

Supplementary Online Content

Kok P-S, Cho D, Yoon W-H, et al. Validation of progression-free survival rate at 6 months and objective response rate for estimating overall survival in immune checkpoint inhibitor trials: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(9):e2011809. doi:10.1001/jamanetworkopen.2020.11809

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Predictive Models Developed From Training Data Set to Estimate End Points

Model from 20 RCTs	Model equation
PFS6 to predict OS12	$OS12 = (1.06 \times PFS6) + 0.16 + (0.04 \times \text{melanoma}) - (0.03 \times \text{NSCLC}) + (0 \times \text{other tumors})$
ORR to predict OS12	$OS12 = (0.15 \times \text{ORR}) + 0.52 + (0 \times \text{melanoma}) - (0.02 \times \text{NSCLC}) - (0.01 \times \text{other tumors})$
Refitted model from 60 RCTs	
ORR to predict OS12	$OS12 = (1.012324 \times \text{ORR}) + 0.3006825 + (0 \times \text{melanoma}) + (0.0021079 \times \text{NSCLC}) - (0.038521 \times \text{other tumors})$

Abbreviation: PFS6, 6-month progression-free survival rate; OS12, 12-month overall survival rate; ORR, objective response rate; NSCLC, non-small cell lung cancer

eTable 2. Summary of Included Trials

Trial	Treatment comparisons	Phase	Tumour	Line	Experimental arm	Selected PD-L1 population	Sample size of ICI arm
Training dataset							
Checkmate 017 ¹	ICI vs C	3	NSCLC	2	Nivolumab	No	135
Checkmate 025 ²	ICI vs C	3	Renal	2	Nivolumab	No	410
Checkmate 037 ^{3,4}	ICI vs C	3	Melanoma	2	Nivolumab	No	272
Checkmate 057 ⁵	ICI vs C	3	NSCLC	2	Nivolumab	No	292
Checkmate 141 ⁶	ICI vs C	3	Head and Neck SCC	2	Nivolumab	No	240
Checkmate 066 ⁷	ICI-C vs C	3	Melanoma	1	Nivolumab + Dacarbazine	No	210
Checkmate 026 ⁸	ICI vs C	3	NSCLC	1	Nivolumab	Yes	271
Attraction2 ⁹	ICI vs Placebo	3	Gastric/ Oesophageal	3	Nivolumab	No	330
CA184-024 ¹⁰	ICI-C vs C	3	Melanoma	1	Ipilimumab + Dacarbazine, followed by Dacarbazine, followed by Ipilimumab	No	250
CA 184-095 ¹¹	ICI vs Placebo	3	Prostate	1	Ipilimumab	No	400
Keynote 010 ¹²	ICI vs C	2/3	NSCLC	2	Pembrolizumab	Yes	346
Keynote 010 ¹²	ICI vs C	2/3	NSCLC	2	Pembrolizumab	Yes	345
Keynote 024 ^{13,14}	ICI vs C	3	NSCLC	1	Pembrolizumab	No	154
Keynote 002 ^{15,16}	ICI vs C	2	Melanoma	3	Pembrolizumab	No	181
Keynote 002 ^{15,16}	ICI vs C	2	Melanoma	3	Pembrolizumab	No	180
Keynote 021 ^{17,18}	ICI-C vs C	2	NSCLC	1	Pembrolizumab + Carboplatin + Pemetrexed, followed by Pembrolizumab + Pemetrexed	No	60
OAK ¹⁹	ICI vs C	3	NSCLC	2	Atezolizumab	No	425
Poplar ²⁰	ICI vs C	2	NSCLC	2	Atezolizumab	No	144
NCT00257205 ²¹	ICI vs C	3	Melanoma	1	Tremelimumab	No	328

DETERMINE ²²	ICI vs Placebo	2	Malignant Mesothelioma	2	Tremelimumab	No	382
CA 184-041 ²³	ICI-C vs C	2	NSCLC	1	Carboplatin + Paclitaxel, followed by Ipilimumab + Carboplatin + Paclitaxel, followed by Ipilimumab	No	68
CA 184-041 ²³	ICI-C vs C	2	NSCLC	1	Ipilimumab+ Carboplatin+ Paclitaxel, followed by Carboplatin + Paclitaxel, followed by Ipilimumab	No	70
CA 184-041 ¹⁶	ICI-C vs C	2	SCLC	1	Carboplatin + Paclitaxel, followed by Ipilimumab + Carboplatin + Paclitaxel, followed by Ipilimumab	No	45
CA 184-041 ²⁴	ICI-C vs C	2	SCLC	1	Ipilimumab+ Carboplatin+ Paclitaxel, followed by Carboplatin + Paclitaxel, followed by Ipilimumab	No	45
CA 184-056 ²⁵	ICI-C vs C	3	SCLC	1	Ipilimumab + Carboplatin/ Cisplatin and Etoposide, followed by Ipilimumab	No	566
Validation dataset							
IMPower 150 ²⁶	ICI-C vs C	3	NSCLC	1	Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin	No	356
Keynote 189 ²⁷	ICI-C vs C	3	NSCLC	1	Pembrolizumab + Platinum + Pemetrexed	No	410
Keynote 407 ²⁸	ICI-C vs C	3	NSCLC	1	Pembrolizumab+ Carboplatin + Paclitaxel/ nab-paclitaxel, followed by Pembrolizumab	No	278
Checkmate 227 ²⁹	ICI-C vs C	3	NSCLC	1	Nivolumab + Chemotherapy	No	177
IMPassion 130 ³⁰	ICI-C vs C	3	Triple negative breast cancer	1	Atezolizumab + nab-paclitaxel	Yes	451
IMPower 133 ³¹	ICI-C vs C	3	SCLC	1	Atezolizumab + Carboplatin + Etoposide	No	201
Keynote 048 ³²	ICI-C vs C	3	Head and Neck SCC	1	Pembrolizumab + Carboplatin/ Cisplatin + 5FU, followed by Pembrolizumab	No	281
IMPower 131 ³³	ICI-C vs C	3	NSCLC	1	Atezolizumab+ Carboplatin + nab-paclitaxel	No	343
IMPower 132 ³⁴	ICI-C vs C	3	NSCLC	1	Atezolizumab + Cisplatin/ Carboplatin + Pemetrexed, followed by Atezolizumab + Pemetrexed	No	292
Kate2 ³⁵	ICI-C vs C	2	Triple negative breast cancer	2+	Atezolizumab + TDM1	No	133
Keynote 062 ³⁶	ICI-C vs C	3	Gastric/ Oesophageal	1	Pembrolizumab+ Chemotherapy (Cisplatin + 5FU/ Capecitabine)	Yes	257

IMpower 130 ³⁷	ICI-C vs C	3	NSCLC	1	Atezolizumab + Carboplatin + nab-paclitaxel, followed by Atezolizumab	No	451
Javelin Renal 101 ³⁸	ICI-TKI vs TKI	3	Renal	1	Avelumab + Axitinib	Yes	270
Keynote 426 ²¹	ICI-TKI vs TKI	3	Renal	1	Pembrolizumab + Axitinib	No	432
ImBlaze370 ³⁹	ICI-TKI vs TKI	3	CRC	3	Atezolizumab + Cobimetinib	No	183
CCTG CO.26 ³⁹	ICI vs BSC	2	CRC	3+	Durvalumab + Tremelimumab, followed by Durvalumab	No	119
Keynote 240 ⁴⁰	ICI vs BSC	3	HCC	2	Pembrolizumab + BSC	No	278
Checkmate 227 ⁴¹	ICI vs C	3	NSCLC	1	Ipilimumab + Nivolumab	Yes	139
Keynote 048 ³²	ICI vs C	3	Head and Neck SCC	1	Pembrolizumab	No	301
Javelin Lung 200 ⁴²	ICI vs C	3	NSCLC	2	Avelumab	Yes	264
ARCTIC ⁴³	ICI vs C	3	NSCLC	3	Durvalumab	Yes	62
ARCTIC ⁴³	ICI vs C	3	NSCLC	3	Durvalumab + Tremelimumab, followed by Durvalumab	Yes	174
Checkmate 214 ⁴⁴	ICI vs C	3	Renal	1	Ipilimumab + Nivolumab, followed by Nivolumab	No	425
IMMOTION 151 ⁴⁵	ICI vs C	3	Renal	1	Atezolizumab + Bevacizumab	Yes	178
Keynote 040 ⁴⁶	ICI vs C	3	Head and Neck SCC	2	Pembrolizumab	Yes	247
Javelin Gastric 300 ⁴⁷	ICI vs C	3	Gastric/ Oesophageal	3	Avelumab	No	185
IMvigor 211 ⁴⁸	ICI vs C	3	Urothelial	2	Atezolizumab	Yes	116
IMMOTION 150 ⁴⁹	ICI vs C	2	Renal	1	Atezolizumab	Yes	103
IMMOTION 150 ⁴⁹	ICI vs C	2	Renal	1	Atezolizumab + Bevacizumab	Yes	101
Checkmate 331 ⁵⁰	ICI vs C	3	SCLC	2	Nivolumab	No	284
Mystic ⁵¹	ICI vs C	3	NSCLC	1	Durvalumab + Tremelimumab	Yes	163
Mystic ⁵¹	ICI vs C	3	NSCLC	1	Durvalumab	Yes	163
Keynote 181 ^{52, 53}	ICI vs C	3	Gastric/ Oesophageal	2	Pembrolizumab	Yes	107

Keynote 061 ⁵⁴	ICI vs C	3	Gastric/ Oesophageal	2	Pembrolizumab	Yes	196
Keynote 042 ⁵⁵	ICI vs C	3	NSCLC	1	Pembrolizumab	Yes	637
IMBlaze370 ³⁹	ICI vs C	3	CRC	3	Atezolizumab	No	90
EAGLE ⁵⁶	ICI vs C	3	Head and Neck SCC	2+	Durvalumab	No	240
EAGLE ⁵⁶	ICI vs C	3	Head and Neck SCC	2+	Durvalumab + Tremelimumab	No	247
Keynote 062 ³⁶	ICI vs C	3	Gastric/ Oesophageal	1	Pembrolizumab	Yes	256
Checkmate 078 ⁵⁷	ICI vs C	3	NSCLC	2	Nivolumab	No	338
Keynote 045 ⁵⁸	ICI vs C	3	Urothelial	2	Pembrolizumab	Yes	270
Checkmate 067 ⁵⁹	ICI vs ICI	3	Melanoma	1	Ipilimumab + Nivolumab, followed by Nivolumab	No	314
Checkmate 067 ⁵⁹	ICI vs ICI	3	Melanoma	1	Nivolumab	No	316
NCT01927419 ⁶⁰	ICI vs ICI	2	Melanoma	1	Ipilimumab + Nivolumab, followed by Nivolumab	No	72
Keynote 006 ⁶¹	ICI vs ICI	3	Melanoma	1	Pembrolizumab	No	279
Keynote 006 ⁶¹	ICI vs ICI	3	Melanoma	1	Pembrolizumab	No	277
NCT01740297 ⁶²	ICI vs T-Vec	2	Melanoma	1-2	Ipilimumab + Talimogene laherparepvec	No	98
LUNG-MAP ⁶³	ICI vs ICI	3	NSCLC	1-3	Ipilimumab + Nivolumab	No	125
IFCT-1501 MAPS2 ⁶⁴	ICI vs ICI	2	Malignant Mesothelioma	2+	Nivolumab	No	63

Abbreviations: ICI, immune checkpoint inhibitor; C, Chemotherapy; ICI-C, combination of immune checkpoint inhibitor and chemotherapy; ICI-TKI, combination of immune checkpoint inhibitor and tyrosine kinase inhibitor; BSC, best supportive care; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CRC, colorectal cancer; SCC, squamous cell carcinoma.

eTable 3. Summary of Immune Checkpoint Inhibitor Arms in Included Trials

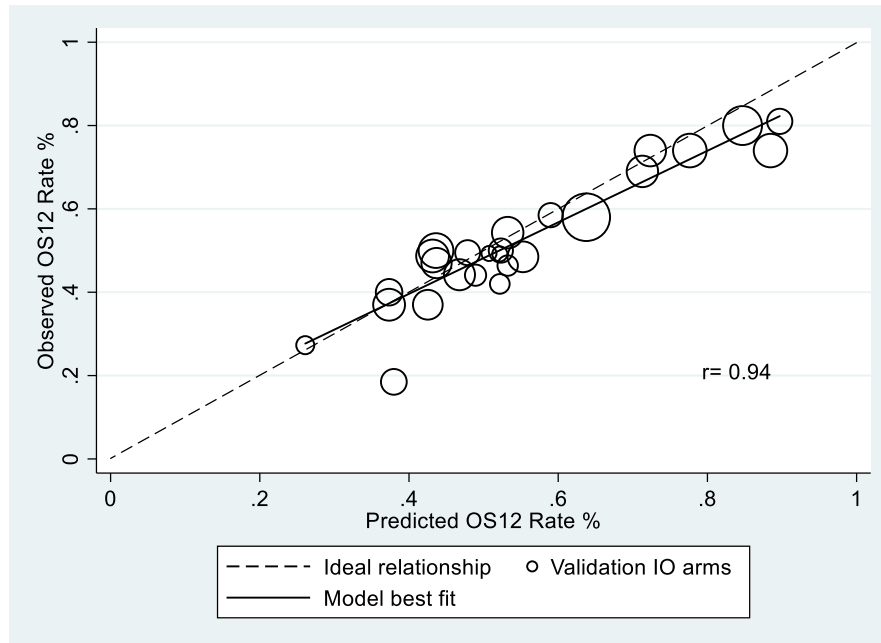
Summary of ICI arms	Training dataset (n=25)	Validation dataset (n=49)	Combined dataset (n=74)
Phase			
3	14 (56)	42 (86)	56 (76)
2 or 2/3	11 (44)	7 (14)	18 (24)
ICI regimen			
ICI combined with chemotherapy or TKI	8 (32)	15 (30)	23 (31)
ICI-only (singlet/ doublet)	17 (68)	34 (70)	51 (69)
Line of treatment			
First line	12 (48)	28 (57)	40 (54)
Second and subsequent line	13 (52)	21 (43)	34 (46)
Tumour			
Melanoma	6 (24)	6 (12)	12 (16)
NSCLC	11 (44)	16 (33)	27 (36)
Others	8 (32)	27 (55)	35 (47)
PD-L1 selection			
PD-L1 selected	3 (12)	19 (39)	22 (30)
PD-L1 unselected	22 (88)	30 (61)	52 (70)

Note. Values are No. (%) unless otherwise indicated.

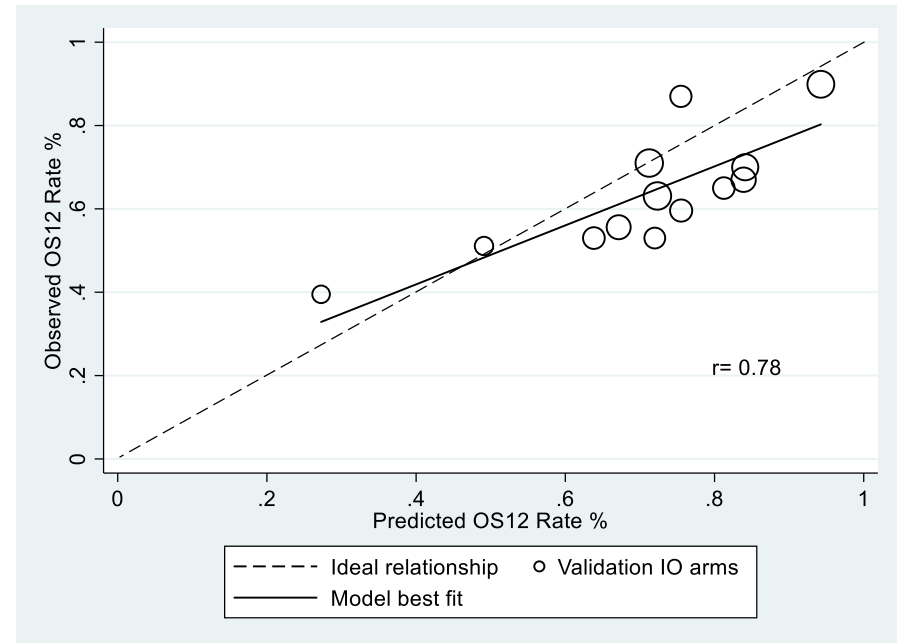
Abbreviation: ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer

eFigure 1. Six-Month Progression Free Survival Model–Predicted vs Observed 12-Month Overall Survival in Immune Checkpoint Inhibitor Arms in the Subgroups and Validation Trial Data Set

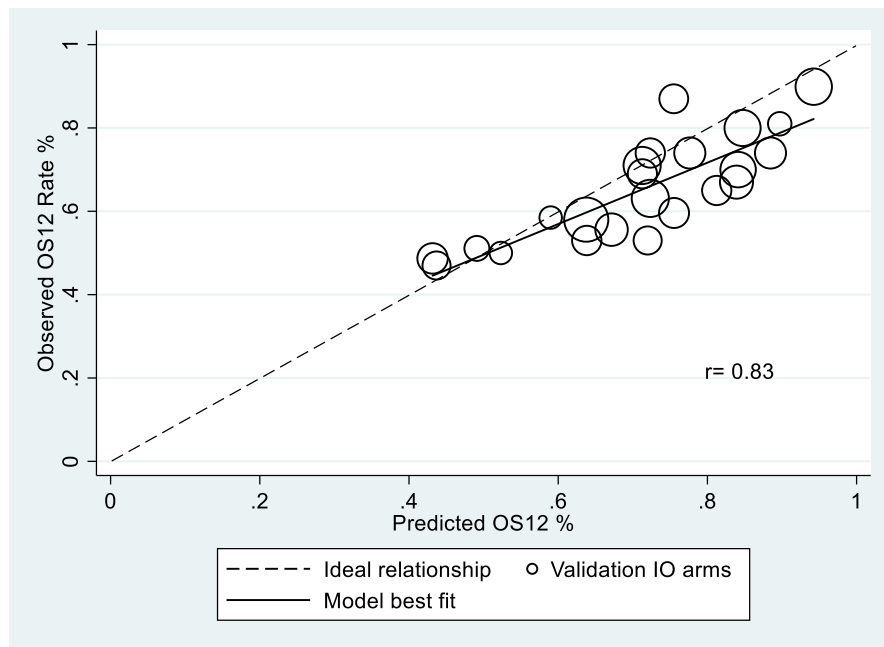
A. ICI-only



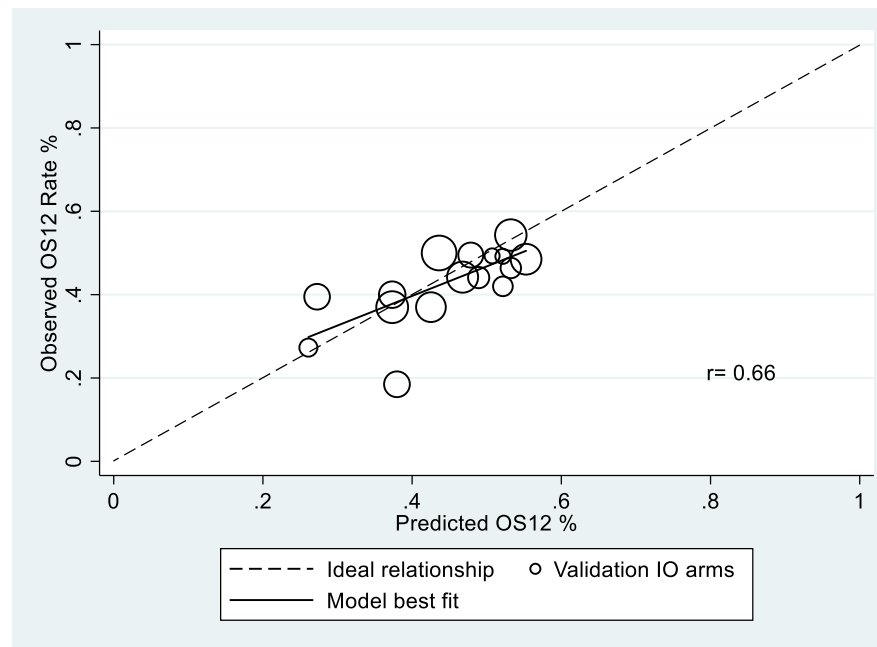
B. ICI-C



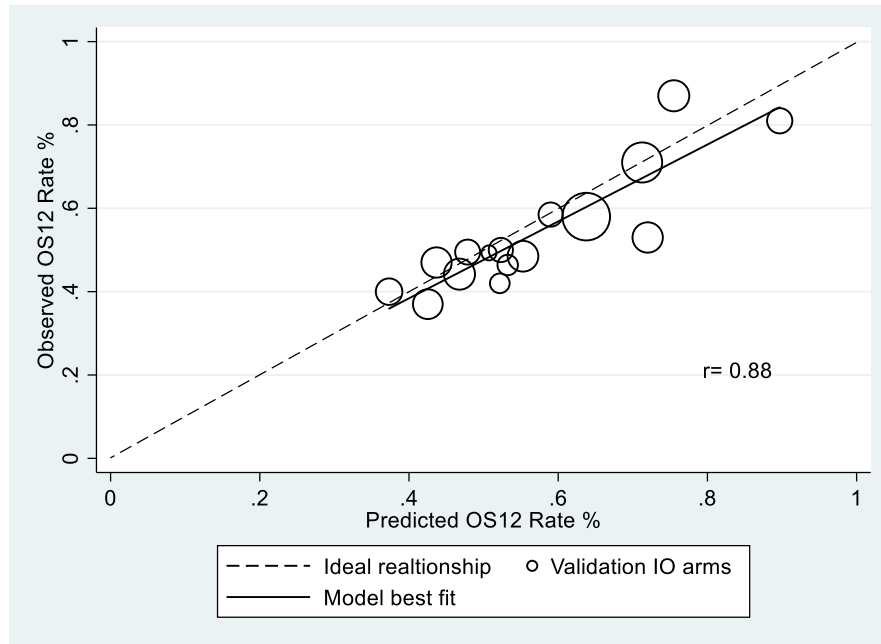
C. First line



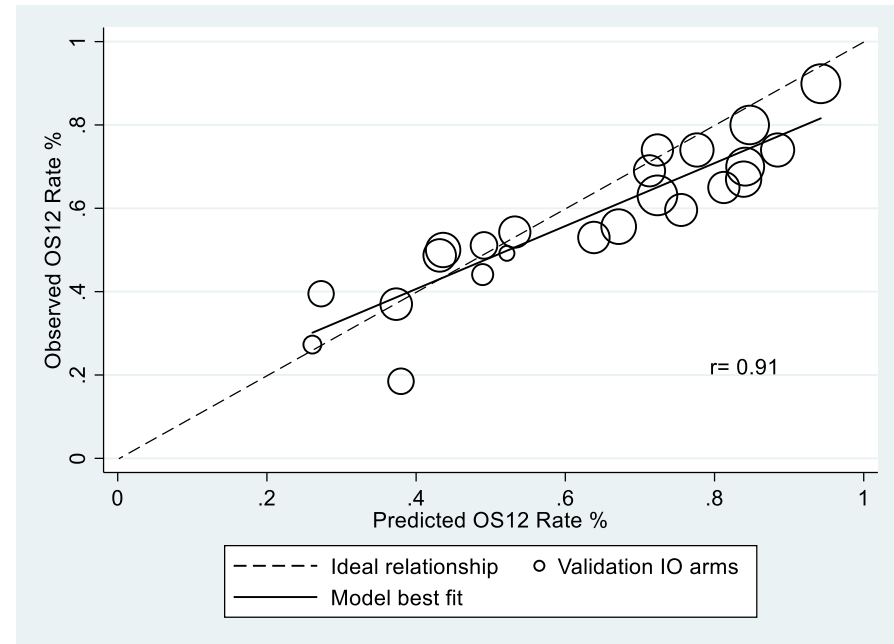
D. Second and subsequent line



E. PD-L1 selected



F. PD-L1 unselected

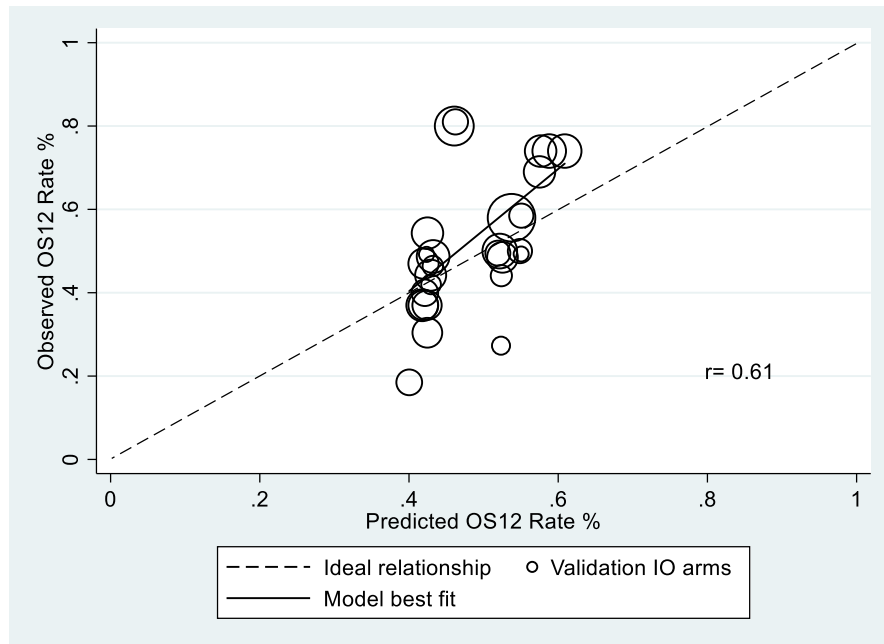


A: ICI-only B: ICI-C C: First line. D: Second and subsequent line. E. PD-L1 selected. F. PD-L1 unselected. Size of each circle represents size of immune checkpoint inhibitor arm.

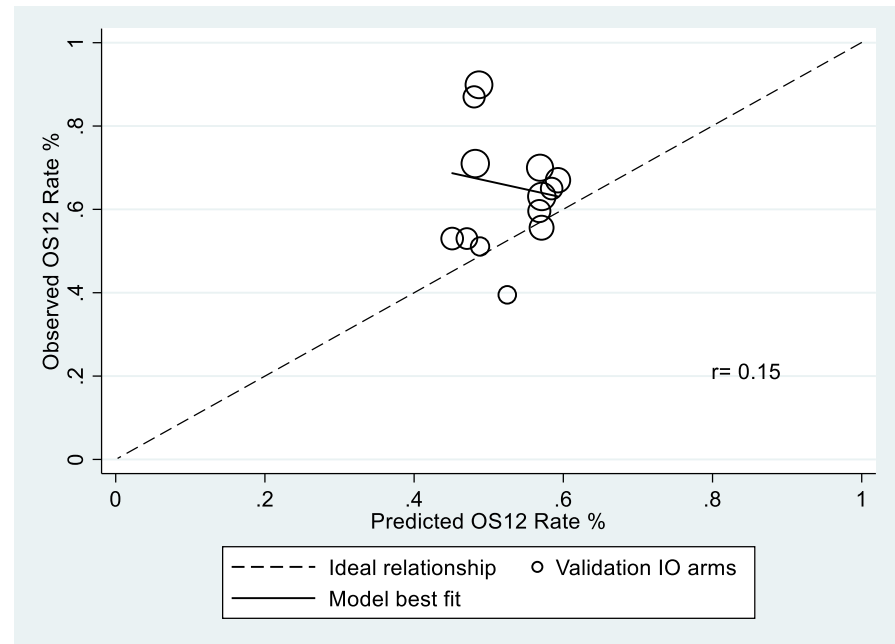
Abbreviations: PFS6, 6-month progression-free survival; OS, overall survival; OS12, 12-month overall survival rate; ICI, immune checkpoint inhibitor; ICI-C, combination of immune checkpoint inhibitor and chemotherapy or tyrosine kinase inhibitor; PD-L1, programmed death-ligand 1

eFigure 2. Objective Response Rate Model–Predicted vs Observed 12-Month Overall Survival in Immune Checkpoint Inhibitor Arms in the Subgroups and Validation Trial Data Set

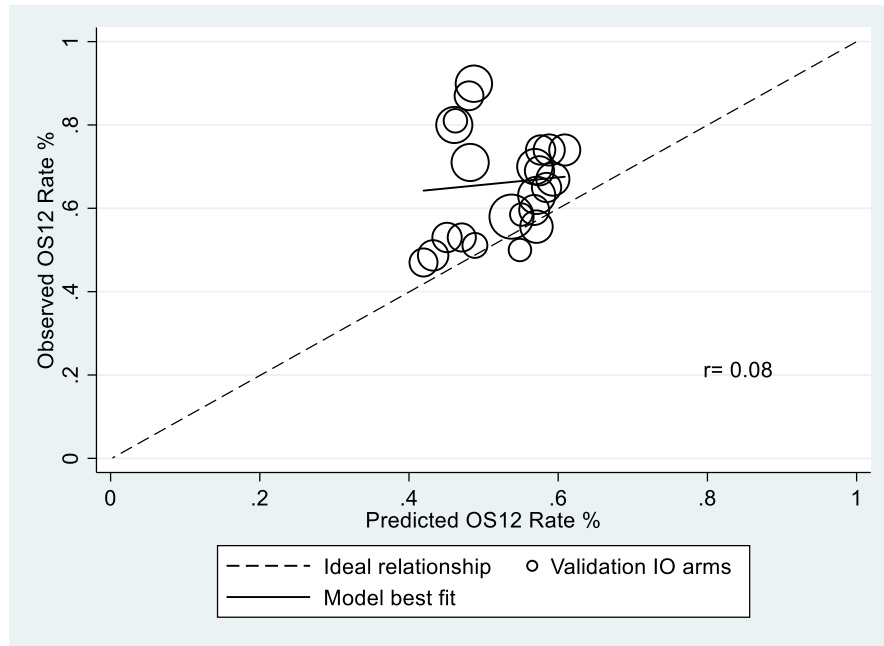
A. ICI-only



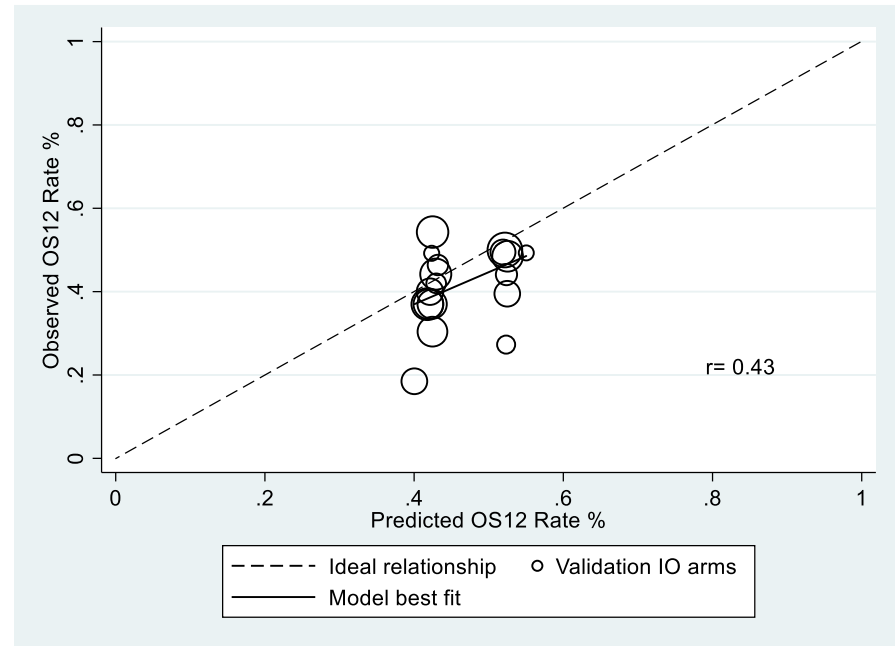
B. ICI-C



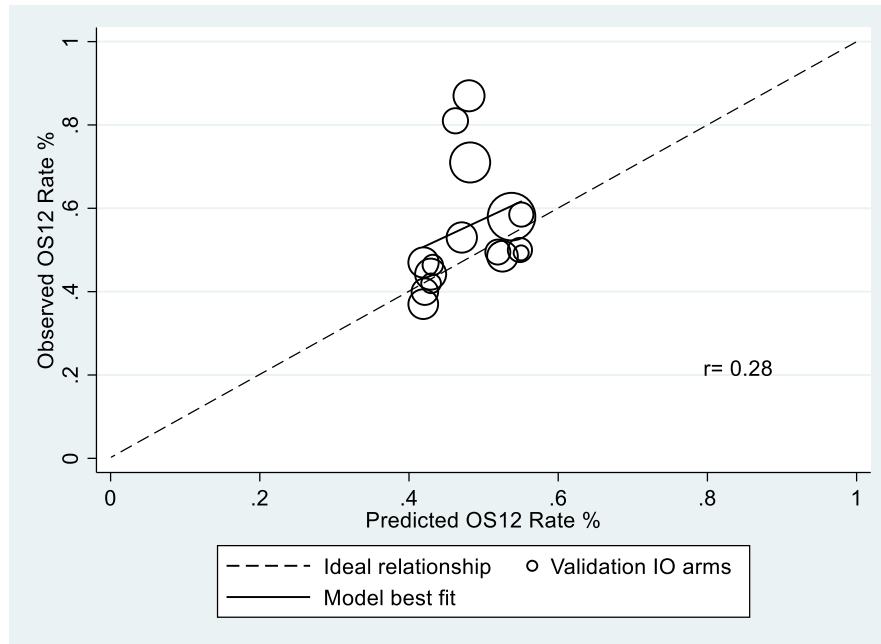
C. First line



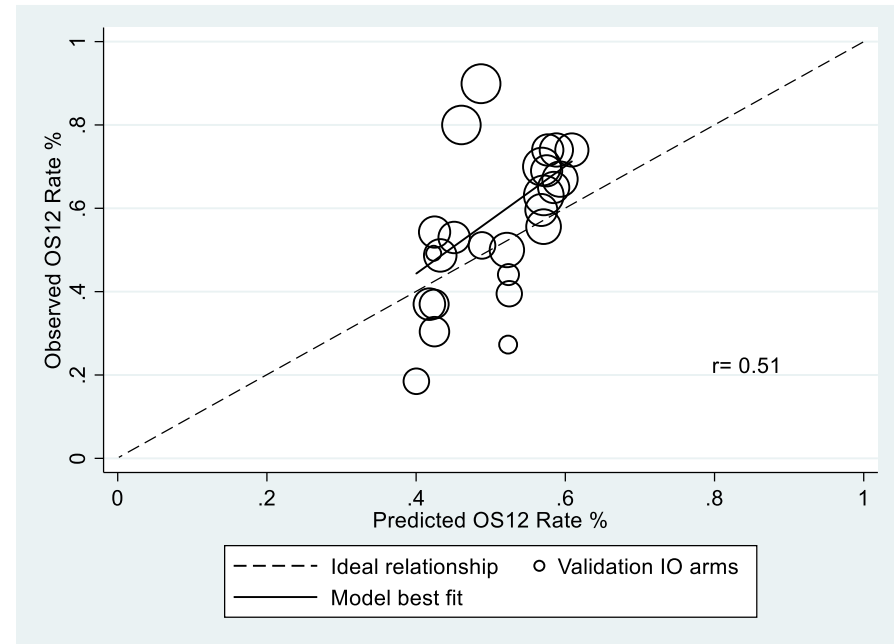
D. Second and subsequent line



E. PD-L1 selected



F. PD-L1 unselected

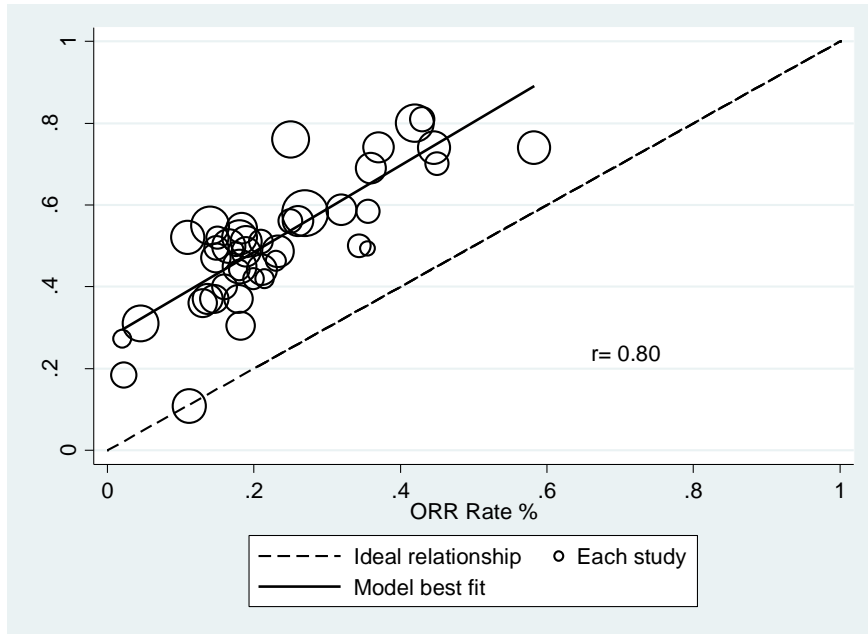


A: ICI-only B: ICI-C C: First line D: Second and subsequent line E. PD-L1 selected F. PD-L1 unselected. Size of each circle represents size of immune checkpoint inhibitor arm.

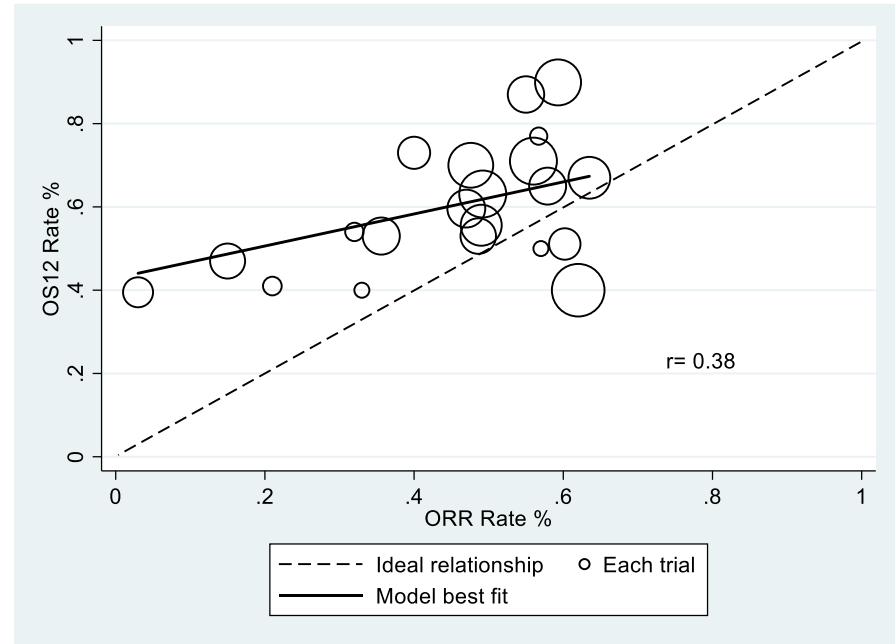
Abbreviations: ORR, objective response rate; OS, overall survival; OS12, 12-month overall survival rate; ICI, immune checkpoint inhibitor; ICI-C, combination of immune checkpoint inhibitor and chemotherapy or tyrosine kinase inhibitor; PD-L1, programmed death-ligand 1.

eFigure 3. Correlations Between Objective Response Rate and 12-Month Overall Survival in Immune Checkpoint Inhibitor Arms in the Subgroups and Entire Trial Data Set

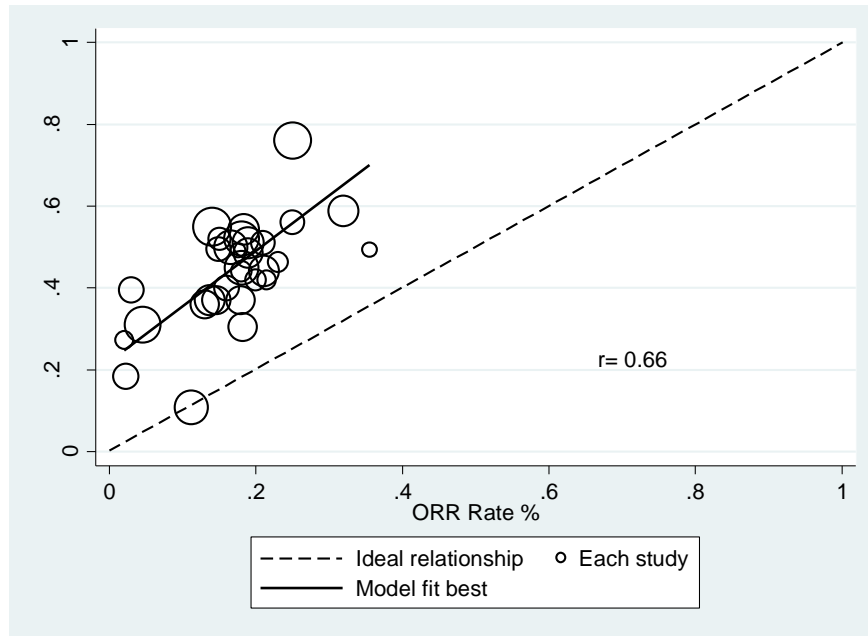
A. ICI-only



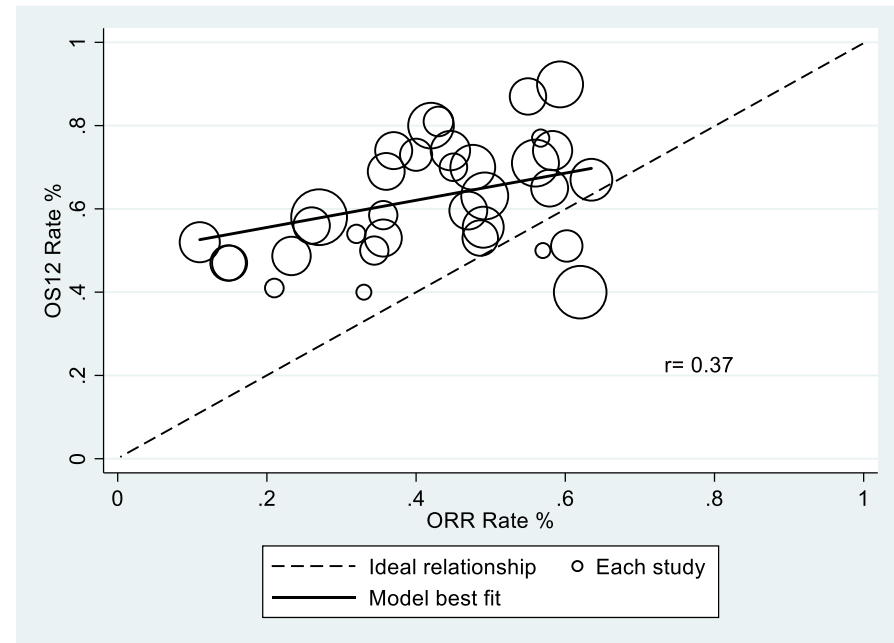
B. ICI-C



C. Second and subsequent line



D. First line



A: ICI-only B: ICI-C C: First line D: Second and subsequent line. Size of each circle represents size of immune checkpoint inhibitor arm.

Abbreviations: ORR, objective response rate; OS, overall survival; OS12, 12-month overall survival rate; ICI, immune checkpoint inhibitor; ICI-C, combination of immune checkpoint inhibitor and chemotherapy or tyrosine kinase inhibitor.

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