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Exposure-response analysis for nivolumab + ipilimumab combination therapy in patients with advanced hepatocellular carcinoma (CheckMate 040)

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Introduction

- Optimal benefit-risk profiles in different indications have been achieved with different nivolumab (NIVO) plus ipilimumab (IPI) combination regimens
- A flat dose-response relationship was observed for NIVO monotherapy in patients with non-small cell lung cancer, melanoma, and renal cell carcinoma within a 1 to 10 mg/kg dose range[1]
- A positive dose-response relationship was observed for IPI monotherapy in patients with melanoma within a 0.3 to 10 mg/kg dose range[2]
- Of the 3 regimens evaluated in CheckMate 040 (NCT01658878),[3] the NIVO 1 mg/kg + IPI 3 mg/kg (NIVO1+IPI3) Q3W regimen provided the most favorable outcomes, with an objective response rate (ORR) of 32% and median overall survival (OS) of 22.8 months
  - For the other 2 regimens, ORR was 31% in each arm and median OS was 12.5 months in the NIVO 3 mg/kg + IPI 1 mg/kg (NIVO3+IPI1) Q3W arm and 12.7 months in the NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W (NIVO3 Q2W + IPI1 Q6W) arm
- The NIVO1+IPI3 Q3W regimen is approved in the United States to treat advanced hepatocellular carcinoma (aHCC) in patients previously treated with sorafenib
- The objective of this analysis was to investigate the relationship between the intensity of NIVO and IPI exposure and clinical outcomes to identify the dosing regimen that provides the most favorable benefit-risk profile in patients with aHCC

Methods

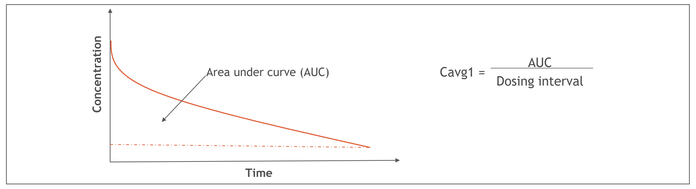
CheckMate 040 NIVO plus IPI cohort study design and patient population

- Key eligibility criteria included aHCC; sorafenib treated intolerant or progressors; uninfected, hepatitis C virus infected, or hepatitis B virus infected; Child-Pugh score A5 or A6; Eastern Cooperative Group performance status 0 or 1
- Primary endpoints were safety and tolerability (using National Cancer Institute Common Terminology Criteria for Adverse Events v4.0), ORR (using Response Evaluation Criteria in Solid Tumors v1.1), and duration of response based on investigator assessment
- At the data cutoff of January 19, 2019, the minimum follow-up was 28 months

Exposure parameters

- Average NIVO and IPI concentrations after the first dose (Cavg1) were derived across the regimens through a population pharmacokinetic analysis **(Figure 1)**

Figure 1. Calculation of NIVO and IPI Cavg1



- Cavg1 was treated as a continuous variable or categorical variable for exposure-response analyses
  - When Cavg1 was treated categorically, the median IPI Cavg1 was used as a cutoff to differentiate high-IPI and low-IPI exposure groups in the NIVO1+IPI3 arm (above or below the median) to compare clinical outcomes

Clinical endpoints

- Efficacy endpoints evaluated in this analysis in relation to NIVO and IPI exposures were ORR by blinded independent central review and OS
  - Odds ratios (ORs) for associations between ORR and NIVO and IPI exposures were derived using multivariate logistic regression
  - Hazard ratios (HRs) for associations between OS and NIVO and IPI exposures were derived from Cox proportional-hazards models
- Safety endpoints evaluated in relation to IPI exposure included any-grade and grade 3-4 hepatic treatment-related adverse events (TRAEs) and any-grade and grade 3–4 immune-mediated adverse events (IMAEs)

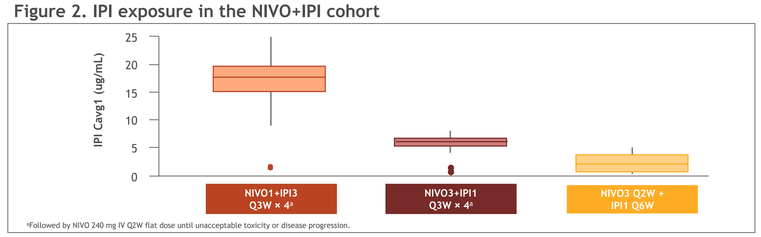
Results

- This analysis included patients who randomly received NIVO1+IPI3 Q3W (n = 49), NIVO3+IPI1 Q3W (n = 49), or NIVO3 Q2W + IPI1 Q6W (n = 48)

IPI exposure

- Increases in IPI dose and treatment frequency were associated with increases in IPI exposure **(Figure 2)**
- There was no overlap in IPI exposure between the different NIVO+IPI regimens; moreover, Cavg1 in the low-IPI exposure group in the NIVO1+IPI3 arm was higher than Cavg1 in the higher-IPI exposure levels in the other 2 arms **(Figure 2)**

Figure 2. IPI exposure in the NIVO+IPI cohort



Efficacy endpoints and exposure

- In patients across all treatment arms, improvements in ORR and OS were associated with increases in IPI exposure but not increases in NIVO exposure **(Figure 3A, Figure 4A)**
- In the NIVO1+IPI3 treatment arm, response appeared to be independent of IPI exposure, whereas, in the other treatment arms, there was a higher frequency of responders at higher IPI exposure levels (Figure 3B)
- The greatest OS benefit was observed in the high-IPI exposure group of the NIVO1+IPI3 Q3W treatment arm **(Figure 4B)**

Figure 3. Relationship between NIVO and IPI exposure and response

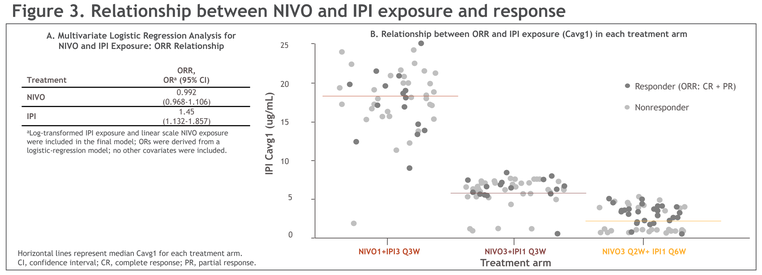
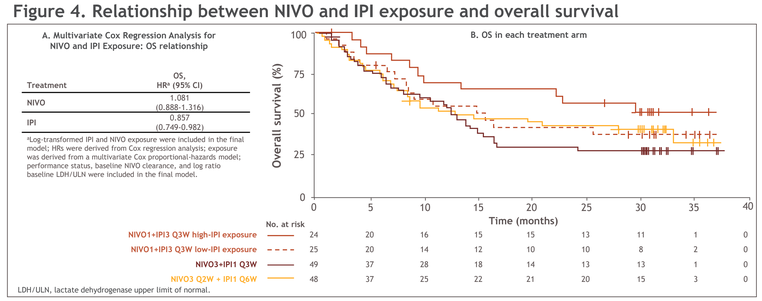


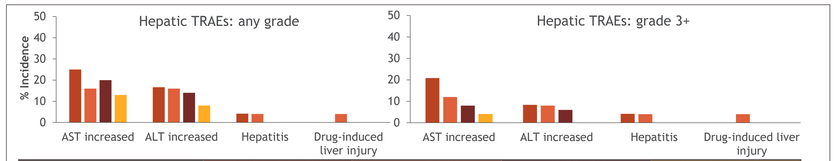
Figure 4. Relationship between NIVO and IPI exposure and overall survival



Safety endpoints and exposure

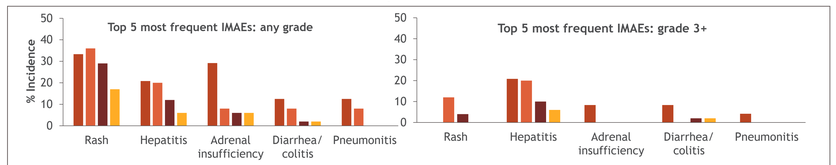
- Hepatic TRAEs occurred regardless of IPI exposure level **(Table 1)**
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increases were reported for similar proportions of patients in the high-IPI and low-IPI exposure groups
- The most frequent IMAEs of any grade were rash, hepatitis, adrenal insufficiency, diarrhea/colitis, and pneumonitis **(Table 2)**
- Of the 5 most frequent IMAEs
  - Incidence of any-grade rash and hepatitis was similar in patients with high-IPI and low-IPI exposure
  - Incidence of any-grade and grade 3-4 adrenal insufficiency, diarrhea/colitis, and pneumonitis were more frequent with high-IPI exposure than with low-IPI exposure
- IMAEs occurred regardless of IPI exposure level

Table 1. Association between hepatic TRAEs and IPI exposure



System organ class, n (%)	NIVO1+IPI3 Q3W high-IPI exposure n = 24		NIVO1+IPI3 Q3W low-IPI exposure n = 25		NIVO3+IPI1 Q3W n = 49		NIVO3 Q2W+IPI1 Q6W n = 48	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
AST increased	6 (25)	5 (21)	4 (16)	3 (12)	10 (20)	4 (8)	6 (13)	2 (4)
ALT increased	4 (17)	2 (8)	4 (16)	2 (8)	7 (14)	3 (6)	4 (8)	0
Hepatitis	1 (4)	1 (4)	1 (4)	1 (4)	0	0	0	0
Drug-induced liver injury	0	0	1 (4)	1 (4)	0	0	0	0

Table 2. Association between IMAEs and IPI exposure



System organ class, n(%)	NIVO1+IPI3 Q3W high-IPI exposure n = 24		NIVO1+IPI3 Q3W low-IPI exposure n = 25		NIVO3+IPI1 Q3W n = 49		NIVO3 Q2W+IPI1 Q6W n = 48	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Rash	8 (33)	0	9 (36)	3 (12)	14 (29)	2 (4)	8 (17)	0
Hepatitis	5 (21)	5 (21)	5 (20)	5 (20)	6 (12)	5 (10)	3 (6)	3 (6)
Adrenal insufficiency	7 (29)	2 (8)	2 (8)	0	3 (6)	0	3 (6)	0
Diarrhea/colitis	3 (13)	2 (8)	2 (8)	0	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis	3 (13)	1 (4)	2 (8)	0	0	0	0	0

Conclusions

- We observed a positive association between OS and IPI exposure but not NIVO exposure
- The greatest OS benefit was seen with high-IPI exposures among patients who received NIVO1+IPI3 Q3W
- In the NIVO1+IPI3 Q3W arm, ORR benefit was seen regardless of IPI exposure level
- IMAEs of adrenal insufficiency, diarrhea/colitis, and pneumonitis occurred in a higher proportion of patients in the high-IPI exposure group of the NIVO1+IPI3 arm compared with other treatment arms, while the incidence of rash and hepatitis were generally similar in the NIVO1+IPI3 high-IPI and low-IPI exposure groups
- Incidence of AST and ALT increases were generally similar in both IPI exposure groups of the NIVO1+IPI3 arm and in the NIVO3+IPI1 Q3W arm despite differences in IPI exposure, suggesting that there may be risk factor(s) other than IPI exposure
- Findings from the exploratory exposure response analyses support the NIVO1+IPI3 Q3W combination regimen as offering the most favorable benefit-risk profile for the second-line treatment of patients with aHCC

References

1. Feng Y, et al. *Clin Cancer Res* 2017;23:5394-5405.
2. Feng Y, et al. *Clin Cancer Res* 2013;19:3977-3986.
3. Yau T, et al. *J Clin Oncol* 2019;37(15 suppl):4012-4012.

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