Evaluation of flat dosing for nivolumab + ipilimumab in first-line unresectable malignant pleural mesothelioma: CheckMate 743

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*Study performed while at Bristol Myers Squibb.

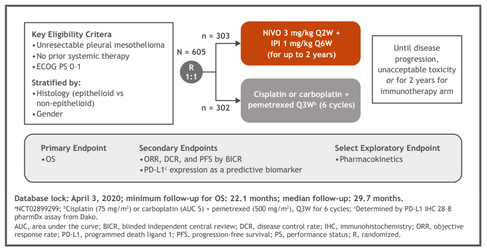
Introduction

- CheckMate 743 is the first positive randomized trial of dual immunotherapy where a significant improvement in overall survival (OS) was observed with nivolumab (NIVO) + ipilimumab (IPI) vs chemo in first-line (1L) unresectable malignant pleural mesothelioma (MPM)
  - Patients in the NIVO plus IPI arm received NIVO 3 mg/kg every 2 weeks (Q2W) plus IPI 1 mg/kg every 6 weeks (Q6W)[1]
- These results led to the approval of NIVO + IPI as 1L treatment of patients with unresectable MPM in the USA[2]
  - The approval for 1L treatment of MPM includes flat-dose NIVO 360 mg every 3 weeks (Q3W) in combination with IPI 1 mg/kg Q6W based on pharmacometric and CheckMate 743 clinical subgroup analyses[2]
  - Similar analyses have supported approval of flat-dose NIVO monotherapy for multiple tumor types by various health authorities[3]
- Here we present results from pharmacometric and clinical subgroup analyses by body weight which were used to support flat-dose NIVO in combination with IPI for the 1L treatment of patients with MPM
  - Subgroup analysis by body weight was performed to assess any potential associations between body weight with efficacy or safety of NIVO + IPI, with focus on higher body weight for efficacy and lower body weight for safety

Methods

- Adult patients with previously untreated unresectable MPM were enrolled (**Figure 1**)

Figure 1. CheckMate 743 study design[a]



Database lock: April 3, 2020; minimum follow-up for OS: 22.1 months; median follow-up: 29.7 months.

[a]NCT02899299; [b]Cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2), Q3W for 6 cycles; [c]Determined by PD-L1 IHC 28-8 pharmDx assay from Dako.

AUC, area under the curve; BICR, blinded independent central review; DCR, disease control rate; IHC, immunohistochemistry; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; PS, performance status; R, randomized.

Pharmacometric analyses

- Previous model-informed analyses of predicted exposures, exposure-response (E-R) efficacy and safety data from clinical studies were used to predict the benefit-risk profile of flat vs weight-based dosing of NIVO
- Based on a previously developed population pharmacokinetics model,[3,4] mean NIVO exposures were predicted for patients in the CheckMate 743 trial for the combination of IPI 1 mg/kg Q6W with:
  - NIVO 3 mg/kg Q2W
  - NIVO 240 mg Q2W
  - NIVO 360 mg Q3W
- Key summary measures (see definitions in footnote to **Table 2**) of exposure after first dose (Cmax1, Cmin1, and Cavg1) and at steady-state (Cavgss, Cmaxss, and Cminss) were calculated using the simulations of concentration-time profiles
- E-R efficacy and safety were evaluated by characterizing the relationships between simulations of NIVO exposure and OS or grade ≥ 2 immune-mediated adverse events (grade 2+ IMAEs), respectively, using the multivariate Cox proportional-hazard model
- Baseline covariates for E-R efficacy and safety analyses included:
  - Continuous: age, body weight, albumin, baseline tumor size, and lactate dehydrogenase
  - Categorical: sex, performance status, disease stage, smoking status, and histology

Clinical subgroup analyses

- OS was analyzed for clinical subgroups based on baseline body weight categories (< 60 kg, ≥ 60 to < 70 kg, ≥ 70 to < 80 kg, and ≥ 80 kg) for patients with previously untreated unresectable MPM from the CheckMate 743 trial
- Safety analyses based on baseline body weight categories included grade 2+ IMAEs, grade 3–4 adverse events (AEs), and serious AEs (SAEs)

Results

Patients

- Baseline characteristics for the treatment arms and across body weight categories are presented in **Table 1**
  - Numerical differences were observed for a few baseline characteristics (eg, sex, histology, ECOG PS, PD-L1 expression) across body weight categories
- Patients in the NIVO + IPI arm had a median body weight of 72 kg (range, 40–123 kg)

Table 1. Demographics and baseline disease characteristics by body weight (CheckMate 743)

	All randomized		< 60 kg		≥ 60 to < 70 kg		≥ 70 to < 80 kg		≥ 80 kg	
	NIVO + IPI (n = 303)	Chemo (n = 302)	NIVO + IPI (n = 56)	Chemo (n = 56)	NIVO + IPI (n = 76)	Chemo (n = 86)	NIVO + IPI (n = 78)	Chemo (n = 63)	NIVO + IPI (n = 90)	Chemo (n = 79)
Age, median (range), years	69 (32-85)	69 (25-89)	70 (32-82)	68 (25-83)	69 (47-85)	70 (30-87)	70 (42-81)	72 (47-89)	69 (41-83)	69 (39-83)
Male, %	77	77	54	50	70	78	85	84	92	92
ECOG PS,[a] %										
0	38	42	45	45	26	36	33	46	47	46
1	62	57	55	55	74	64	67	52	53	54
Smoking status,[b] %										
Never	42	40	46	39	43	52	49	38	30	32
Current / former	57	57	54	61	57	44	50	57	68	67
Tumor histology, %										
Epithelioid	76	75	75	84	83	70	81	71	64	75
Non-epithelioid	24	25	25	16	17	30	19	29	36	25
PD-L1 quantifiable at baseline,[c] n	289	297	54	55	72	84	75	61	85	79
< 1%,[d] %	20	26	15	27	25	24	27	25	13	33
≥ 1%,[d] %	80	74	85	73	75	76	73	75	87	67

[a]ECOG PS ≥ 2 for < 1% of patients in the chemo arm of the all-randomized population. ECOG PS ≥ 2 for 2% of patients in the chemo arm of the subgroup ≥ 70 to < 80 kg; [b]Unknown for 1% (NIVO + IPI) and 3% (chemo) of patients in the all-randomized population. Unknown for 4% (chemo) of patients in the subgroup ≥ 60 to < 70 kg. Unknown for 1% (NIVO + IPI) and 5% (chemo) of patients in the subgroup ≥ 70 to < 80 kg. Unknown for 2% (NIVO + IPI) and 1% (chemo) of patients in the subgroup ≥ 80 kg; [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [d]Based on PD-L1 quantifiable at baseline; for all randomized 95% and 98% of patients in the NIVO + IPI and chemo arms, respectively.

Population pharmacokinetics

- The NIVO exposure simulations were similar (≤ 20% difference) for Cmin1, Cminss, and Cavgss or higher (> 20% difference) for Cavg1, Cmax1, and Cmaxss with NIVO 360 mg Q3W relative to NIVO 3 mg/kg Q2W in combination with IPI 1 mg/kg Q6W (**Table 2**)
  - Greatest difference was observed with Cmax1 (peak serum concentration after the first dose; 67.4% higher with 360 mg Q3W)
  - However, this was ~82% below the median Cmaxss when administered as NIVO 10 mg/kg Q2W, a dosing regimen previously demonstrated to be safe and well tolerated

Table 2. Population pharmacokinetics predicted exposures for weight-based and flat-dose NIVO in combination with IPI

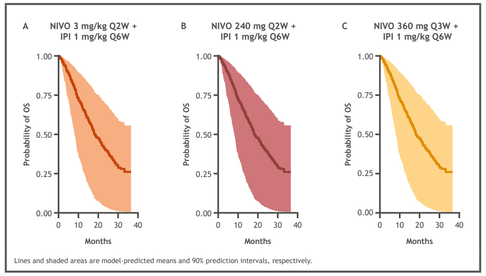
Summary exposure,[a] µg/mL	GM (% CV)			Percent difference GM G2 – G1[b]	Percent difference GM G3 – G1[c]
	NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W	NIVO 240 mg Q2W + IPI 1 mg/kg Q6W	NIVO 360 mg Q3W + IPI 1 mg/kg Q6W		
Cmax1	55.6 (18.3)	62.1 (21.6)	93.1 (21.6)	11.7	67.4
Cmin1	13.7 (27.0)	15.3 (27.9)	16.0 (33.2)	11.7	16.8
Cavg1	23.8 (19.4)	26.6 (20.9)	33.1 (22.4)	11.8	39.1
Cmaxss	114.0 (26.2)	127.0 (25.5)	151.0 (24.1)	11.4	32.5
Cminss	56.6 (39.1)	63.2 (37.3)	55.8 (40.2)	11.7	−1.41
Cavgss	74.9 (32.8)	83.7 (31.1)	83.7 (31.1)	11.7	11.7

[a]Geometric mean exposures were predicted for 297 patients with MPM in the CheckMate 743 study; [b]Percent difference in geometric mean of 240 mg Q2W (G2) relative to 3 mg/kg Q2W (G1); [c]Percent difference in geometric mean of NIVO 360 mg Q3W (G3) relative to NIVO 3 mg/kg Q2W (G1). Cavg1, NIVO concentration over the first dosing interval (Cavg1 is equivalent to Cavgd14 for Q2W and Cavgd21 for Q3W); Cmax1, maximum NIVO serum concentration after the first dose; Cmin1, trough concentration after the first NIVO dose (Cmin1 is equivalent to Cmind14 for Q2W and Cmind21 for Q3W); CV, coefficient of variation; GM, geometric mean; SS, steady state.

E-R efficacy and safety analyses

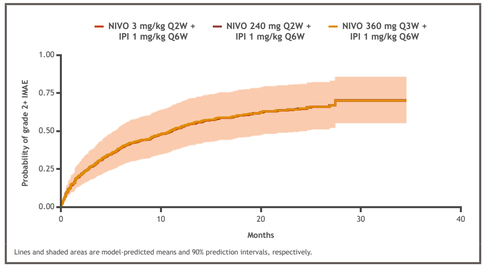
- Model-predicted mean probabilities of OS using the predicted averaged serum concentration after the first dose (Cavg1) were similar for NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W and NIVO 360 mg Q3W + IPI 1 mg/kg Q6W (**Figure 2**)
- Model-predicted mean probabilities of grade 2+ IMAEs using the predicted daily averaged concentration were similar for NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W and NIVO 360 mg Q3W + IPI 1mg/kg Q6W (**Figure 3**)

Figure 2. E-R predicted mean probability of OS



Lines and shaded areas are model-predicted means and 90% prediction intervals, respectively.

Figure 3. E-R predicted mean probability of grade 2+ IMAEs

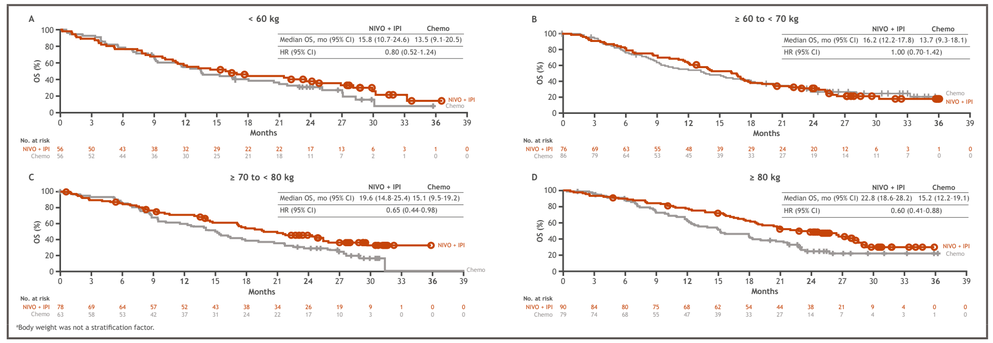


Lines and shaded areas are model-predicted means and 90% prediction intervals, respectively.

Clinical efficacy and safety by body weight categories

- The trend observed for OS benefit with NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W) was not different across body weight categories (**Figure 4**); however, these results should be interpreted with caution as body weight was not a stratification factor
- No worsening of toxicity was observed in lower body weight categories (**Table 3**)
  - A numerical increase in incidence in hepatitis and hypothyroidism/thyroiditis was observed in the highest body weight category
- Safety endpoints by body weight categories were not assessed for patients who received chemo

Figure 4. OS based on baseline body weight categories[a]



[a]Body weight was not a stratification factor.

Table 3. Safety with NIVO + IPI based on baseline body weight categories (CheckMate 743)

Patients with AE, n (%)	< 60 kg (n = 56)	≥ 60 to < 70 kg (n = 76)	≥ 70 to < 80 kg (n = 78)	≥ 80 kg (n = 90)	Total (N = 300)
Grade 3-4 AEs	27 (48)	40 (53)	40 (51)	52 (58)	159 (53)
95% CI	35-62	41-64	40-63	47-68	-
All SAEs	33 (59)	37 (49)	44 (56)	50 (56)	164 (55)
95% CI	45-72	37-60	45-68	45-66	-
Grade 2+ IMAEs					
Pneumonitis	4 (7)	3 (4)	6 (8)	6 (7)	19 (6)
Diarrhea/colitis	6 (11)	5 (7)	7 (9)	5 (6)	23 (8)
Hepatitis	2 (4)	2 (3)	4 (5)	9 (10)	17 (6)
Nephritis/renal dysfunction	1 (2)	2 (3)	0	3 (3)	6 (2)
Rash	3 (5)	9 (12)	5 (6)	8 (9)	25 (8)
Hypersensitivity	1 (2)	0	1 (1)	2 (2)	4 (1)
Adrenal insufficiency	1 (2)	0	3 (4)	3 (3)	7 (2)
Hypothyroidism/ thyroiditis	2 (4)	1 (1)	2 (3)	12 (13)	17 (6)
Diabetes mellitus	0	0	0	1 (1)	1 (< 1)
Hyperthyroidism	0	0	2 (3)	0	2 (1)
Hypophysitis	3 (5)	3 (4)	3 (4)	1 (1)	10 (3)

Discussion and limitations

Discussion

- With higher exposures (Cmax1, Cmin1, Cavg1, Cmaxss, Cavgss) or similar (Cminss) for NIVO 360 mg Q3W vs NIVO 3 mg/kg Q2W in combination with IPI 1 mg/kg Q6W, efficacy is not expected to be compromised with the flat-dose regimen
- Efficacy in patients with higher body weight (≥ 80 kg) was not compromised compared to those with lower body weight (< 60 kg)
- Subgroup analysis by baseline body weight showed a similar safety profile in patients regardless of body weight. No additional safety concerns were seen in patients with lower body weight

Limitations

- Clinical subgroup analysis by baseline body weight was a post hoc analysis and is descriptive in nature
- Baseline body weight subgroups had a limited sample size (n = 56–90)
- Body weight was not a stratification factor in CheckMate 743 and potential imbalances in known or unknown prognostic factors could influence outcomes

Conclusions

- Model-predicted mean probabilities for OS and grade 2+ IMAEs were comparable between NIVO 360 mg Q3W, 240 mg Q2W, and 3 mg/kg Q2W, in combination with IPI 1 mg/kg Q6W
- Clinical subgroup analysis from CheckMate 743 showed that survival was not compromised in patients with higher body weight
- Conversely, no additional safety concerns were observed in patients with lower body weight
- The subgroup analysis was post hoc, descriptive, and limited by small sample size
- Overall these results suggest that the benefit-risk of flat-dose NIVO + IPI regimens evaluated here could be comparable with NIVO 3 mg/kg Q2W + IPI, supporting alternative dosing regimens in patients with previously untreated, unresectable MPM

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Disclosures

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