

Five-year survival with neoadjuvant therapy in melanoma: updated pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

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Supplementary Results

Supplementary Results 1 | Radiological and metabolic response

Radiological (CT; RECIST version 1.1¹) and metabolic (FDG-PET; EORTC categories²) responses are shown in **Extended Data Table 5**. The objective response rate as per RECIST 1.1 was 49.8% (95% CI 45.8–53.8) with ICI, 83.0% (95% CI 75.0–89.3) with BRAF/MEKi, and 54.7% (95% CI 47.2–62.2) with ICI + TT, with progressive disease (PD) rates of 16.8%, 0.8%, and 8.4%, respectively. On FDG-PET, the objective metabolic response rate was 63.6% (95% CI 56.2–70.5) with ICI, 85.7% (95% CI 57.2–98.2) with BRAF/MEKi, and 75.2% (95% CI 65.7–83.3) with ICI + TT, and progressive metabolic disease (PMD) rates were 22.8%, 0%, and 7.9%, respectively. Pathological response and RFS rates by imaging response category are shown in **Supplementary Fig. 1**.

In 121 ICI-treated patients with available percent change from baseline data per CT (sum-of-diameters) and FDG-PET (SUVmax), plus recurrence data, we found that CT alone, PET alone, and CT plus PET models had similar, modest ability to predict recurrence at 1 year (AUC of 0.54, 0.49, and 0.54, respectively; $p=0.821$), 2 years (AUC of 0.69, 0.73, and 0.72; $p=0.964$), and 3 years (AUC of 0.68, 0.72, and 0.69; $p=0.246$). **Supplementary Fig. 3** contains an alluvial plot visualizing the relationship between complete imaging response on CT and/or FDG-PET and recurrence in patients treated with ICI.

Of the 308 ICI-treated patients with an objective CT response, surgery was omitted in 12 (3.9%). One 86-year-old male, who received neoadjuvant anti-CTLA-4 10 mg/kg, died due to melanoma after 7.7 years. The remaining 11 (91.7%) patients were alive and recurrence-free.

Supplementary Table 1 | Contributing sites (N=1,038)

	Trial (N=755)	Non-trial (N=283)	Overall (N=1,038)
≥10% of patients			
Melanoma Institute Australia, Australia	288 (38.1)	15 (5.3)	303 (29.2)
Netherlands Cancer Institute, The Netherlands	143 (18.9)	0 (0)	143 (13.8)
≥5% and <10% of patients			
National Tumour Institute Pascale Foundation, Italy	94 (12.4)	0 (0)	94 (9.1)
MD Anderson Cancer Center, TX, USA	92 (12.2)	0 (0)	92 (8.9)
Mayo Clinic Comprehensive Cancer Center, MN, USA	19 (2.5)	44 (15.6)	63 (6.1)
Gustave Roussy, France	27 (3.6)	25 (8.9)	52 (5.0)
<5% of patients			
Ludwig Maximilian University Hospital, Germany	0 (0)	35 (12.4)	35 (3.4)
Peter MacCallum Cancer Centre, Australia	12 (1.6)	23 (8.1)	35 (3.4)
AC Camargo Cancer Center, Brazil	0 (0)	28 (9.9)	28 (2.7)
University of Pennsylvania, PA, USA	26 (3.4)	0 (0)	26 (2.5)
Moffitt Cancer Center, FL, USA	0 (0)	21 (7.4)	21 (2.0)
N. N. Blokhin National Medical Research Centre of Oncology, Russia	0 (0)	21 (7.4)	21 (2.0)
University Hospital Tübingen, Germany	0 (0)	19 (6.7)	19 (1.8)
Saint-Louis Hospital, France	4 (0.5)	14 (5.0)	18 (1.7)
Maria Skłodowska-Curie National Research Institute of Oncology, Poland	0 (0)	13 (4.6)	13 (1.3)
Vanderbilt University Medical Center, TN, USA	0 (0)	14 (5.0)	14 (1.3)
Vall Hebron University Hospital, Spain	2 (0.3)	8 (2.8)	10 (1.0)
The Angeles Clinic and Research Institute, LA, USA	6 (0.8)	3 (1.1)	9 (0.9)
Blacktown Hospital, Australia	8 (1.1)	0 (0)	8 (0.8)
University Medical Center Groningen, The Netherlands	8 (1.1)	0 (0)	8 (0.8)
European Institute of Oncology Multimedica Group, Italy	6 (0.8)	0 (0)	6 (0.6)
Memorial Sloan Kettering Cancer Center, NY, USA	6 (0.8)	0 (0)	6 (0.6)
Leiden University Medical Center, The Netherlands	5 (0.7)	0 (0)	5 (0.5)
Erasmus Medical Center, The Netherlands	4 (0.5)	0 (0)	4 (0.4)
Utrecht Medical Center, The Netherlands	3 (0.4)	0 (0)	3 (0.3)
ESweden, Sweden	2 (0.3)	0 (0)	2 (0.2)

Final included patients per site.

Supplementary Table 2 | Neoadjuvant regimens (N=1,038)

	Abbreviation for Results, Tables, and Figs.	Trial (N=755)	Non-trial (N=283)	Overall (N=1,038)
ICI*, n (%)				
Anti-CTLA-4 alone	CTLA-4 alone	0 (0)	4 (1.4)	4 (0.4)
Anti-PD-1 alone	PD-1 alone	87 (11.5)	155 (54.8)	242 (23.3)
Anti-PD-1 + IO†	PD-1 + IO	376 (49.8)	113 (39.9)	489 (47.1)
<i>Anti-PD-1 + anti-CTLA-4</i>	PD-1 + CTLA-4	275 (36.4)	111 (39.2)	386 (37.2)
<i>Anti-PD-1 + anti-LAG3</i>	PD-1 + LAG3	56 (7.4)	2 (0.7)	58 (5.6)
<i>Anti-PD-1 + other IO</i>	PD-1 + other IO	45 (6.0)	0 (0)	45 (4.3)
BRAF/MEKi, n (%)				
BRAF alone	BRAF alone	0 (0)	1 (0.4)	1 (0.1)
BRAF/MEKi	BRAF/MEKi	112 (14.8)	6 (2.1)	118 (11.4)
ICI + TT*, n (%)				
ICI + TT	ICI + TT			
Anti-PD-1 + MEKi	PD-1 + MEKi	44 (5.8)	0 (0)	44 (4.2)
Anti-PD-1 + BRAF/MEKi	PD-1 + BRAF/MEKi	80 (10.6)	0 (0)	80 (7.7)
Anti-PD-1 + VEGFi	PD-1 + VEGFi	22 (2.9)	0 (0)	22 (2.1)
Anti-PD-1 + HDACi‡	PD-1 + HDACi	20 (2.6)	0 (0)	20 (1.9)
Anti-PD-1 + anti-CTLA-4 + HDACi‡	PD-1 + CTLA-4 + HDACi	14 (1.9)	0 (0)	14 (1.3)
Anti-PD-1 + anti-CTLA-4 + BRAF/MEKi	PD-1 + CTLA-4 + BRAF/MEKi	0 (0)	2 (0.7)	2 (0.2)
Anti-PD-1 + anti-LAG3 + BRAF/MEKi	PD-1 + LAG3 + BRAF/MEKi	0 (0)	2 (0.7)	2 (0.2)

Breakdown of neoadjuvant regimens included in the study by treatment setting (trial or non-trial). Each regimen and drug target includes a range of agents, dosing schedules, and treatment duration. Patients receiving intralesional therapies or chemotherapy were excluded. Italicized regimens are subsets of the preceding, but all percentages are calculated using the denominator in the column header. *PD-1 includes both anti-PD-1 and anti-PD-L1 agents. †IO includes any immuno-oncology agent(s), including other ICIs. ‡Patients receiving HDACi were from the DONIMI trial (NCT04133948) and stratified via IFN γ high or low. BRAF/MEKi, BRAF/MEK inhibitors; BRAFi, BRAF inhibitors; HDACi, HDAC inhibitors; ICI, immune checkpoint inhibitors; IFN, interferon; IO, immuno-oncology agent(s); MEKi, MEK inhibitors; TT, targeted therapy; VEGFi, VEGF inhibitors.

Supplementary Table 3 | Clinical trials (N=1,038)

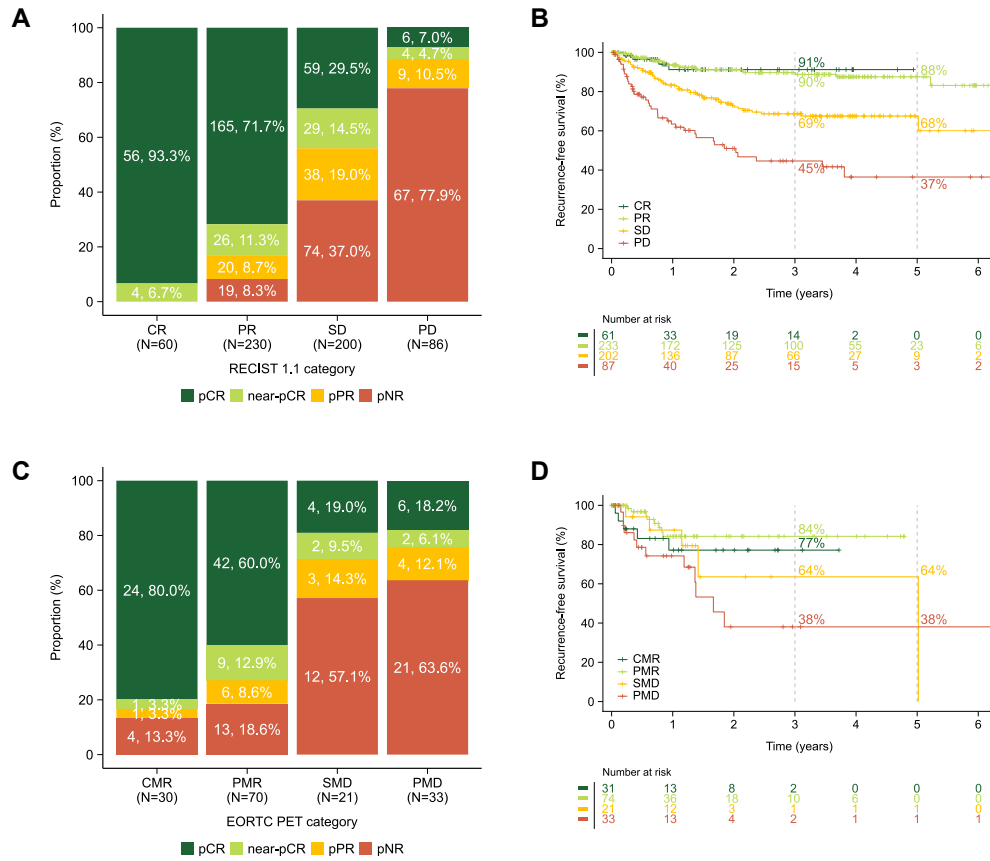
	ICI (N=735)			BRAF/MEKi (N=119)	ICI + TT (N=184)	Overall (N=1,038)
	All (N=735)	PD-1 alone (N=242)	PD-1 + IO (N=489)			
Non-trial patients, n (%)	272 (37.0)	155 (64.0)	113 (23.1)	7 (5.9)	4 (2.2)	283 (27.3)
Trial patients, n (%)	463 (63.0)	87 (36.0)	376 (76.9)	112 (94.1)	180 (97.8)	755 (72.7)
PRADO ³	99 (13.5)	0 (0)	99 (20.2)	0 (0)	0 (0)	99 (9.5)
NEO-TIM ⁴	0 (0)	0 (0)	0 (0)	29 (24.4)	65 (35.3)	94 (9.1)
OpACIN-neo ⁵	86 (11.7)	0 (0)	86 (17.6)	0 (0)	0 (0)	86 (8.3)
NeoTrio ⁶	20 (2.7)	20 (8.3)	0 (0)	0 (0)	40 (21.7)	60 (5.8)
Morpheus-Melanoma ⁷	57 (7.8)	1 (0.4)	56 (11.5)	0 (0)	0 (0)	57 (5.5)
NADINA ⁸	52 (7.1)	0 (0)	52 (10.6)	0 (0)	0 (0)	52 (5.0)
BMS CA209-291 ⁹	49 (6.7)	11 (4.5)	38 (7.8)	0 (0)	0 (0)	49 (4.7)
Combi-Neo ¹⁰	0 (0)	0 (0)	0 (0)	49 (41.2)	0 (0)	49 (4.7)
DONIMI ¹¹	10 (1.4)	10 (4.1)	0 (0)	0 (0)	34 (18.5)	44 (4.2)
KEYMAKER-U02C ¹²	41 (5.6)	17 (7.0)	24 (4.9)	0 (0)	0 (0)	41 (4.0)
NeoCombi ¹³	0 (0)	0 (0)	0 (0)	34 (28.6)	0 (0)	34 (3.3)
UPenn study ¹⁴	26 (3.5)	26 (10.7)	0 (0)	0 (0)	0 (0)	26 (2.5)
NeoPeLe ¹⁵	0 (0)	0 (0)	0 (0)	0 (0)	22 (12.0)	22 (2.1)
NeoACTIVATE ¹⁶	0 (0)	0 (0)	0 (0)	0 (0)	19 (10.3)	19 (1.8)
OpACIN ¹⁸	10 (1.4)	0 (0)	10 (2.0)	0 (0)	0 (0)	10 (1.0)
IEO838 ¹⁹	6 (0.8)	0 (0)	6 (1.2)	0 (0)	0 (0)	6 (0.6)
IOB-032/PN-E40 ¹⁷	6 (0.8)	1 (0.4)	5 (1.0)	0 (0)	0 (0)	6 (0.6)
SWOG S1801 ²⁰	1 (0.1)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.1)

Final included clinical trials. BRAF/MEKi, BRAF/MEK inhibitors; ICI, immune checkpoint inhibitors; IO, immuno-oncology agent(s); TT, targeted therapy.

Supplementary Table 4 | Clinicopathological factors associated with pCR in patients treated with ICI (N=735)

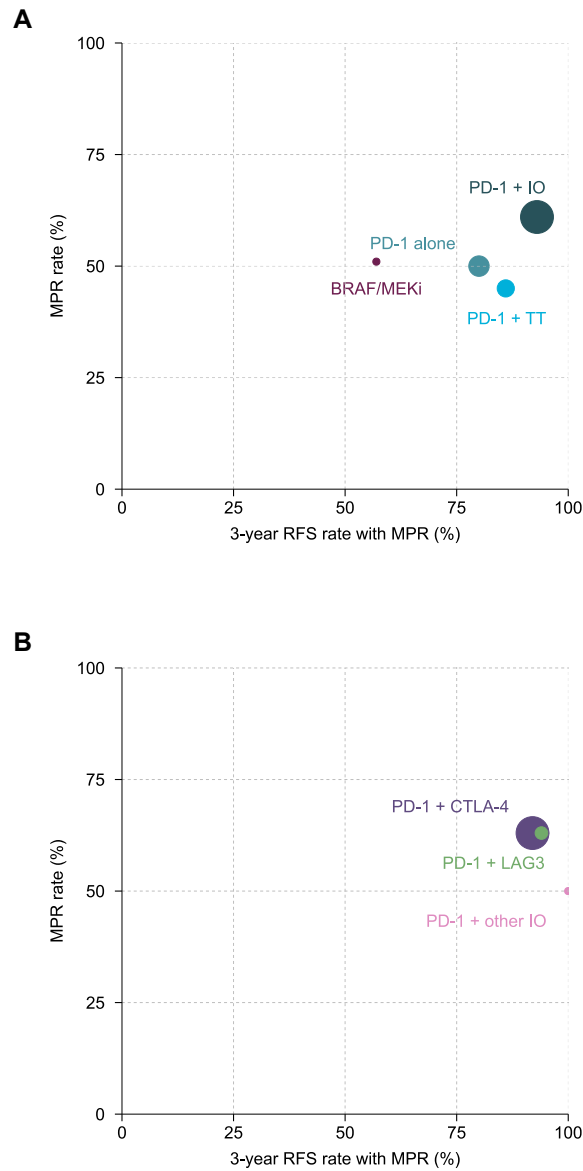
	Univariate		Multivariate*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.01 (1.00, 1.02)	0.2062		
Sex				
Female	1	0.4984		
Male	1.11 (0.82, 1.52)			
Primary site				
Extremity	1	0.0098		
Trunk	0.73 (0.47, 1.14)			
Head and neck	1.50 (0.92, 2.46)			
Acral	0.26 (0.08, 0.80)			
Occult	0.91 (0.58, 1.41)			
BRAF mutation status				
Wildtype	1	0.0368	1	0.0438
V600	0.67 (0.48, 0.93)		0.67 (0.48, 0.93)	
Non-V600	1.04 (0.47, 2.30)		1.03 (0.45, 2.36)	
Baseline disease				
Nodal only	1	0.6401	1	0.0005
In-transits only	0.99 (0.50, 1.93)		0.52 (0.35, 0.78)	
Nodal plus in-transits	0.75 (0.41, 1.37)		0.44 (0.28, 0.68)	
Nodal site				
Neck	1	0.0008		
Axilla	0.57 (0.39, 0.84)			
Groin	0.46 (0.30, 0.69)			
AJCC 8th ed. stage				
IIIB	1	0.0303		
IIIC	0.68 (0.49, 0.94)			
IIID	0.34 (0.10, 1.10)			
IV	0.46 (0.17, 1.28)			
SOD largest nodes (mm)	0.99 (0.98, 1.00)	0.0379		
Neoadjuvant ICI treatment type				
PD-1 alone	1	0.0272		
PD-1 + IO	1.45 (1.04, 2.02)			
Neoadjuvant therapy duration (weeks)	1.00 (0.99, 1.02)	0.6336		
Treatment course				
Completed	1	0.8662		
Ceased early	0.96 (0.58, 1.57)			
Treatment setting				
Non-trial	1	0.6538		
Trial	0.93 (0.68, 1.28)			

Analysis included 682 ICI-treated patients with an available pathological response assessment, of whom 319 had pCR events. Age is at start of neoadjuvant treatment. *Variable selection for the multivariate model was performed using the penalized Least Absolute Shrinkage and Selection Operator (LASSO) method. All p-values were calculated using two-sided Wald tests. AJCC, American Joint Committee on Cancer; ICI, immune checkpoint inhibitors; IO, immuno-oncology agent(s); OR, odds ratio; pCR, pathological complete response; SOD, sum-of-diameters.



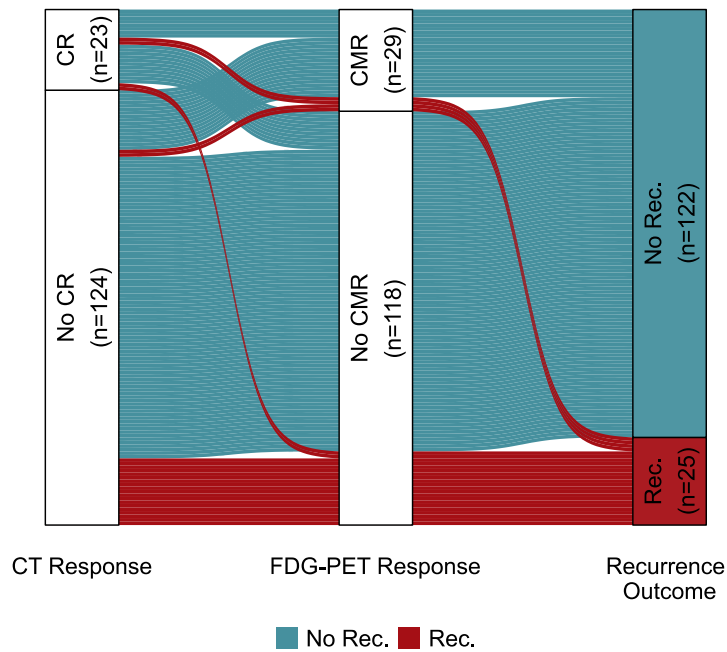
Supplementary Fig. 1 | RFS and pathological response by CT and FDG-PET response in patients treated with ICI (N=735)

Association of imaging response with pathological response and RFS in ICI-treated patients. Pathological response data shown in 100% stacked column graphs; white data labels are n, %. CT response as per RECIST 1.1¹ and FDG-PET response as per EORTC PET² categories. **A** See data labels. **B** Per RECIST 1.1: At 3 years, RFS rates were 91.2% (95% CI 83.2–100) with CR, 89.6% (85.3–94.2) with PR, 68.7% (61.7–76.5) with SD, and 44.6% (33.6–59.3) with PD. At 5 years, RFS rates were 87.5% (95% CI 82.4–93.0), 67.5% (60.3–75.6), and 36.5% (24.2–54.9) with PR, SD, and PD, respectively; 5-year data was not available for CR. **C** See data labels. **D** Per FDG-PET: At 3 years, RFS rates were 77.2% (95% CI 61.1–97.5) with CMR, 84.2% (74.6–95.0) with PMR, 63.6% (38.1–100) with SMD, and 38.1% (20.0–72.6) with PMD. At 5 years, RFS rates were 63.6% (95% CI 38.1–100) and 38.1% (20.0–72.6) with SMD and PMD, respectively; 5-year data was not available for CMR or PMR. CMR, complete metabolic response; CR, complete response; CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; ICI, immune checkpoint inhibitors; pCR, pathological complete response; PD, progressive disease; PMD, progressive metabolic disease; PMR, partial metabolic response; pNR, pathological non-response; pPR, pathological partial response; PR, partial response; RFS, recurrence-free survival; SD, stable disease; SMD, stable metabolic disease.



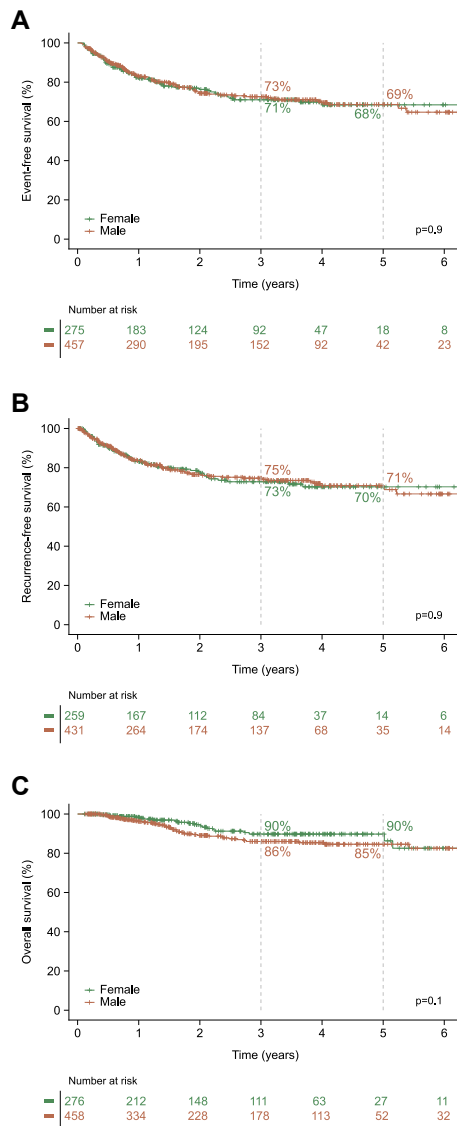
Supplementary Fig. 2 | Bubble plots of MPR rate versus 3-year RFS rate with MPR by treatment regimen (N=1,038)

Bubble plots of MPR rate (y-axis) and 3-year RFS rate in patients with MPR (x-axis) in 959 patients with pathological response data. Bubble size reflects number of patients. **A PD-1 alone:** MPR rate of 49.5% (103/208) and 3-year RFS rate with MPR of 95.6% (95% CI 89.2–100); **PD-1 + IO:** MPR rate of 61.4% (290/472) and 3-year RFS rate with MPR of 92.8% (89.7–96.1); **BRAF/MEKi:** MPR rate of 51.4% (57/111) and 3-year RFS rate with MPR of 60.4% (48.4–75.5); **ICI + TT:** MPR rate of 44.6% (74/166) and 3-year RFS rate with MPR of 89.6% (81.5–98.5). **B PD-1 + CTLA-4:** MPR rate of 62.5% (233/373) and 3-year RFS rate with MPR of 92.2% (88.6–96.0); **PD-1 + LAG3:** MPR rate of 63.2% (36/57) and 3-year RFS rate with MPR of 92.8% (83.4–100); **PD-1 + other IO:** MPR rate of 50.0% (21/42) and 3-year RFS rate with MPR of 100%. BRAF/MEKi, BRAF/MEK inhibitors; ICI, immune checkpoint inhibitors; IO, immuno-oncology agent/s; MPR, major pathological response; RFS, recurrence-free survival; TT, targeted therapy.



Supplementary Fig. 3 | Alluvial plot of imaging responses and recurrence in patients treated with ICI (N=735)

Alluvial plot of 147 ICI-treated patients with CT and FDG-PET response categories, plus recurrence data (including some patients where precise change-from-baseline is unknown). CT response as per RECIST 1.1¹ and PET-FDG response as per EORTC PET² categories. CMR, complete metabolic response on FDG-PET; CR, complete response on CT; CT, computed tomography; EORTC, European Organization for Research and Treatment of Cancer; FDG-PET, fluorodeoxyglucose positron emission tomography; ICI, immune checkpoint inhibitors; Rec., recurrence; RECIST, Response Evaluation Criteria in Solid Tumors.



Supplementary Fig. 4 | EFS, RFS, and OS by sex in patients treated with ICI (N=735)

Survival rates for patients of female sex versus male sex treated with neoadjuvant ICI. **A** At 3 years, EFS rates were 71.0% (95% CI 65.1–77.5) in females and 72.6% (68.0–77.5) in males. At 5 years, EFS rates were 68.4% (95% CI 61.8–75.8) and 68.6% (63.3–74.4), respectively. **B** At 3 years, RFS rates were 72.8% (95% CI 66.7–79.5) in females and 74.7% (70.0–79.6) in males. At 5 years, RFS rates were 70.2% (95% CI 63.4–77.7) and 70.9% (65.4–76.8), respectively. **C** At 3 years, OS rates were 89.8% (95% CI 85.3–94.5) in females and 86.0% (82.1–90.1) in males. At 5 years, OS rates were 89.8% (95% CI 85.3–94.5) and 84.6% (80.3–89.1), respectively. EFS, event-free survival; ICI, immune checkpoint inhibitors; OS, overall survival; RFS, recurrence-free survival.

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