

Proton Pump Inhibitor Use and Efficacy of Nivolumab and Ipilimumab in Advanced Melanoma

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Table S1. Multivariable logistic regression models of ORR by study and treatment.

Parameter	CheckMate 066		CheckMate 067			CheckMate 069	
	Dacarbazine (N = 198)	Nivolumab (N = 199)	Ipilimumab (N = 309)	Nivolumab (N = 309)	Nivolumab + Ipilimumab (N = 313)	Ipilimumab (N = 46)	Nivolumab + Ipilimumab (N = 93)
PPI at baseline (yes vs no)	0.975 (0.362-2.625) [0.96]	0.605 (0.295-1.239) [0.17]	1.395 (0.678-2.866) [0.37]	1.116 (0.539-2.310) [0.77]	1.444 (0.756-2.756) [0.27]	0.000 (0.000-infinity) [0.97]	0.256 (0.090-0.731) [0.01]
Metastatic disease stage (M1c vs M0/M1a/M1b)	0.682 (0.280-1.661) [0.40]	0.790 (0.407-1.533) [0.49]	0.722 (0.384-1.358) [0.31]	0.967 (0.561-1.667) [0.90]	0.624 (0.317-1.050) [0.08]	189045 (0.000-infinity) [0.93]	0.997 (0.381-2.606) [0.99]
Sex (male vs female)	0.395 (0.173-0.904) [0.03]	1.437 (0.782-2.642) [0.24]	1.490 (0.775-2.864) [0.23]	1.960 (1.155-3.327) [0.01]	1.427 (0.864-2.357) [0.16]	107150 (0.000-infinity) [0.94]	1.955 (0.751-5.087) [0.17]
LDH (> ULN vs ≤ ULN)	0.877 (0.341-2.252) [0.78]	0.572 (0.300-1.093) [0.09]	0.349 (0.168-0.723) [0.005]	0.487 (0.277-0.856) [0.01]	0.466 (0.280-0.777) [0.003]	0.258 (0.018-3.618) [0.31]	0.507 (0.182-1.412) [0.19]
AJCC disease stage (IV vs III)	0.289 (0.098-0.857) [0.03]	0.972 (0.392-2.409) [0.95]	0.517 (0.179-1.496) [0.22]	0.462 (0.182-1.169) [0.10]	0.684 (0.216-2.161) [0.52]	1.393 (0.000-infinity) [1.00]	2.359 (0.537-10.363) [0.26]
PD-L1-positive (≥ 1% vs indetermi- nate/negative)	0.981 (0.426-2.257) [0.96]	2.126 (1.178-3.840) [0.01]	1.058 (0.574-1.950) [0.86]	2.068 (1.240-3.448) [0.01]	1.479 (0.915-2.391) [0.11]	2.392 (0.218-26.201) [0.48]	1.922 (0.727-5.085) [0.19]

Region								
western Europe/Canada	Rest of world vs	1.343	1.242					
		(0.572-3.152)	(0.651-2.371)	-	-	-	-	-
		[0.50]	[0.51]					
US	Rest of world vs	-	-	0.486	1.462	0.684	-	-
				(0.177-1.335)	(0.618-3.457)	(0.280-1.666)		
				[0.16]	[0.39]	[0.40]		
EU vs US				0.337	0.783	0.827		
				(0.169-0.672)	(0.419-1.462)	(0.447-1.530)	-	-
				[0.002]	[0.44]	[0.55]		
Australia vs US				0.291	3.092	1.852		
				(0.096-0.877)	(1.216-7.865)	(0.741-4.632)	-	-
				[0.03]	[0.02]	[0.19]		
France vs US							0.000	2.000
							(0.000-infinity)	(0.455-8.792)
							[0.96]	[0.36]

Data are odds ratio (95% CI) [P value]. AJCC, American Joint Committee on Cancer; EU, European Union; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor; ULN, upper limit of normal; US, United States.

Table S2. Multivariable Cox proportional hazards models of PFS by study and treatment.

Parameter	CheckMate 066		CheckMate 067			CheckMate 069	
	Dacarbazine (N = 198)	Nivolumab (N = 199)	Ipilimumab (N = 309)	Nivolumab (N = 309)	Nivolumab + Ipilimumab (N = 313)	Ipilimumab (N = 46)	Nivolumab + Ipilimumab (N = 93)
PPI at baseline (yes vs no)	1.286 (0.869-1.903) [0.21]	1.126 (0.741-1.713) [0.58]	0.926 (0.669-1.282) [0.65]	0.741 (0.464-1.183) [0.21]	1.032 (0.700-1.520) [0.87]	0.818 (0.264-2.529) [0.73]	2.167 (1.105-4.251) [0.02]
History of brain metas- tases (yes vs no)	1.240 (0.556-2.767) [0.60]	1.269 (0.466-3.456) [0.64]	0.766 (0.395-1.486) [0.43]	0.846 (0.304-2.357) [0.75]	0.428 (0.134-1.363) [0.15]	NA NA	1.220 (0.262-5.680) [0.80]
Metastatic disease stage (M1c vs M0/M1a/M1b)	1.283 (0.906-1.817) [0.16]	1.107 (0.744-1.646) [0.62]	1.357 (1.043-1.766) [0.02]	1.230 (0.906-1.669) [0.18]	1.561 (1.127-2.163) [0.01]	0.568 (0.265-1.215) [0.15]	1.263 (0.676-2.362) [0.46]
Sex (male vs female)	1.430 (1.024-1.997) [0.04]	0.747 (0.515-1.084) [0.12]	1.079 (0.830-1.402) [0.57]	0.762 (0.566-1.024) [0.07]	0.798 (0.586-1.086) [0.15]	0.556 (0.250-1.237) [0.15]	0.638 (0.337-1.208) [0.17]
ECOG PS (≥ 1 vs 0)	1.095 (0.768-1.562) [0.62]	1.280 (0.839-1.951) [0.25]	1.189 (0.898-1.574) [0.23]	1.451 (1.019-2.065) [0.04]	1.295 (0.924-1.814) [0.13]	0.918 (0.313-2.696) [0.88]	1.239 (0.513-2.995) [0.63]
LDH (> ULN vs ≤ ULN)	1.703 (1.187-2.443) [0.004]	1.530 (1.007-2.325) [0.05]	2.044 (1.570-2.661) [0.0000]	1.468 (1.063-2.028) [0.02]	1.657 (1.208-2.273) [0.002]	2.316 (0.839-6.396) [0.11]	1.447 (0.713-2.936) [0.31]
PD-L1-positive (≥1% vs indetermi- nate/negative)	1.183 (0.856-1.635) [0.31]	0.609 (0.425-0.872) [0.01]	0.676 (0.524-0.873) [0.003]	0.663 (0.491-0.894) [0.01]	0.855 (0.637-1.150) [0.30]	1.059 (0.482-2.331) [0.89]	0.751 (0.394-1.430) [0.38]
Region							
western Europe/Canada	Rest of world vs	0.671	0.893				
		(0.461-0.978)	(0.586-1.363)	-	-	-	-
		[0.04]	[0.60]				
US	Rest of world vs	-	-	1.068	0.780	1.755	-
				(0.678-1.681)	(0.460-1.325)	(1.027-2.999)	-
				[0.78]	[0.36]	[0.04]	
EU vs US				1.368	1.184	1.332	
				(0.996-1.879)	(0.813-1.723)	(0.899-1.972)	-
				[0.05]	[0.38]	[0.15]	

Australia vs US	-	-	1.334 (0.862-2.063) [0.20]	0.708 (0.403-1.245) [0.23]	0.639 (0.346-1.180) [0.15]	-	-
France vs US	-	-	-	-	-	0.762 (0.224-2.598) [0.66]	0.621 (0.187-2.062) [0.44]

Data are hazard ratio (95% CI) [P value]. AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; LDH, lactate dehydrogenase; NA, not applicable (no patients in the CheckMate 069 ipilimumab arm had brain metastases at baseline); PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor; ULN, upper limit of normal; US, United States.

Table S3. Multivariable Cox proportional hazards models of OS by study and treatment.

Parameter	CheckMate 066		CheckMate 067		CheckMate 069		
	Dacarbazine (N = 198)	Nivolumab (N = 199)	Ipilimumab (N = 309)	Nivolumab (N = 309)	Nivolumab + Ipilimumab (N = 313)	Ipilimumab (N = 46)	Nivolumab + Ipilimumab (N = 93)
PPI at baseline (yes vs no)	1.077 (0.719-1.613) [0.72]	1.069 (0.673-1.697) [0.78]	1.309 (0.922-1.857) [0.13]	0.766 (0.468-1.254) [0.29]	0.903 (0.573-1.425) [0.66]	0.538 (0.103-2.811) [0.46]	1.996 (0.936-4.256) [0.07]
History of brain metas- tases (yes vs no)	0.784 (0.309-1.991) [0.61]	1.028 (0.336-3.140) [0.96]	0.824 (0.410-1.659) [0.59]	0.922 (0.331-2.569) [0.88]	0.777 (0.275-2.197) [0.63]	NA NA	2.919 (0.581-14.667) [0.19]
<i>BRAF</i> mutation status (mutant vs wild type)	-	-	0.971 (0.713-1.323) [0.85]	0.709 (0.493-1.019) [0.06]	0.661 (0.448-0.974) [0.04]	0.190 (0.044-0.829) [0.03]	2.594 (1.118-6.018) [0.03]
Metastatic disease stage (M1c vs M0/M1a/M1b)	1.599 (1.112-2.302) [0.01]	1.181 (0.773-1.805) [0.44]	1.667 (1.238-2.245) [0.001]	1.697 (1.195-2.410) [0.003]	1.671 (1.148-2.432) [0.007]	0.443 (0.155-1.266) [0.13]	1.575 (0.800-3.101) [0.19]
Age group (≥ 65–< 75 vs < 65)	1.017 (0.696-1.486) [0.93]	0.814 (0.534-1.242) [0.34]	0.785 (0.565-1.091) [0.15]	0.945 (0.644-1.387) [0.77]	1.194 (0.814-1.750) [0.36]	0.351 (0.118-1.047) [0.06]	1.730 (0.798-3.749) [0.16]
Age group (≥ 75 vs < 65)	1.798 (1.132-2.858) [0.01]	0.697 (0.366-1.328) [0.27]	1.252 (0.817-1.920) [0.30]	1.427 (0.893-2.280) [0.14]	1.256 (0.747-2.113) [0.39]	1.503 (0.380-5.936) [0.56]	3.733 (1.291-10.797) [0.02]
Sex (male vs female)	1.190 (0.839-1.688) [0.33]	0.681 (0.460-1.008) [0.05]	1.105 (0.826-1.479) [0.50]	0.799 (0.573-1.114) [0.19]	0.758 (0.537-1.070) [0.11]	1.156 (0.374-3.569) [0.80]	0.596 (0.303-1.171) [0.13]
ECOG PS (≥ 1 vs 0)	1.417 (0.989-2.031) [0.06]	2.225 (1.393-3.554) [0.001]	1.587 (1.168-2.157) [0.003]	1.936 (1.345-2.786) [0.0004]	2.079 (1.458-2.963) [0.0001]	2.957 (0.752-11.634) [0.12]	1.216 (0.515-2.866) [0.66]
LDH (> ULN vs ≤ ULN)	2.437 (1.668-3.562) [0.0000]	1.713 (1.115-2.632) [0.01]	2.134 (1.596-2.855) [0.0000]	1.494 (1.043-2.141) [0.03]	1.970 (1.385-2.801) [0.0002]	10.914 (2.823-42.197) [0.0005]	1.651 (0.708-3.851) [0.25]
PD-L1–positive (≥ 1% vs indetermi- nate/negative)	1.615 (1.151-2.266) [0.01]	0.647 (0.440-0.951) [0.03]	0.728 (0.549-0.965) [0.03]	0.671 (0.482-0.933) [0.02]	0.914 (0.654-1.278) [0.60]	0.765 (0.303-1.935) [0.57]	0.491 (0.238-1.013) [0.05]
Region							
Rest of world vs western Europe/Can- ada	0.914 (0.632, 1.322) [0.63]	0.732 (0.463, 1.155) [0.18]	-	-	-	-	-
Rest of world vs US	-	-	1.098 (0.655, 1.840) [0.72]	0.936 (0.534, 1.642) [0.82]	2.481 (1.344, 4.580) [0.004]	-	-

EU vs US	-	-	1.366 (0.960-1.944) [0.08]	1.270 (0.846-1.907) [0.25]	1.609 (1.011-2.562) [0.04]	-	-
Australia vs US	-	-	0.801 (0.470-1.364) [0.41]	0.634 (0.335-1.201) [0.16]	0.716 (0.351-1.464) [0.36]	-	-
France vs US	-	-	-	-	-	0.114 (0.017-0.739) [0.02]	0.629 (0.211-1.873) [0.40]

Data are hazard ratio (95% CI) [P value]. AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; LDH, lactate dehydrogenase; NA, not applicable (no patients in the CheckMate 069 ipilimumab arm had brain metastases at baseline); PD-L1, programmed death-ligand 1; PPI, proton pump inhibitor; ULN, upper limit of normal; US, United States.

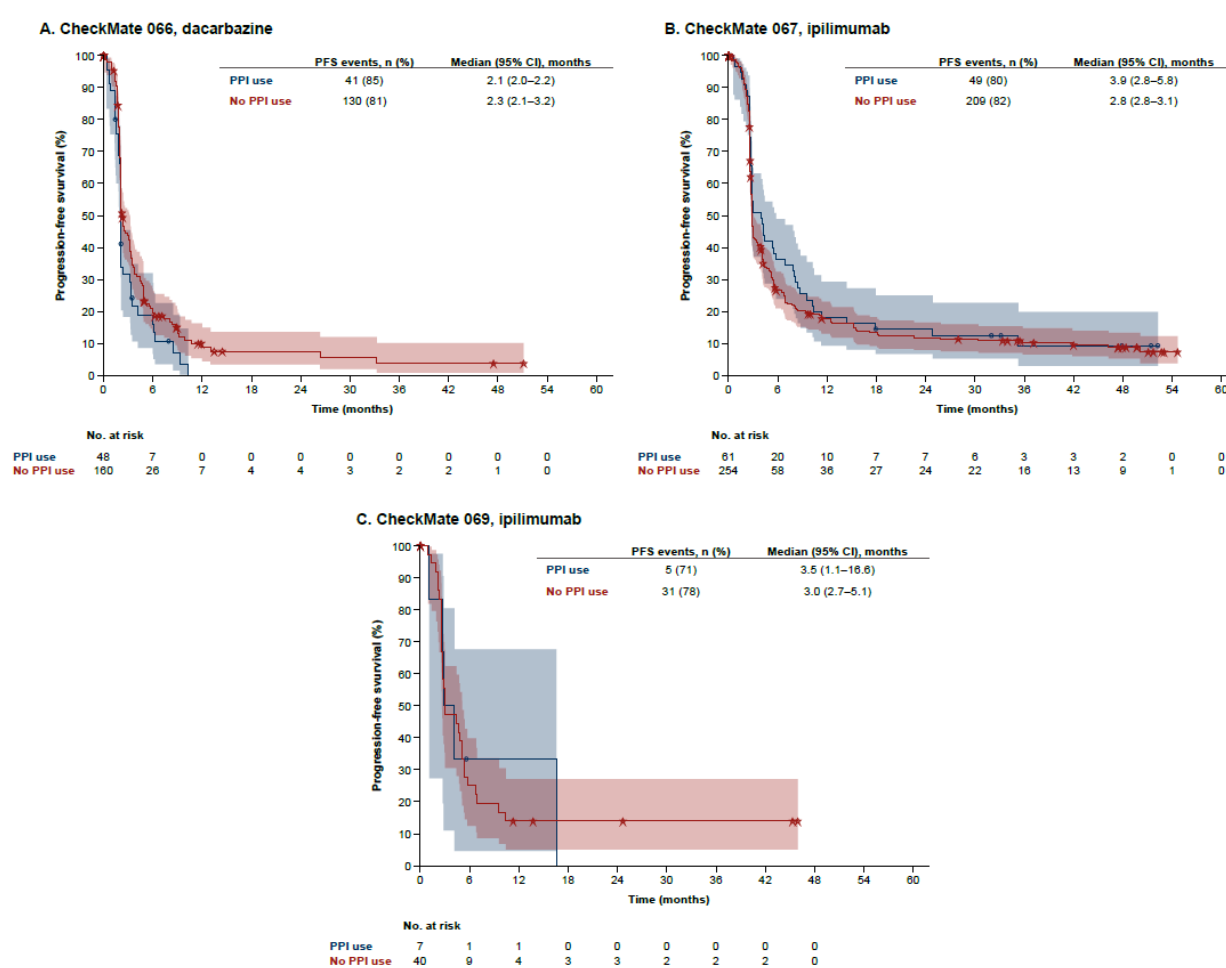


Figure S1. Progression-free survival by baseline PPI use in the control arms of CheckMate 066, 067, and 069. Kaplan–Meier estimates of progression-free survival in the dacarbazine arm of CheckMate 066 (A) and the ipilimumab arms of CheckMate 067 (B) and CheckMate 069 (C). Shaded areas are 95% log–log confidence bands. CI, confidence interval; PFS, progression-free survival; PPI, proton pump inhibitor.

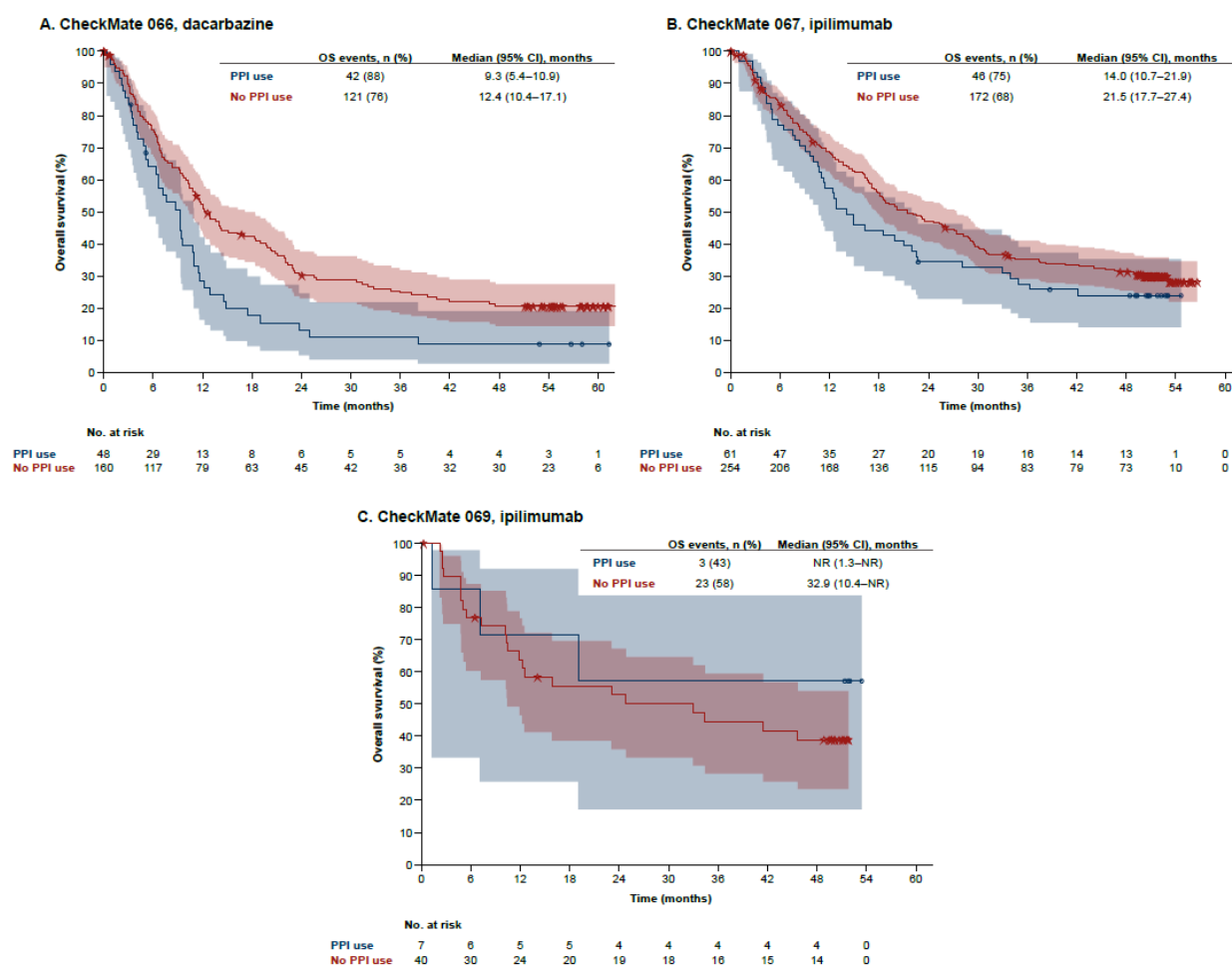


Figure S2. Overall survival by baseline PPI use in the control arms of CheckMate 066, 067, and 069. Kaplan–Meier estimates of overall survival in the dacarbazine arm of CheckMate 066 (A) and the ipilimumab arms of CheckMate 067 (B) and CheckMate 069 (C). Shaded areas are 95% log–log confidence bands. CI, confidence interval; OS, overall survival; PPI, proton pump inhibitor.