab + ipilimumab) based on OS, and 9–13%, 29–33%, and 38–40%, based on PFS.[2]
- Identifying biomarkers associated with long-term response to ICIs remains a key research goal.
- BRAF mutation status and PD-L1 expression are among the most studied biomarkers in advanced melanoma with potential prognostic value.
- In the CheckMate-067 trial, 10-year melanoma-specific survival (MSS)—death from melanoma, censoring death from other causes—in the overall population was 52% with nivolumab + ipilimumab, 44% with nivolumab, and 23% with ipilimumab.[3]
- Subgroup analyses showed noticeable and clinically meaningful differences in 10-year MSS rates according to BRAF status and PD-L1 expression:
  - **BRAF (mutant vs. wildtype):** 56% vs. 50% with nivolumab + ipilimumab, 42% vs. 45% with nivolumab, 27% vs. 22% with ipilimumab.
  - **PD-L1 expression (≥5% vs. <5%):** 59% vs. 50% with nivolumab + ipilimumab, 54% vs. 43% with nivolumab, 34% vs. 20% with ipilimumab.
- While these findings suggest a potential prognostic role for BRAF and PD-L1 in treatment with ICIs, further research was needed to clarify their role in underlying survival heterogeneity and long-term survival benefit.

Objective

- This study investigated the impact of the BRAF and PD-L1 biomarkers on long-term survivorship (LTS) rates among treatment-naïve advanced melanoma patients receiving ICIs in the CheckMate-067 study.

Methods

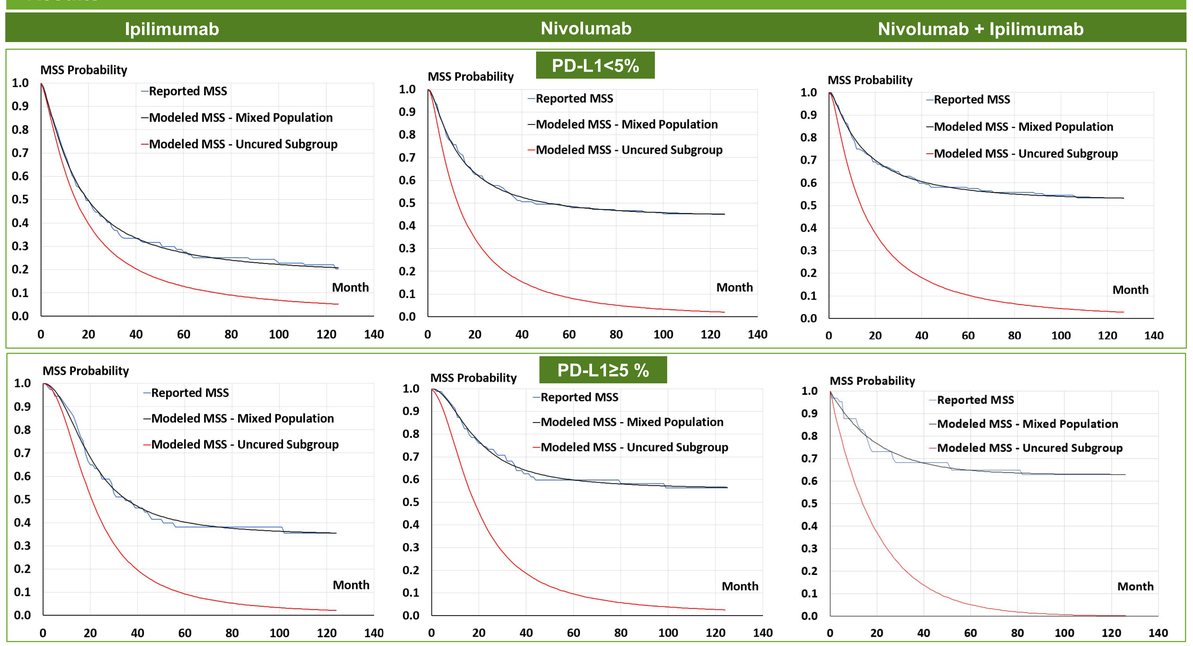
Input Data

- Minimum follow-up in the study was 10 years.
- Patients were classified in PD-L1<5%, PD-L1≥5%, BRAF-Wild Type, and BRAF-Mutant subgroups based on data availability.
- Publicly available Kaplan-Meier (KM) curves for MSS from the Phase III CheckMate-067 study[3] were digitized to reconstruct time-to-event data using the Guyot algorithm[4] for each subgroup.

Modelling

- MCMs were applied to reconstructed MSS data for each subgroup in each arm.
- In the MCMs, patients were classified into two exclusive, latent subpopulations as cured (long-term survivors) and uncured, where cured (uncured) patients were free from (at) the risk of melanoma-related deaths.
- As definition of MSS censors non-melanoma-related deaths, MCMs did not require generation of background mortality rates
- MSS for the uncured was modeled via standard parametric distributions which were characterized simultaneously with LTS rates using maximum likelihood estimation.
- Statistical goodness-of-fit metrics (Akaike Information Criteria [AIC], Bayesian Information Criteria [BIC]), and visual inspection of candidate fits to reported KM curves guided model selection.

Results



PD-L1 Status				
Arm	PD-L1<5%		PD-L1≥5%	
	Best-Fitting MCM	% Cure Fraction (95% CI)	Best-Fitting MCM	% Cure Fraction (95% CI)
Ipilimumab	Loglogistic	16.5 (10.4-25.1)	Loglogistic	34.1 (22.8-44.7)
Nivolumab	Lognormal	43.9 (36.5-51.6)	Loglogistic	55.4 (43.5-66.7)
Nivolumab + Ipilimumab	Lognormal	51.9 (44.4-59.4)	Exponential	63 (50.3-74.1)
BRAF Status				
Arm	BRAF-Mutant		BRAF-Wild Type	
	Best-Fitting MCM	% Cure Fraction (95% CI)	Best-Fitting MCM	% Cure Fraction (95% CI)
Ipilimumab	Loglogistic	20.3 (11.6-33.1)	Loglogistic	15.7 (9.2-25.5)
Nivolumab	Exponential	41 (29.4-52.6)	Exponential	46 (39.3-52.9)
Nivolumab + Ipilimumab	Loglogistic	55 (43.5-65.9)	Loglogistic	47.2 (39.0-55.5)

Results (continued)

- Estimated LTS rates for (PD-L1<5%, PD-L1≥5%) subgroups from the best-fitting MCMs were (16.5%, 34.1%), (43.9%, 55.4%) and (51.9%, 63.0%) in the ipilimumab, nivolumab and nivolumab + ipilimumab arms, respectively.
  - PD-L1+ patients had higher long-term survival benefit from ICIs than PD-L1- patients.
- Estimated LTS rates for (BRAF-Wild Type, BRAF-Mutant) subgroups from the best-fitting models were (15.7%, 20.3%), (46.0%, 41.0%) and (47.2%, 55.0%) in the ipilimumab, nivolumab and nivolumab + ipilimumab arms, respectively.
  - BRAF-Mutant patients had higher long-term survival benefit from ipilimumab-containing regimens than BRAF-Wild Type patients, but lower survival benefit from nivolumab monotherapy
- In all arms, overlapping 95% CIs for LTS rates between the contrasting subgroups (PD-L1<5% vs. PD-L1≥5%; BRAF-Wild Type vs BRAF-Mutant) implied statistical insignificance for biomarkers' impact on estimated LTS rates.
- Estimated median MSS, in months, for the uncured subgroup in (PD-L1<5%, PD-L1≥5%) subpopulations from the best-fitting MCMs were (14.6, 20.6), (12.8, 19.1) and (13.9, 14) in the ipilimumab, nivolumab and nivolumab + ipilimumab arms, respectively.
  - PD-L1+ patients had substantially longer median MSS than PD-L1- patients in the monotherapy arms.
- Estimated median MSS, in months, for (BRAF-Wild Type, BRAF-Mutant) subgroups from the best-fitting MCMs were (15.0, 20.4), (13.0, 23.0) and (12.9, 21.3) in the ipilimumab, nivolumab and nivolumab + ipilimumab arms, respectively.
  - BRAF-Mutant patients had substantially longer median MSS than BRAF-Wild Type patients across all arms.
- With the exception of BRAF-Wild Type subgroup in nivolumab arm and BRAF-Mutant subgroup in nivolumab + ipilimumab arm, across all arms and subgroups, in the selection of best-fitting model according to statistical fit criteria, there was a consensus between AIC and BIC.
- Compared to using OS data, estimation of cure rates from MSS curves is free from potential bias borne by the assumptions in deriving general population mortality rates, allowing for disease-specific interpretations of treatment effects and long-term outcomes.
- Cure rates and MSS curves for the uncured subgroup derived from this analysis had limited applicability for extrapolating long-term OS outcomes from the study and would still require generation of non-melanoma-related mortality rates for their integration into potential cost-effectiveness analyses.

Conclusions

- PD-L1≥5% status had meaningful impact on LTS rates (≥11.1% increase across all arms) whereas BRAF mutation status had relatively more modest impact on LTS rates (≥4.6% increase across ipilimumab containing arms).
- While prior research[2] examined the LTS rates in CheckMate-067 study using 5-year follow-up data, impacts of PD-L1 and BRAF biomarkers on LTS rates have not been explored previously.
- Results highlight clinical importance and predictive value of PD-L1 and BRAF biomarkers in selection of advanced melanoma patients for ICI treatment.

References

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