Supplementary Appendix

Nivolumab Monotherapy or Combination with Ipilimumab with or without Cobimetinib in Previously Treated Patients with Pancreatic Adenocarcinoma (CheckMate 032)

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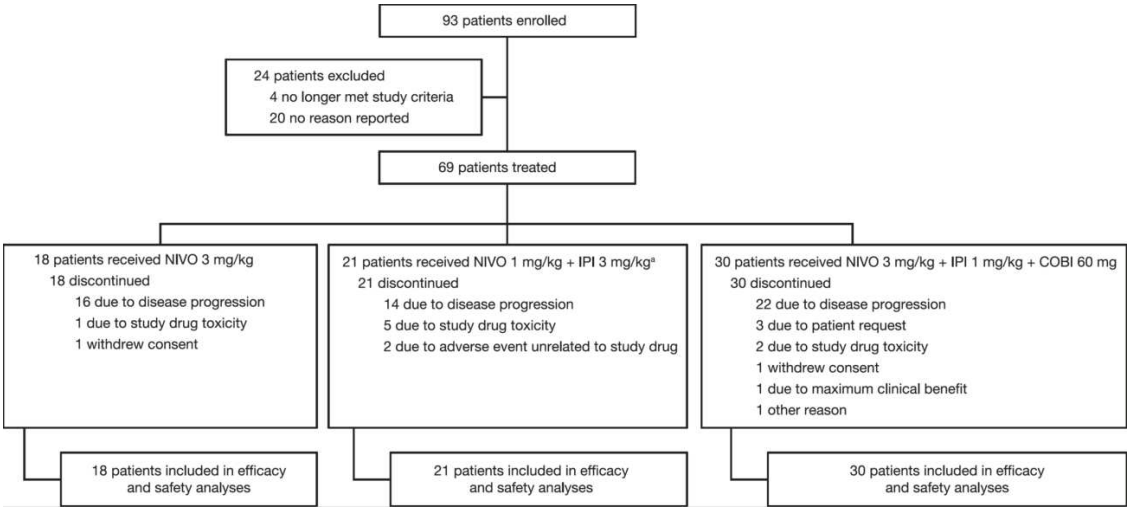
*At the time the study was conducted.

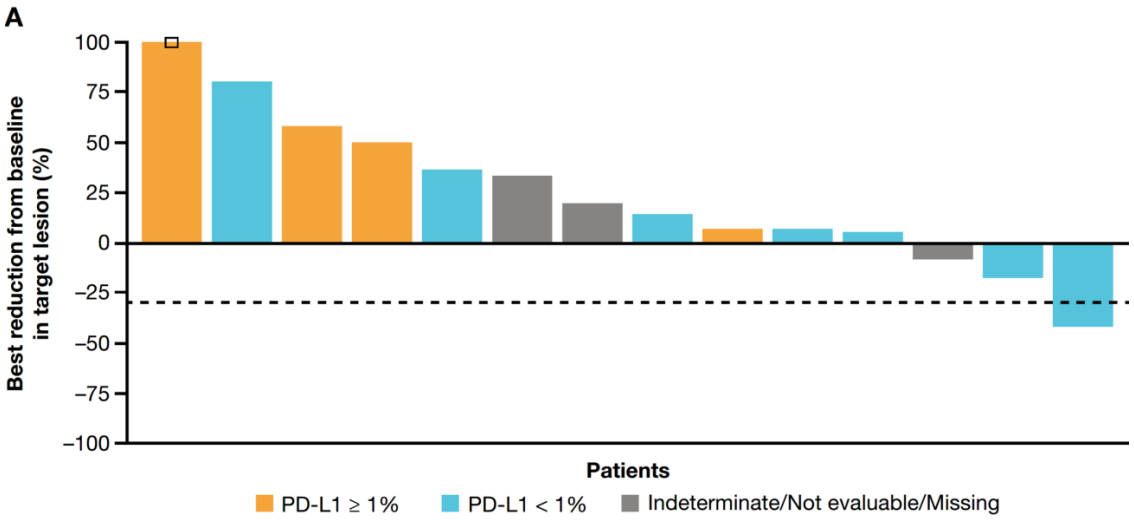
Supplemental Figure 1 Patient disposition. Two crossover patients discontinued treatment due to disease progression and are not counted in the patient status at the end of treatment below.

[a]Includes three patients who received nivolumab 1 mg/kg + ipilimumab 1 mg/kg.

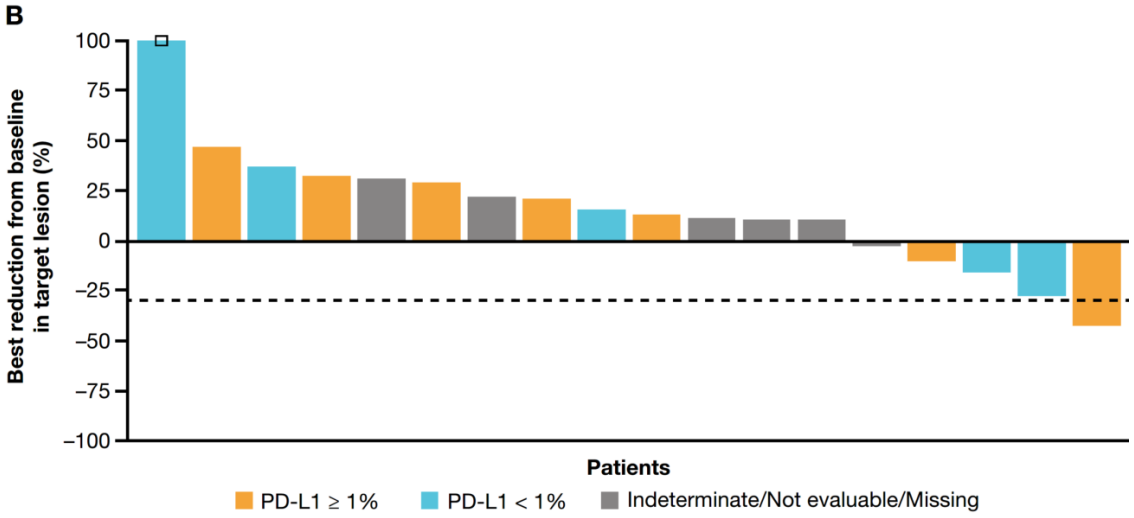


Supplemental Figure 2 Maximum percentage change from baseline in tumor size with nivolumab monotherapy (**A**), nivolumab plus ipilimumab (**B**), and nivolumab plus ipilimumab plus cobimetinib (**C**). Patients with target lesion at baseline and at least one on-treatment tumor assessment. Negative/positive values mean maximum tumor reduction/minimum tumor increase. Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy/crossover. Horizontal reference line indicates the 30% reduction consistent with a RECIST v1.1 response. Asterisk (*) indicates responders. Symbol □ represents % change truncated to 100%. [a]Nivolumab 1 mg/kg plus ipilimumab 1 mg/kg not shown as n=2.

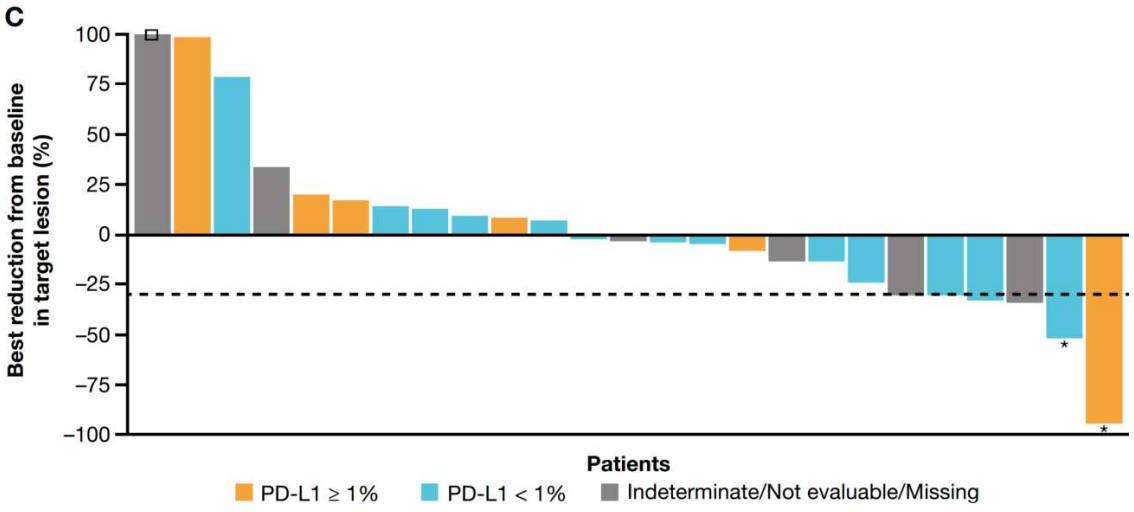
A. Nivolumab 3 mg/kg monotherapy



B. Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg[a]

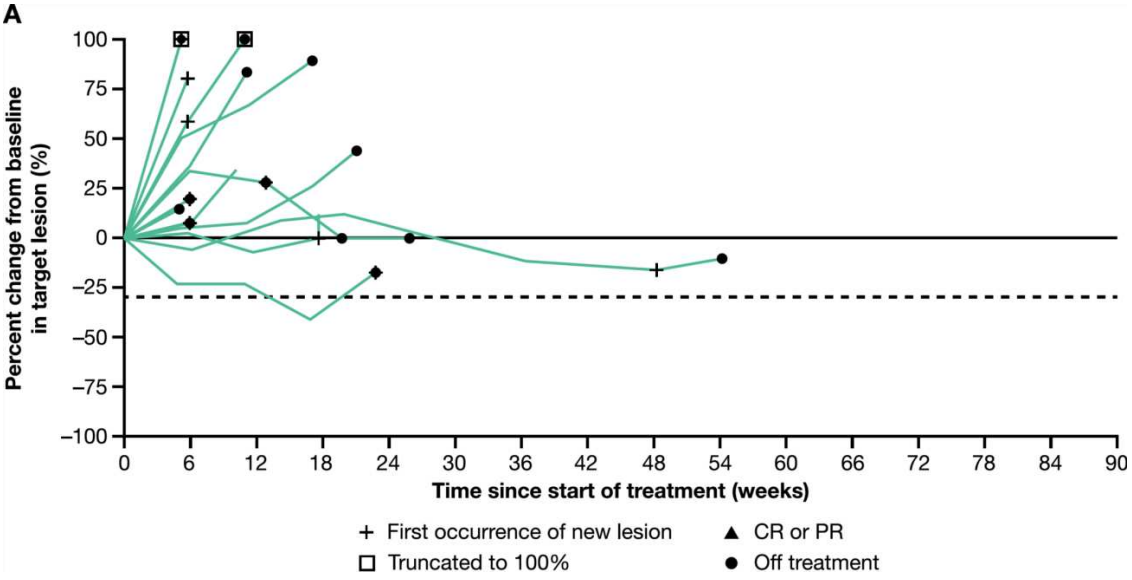


C. Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg plus cobimetinib 60 mg

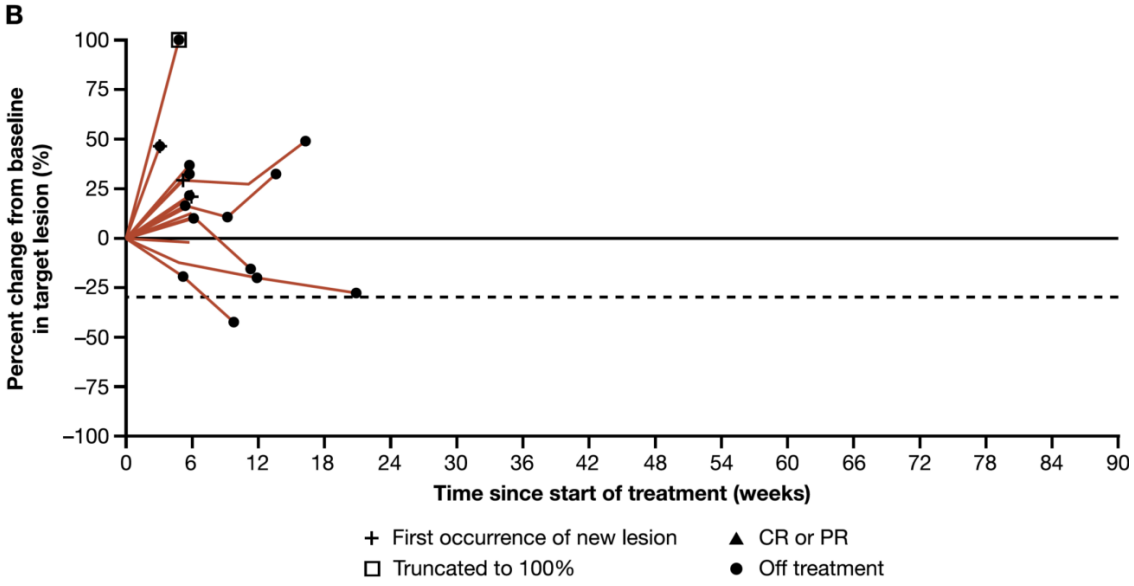


Supplemental Figure 3 Change in tumor burden over time in individual patients per investigator assessment. Percentage change from baseline in target lesions over time with nivolumab monotherapy (**A**; n= 14), nivolumab plus ipilimumab (**B**; n=16), and nivolumab plus ipilimumab plus cobimetinib (**C**; n=26). The horizontal reference line indicates the 30% reduction consistent with a protocol-defined criteria response. [a]Nivolumab 1 mg/kg plus ipilimumab 1 mg/kg not shown as n=2.

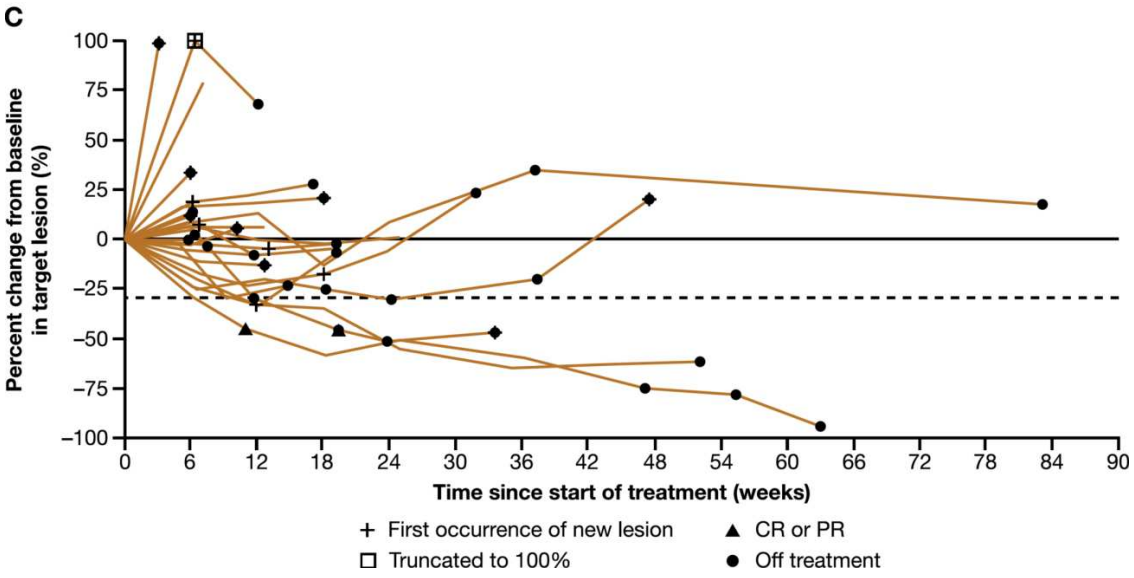
A. Nivolumab 3 mg/kg



B. Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg[a]



C. Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg plus cobimetinib 60 mg



Supplemental Table 1 Prior systemic cancer therapy in the neoadjuvant and adjuvant settings

	Nivolumab (n=18)	Nivolumab plus ipilimumab (n=21)	Nivolumab plus ipilimumab plus cobimetinib (n=30)
Patients with prior regimen in neoadjuvant setting, n (%)[a]	**3 (17)**	**1 (5)**	**5 (17)**
Fluorouracil/irinotecan/leucovorin/oxaliplatin	3 (17)	0	3 (10)
Gemcitabine	1 (6)	0	1 (3)
Capcitabine	1 (6)	0	0
Gemcitabine/Paclitaxel	0	1 (5)	0
Cisplatin/irinotecan	0	0	1 (3)
Patients with prior regimen in adjuvant setting, n (%)[a]	**7 (39)**	**5 (24)**	**11 (37)**
Capcitabine/gemcitabine	0	2 (10)	4 (13)
Gemcitabine	4 (22)	1 (5)	0
Capcitabine	1 (6)	0	1 (3)

	Nivolumab (n=18)	Nivolumab plus ipilimumab (n=21)	Nivolumab plus ipilimumab plus cobimetinib (n=30)
Gemcitabine/paclitaxel	0	0	2 (7)
Capcitabine/gemcitabine/paclitaxel	1 (6)	0	0
Fluorouracil/irinotecan/leucovorin/oxaliplatin	1 (6)	0	0
Capcitabine/cisplatin/gemcitabine	0	1 (5)	0
Fluorouracil/leucovorin/oxaliplatin	0	1 (5)	0
Capcitabine/fluorouracil/irinotecan/leucovorin	0	0	1 (3)
Cisplatin/irinotecan	0	0	1 (3)
Dexamethasone/fluorouracil/leucovorin/ondansetron	0	0	1 (3)
Fluorouracil/gemcitabine	0	0	1 (3)

[a]One patient in the nivolumab arm and five patients in the nivolumab plus ipilimumab plus cobinetinib arm received systemic therapies in both neoadjuvant and adjuvant settings.

Supplemental Table 2 Cumulative dose and relative dose intensity for all treated patients

	Nivolumab (n=18)	**Nivolumab plus ipilimumab (n=21)**		**Nivolumab plus ipilimumab plus cobimetinib (n=30)**		
	Nivolumab	**Nivolumab**	**Ipilimumab**	**Nivolumab**	**Ipilimumab**	**Cobimetinib**
Relative dose intensity, n (%)						
90% to <110%	16 (89)	18 (86)	18 (86)	21 (70)	24 (80)	5 (17)
70% to <90%	2 (11)	3 (14)	3 (14)	6 (20)	6 (20)	9 (30)
50% to <70%	0	0	0	2 (7)	0	11 (37)
<50%	0	0	0	1 (3)	0	4 (13)
Not reported	0	0	0	0	0	1 (3)
No. of doses received, median (range)	3.5 (1–26)	2.0 (1–5)	2.0 (1–4)	5.0 (1–20)	2.0 (1–7)	–
No. of doses received, n (%)						
1	4 (22)	3 (14)	3 (14)	5 (17)	12 (40)	–
2	0	8 (38)	8 (38)	2 (7)	9 (30)	–
3	5 (28)	6 (29)	6 (29)	3 (10)	5 (17)	–
4	1 (6)	3 (14)	4 (19)	2 (7)	1 (3)	–

	Nivolumab (n=18)	**Nivolumab plus ipilimumab (n=21)**		**Nivolumab plus ipilimumab plus cobimetinib (n=30)**		
	Nivolumab	**Nivolumab**	**Ipilimumab**	**Nivolumab**	**Ipilimumab**	**Cobimetinib**
>4	8 (44)	1 (5)	0	18 (60)	3 (10)	–
Cumulative dose						
Mean (SD)	18.7 (18.7)	2.7 (1.4)	6.7 (3.2)	18.4 (14.3)	2.2 (1.5)	2735.9 (2484.2)
Median (range)[a]	10.7 (3.0–78.9)	2.0 (1.0–7.1)	6.0 (1.9–12.4)	15.1 (3.0–60.1)	2.0 (1.0–7.0)	1980.0 (240.0–11800.0)

[a]Dose units: nivolumab and ipilimumab are mg/kg and cobimetinib in mg.

SD, standard deviation.

Supplemental Table 3 Summary of responses per RECIST v1.1 by baseline PD-L1 status

	Nivolumab (n=18)	**Nivolumab plus ipilimumab (n=21)**	**Nivolumab plus ipilimumab plus cobimetinib (n=30)**
Tumor cell PD-L1 expression ≥5%, n (%)	**2 (11)**	**6 (29)**	**6 (20)**
Objective response rate, n (%)	0	0	1 (16.7)
95% CI	0–84.2	0–45.9	0.4–64.1
Best overall response, n (%)			
Complete response	0	0	0
Partial response	0	0	1 (17)
Stable disease	0	1 (17)	2 (33)
Progressive disease	2 (100)	5 (83)	2 (33)
Unable to determine	0	0	1 (17)
Median PFS (95% CI) per investigator, months	1.2 (1.2–1.2)	1.35 (0.7–4.4)	2.8 (0.7–NE)

	Nivolumab (n=18)	Nivolumab plus ipilimumab (n=21)	Nivolumab plus ipilimumab plus cobimetinib (n=30)
Median PFS (95% CI) per BICR, months	–	–	2.1 (0.7–NE)
Median OS (95% CI), months	8.6 (2.0–15.2)	4.45 (1.5–6.7)	6.1 (1.2–NE)
Tumor cell PD-L1 expression <5%, n (%)	**13 (72)**	**8 (38)**	**16 (53)**
Objective response rate, n (%)	0	0	1 (6.3)
95% CI	0–24.7	0–36.9	0.2–30.2
Best overall response, n (%)			
Complete response	0	0	0
Partial response	0	0	1 (6)
Stable disease	4 (31)	3 (38)	9 (56)
Progressive disease	5 (38)	4 (50)	5 (31)
Unable to determine	4 (31)	1 (13)	1 (6)

	Nivolumab (n=18)	Nivolumab plus ipilimumab (n=21)	Nivolumab plus ipilimumab plus cobimetinib (n=30)
Median PFS (95% CI) per investigator, months	1.45 (1.3–2.3)	1.3 (0.7–17.15)	3.0 (1.5–5.5)
Median PFS (95% CI) per BICR, months	–	–	3.9 (1.4–7.7)
Median OS (95% CI), months	3.35 (1.5–9.0)	2.4 (0.9–4.9)	11.4 (3.65–NE)
Tumor cell PD-L1 expression ≥1%, n (%)	**5 (28)**	**8 (38)**	**8 (27)**
Objective response rate, n (%)	0	0	1 (12.5)
95% CI	0–52.2	0–36.9	0.3–52.7
Best overall response, n (%)			
Complete response	0	0	0
Partial response	0	0	1 (13)
Stable disease	1 (20)	1 (13)	2 (25)
Progressive disease	3 (60)	6 (75)	4 (50)

	Nivolumab (n=18)	Nivolumab plus ipilimumab (n=21)	Nivolumab plus ipilimumab plus cobimetinib (n=30)
Unable to determine	1 (20)	1 (13)	1 (13)
Median PFS (95% CI) per investigator, months	1.3 (1.2–2.3)	1.25 (0.7–1.4)	1.5 (0.7–NE)
Median PFS (95% CI) per BICR, months	–	–	1.5 (0.7–NE)
Median OS (95% CI), months	7.0 (1.45–15.2)	4.1 (0.9–6.7)	8.9 (1.2–12.9)
Tumor cell PD-L1 expression <1%, n (%)	**10 (56)**	**6 (29)**	**14 (47)**
Objective response rate, n (%)	0	0	1 (7.1)
95% CI	0–30.8	0–45.9	0.2–33.9
Best overall response, n (%)			
Complete response	0	0	0
Partial response	0	0	1 (7)
Stable disease	3 (30)	3 (50)	9 (64)

	Nivolumab (n=18)	**Nivolumab plus ipilimumab (n=21)**	**Nivolumab plus ipilimumab plus cobimetinib (n=30)**
Progressive disease	4 (40)	3 (50)	3 (21)
Unable to determine	3 (30)	0	1 (7)
Median PFS (95% CI) per investigator, months	1.5 (0.6–3.9)	2.1 (1.1–17.15)	3.9 (1.6–7.7)
Median PFS (95% CI) per BICR, months	–	–	3.9 (1.4–7.7)
Median OS (95% CI), months	2.9 (0.6–11.9)	3.4 (1.8–17.15)	7.4 (3.1–NE)
Patients without quantifiable tumor cell PD-L1 expression at baseline, n (%)	**3 (17)**	**7 (33)**	**8 (27)**
Objective response rate, n (%)	0	0	0
95% CI	0–70.8	0–41.0	0–36.9
Best overall response, n (%)			
Complete response	0	0	0

	Nivolumab (n=18)	Nivolumab plus ipilimumab (n=21)	Nivolumab plus ipilimumab plus cobimetinib (n=30)
Partial response	0	0	0
Stable disease	1 (33)	3 (43)	4 (50)
Progressive disease	2 (67)	3 (43)	2 (25)
Unable to determine	0	1 (14)	2 (25)

BICR, blinded independent central review; CI, confidence interval; NE, not estimable; PD-L1, programmed death ligand 1; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

List of sites and investigators

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United Kingdom	Thomas Evans
	Ian Chau
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	Rathi Pillai
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	Asim Amin
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	Patrick Ott
	Margaret Callahan
	Neil Segal
	Shivaani Kummar
	Matthew Taylor
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	Merry Markham
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