Indirect estimation of post-distant recurrence survival for resected stage II/III melanoma: a network meta-analysis approach

MSR97

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Background

- Adjuvant immunotherapy represents an important option for patients with completely resected melanoma to prevent recurrence from micrometastatic disease
- In 2023, nivolumab (NIVO; a programmed death [PD]-1 protein inhibitor) was approved by both the European Medicines Agency and the US Food and Drug Administration as an adjuvant therapy for patients with completely resected stage IIB/C melanoma based on results from the phase 3 CheckMate 76K trial (NCT04099251)[1]
  - In CheckMate 76K, nivolumab significantly prolonged recurrence-free survival (hazard ratio [HR], 0.42; 95% CI, 0.30-0.59) and distant metastasis-free survival (HR, 0.47; 95% CI, 0.30-0.72) compared with placebo, with a manageable safety profile[1]
- However, longer follow-up times are needed to evaluate overall survival (OS) which has precluded drawing any conclusions regarding OS in CheckMate 76K to date
  - The lack of OS results represents a key data gap for estimating post-locoregional recurrence and post-distant recurrence survival (PDRS)
    - In addition, there have been very few distant recurrence events to date, which has also precluded estimating PDRS in CheckMate 76K
  - This data gap is present in many adjuvant indications, where OS and PDRS data are often immature, and poses challenges for clinical and economic evaluation of emerging therapies in patients with completely resected melanoma
    - However, there are few approaches for estimating PDRS in the absence of mature OS data and sufficient distant recurrence events

Objective

- The objective of this study was to evaluate a network meta-analysis (NMA)-based approach for predicting PDRS in patients with primary completely resected stage II/III melanoma using data from both a randomized clinical trial (RCT) and a real-world (RW) setting

Methods

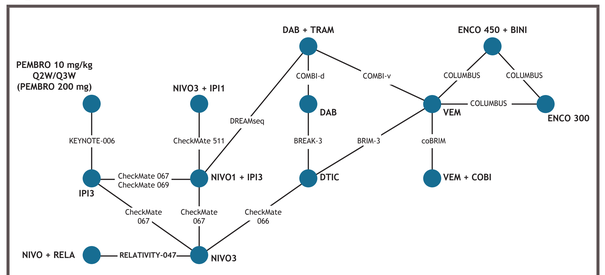
Patient populations

- The RCT dataset was derived from the following 2 trials involving patients who received adjuvant therapy for completely resected stage III/IV melanoma: the CheckMate 238 trial (NCT02388906; which assessed nivolumab versus ipilimumab)[2] and the European Organisation for Research and Treatment of Cancer (EORTC) 18071 trial (NCT00636168; which assessed ipilimumab versus placebo)[3]
  - These trials were selected because they assessed an indication for which patients are expected to have a similar post-recurrence prognosis to those with a primary stage IIB/C melanoma diagnosis (ie, those enrolled in CheckMate 76K)
  - Specifically, this dataset was created using individual patient-level data (IPD) from the nivolumab arm of CheckMate 238 and the placebo arm of EORTC 18071 for those patients that had experienced a distant recurrence after a primary diagnosis of stage IIIA/B/C melanoma (n=232; n=215 for stage IIIB/C only)
    - CheckMate 238 included patients with stage IIIB/C and stage IV disease, of which stage IV patients were excluded for these analyses
    - The EORTC 18071 trial included patients with stage IIIA/B/C disease, of which all patients were included in the base-case; but a scenario was explored only including patients with stage IIIB/C disease
      - American Joint Committee on Cancer, *Cancer Staging Manual* (AJCC) 7th edition criteria were used for staging in these trials, while AJCC 8th edition was used for CheckMate 76K
- In the RW dataset, patients with stage II (n = 311) or stage III (n = 85) disease from the retrospective, Flatiron Health electronic health record (EHR)-derived, de-identified, advanced melanoma database were pooled into 2 cohorts, with stage II and stage III disease only

NMA in first-line (1L) advanced/unresectable melanoma development

- The network for the evidence base chosen for the 1L NMA of approved 1L treatments for metastatic melanoma is shown in **Figure 1**
- The NMA methodology allowed for time-varying HRs, given the proportional hazards assumption was tested and deemed to be violated[4]
  - Standard parametric models were fit to each arm of each treatment in the network, and differences were estimated on the parameters using dacarbazine as the reference treatment
  - Analysis was conducted in a Bayesian framework and required a single standard parametric function to be selected to characterize the entire evidence network
  - Time-varying treatment effects were applied to the reference (dacarbazine; best fitting model according to Akaike information criterion [AIC]) to estimate absolute survival over time for each treatment
  - Model selection was based primarily on AIC, but validated through visual inspection

Figure 1. Evidence base for 1L advanced/unresectable melanoma NMA



BINI, binimetinib 45 mg twice daily; COBI, cobimetinib; DAB, dabrafenib 150 mg twice daily; DTIC, dacarbazine 1000 mg/m²; ENCO 300, encorafenib 300 mg once daily; ENCO 450, encorafenib 450 mg once daily; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PEMBRO, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks; TRAM, trametinib 2 mg once daily; VEM, vemurafenib 960 mg.

Estimation of PDRS

- Once absolute survival over time was estimated for each treatment in the network, PDRS aggregate was calculated based on a weighted average of PDRS of the treatments over a 40-year time horizon
  - The weighting was based on a subsequent treatment distribution separately for the RCT (**Figure 2**) and the RW setting (**Figure 3**)
- Scenarios were explored using stage IIIA/B/C data as well as restriction to only stage IIIB/C data, in which proportions were altered (there were no updates to the data informing the NMA)

Figure 2. Subsequent treatment distribution in CheckMate 238 and EORTC 18071 by stage

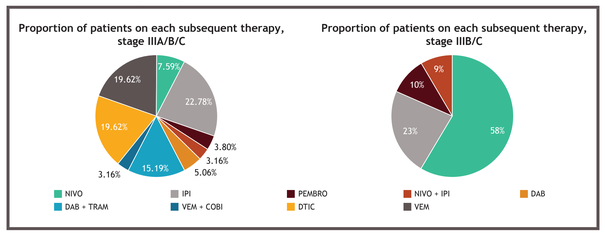
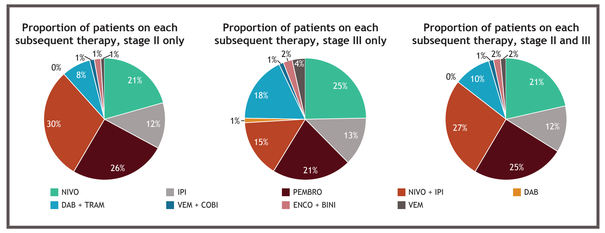


Figure 3. Subsequent treatment distribution in the Flatiron population by stage



Validation of PDRS

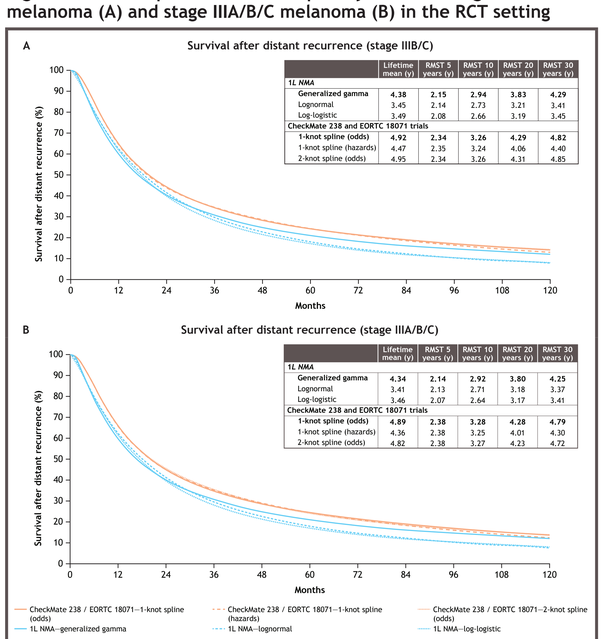
- To validate the estimation of PDRS from the 1L NMA, estimated survival was compared with the IPD from the CheckMate 238 and EORTC 18071 trials, as well as data from the RW setting
- For each dataset, Kaplan-Meier (KM) curves for PDRS were generated using patient-level data; the observed data were then modeled with standard parametric and spline models and model selection was guided by AIC and the visual fit to the generated KM curves; for each dataset and for the sensitivity analysis, the top-3 fitting models were evaluated
- For the validation, restricted mean survival time at multiple follow-up intervals, landmark survival at various time points, and cumulative life-years over the model horizon were compared

Results

Estimation and validation of PDRS in the RCT setting

- For PDRS in the RCT setting, the generalized gamma model was the best fitting model for the NMA (**Figure 4**)
- Mean discounted PDRS projections from the NMA and IPD were 2.84-3.37 and 3.52-3.79 years, respectively, with marginal impact on the results when patients with stage IIIA disease were excluded (**Figure 4**)
  - The NMA was more conservative at all time points
  - There was more variation in the models fit to the NMA compared with the IPD, and extrapolations were most optimistic with the best fitting model; whereas those fit to IPD were similar up to 10 years

Figure 4. PDRS in patients with completely resected stage IIIB/C melanoma (A) and stage IIIA/B/C melanoma (B) in the RCT setting



A	Lifetime mean (y)	RMST 5 years (y)	RMST 10 years (y)	RMST 20 years (y)	RMST 30 years (y)
1L NMA					
Generalized gamma	4.38	2.15	2.94	3.83	4.29
Lognormal	3.45	2.14	2.73	3.21	3.41
Log-logistic	3.49	2.08	2.66	3.19	3.45
CheckMate 238 and EORTC 18071 trials					
1-knot spline (odds)	4.92	2.34	3.26	4.29	4.82
1-knot spline (hazards)	4.47	2.35	3.24	4.06	4.40
2-knot spline (odds)	4.95	2.34	3.26	4.31	4.85

B	Lifetime mean (y)	RMST 5 years (y)	RMST 10 years (y)	RMST 20 years (y)	RMST 30 years (y)
1L NMA					
Generalized gamma	4.34	2.14	2.92	3.80	4.25
Lognormal	3.41	2.13	2.71	3.18	3.37
Log-logistic	3.46	2.07	2.64	3.17	3.41
CheckMate 238 and EORTC 18071 trials					
1-knot spline (odds)	4.89	2.38	3.28	4.28	4.79
1-knot spline (hazards)	4.36	2.38	3.25	4.01	4.30
2-knot spline (odds)	4.82	2.38	3.27	4.23	4.72

Rows in bold indicate best fitting model according to AIC; model time horizon is 40 years.
RMST, restricted mean survival time.

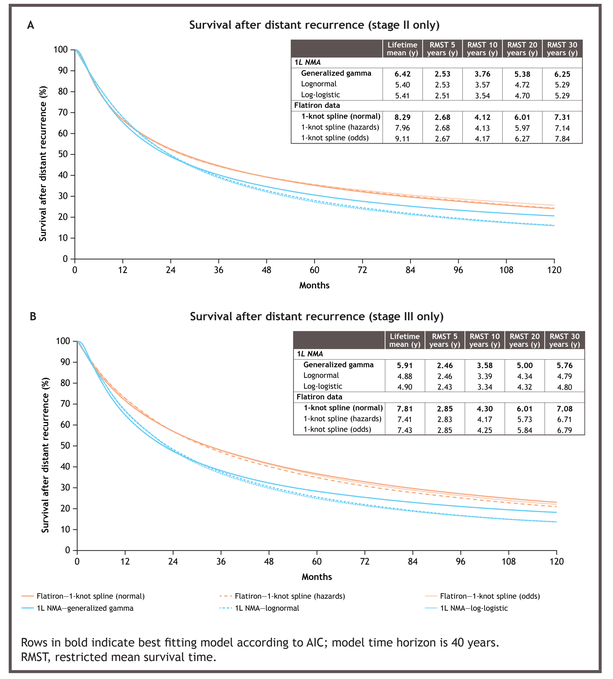
Estimation and validation of PDRS in the RW setting

- In the RW setting, the generalized gamma was the best fitting model for the NMA
- For the RW cohorts, mean discounted PDRS projections from the NMA and IPD were 4.14-4.72 and 5.46-5.94 years, respectively, for patients with stage II disease (**Figure 5A**), and 3.82-4.40 and 5.24-5.48 years, respectively, for patients with stage III disease (**Figure 5B**)
  - The NMA was more conservative at all time points regardless of disease stage, and there was more variation in how the models fit to the NMA compared with the IPD; extrapolations were most optimistic with the best fitting model (**Figure 5**)

Strengths and limitations

- Strengths of this study included the use of both RCT and RW data to comprehensively evaluate the NMA-based approach
- This is also the first analysis of its kind for patients with stage IIB/C or stage III melanoma, which could provide valuable information for clinicians and their patients regarding various types of adjuvant therapy, while OS data remain immature in adjuvant settings
- This study was limited by differences in the characteristics of 2 locally recurrent populations at the time of recurrence that were not addressed before pooling these data
- Another limitation is that the subsequent treatments available to patients enrolled in EORTC 18071 may not reflect the current standard of care
  - Similarly, anti-PD-1 therapy (ie, NIVO) would not have been available as an adjuvant therapy for those enrolled in CheckMate 238 or EORTC 18071
- The approach used in these RW analyses assumed that the type of adjuvant treatment had no impact on PDRS; the impact of specific adjuvant treatments will be examined in future analyses

Figure 5. PDRS in patients with completely resected stage II melanoma (A) and stage III melanoma (B) in the RW setting



A	Lifetime mean (y)	RMST 5 years (y)	RMST 10 years (y)	RMST 20 years (y)	RMST 30 years (y)
1L NMA					
Generalized gamma	6.42	2.53	3.76	5.38	6.25
Lognormal	5.40	2.53	3.57	4.72	5.29
Log-logistic	5.41	2.51	3.54	4.70	5.29
Flatiron data					
1-knot spline (normal)	8.29	2.68	4.12	6.01	7.31
1-knot spline (hazards)	7.96	2.68	4.13	5.97	7.14
1-knot spline (odds)	9.11	2.67	4.17	6.27	7.84

B	Lifetime mean (y)	RMST 5 years (y)	RMST 10 years (y)	RMST 20 years (y)	RMST 30 years (y)
1L NMA					
Generalized gamma	5.91	2.46	3.58	5.00	5.76
Lognormal	4.88	2.46	3.39	4.34	4.79
Log-logistic	4.90	2.43	3.34	4.32	4.80
Flatiron data					
1-knot spline (normal)	7.81	2.85	4.30	6.01	7.08
1-knot spline (hazards)	7.41	2.83	4.17	5.73	6.71
1-knot spline (odds)	7.43	2.85	4.25	5.84	6.79

Rows in bold indicate best fitting model according to AIC; model time horizon is 40 years.
RMST, restricted mean survival time.

Conclusions

- The NMA-based approach provides a conservative, flexible, and scalable framework for estimating PDRS in patients with completely resected stage II/III melanoma in the absence of IPD
- Importantly, projections for PDRS were similar between the NMA-based approach and the IPD in both the RCT and RW settings, underscoring its flexibility
- This NMA-based approach may allow for more in-depth clinical and economic evaluations of future clinical trials of novel agents aimed at treating stage II/III melanoma in the adjuvant setting, for which PDRS estimates often remain premature and unevaluable for many years
- Applying this NMA-approach in lieu of traditional cost-effectiveness models may result in more rapid and informed decision-making by health technology assessment bodies when determining the approval of novel agents for the adjuvant treatment of patients with completely resected stage II/III melanoma

References

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