Treatment-Free Survival in Metastatic Non-Small Cell Lung Cancer Patients Treated With 1L Nivolumab Plus Ipilimumab or Platinum-Doublet Chemotherapy in CheckMate 227

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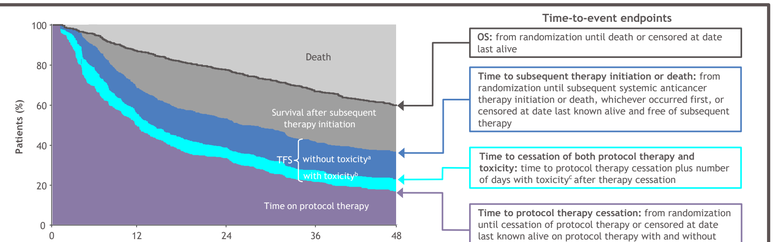
Background

- Immune checkpoint inhibitors elicit distinct patterns of antitumor response[1]
  - However, conventional endpoints, such as progression-free survival (PFS) and overall survival (OS), may not comprehensively address the nuances of immuno-oncology (IO) treatment[2]
- Previous analyses have demonstrated periods of disease control during the off-treatment phase in patients who received IO therapy[2]
  - Treatment-free survival (TFS) is an emerging clinical endpoint that measures the time between treatment cessation and subsequent treatment initiation or death
  - TFS is part of an integrated analysis that comprehensively characterizes how patients spend survival time on and off treatment, with and without treatment-related toxicity
  - Thus, TFS also captures the durability of clinical benefit following treatment discontinuation
- The randomized phase 3 CheckMate 227 Part 1 study (NCT02477826) evaluated first-line treatment with nivolumab plus ipilimumab (NIVO + IPI) versus platinum-doublet chemotherapy (chemo) in patients with metastatic non-small cell lung cancer
  - The study met its primary endpoint in the PD-L1 ≥ 1% population, with prolonged OS observed with NIVO + IPI versus chemo (hazard ratio [HR] 0.79; 97.72% confidence interval [CI], 0.65–0.96)[3]
  - After a minimum follow-up of > 48 months, OS benefit was maintained with NIVO + IPI versus chemo regardless of tumor PD-L1 expression; 4-year OS rates were 27% versus 15% (HR 0.72, 95% CI, 0.63–0.82)[4]
- Here, we present TFS results from CheckMate 227 Part 1 in the all randomized population after a minimum follow-up of 48 months (database lock: February 2021)

Methods

- Analysis included all patients who were randomized to NIVO + IPI (n = 583) or chemo (n = 583) in CheckMate 227 Part 1
  - NIVO 3 mg/kg every 2 weeks + IPI 1 mg/kg every 6 weeks were administered for up to 2 years
  - Chemo was administered every 3 weeks for up to 4 cycles, with optional maintenance for patients with non-squamous histology
  - Treatment continued until disease progression or unacceptable toxicity or, for NIVO + IPI, until a maximum of 2 years
- Restricted mean (*r*-mean) survival was calculated for on- and off-treatment periods, both with and without toxicity. TFS was estimated at the 12-, 24-, 36-, and 48-month landmarks
  - 48-month landmark rates were calculated
- How patients spent OS time during the 48-month period since randomization was characterized by the following calculations (see schematic illustration):
  - Kaplan-Meier (KM) estimates of time-to-event endpoints
  - Areas under each KM curve, estimated by 48-month *r*-mean times of endpoints and expressed as a percentage of the period
  - Areas between KM curves, as 48-month mean times in survival states
  - Between-group differences in mean survival state times, with bootstrapped 95% CIs
- In the schematic illustration, TFS (blue areas) is:
  - Represented by the area between KM curves for 2 time-to-event endpoints defined from randomization: time to protocol therapy cessation and time to subsequent therapy or death
  - Subdivided to represent time spent with (lighter blue) and without (darker blue) toxicity (ie, grade ≥ 3 treatment-related adverse events [TRAEs])
- Time on protocol therapy with and without toxicity (purple area) were computed as the mean number of months on therapy with and without toxicity, respectively. This subdivision is not illustrated as a KM curve in the schema, as toxicities could occur and resolve during the treatment period
- Between-group differences in mean TFS and survival state times were estimated at the 12-, 24-, 36-, and 48-month landmarks

Schematic illustration: Characterization of patients' treatment and survival experience during OS



Areas are restricted mean times. (Adapted from Regan MM, et al. *J Clin Oncol*[2] under Creative Commons License 4.0 [CC BY 4.0].)

[a]Time after cessation of protocol therapy without toxicity (defined as grade ≥ 3 TRAEs), before initiation of subsequent systemic anticancer therapy or death. [b]Time after cessation of protocol therapy with toxicity while treatment-free. [c]Includes toxicity persisting since protocol therapy and toxicity newly presenting after protocol therapy cessation. [d]Time on protocol therapy with toxicity was estimated as the number of days on protocol therapy with grade ≥ 3 TRAEs.

Results

- **Figure 1** summarizes the percentage of patients in TFS and other survival states over the 48-month period since randomization in the NIVO + IPI and chemo arms, revealing different patterns of time spent for each of the treatment arms
  - Estimated mean times over the 48-month period and means as percentages of 48 months are provided in the inset table
  - Differences in mean times between the NIVO + IPI and chemo arms are also provided
- **Figure 2** presents TFS and survival state means as percentages of 48 months (using values from the **Figure 1** inset table), compared with percentages calculated over a 24-month period of follow-up to illustrate changes in survival states with increased follow-up time
- **Figure 3** presents TFS and survival-state differences in mean times between NIVO + IPI and chemo at the 12-, 24-, 36-, and 48-month landmarks
  - In these analyses, mean times with and without toxicity were combined for TFS and for time on protocol therapy
  - These analyses provide insight into treatment-group differences depending on time of analysis and between-treatment differences in TFS and OS

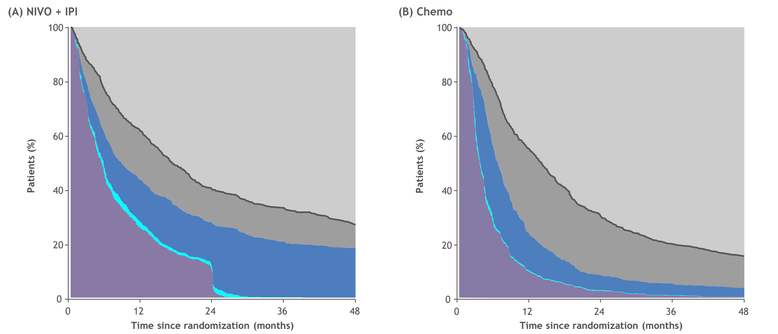
NIVO + IPI versus chemo

- Over the 48-month period since randomization, patients' *r*-mean OS was 23.3 versus 19.1 months for NIVO + IPI versus chemo, respectively (mean difference, 4.2 months; 95% CI, 2.2–6.2) (**Figure 1**, inset table)
- Patients' mean TFS was 8.7 versus 4.4 months for NIVO + IPI versus chemo, respectively (mean difference, 4.3 months; 95% CI, 2.5–6.2) (**Figure 1**, inset table)
  - *r*-mean TFS without toxicity was 8.3 versus 4.3 months (mean difference, 4.0 months; 95% CI, 2.2–5.9)
  - Patients spent 18% versus 9% of the 48-month period in TFS
  - The 48-month TFS rates were 18.4% versus 3.5% in the NIVO + IPI versus chemo arms, respectively
- Overall, the *r*-mean time on protocol therapy was longer with NIVO + IPI versus chemo (8.3 vs 5.6 months; mean difference, 2.7 months [95% CI, 1.9–3.5]) (**Figure 1**, inset table)
- The proportion of time spent in TFS appeared to increase from the 24-month to the 48-month time point in the NIVO + IPI arm (15% to 18%) but appeared to decrease in the chemo arm (14% to 9%) (**Figure 2**)
- The difference in TFS in the NIVO + IPI versus chemo arms was greater when measured over the 48-month period compared with the previous time points, with a steep increase after 24 months, following cessation of NIVO + IPI treatment per protocol (**Figure 3**)

Grade ≥ 3 TRAEs

- Mean TFS with grade ≥ 3 TRAEs constituted a small proportion of the 48-month period: 0.9% with NIVO + IPI and 0.3% with chemo; *r*-mean TFS was 0.4 versus 0.1 months (mean difference, 0.3 months [95% CI, −0.9 to 1.5]) (**Figure 2**)

Figure 1. TFS and survival states over the 48-month follow-up period



Survival state	NIVO + IPI: 48-mo mean time (mo)	NIVO + IPI: Percent of 48-mo period	Chemo: 48-mo mean time (mo)	Chemo: Percent of 48-mo period	Mean difference (95% CI): NIVO + IPI vs chemo (mo)
Overall survival	23.3	48	19.1	40	4.2 (2.2 to 6.2)
Survival after subsequent therapy initiation	6.3	13	9.1	19	−2.8 (−5.4 to −0.2)
TFS	8.7	18	4.4	9	4.3 (2.5 to 6.2)
Without grade ≥ 3 TRAEs	8.3	17	4.3	9	4.0 (2.2 to 5.9)
With grade ≥ 3 TRAEs	0.4	1	0.1	< 1	0.3 (−0.9 to 1.5)
Time on protocol therapy	8.3	17	5.6	12	2.7 (1.9 to 3.5)
Without grade ≥ 3 TRAEs	8.0	17	5.4	11	2.6 (1.8 to 3.4)
With grade ≥ 3 TRAEs	0.3	< 1	0.2	< 1	0.1 (0.02 to 0.2)

Figure 2. Percentage of mean times in TFS state by follow-up period: 24 and 48 months

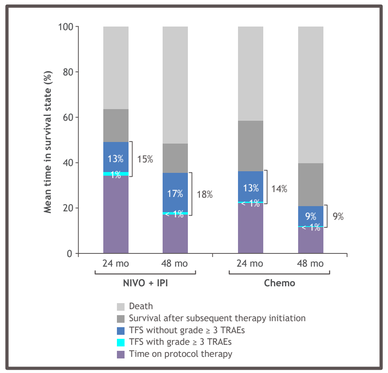
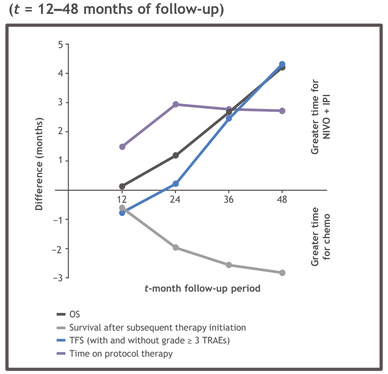


Figure 3. Differences in *t*-month TFS and survival state mean times by analysis time point (*t* = 12–48 months of follow-up)



Conclusions

- In this analysis of CheckMate 227 Part 1, NIVO + IPI conferred longer *r*-mean TFS both with and without toxicity over 48 months when compared with chemo
  - TFS was twice as long with NIVO + IPI versus chemo, due to continued benefit following treatment cessation
  - The sustained long-term OS benefit previously observed with NIVO + IPI versus chemo[4] was accompanied by sustained TFS
- The majority of TFS time was spent without grade ≥ 3 TRAEs in both treatment arms
- Difference in time spent in TFS between treatment arms appears to increase with extended follow-up, particularly after the 2-year time point (maximum duration of NIVO + IPI treatment)
- Given longer OS with dual immunotherapy (and durable responses after cessation of therapy) relative to a chemotherapy-based regimen,[2,4] this comprehensive analysis of CheckMate 227 Part 1 establishes the importance of assessing the quality of OS time to capture patient experiences more completely
  - Furthermore, TFS analyses (vs the conventional endpoints of PFS and OS) may provide additional clinical insights when investigating regimens with a defined therapy duration

References

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