

Odds ratio (CI; p-val; N)**Biomarker (cohort)**

response ←

→ resistance

0.21 (0.14, 0.32; p=1e-16; 731)

PDL1-TC (cpi)

0.72 (0.51, 1.01; p=0.06; 1004)

PDL1-TC (chemo)

0.42 (0.32, 0.57; p=8e-10; 1252)

TMB (cpi)

1.17 (0.71, 1.93; p=0.5; 446)

TMB (chemo)

0.68 (0.54, 0.85; p=5e-04; 2016)

ALB (cpi)

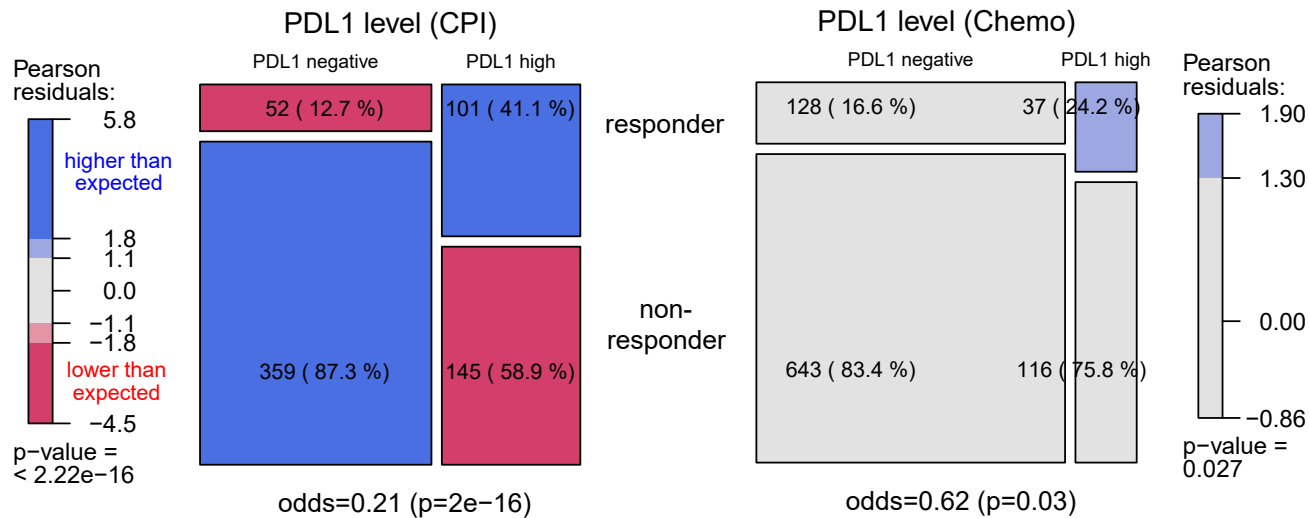
0.48 (0.36, 0.64; p=2e-07; 1398)

ALB (chemo)

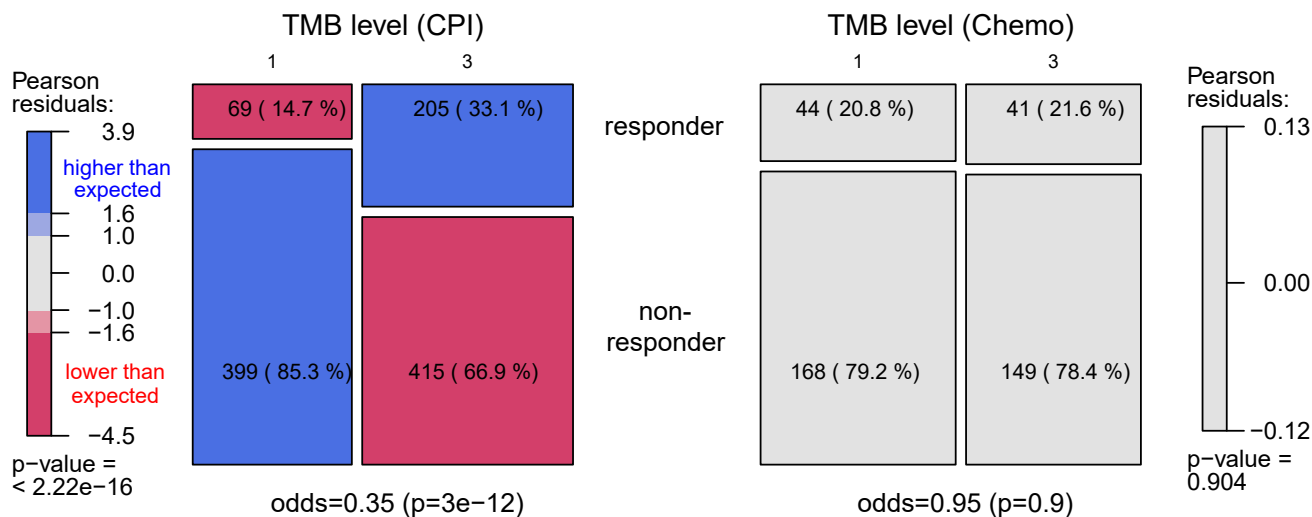
0.12 0.25 0.50 1.0 2.0
Odds Ratio (log scale)

suppFig1

A

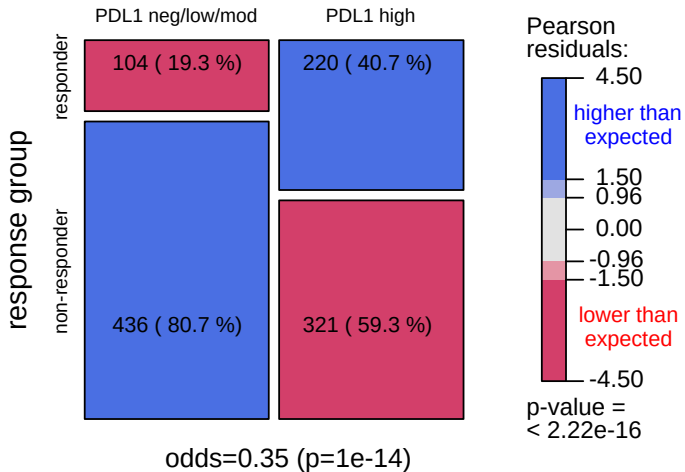


B



area: proportion of patients; color: deviation from expected frequency

suppFig2



suppFig3

Supplemental Material Predictive biomarkers for checkpoint inhibitor response in NSCLC

Supplementary Figure 1. Association of biomarker levels with treatment outcome without removing patients with early deaths.

Forest plot of association of baseline tumor PD-L1 and TMB, and serum albumin with response to CPI versus chemotherapy in CGDB and atezolizumab trial patients. PDL1 and TMB showed the same pattern of predictive effect on CPI response, and weak or no effect on chemotherapy response. On the other hand, albumin had an increased effect (a left shift of the ORs) for both CPI and chemotherapy responses compared to Figure 3C (analysis restricted to patients survived ≥ 18 weeks after treatment start).

Supplementary Figure 2. Predictive effect of PD-L1 and TMB for responses to CPI or chemotherapy using unbalanced cohorts.

A) Distribution of CPI (left plot) and chemotherapy (right plot) durable responders and non-responders among the PD-L1-high and PD-L1-negative patients in CGDB and atezolizumab trials. B) Distribution of CPI (left plot) and chemotherapy (right plot) durable responders and non-responders among the TMB high and low patients in CGDB and atezolizumab trials.

Supplementary Figure 3. Correlation of PDL1 high versus combined moderate/low/negative expression with response to CPI.

Distribution of CPI durable responders and non-responders among the PD-L1-high and combined PD-L1-negative and PD-L1-low/mod patients in CGDB and atezolizumab trials.

Refer to Figure 3A for mosaic plot legends.

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Supplementary Tables

Supplementary Table 1. Characteristics of all the starting NSCLC patient cohorts considered for the analysis from the three data sources (the 71850 patients in the top box in Figure 1A).

	atezo⁴ (N=6437)	CGDB⁵ (N=9439)	FH⁶ (N=55974)
Age¹			
Mean (SD)	63.3 (9.33)	67.4 (10.4)	68.5 (9.48)
Median [Min, Max]	64.0 [18.0, 90.0]	68.0 [23.0, 86.0]	70.0 [11.0, 85.0]
Missing	9 (0.1%)	5 (0.1%)	0 (0%)
Sex			
F	2257 (35.1%)	4837 (51.2%)	26460 (47.3%)
M	4180 (64.9%)	4602 (48.8%)	29508 (52.7%)
Unknown	0 (0%)	0 (0%)	6 (0.0%)
Race			
African American	124 (1.9%)	522 (5.5%)	4824 (8.6%)
Asian	1015 (15.8%)	286 (3.0%)	1399 (2.5%)
Caucasian	5001 (77.7%)	6485 (68.7%)	39159 (70.0%)
Other	33 (0.5%)	1314 (13.9%)	0 (0%)
Unknown	264 (4.1%)	832 (8.8%)	10592 (18.9%)
ECOG PS²			
0	2344 (36.4%)	2988 (31.7%)	11760 (21.0%)
1	4052 (62.9%)	3600 (38.1%)	16067 (28.7%)
2	30 (0.5%)	1022 (10.8%)	6576 (11.7%)
3	3 (0.0%)	274 (2.9%)	2025 (3.6%)
4	2 (0.0%)	17 (0.2%)	150 (0.3%)
Missing	6 (0.1%)	1538 (16.3%)	19396 (34.7%)
Disease Stage³			
Stage 0	0 (0%)	1 (0.0%)	4 (0.0%)
Stage I	390 (6.1%)	1003 (10.6%)	5050 (9.0%)
Stage II	403 (6.3%)	757 (8.0%)	2917 (5.2%)
Stage III	972 (15.1%)	2093 (22.2%)	11562 (20.7%)
Stage IV	4564 (70.9%)	5209 (55.2%)	34442 (61.5%)
Unknown	108 (1.7%)	376 (4.0%)	1999 (3.6%)
Smoking History			
Previous/Current	5449 (84.7%)	7758 (82.2%)	48720 (87.0%)
Never	988 (15.3%)	1644 (17.4%)	6557 (11.7%)
Unknown	0 (0%)	37 (0.4%)	697 (1.2%)
Histology			

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NonSquamous	4593 (71.4%)	7106 (75.3%)	38356 (68.5%)
Squamous	1763 (27.4%)	1925 (20.4%)	14567 (26.0%)
Unknown	81 (1.3%)	408 (4.3%)	3051 (5.5%)

¹ Age - age data at advanced diagnosis time for the RWD sources (FH and CGDB), and at study start for the atezolizumab trials.

² ECOG PS - Eastern Cooperative Oncology Group Performance Status at advanced diagnosis time for the RWD sources (FH and CGDB), and at study start for the atezolizumab trials.

³ Disease stage - Group stage at initial diagnosis for the RWD sources (FH and CGDB), and at study start for the atezolizumab trials.

⁴ atezo - atezolizumab NSCLC trials

⁵ CGDB - Clinicogenomic database by Flatiron Health-Foundation Medicine Inc

⁶ FH - Flatiron Health database

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Supplementary Table 2. Characteristics of patients who were analyzed for tumor PD-L1 data

	CPI					chemo				
	atezo response (N=800)	CGDB response (N=310)	atezo progression (N=927)	CGDB progression (N=328)	FH progression (N=2166)	atezo response (N=1183)	CGDB response (N=48)	atezo progression (N=1366)	CGDB progression (N=50)	FH progression (N=943)
Age¹										
Mean (SD)	62.5 (9.95)	68.2 (10.1)	62.9 (9.77)	68.6 (10.0)	69.7 (9.31)	63.1 (8.86)	61.5 (11.5)	63.1 (8.86)	61.1 (11.3)	68.4 (9.30)
Median [Min, Max]	63.0 [28.0, 86.0]	69.0 [38.0, 85.0]	64.0 [28.0, 86.0]	69.0 [38.0, 85.0]	71.0 [38.0, 85.0]	64.0 [30.0, 87.0]	63.5 [35.0, 83.0]	64.0 [30.0, 87.0]	61.0 [35.0, 83.0]	69.0 [34.0, 84.0]
Sex										
F	309 (38.6%)	156 (50.3%)	360 (38.8%)	169 (51.5%)	1047 (48.3%)	400 (33.8%)	24 (50.0%)	466 (34.1%)	25 (50.0%)	444 (47.1%)
M	491 (61.4%)	154 (49.7%)	567 (61.2%)	159 (48.5%)	1119 (51.7%)	783 (66.2%)	24 (50.0%)	900 (65.9%)	25 (50.0%)	499 (52.9%)
Race										
Caucasian	627 (78.4%)	217 (70.0%)	731 (78.9%)	235 (71.6%)	1529 (70.6%)	934 (79.0%)	36 (75.0%)	1084 (79.4%)	36 (72.0%)	647 (68.6%)
African American	13 (1.6%)	22 (7.1%)	19 (2.0%)	22 (6.7%)	183 (8.4%)	26 (2.2%)	2 (4.2%)	31 (2.3%)	3 (6.0%)	97 (10.3%)
Asian	136 (17.0%)	11 (3.5%)	150 (16.2%)	9 (2.7%)	42 (1.9%)	159 (13.4%)	2 (4.2%)	183 (13.4%)	2 (4.0%)	31 (3.3%)
Other	7 (0.9%)	60 (19.4%)	8 (0.9%)	62 (18.9%)	212 (9.8%)	4 (0.3%)	8 (16.7%)	5 (0.4%)	9 (18.0%)	86 (9.1%)
Unknown	17 (2.1%)	0 (0%)	19 (2.0%)	0 (0%)	200 (9.2%)	60 (5.1%)	0 (0%)	63 (4.6%)	0 (0%)	82 (8.7%)
ECOG PS²										
0	318 (39.8%)	84 (27.1%)	369 (39.8%)	97 (29.6%)	550 (25.4%)	455 (38.5%)	10 (20.8%)	525 (38.4%)	10 (20.0%)	242 (25.7%)
1	479 (59.9%)	153 (49.4%)	554 (59.8%)	158 (48.2%)	917 (42.3%)	725 (61.3%)	30 (62.5%)	837 (61.3%)	33 (66.0%)	401 (42.5%)
2	2 (0.3%)	39 (12.6%)	3 (0.3%)	38 (11.6%)	347 (16.0%)	2 (0.2%)	4 (8.3%)	3 (0.2%)	4 (8.0%)	126 (13.4%)
3	0 (0%)	15 (4.8%)	0 (0%)	13 (4.0%)	62 (2.9%)	1 (0.1%)	1 (2.1%)	1 (0.1%)	0 (0%)	27 (2.9%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Missing	1 (0.1%)	19 (6.1%)	1 (0.1%)	22 (6.7%)	286 (13.2%)	0 (0%)	3 (6.3%)	0 (0%)	3 (6.0%)	146 (15.5%)
Disease Stage³										
Stage 0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage I	35 (4.4%)	25 (8.1%)	46 (5.0%)	29 (8.8%)	173 (8.0%)	42 (3.6%)	1 (2.1%)	50 (3.7%)	1 (2.0%)	79 (8.4%)
Stage II	51 (6.4%)	22 (7.1%)	59 (6.4%)	23 (7.0%)	114 (5.3%)	41 (3.5%)	0 (0%)	50 (3.7%)	0 (0%)	45 (4.8%)
Stage III	175 (21.9%)	69 (22.3%)	200 (21.6%)	78 (23.8%)	492 (22.7%)	136 (11.5%)	7 (14.6%)	158 (11.6%)	8 (16.0%)	231 (24.5%)
Stage IV	523 (65.4%)	190 (61.3%)	601 (64.8%)	191 (58.2%)	1343 (62.0%)	948 (80.1%)	39 (81.3%)	1089 (79.7%)	40 (80.0%)	573 (60.8%)
Unknown	16 (2.0%)	4 (1.3%)	21 (2.3%)	7 (2.1%)	43 (2.0%)	16 (1.4%)	1 (2.1%)	19 (1.4%)	1 (2.0%)	15 (1.6%)
Smoking History										
Previous/Current	657 (82.1%)	277 (89.4%)	767 (82.7%)	296 (90.2%)	1996 (92.2%)	1033 (87.3%)	29 (60.4%)	1184 (86.7%)	31 (62.0%)	828 (87.8%)
Never	143 (17.9%)	33 (10.6%)	160 (17.3%)	32 (9.8%)	170 (7.8%)	150 (12.7%)	19 (39.6%)	182 (13.3%)	19 (38.0%)	114 (12.1%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
Histology										
NonSquamous	570 (71.3%)	215 (69.4%)	664 (71.6%)	226 (68.9%)	1410 (65.1%)	807 (68.2%)	45 (93.8%)	945 (69.2%)	47 (94.0%)	653 (69.2%)
Squamous	210 (26.3%)	84 (27.1%)	240 (25.9%)	88 (26.8%)	669 (30.9%)	366 (30.9%)	3 (6.3%)	409 (29.9%)	3 (6.0%)	259 (27.5%)
Unknown	20 (2.5%)	11 (3.5%)	23 (2.5%)	14 (4.3%)	87 (4.0%)	10 (0.8%)	0 (0%)	12 (0.9%)	0 (0%)	31 (3.3%)

¹ Age - age at treatment start.² ECOG PS - Eastern Cooperative Oncology Group Performance Status at treatment start.³ Disease stage - Group stage at initial diagnosis for the RWD sources (FH and CGDB), and at study start for the atezolizumab trials.