Survival of responders to nivolumab + ipilimumab as first-line treatment for advanced NSCLC in CheckMate 227 Part 1

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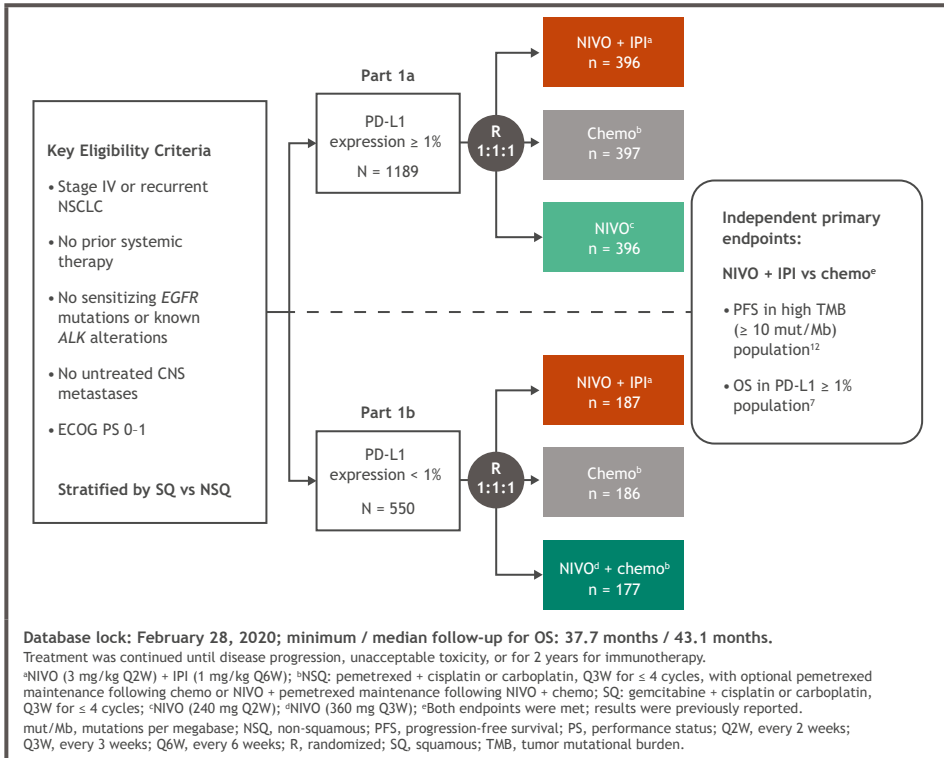
Introduction

- Dual immunotherapy with nivolumab (NIVO) in combination with ipilimumab (IPI), which have distinct but complementary mechanisms of action, has improved long-term survival in patients with melanoma, renal cell carcinoma, malignant pleural mesothelioma, and non-small cell lung cancer (NSCLC)[1-6]
- In the randomized, phase 3 CheckMate 227 Part 1 study, first-line (1L) NIVO + IPI significantly improved overall survival (OS) vs chemo in patients with advanced NSCLC and tumor programmed death ligand-1 (PD-L1) expression ≥ 1% (a primary endpoint) and < 1% (prespecified descriptive analysis)[7]
- NIVO + IPI is approved in the USA as a chemo-free 1L treatment option for adult patients with metastatic NSCLC expressing PD-L1 ≥ 1%, with no *EGFR* or *ALK* genomic tumor aberrations[8]
  - This regimen is also recommended by National Comprehensive Cancer Network and European Society for Medical Oncology guidelines for the treatment of patients regardless of PD-L1 expression[9,10]
- With 3-years' minimum follow-up, 1L NIVO + IPI continued to provide durable and long-term efficacy benefits vs chemo, regardless of PD-L1 expression[11]
  - In an exploratory post-landmark analysis, patients who achieved a complete or partial response (CR/PR) at 6 months had marked OS benefit with NIVO + IPI vs chemo[11]
- Here we present an exploratory analysis describing OS and safety outcomes in patients treated with NIVO + IPI, NIVO, NIVO + chemo, and chemo by response categories and depth of response

Methods

- In CheckMate 227 Part 1 (NCT02477826), adult patients with previously untreated stage IV or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations were enrolled (Figure 1)

Figure 1. CheckMate 227 Part 1 study design

Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.
Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy.
[a]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [b]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; SQ: gemcitabine + cisplatin or carboplatin, Q3W for ≤ 4 cycles; [c]NIVO (240 mg Q2W); [d]Both endpoints were met; results were previously reported.
mut/Mb, mutations per megabase; NSQ, non-squamous; PFS, progression-free survival; PS, performance status; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomized; SQ, squamous; TMB, tumor mutational burden.

- Best overall responses (BOR) were assessed by blinded independent central review (BICR) using RECIST v1.1
  - Patients were categorized as responders (CR/PR) or non-responders (stable disease [SD] or progressive disease [PD])
  - Responders were further grouped by depth of best change from baseline in tumor burden (30 to < 50%, 50 to < 80%, and ≥ 80% reduction) for an exploratory analysis assessing OS by best response and tumor burden reduction
  - The proportion of patients with a response for each tumor burden reduction category was calculated as a percentage of evaluable patients in each treatment arm
- Hazard ratios (HRs) for OS between responders vs non-responders were estimated using a Cox proportional-hazard model with time to tumor reduction category as a time-dependent covariate to account for the difference in time taken to reach a given response

Results

Patients

- Baseline characteristics for responders were generally balanced between treatment arms, and were also consistent with the all randomized population (NIVO + IPI and chemo, Table 1; NIVO monotherapy [PD-L1 ≥ 1%] and NIVO + chemo [PD-L1 < 1%], data not shown)
  - There were no notable differences in baseline characteristics between responders and non-responders

Table 1. Baseline characteristics by response in all randomized patients (PD-L1 ≥ 1% and < 1%)

	All randomized[a]		Responders (CR/PR)		Patients with SD		Patients with PD	
	NIVO + IPI (n = 583)	Chemo (n = 583)	NIVO + IPI (n = 195)	Chemo (n = 163)	NIVO + IPI (n = 187)	Chemo (n = 286)	NIVO + IPI (n = 135)	Chemo (n = 74)
Age, median (range), years	64 (26-87)	64 (29-87)	65 (31-84)	66 (29-87)	63 (26-87)	64 (30-87)	63 (32-79)	62 (39-78)
Female	33	34	28	37	35	35	37	23
ECOG PS[b]								
0	35	33	40	42	36	30	30	30
1	65	66	60	58	63	69	69	66
Smoking status[c]								
Smoker	85	86	91	86	80	83	84	93
Never smoker	14	13	8	14	18	16	15	7
Histology								
SQ	28	28	30	25	27	31	29	23
NSQ	72	72	70	75	73	69	71	77
Tumor PD-L1 expression								
< 1%	32	32	26	26	39	34	33	32
≥ 1%	68	68	74	74	61	66	67	68
1-49%	33	33	26	32	37	40	34	31
≥ 50%	35	33	48	42	24	27	33	36

Data as % unless otherwise noted.
[a]Not evaluable for response: NIVO + IPI, n = 66; chemo, n = 60; [b]ECOG PS ≥ 2 for ≤ 1% of patients in the NIVO + IPI arm, including 1 patient with SD and 1 patient with PD and 1% in the chemo arm, including 1 patient with SD and 3 patients with PD, and not reported for < 1% of patients in the chemo arm of the all-randomized population; [c]Unknown for 1% of patients in each treatment arm in the all-randomized population, 1% of patients including 2 responders, 4 patients with SD, and 1 patient with PD in the NIVO + IPI arm, and 4 patients with SD in the chemo arm.

Subsequent systemic therapy

- Among patients who responded (CR or PR as BOR), then had disease progression, 62/134 (46%) in the NIVO + IPI arm and 103/154 (67%) in the chemo arm received subsequent systemic therapy; 19% and 56% received subsequent immunotherapy, respectively
- Among patients who had SD as BOR, then had disease progression, 84/181 (46%) in the NIVO + IPI arm and 165/278 (59%) in the chemo arm received subsequent systemic therapy; 5% and 43% received subsequent immunotherapy, respectively
- Among patients with PD as BOR, 65/134 (48%) in the NIVO + IPI arm and 38/74 (51%) in the chemo arm received subsequent systemic therapy; 4% and 39% received subsequent immunotherapy, respectively

Efficacy

- Among all randomized patients (PD-L1 ≥ 1% and < 1%), ORR was 195/583 (33%) in the NIVO + IPI arm vs 163/583 (28%) in the chemo arm
  - In patients with PD-L1 ≥ 1%, ORR was 144/396 (36%) with NIVO + IPI, 109/396 (28%) with NIVO, and 120/397 (30%) with chemo; in patients with PD-L1 < 1%, ORR was 51/187 (27%) with NIVO + IPI, 66/177 (38%) with NIVO + chemo, and 43/186 (23%) with chemo[11]
- Responders to NIVO + IPI achieved greater depths of tumor burden reduction than responders to chemo, regardless of PD-L1 expression level (Figure 2A, Figure 3A)
- OS was longer in responders than in non-responders with PD-L1 ≥ 1% (Figure 2B), and PD-L1 < 1% (Figure 3B) regardless of the treatment arm
  - Patients with greater depths of response had longer OS with both NIVO + IPI and chemo (although patient numbers were small in some subgroups). This correlation was more pronounced with NIVO + IPI treatment than chemo
- In PD-L1 ≥ 1%, patients treated with NIVO + IPI achieved deeper responses than those treated with NIVO, and the depth of response with NIVO + IPI or NIVO were both associated with longer OS (Figure 2)
- In PD-L1 < 1%, patients treated with NIVO + chemo had a higher response rate, but deeper responses with NIVO + IPI were associated with longer OS, which was not clearly observed with NIVO + chemo or chemo (Figure 3)

Safety

- Median duration of treatment (mDOT) was 4.2 months for the NIVO + IPI arm and 2.6 months for the chemo arm in all randomized patients and, as expected, was longer for those who were responders (12.6 months and 5.3 months, respectively)
  - In patients with SD, mDOT was 4.5 months with NIVO + IPI and 2.8 months with chemo, but was similar for both treatment arms in patients with PD (1.5 and 1.4 months, respectively)
- The exposure-adjusted incidence of treatment-related adverse events (TRAEs) was lower with NIVO + IPI than with chemo in responders and non-responders (Table 2), in contrast to the previously reported overall similar incidence rate (IR) of TRAEs with NIVO + IPI and chemo for the all-treated population[7]
  - Similar results were observed in the PD-L1 ≥ 1% and the PD-L1 < 1% populations
- The exposure-adjusted incidence of TRAEs with NIVO monotherapy (PD-L1 ≥ 1%) in responders, patients with SD, and those with PD were 299.9, 391.7, and 392.4 per 100 person-years (P-Y), respectively
- For patients treated with NIVO + chemo (PD-L1 < 1%), these were 810.3, 981.7, and 1682.9 per 100 P-Y, respectively
- In the NIVO + IPI arm, the exposure-adjusted incidence of treatment-related select adverse events (AEs) in responders and non-responders was generally consistent with the incidence in all treated patients (Figure 4)

Figure 2. Tumor burden reduction[a] (A) and OS by depth of response (B) with NIVO + IPI, NIVO, and chemo (PD-L1 ≥ 1%)

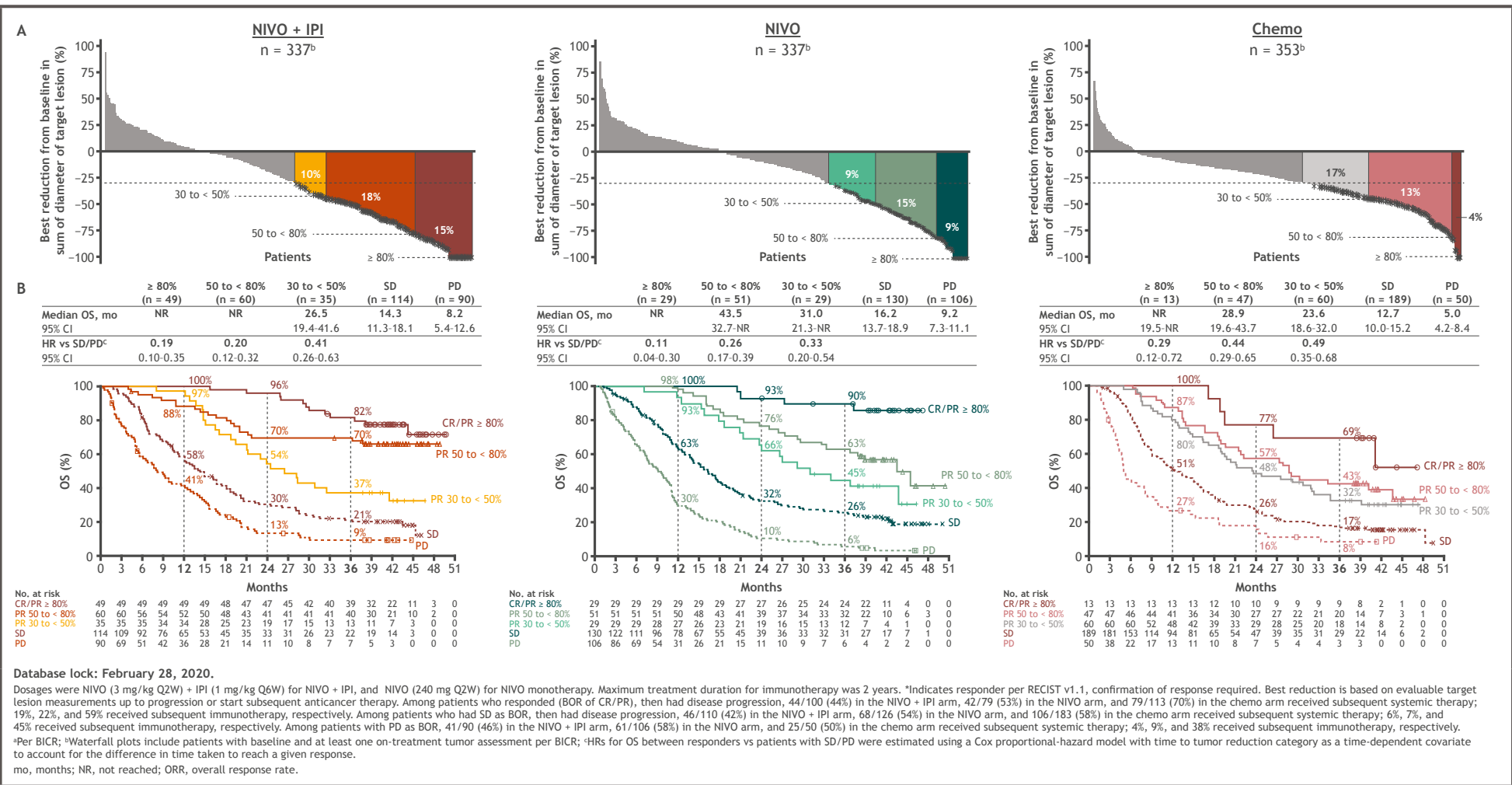Database lock: February 28, 2020.
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W) for NIVO + IPI, and NIVO (240 mg Q2W) for NIVO monotherapy. Maximum treatment duration for immunotherapy was 2 years. [a]Indicates responder per RECIST v1.1, confirmation of response required. Best reduction is based on evaluable target lesion measurements up to progression or start subsequent anticancer therapy. Among patients who responded (BOR of CR/PR), then had disease progression, 44/100 (44%) in the NIVO + IPI arm, 42/79 (53%) in the NIVO arm, and 79/113 (70%) in the chemo arm received subsequent systemic therapy; 19%, 22%, and 59% received subsequent immunotherapy, respectively. Among patients who had SD as BOR, then had disease progression, 46/110 (42%) in the NIVO + IPI arm, 68/126 (54%) on the NIVO arm, and 106/183 (58%) in the chemo arm received subsequent systemic therapy; 6%, 7%, and 45% received subsequent immunotherapy, respectively. Among patients with PD as BOR, 41/90 (46%) in the NIVO + IPI arm, 61/106 (58%) in the NIVO arm, and 25/50 (50%) in the chemo arm received subsequent systemic therapy; 4%, 9%, and 38% received subsequent immunotherapy, respectively. [b]Per BICR; [c]Waterfall plots include patients with baseline and at least one on-treatment tumor assessment per BICR; [d]HRs for OS between responders vs patients with SD/PD were estimated using a Cox proportional-hazard model with time to tumor reduction category as a time-dependent covariate to account for the difference in time taken to reach a given response.
mo, months; NR, not reached; ORR, overall response rate.

Figure 3. Tumor burden reduction[a] (A) and OS by depth of response (B) with NIVO + IPI, NIVO + chemo, and chemo (PD-L1 < 1%)

Database lock: February 28, 2020.
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W) for NIVO + IPI, and NIVO (360 mg Q3W) for NIVO + chemo. Maximum treatment duration for immunotherapy was 2 years. [a]Indicates responder per RECIST v1.1, confirmation of response required. Best reduction is based on evaluable target lesion measurements up to progression or start subsequent anticancer therapy. Among patients who responded (BOR of CR/PR), then had disease progression, 18/34 (53%) in the NIVO + IPI arm, 31/60 (52%) in the NIVO + chemo arm, and 24/41 (58%) in the chemo arm received subsequent systemic therapy; 21%, 8%, and 46% received subsequent immunotherapy, respectively. Among patients who had SD as BOR, then had disease progression, 38/71 (54%) in the NIVO + IPI arm, and 59/95 (62%) in the chemo arm received subsequent systemic therapy; 5% and 38% received subsequent immunotherapy, respectively. Among patients with PD as BOR, 24/44 (54%) in the NIVO + IPI arm, 8/19 (42%) in the NIVO + chemo arm, and 13/24 (54%) in the chemo arm received subsequent systemic therapy; 2%, 0%, and 42% received subsequent immunotherapy, respectively. [b]Per BICR; [c]Waterfall plots include patients with baseline and at least one on-treatment tumor assessment per BICR; [d]Data for NIVO + chemo waterfall not shown due to small number of patients (n = 3); [e]HRs for OS between responders vs patients with SD/PD were estimated using a Cox proportional-hazard model with time to tumor reduction category as a time-dependent covariate to account for the difference in time taken to reach a given response.
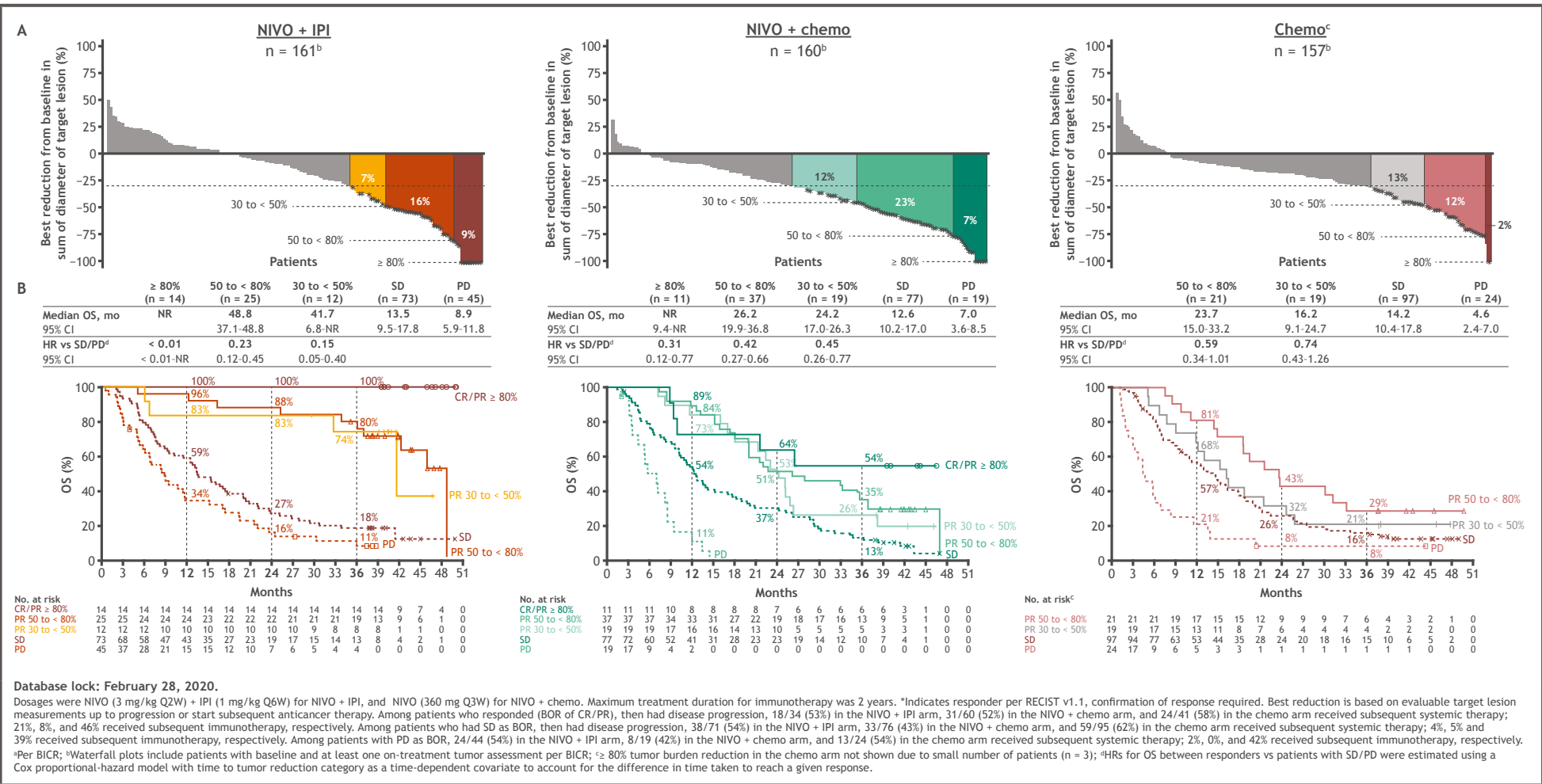
Table 2. Exposure-adjusted TRAEs by response with NIVO + IPI and chemo (PD-L1 ≥ 1% and < 1%)

	All treated		Responders (CR/PR)		Patients with SD		Patients with PD	
	NIVO + IPI (n = 576; P-Y = 401.9)	Chemo (n = 570; P-Y = 275.7)	NIVO + IPI (n = 195; P-Y = 239.8)	Chemo (n = 163; P-Y = 126.2)	NIVO + IPI (n = 187; P-Y = 113.5)	Chemo (n = 286; P-Y = 127.6)	NIVO + IPI (n = 134; P-Y = 38.2)	Chemo (n = 74; P-Y = 15.2)
Any TRAE, IR per 100 P-Y[a]	605.9	1066.2	566.3	920.8	660.9	1143.4	689.0	1364.4

Database lock: February 28, 2020. Dosages were NIVO (3 mg/kg Q6W). Maximum treatment duration for immunotherapy was 2 years. [a]IR per 100 P-Y of exposure (IR/100 P-Y) = event count * 100 / P-Y of exposure; Includes events reported between first dose and 30 days after last dose of study therapy.

Figure 4. Exposure-adjusted treatment-related select[a] AEs by response with NIVO + IPI (PD-L1 ≥ 1% and < 1%)
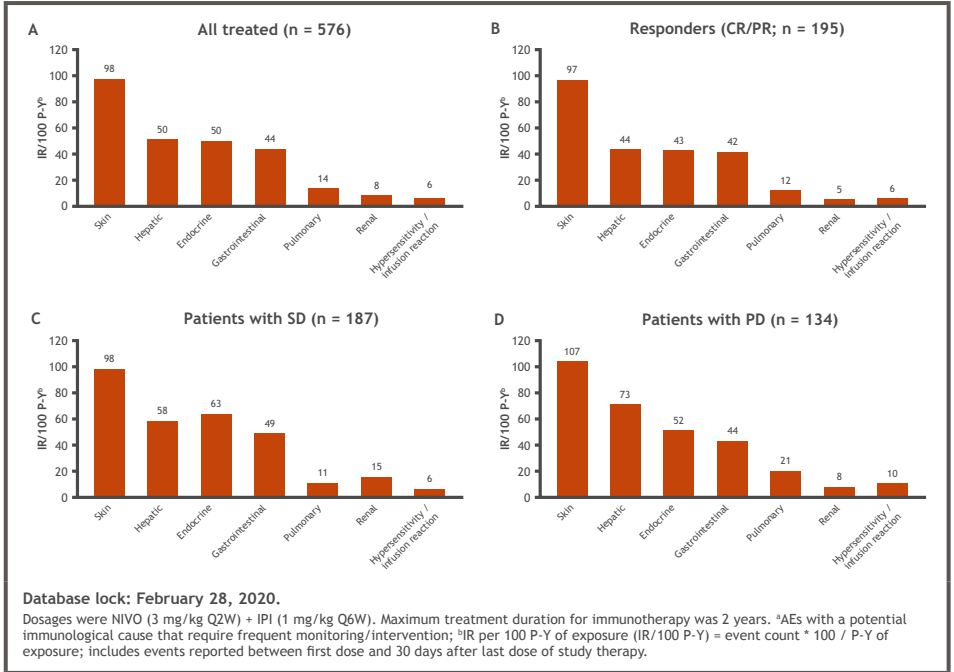
Database lock: February 28, 2020. Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Maximum treatment duration for immunotherapy was 2 years. [a]AEs with a potential immunological cause that require frequent monitoring/intervention; [b]IR per 100 P-Y of exposure (IR/100 P-Y) = event count * 100 / P-Y of exposure; Includes events reported between first dose and 30 days after last dose of study therapy.

Conclusions

- With 3 years' minimum follow-up, patients treated with NIVO + IPI had a higher chance of achieving deeper responses than those treated with chemo (regardless of PD-L1 expression) or with NIVO monotherapy (PD-L1 ≥ 1%)
- Responders with higher tumor burden reduction from baseline had greater long-term OS benefit
  - This correlation was more pronounced with NIVO + IPI treatment vs either chemo (in both PD-L1 ≥ 1% and < 1% populations) or NIVO + chemo (PD-L1 <1%), which reflects the greater durability of responses seen with NIVO + IPI in this study
- The safety profile in responders was consistent with that observed in all treated patients
  - While duration of treatment was longer in responders, when adjusted for exposure this was not associated with higher rates of TRAEs or treatment-related select AEs

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Disclosures