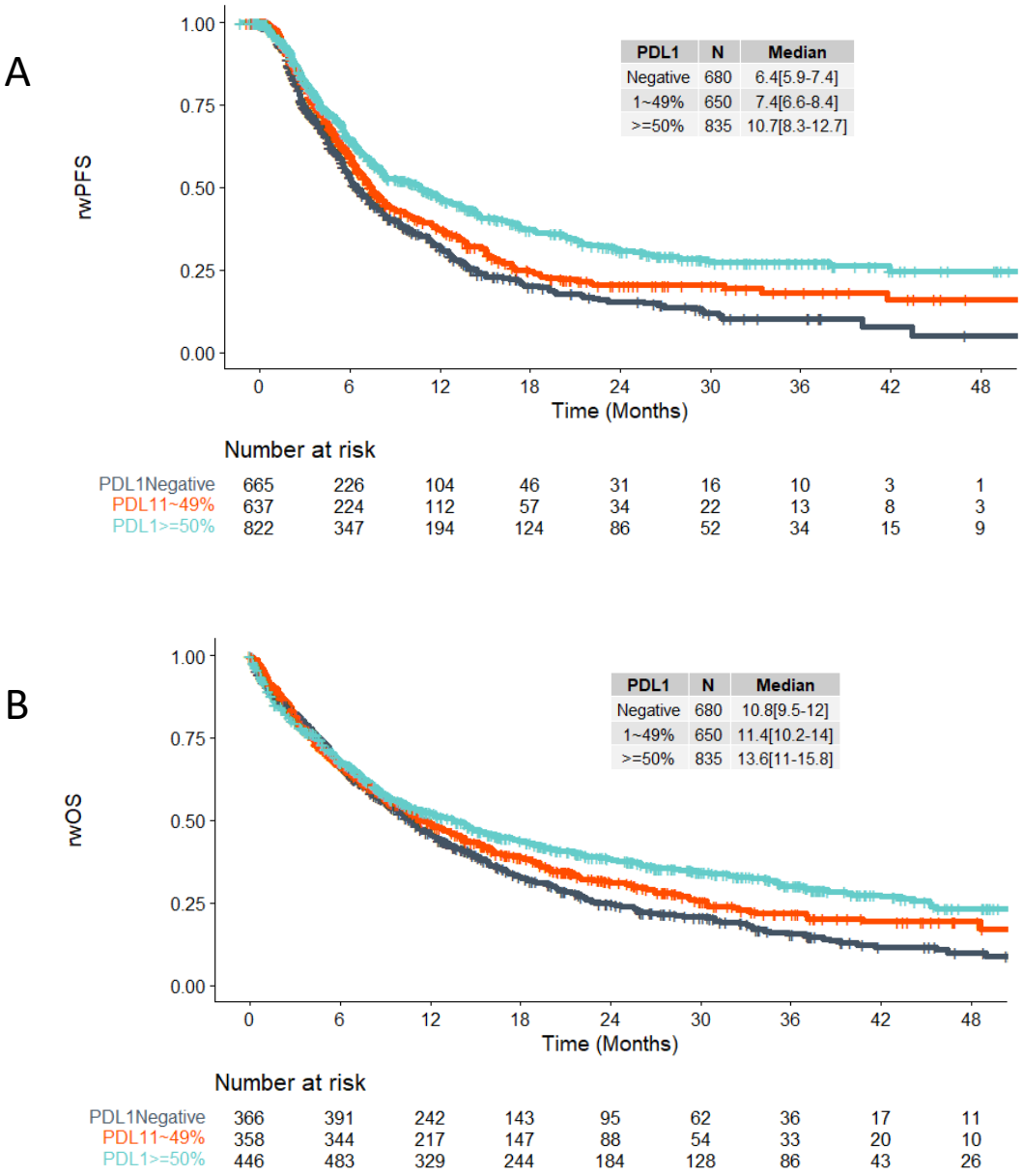
Supplemental Table 1. Patient characteristics of the ICPI and ChemoICPI subgroup

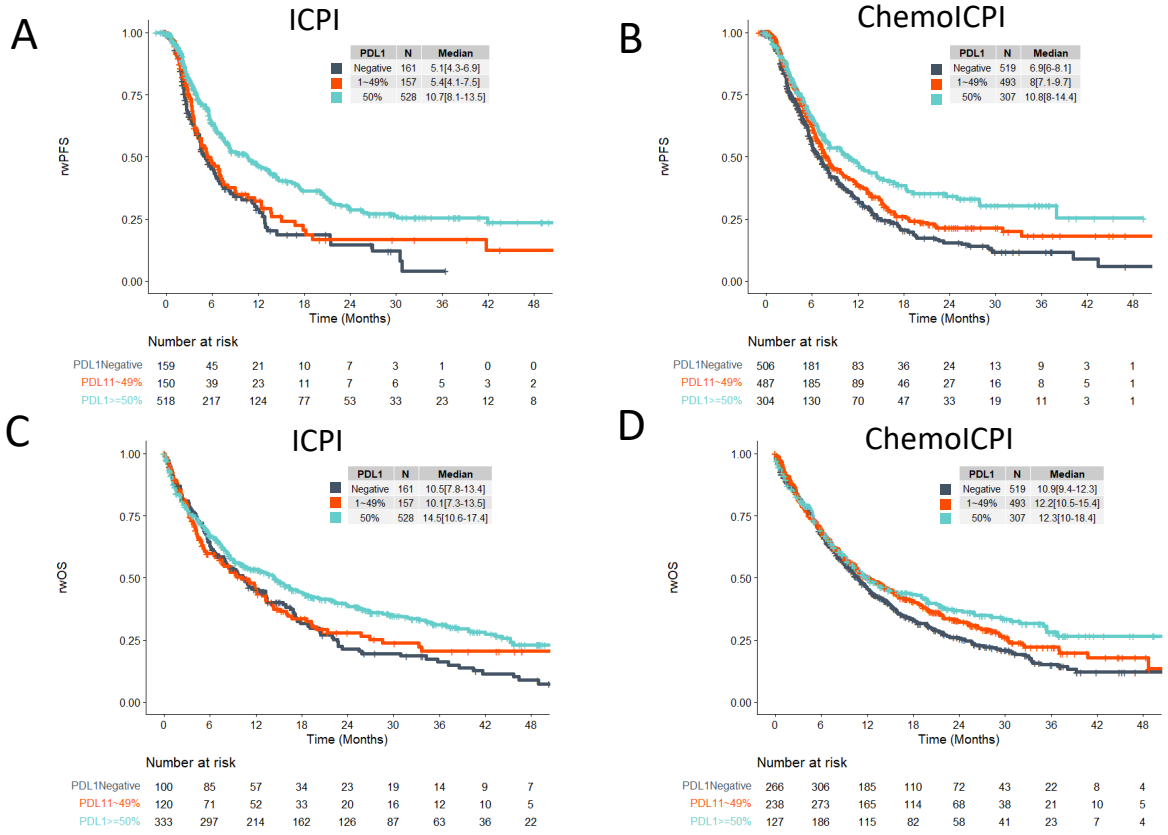
Clinical Characteristics	ALL (N=2165)	ICPI (N=846)	ChemoICPI (N=1319)	p-value
Age at Advanced Diagnosis	70.0 [63.0;76.0]	72.0 [65.0;78.0]	69.0 [62.0;74.0]	<0.001
Gender				<0.001
Female	1035 (47.8%)	446 (52.7%)	589 (44.7%)	
Male	1130 (52.2%)	400 (47.3%)	730 (55.3%)	
Self-Reported Race				0.034
White	1479 (68.3%)	605 (71.5%)	874 (66.3%)	
Black or African American	171 (7.90%)	55 (6.50%)	116 (8.79%)	
Others	515 (23.8%)	186 (22.0%)	329 (24.9%)	
Practice Type				0.724
ACADEMIC	155 (7.16%)	58 (6.86%)	97 (7.35%)	
COMMUNITY	2010 (92.8%)	788 (93.1%)	1222 (92.6%)	
Histology				0.001
Non-squamous cell carcinoma	1577 (72.8%)	586 (69.3%)	991 (75.1%)	
NSCLC histology NOS	93 (4.30%)	32 (3.78%)	61 (4.62%)	
Squamous cell carcinoma	495 (22.9%)	228 (27.0%)	267 (20.2%)	
Stage At Dx				<0.001
I	214 (9.88%)	115 (13.6%)	99 (7.51%)	
II	145 (6.70%)	90 (10.6%)	55 (4.17%)	
III	326 (15.1%)	198 (23.4%)	128 (9.70%)	
IV	1448 (66.9%)	428 (50.6%)	1020 (77.3%)	
Unknown	32 (1.48%)	15 (1.77%)	17 (1.29%)	
History of Smoking				0.171
History of smoking	2032 (93.9%)	802 (94.8%)	1230 (93.3%)	
No history of smoking	133 (6.14%)	44 (5.20%)	89 (6.75%)	
ECOG				0.003
0~1	1486 (68.6%)	548 (64.8%)	938 (71.1%)	
2+	484 (22.4%)	220 (26.0%)	264 (20.0%)	
Unknown	195 (9.01%)	78 (9.22%)	117 (8.87%)	
TMB				<0.001
<10	1307 (60.4%)	470 (55.6%)	837 (63.5%)	
≥10	858 (39.6%)	376 (44.4%)	482 (36.5%)	
PDL1 (TS)				<0.001
<1%	680 (31.4%)	161 (19.0%)	519 (39.3%)	
1-49%	650 (30.0%)	157 (18.6%)	493 (37.4%)	
≥50%	835 (38.6%)	528 (62.4%)	307 (23.3%)	

Supplemental Table 2. PD-L1 IHC Clones and ICPI Regimen Prevalence in Cohort

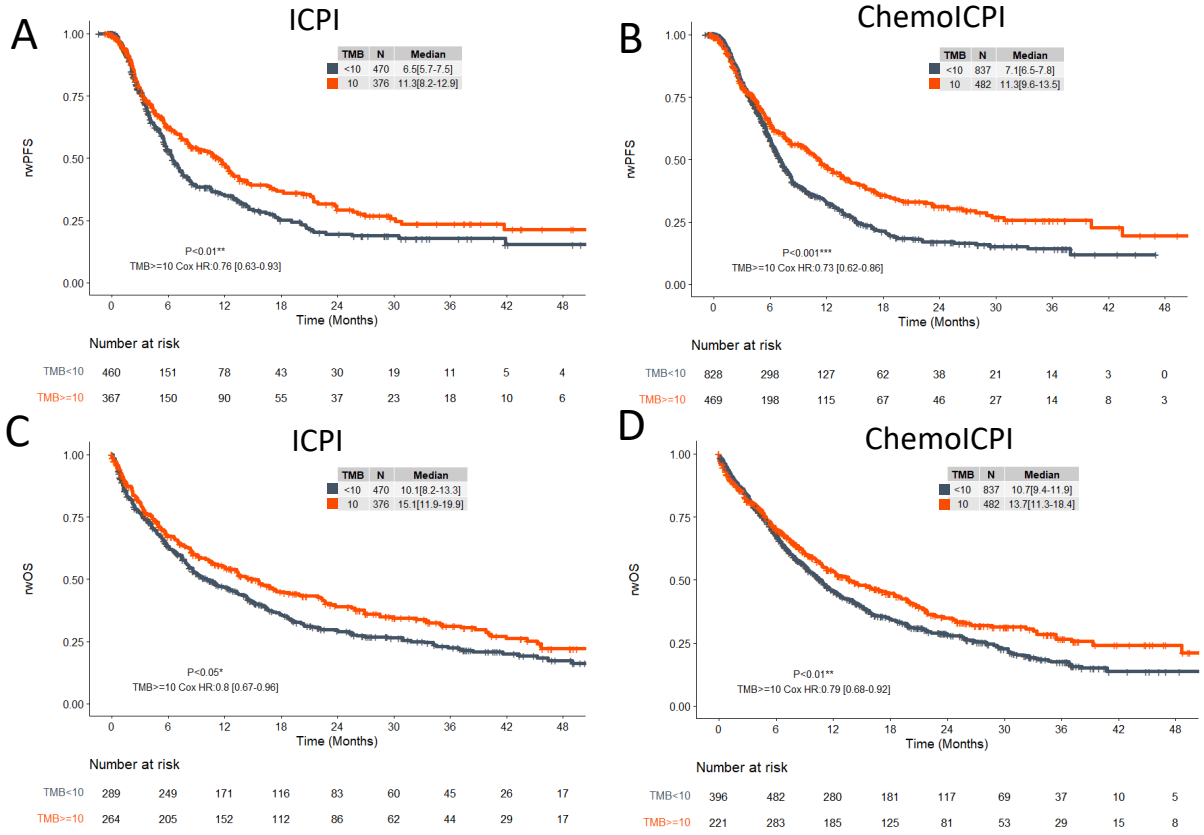
	N=2165
PD-L1 Clones	
DAKO 22C3	2030 (93.8%)
Unknown	79 (3.6%)
VENTANA SP263	26 (1.2%)
DAKO 28-8	15 (0.7%)
VENTANA SP142	15 (0.7%)
ICPI containing regimens	
Pembrolizumab	644 (29.7%)
Nivolumab	141 (6.5%)
Atezolizumab	31 (1.4%)
Durvalumab	30 (1.4%)
Pembrolizumab + Chemotherapy	1304 (60.2%)
Atezolizumab + Chemotherapy	11 (0.5%)
Durvalumab + Chemotherapy	2 (0.1%)
Nivolumab + Chemotherapy	2 (0.1%)



Supplemental Figure 1: 1L NSCLC patients with PD-L1 IHC TS ≥50 exhibited higher rwPFS and rwOS when compared to patients with PD-L1 IHC TS <50 when treated with an ICPI regimens. Unadjusted Kaplan-Meier of (a) rwPFS and (b) in all 2165 patients in the cohort, regardless of therapy received, comparing patients based on PD-L1 score.

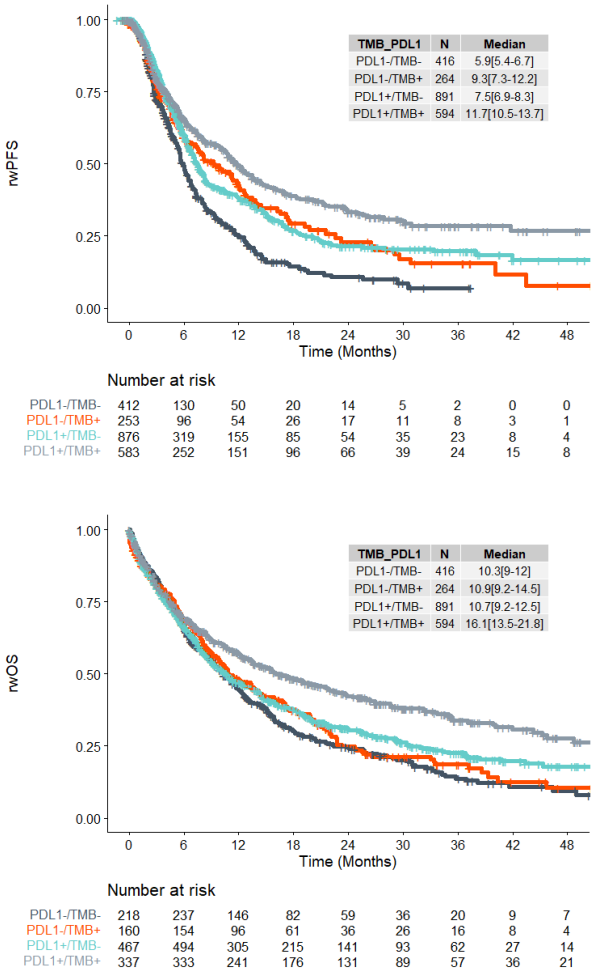


Supplemental Figure 2: 1L NSCLC patients with PD-L1 TS ≥50% exhibited higher rwPFS and rwOS when compared to patients with PD-L1 TS <50% when treated with in both the ICPI and chemoICPI groups. Unadjusted Kaplan-Meier plots of rwPFS (A and B) and rwOS (C and D) for patients who were treated with ICPI (A and C) or chemoICPI (B and D). Outcomes are stratified by PD-L1 TS <1% (black), PD-L1 TS between 1-49% (orange), and PD-L1 TS ≥50% (green).



Supplemental Figure 3: 1L NSCLC patients with TMB ≥10 mutations/Mb exhibited higher rwPFS and rwOS (though less pronounced when compared to the TMB ≥20 mutations/Mb cut-off) when compared to patients with TMB <10 mutations/Mb when treated with ICPI regimens. Kaplan-Meier plots of rwPFS (A and B) and rwOS (C and D) for patients who were treated with ICPI (A and C) or chemoICPI (B and D). Outcomes are stratified by TMB <10 (black) and TMB ≥10 (orange).

A



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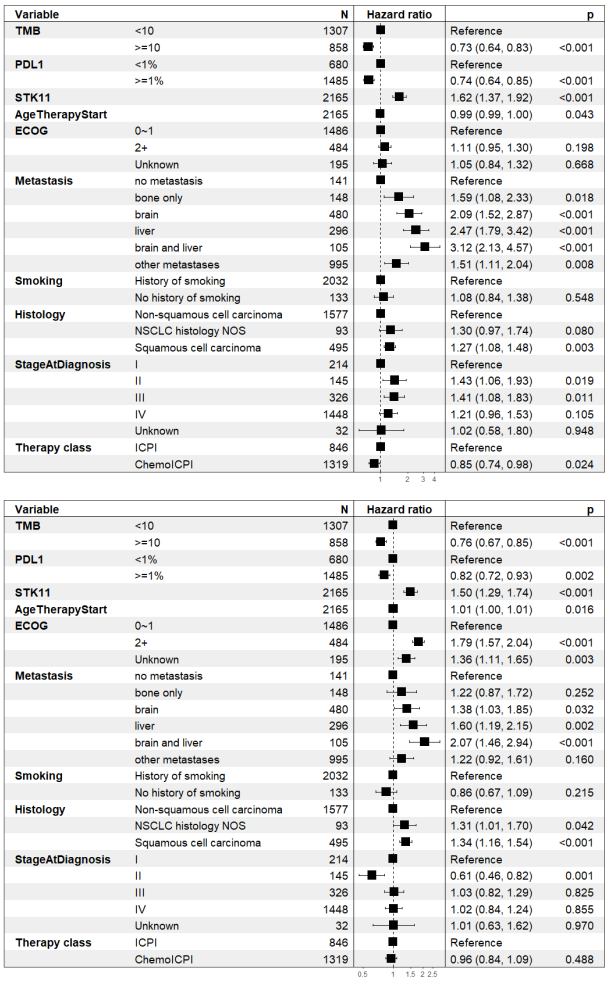
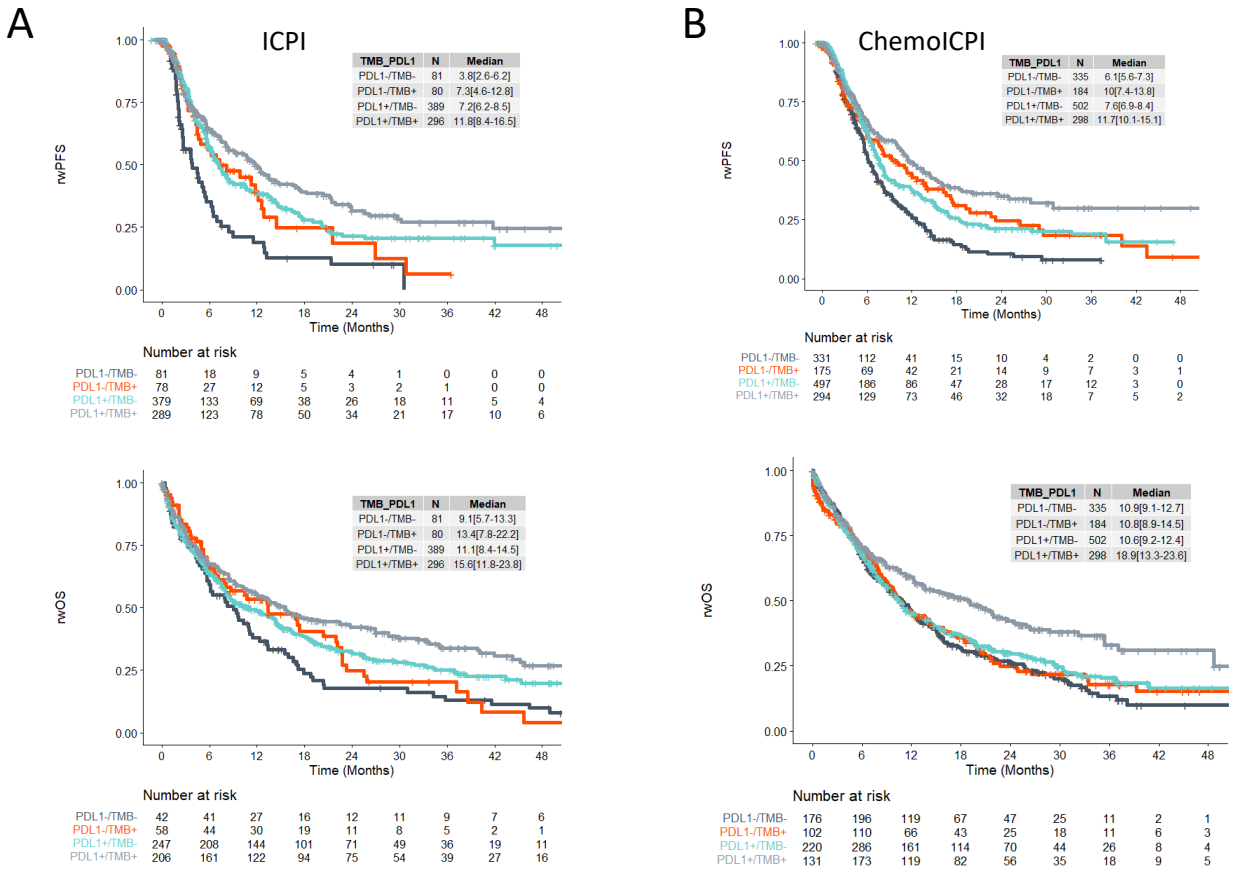
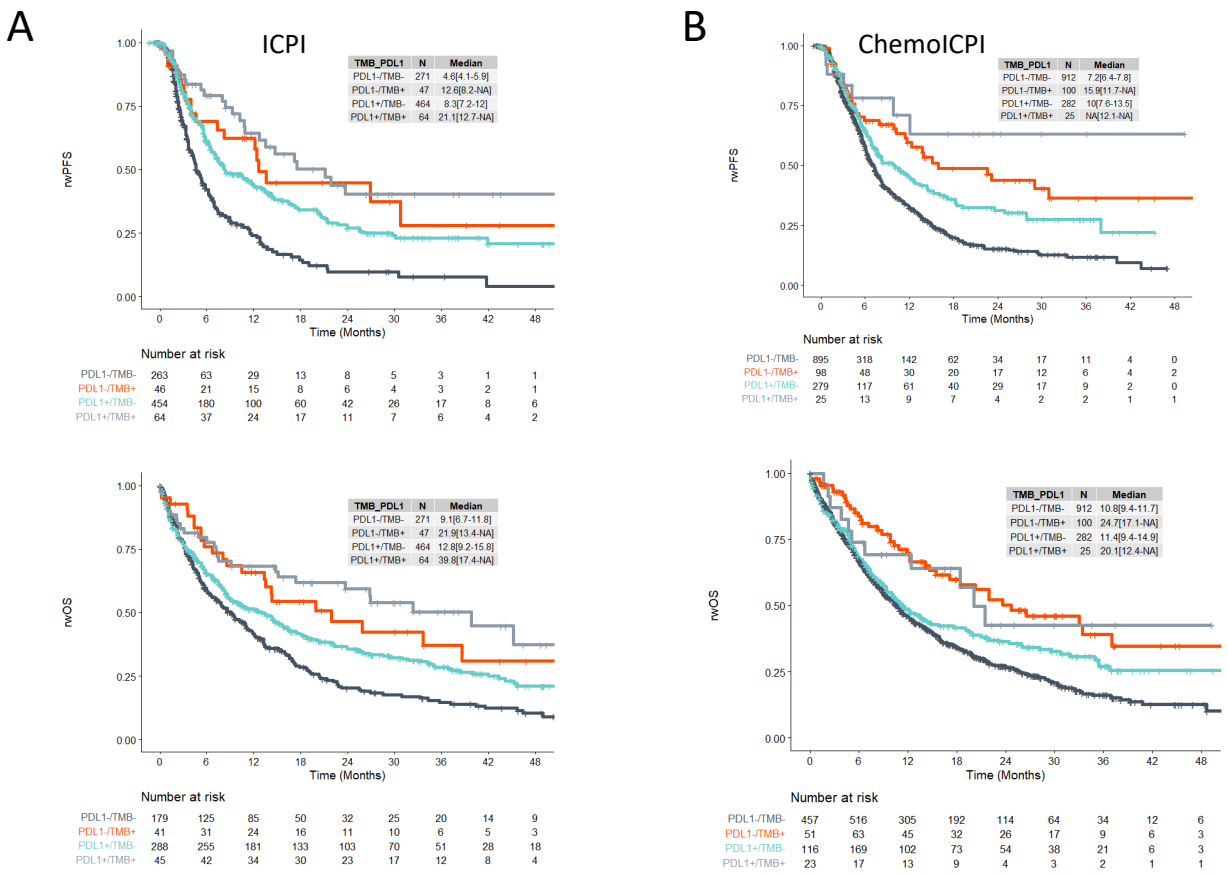


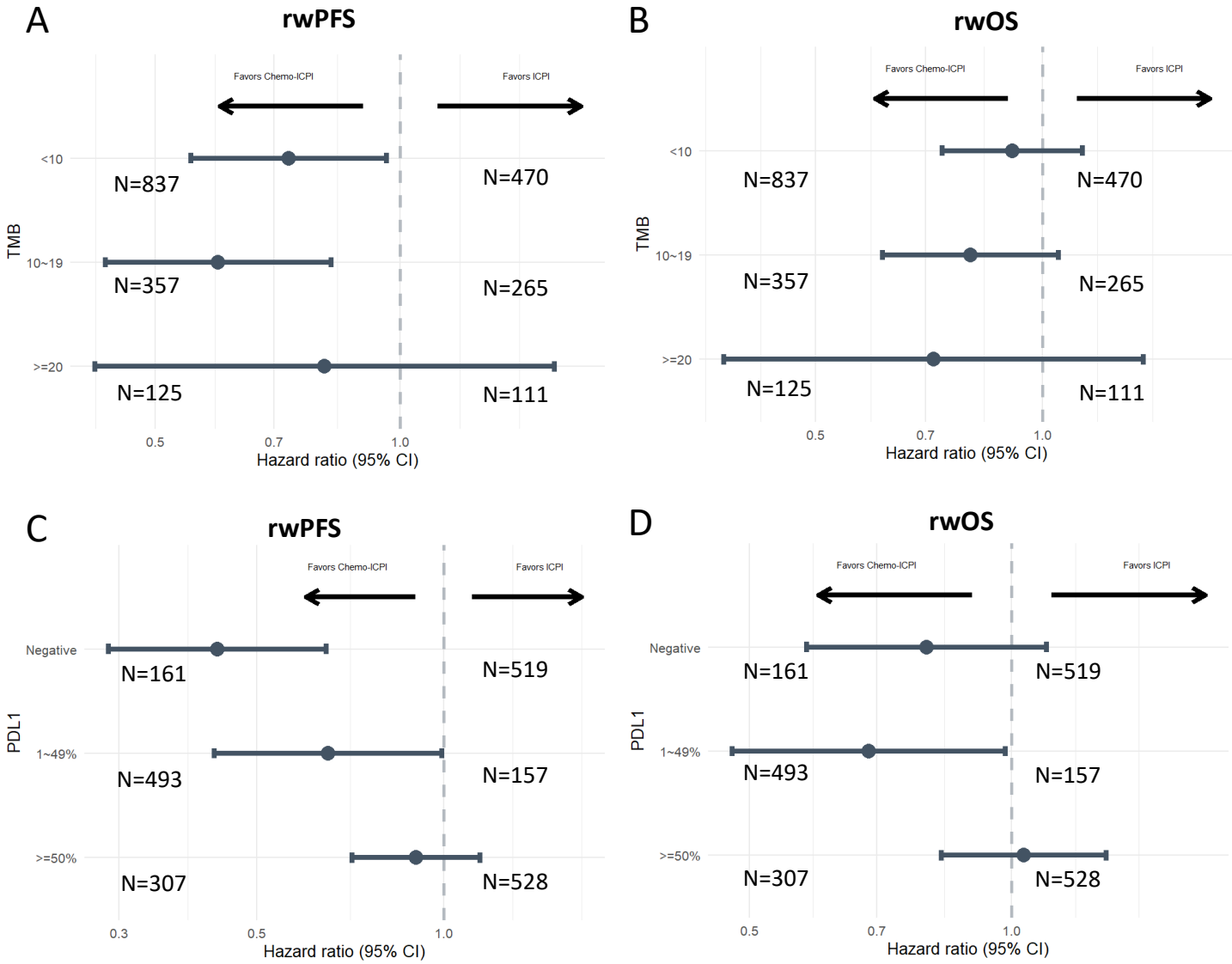
Supplemental Figure 4: Utilizing a less stringent TMB and PD-L1 cut-off (TMB ≥10 and PD-L1 TS ≥1), we still observed that PDL1 IHC and TMB are two independent and complementary biomarkers for predicting durable benefit. (A) Unweighted Kaplan-Meier plots of rwPFS (upper) and rwOS (lower) for patients who were treated with ICPI containing regimens. Outcomes are stratified by TMB and PD-L1 levels: PD-L1 <1% and TMB <10 (black), PD-L1 ≥1% and TMB <10 (green), PD-L1 <1% and TMB ≥10 (orange), PD-L1 ≥1% and TMB ≥10 (gray). (B) Results from multivariate unweighted CoxPH model detecting associations between clinical or genomic features and rwPFS (upper) or rwOS (lower).



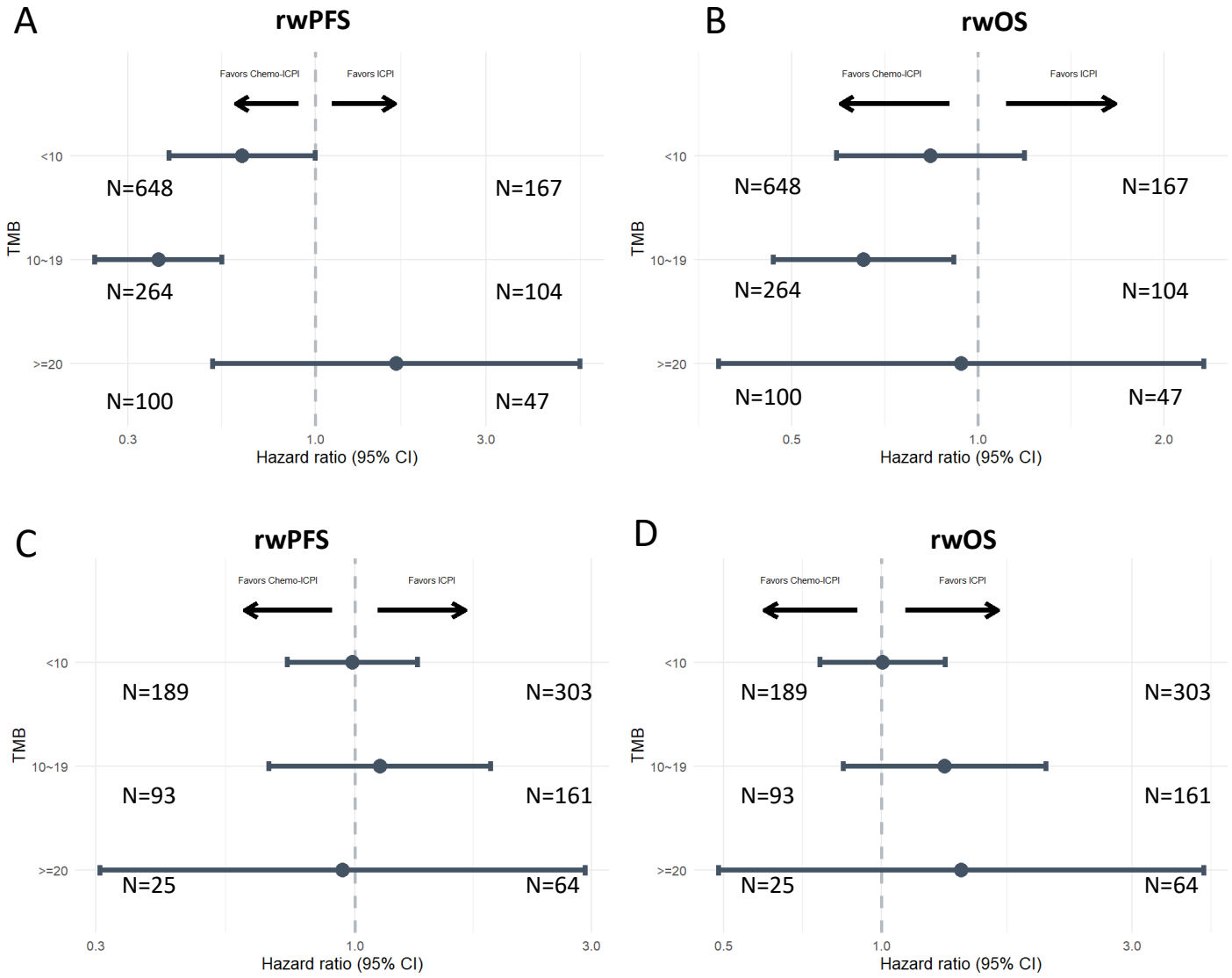
Supplemental Figure 5: **The independent and complementary nature of TMB and PD-L1 IHC in predicting durable benefit is observed in both ICPI and chemoICPI at a PD-L1 TS of 1 and TMB of 10 cut-off.** Clinical value of TMB in addition to PD-L1 in 1L NSCLC in ICPI and chemoICPI cohorts. Kaplan-Meier plots of rwPFS (upper) and rwOS (lower) for patients who were treated with ICPI (A) or chemoICPI (B). Outcomes are stratified by TMB and PD-L1 levels: PD-L1 TS <1% and TMB <10 (black), PD-L1 TS ≥1% and TMB <10 (green), PD-L1 TS <1% and TMB ≥10 (orange), PD-L1 TS ≥1% and TMB ≥10 (gray).



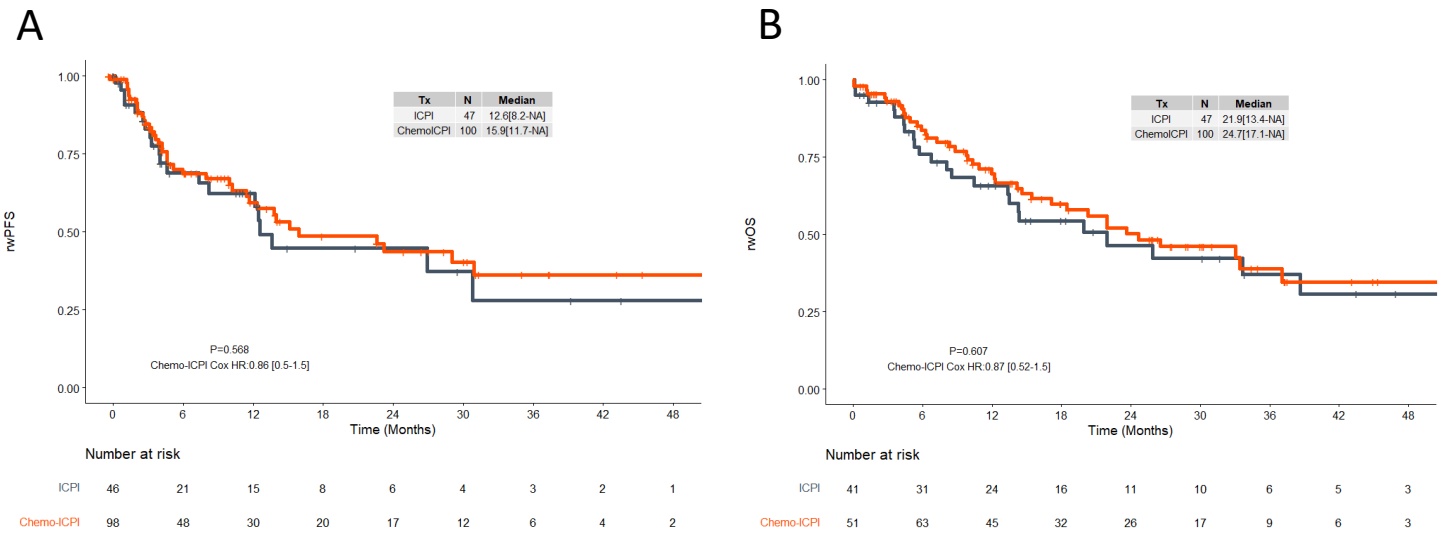
Supplemental Figure 6: **The independent and complementary nature of TMB and PD-L1 IHC in predicting durable benefit is observed in both ICPI monotherapy and chemoICPI at a PD-L1 TS of 50 and TMB of 20 cut-off.** Clinical value of TMB in addition to PD-L1 in 1L NSCLC in ICPI and chemoICPI cohorts. Kaplan-Meier plots of rwPFS (upper) and rwOS (lower) for patients who were treated with ICPI (A) or chemoICPI (B). Outcomes are stratified by TMB and PDL1 levels: PD-L1 TS <50% and TMB <20 (black), PD-L1 TS ≥50% and TMB <20 (green), PD-L1 TS <50% and TMB ≥20 (orange), PD-L1 TS ≥50% and TMB ≥20 (gray).



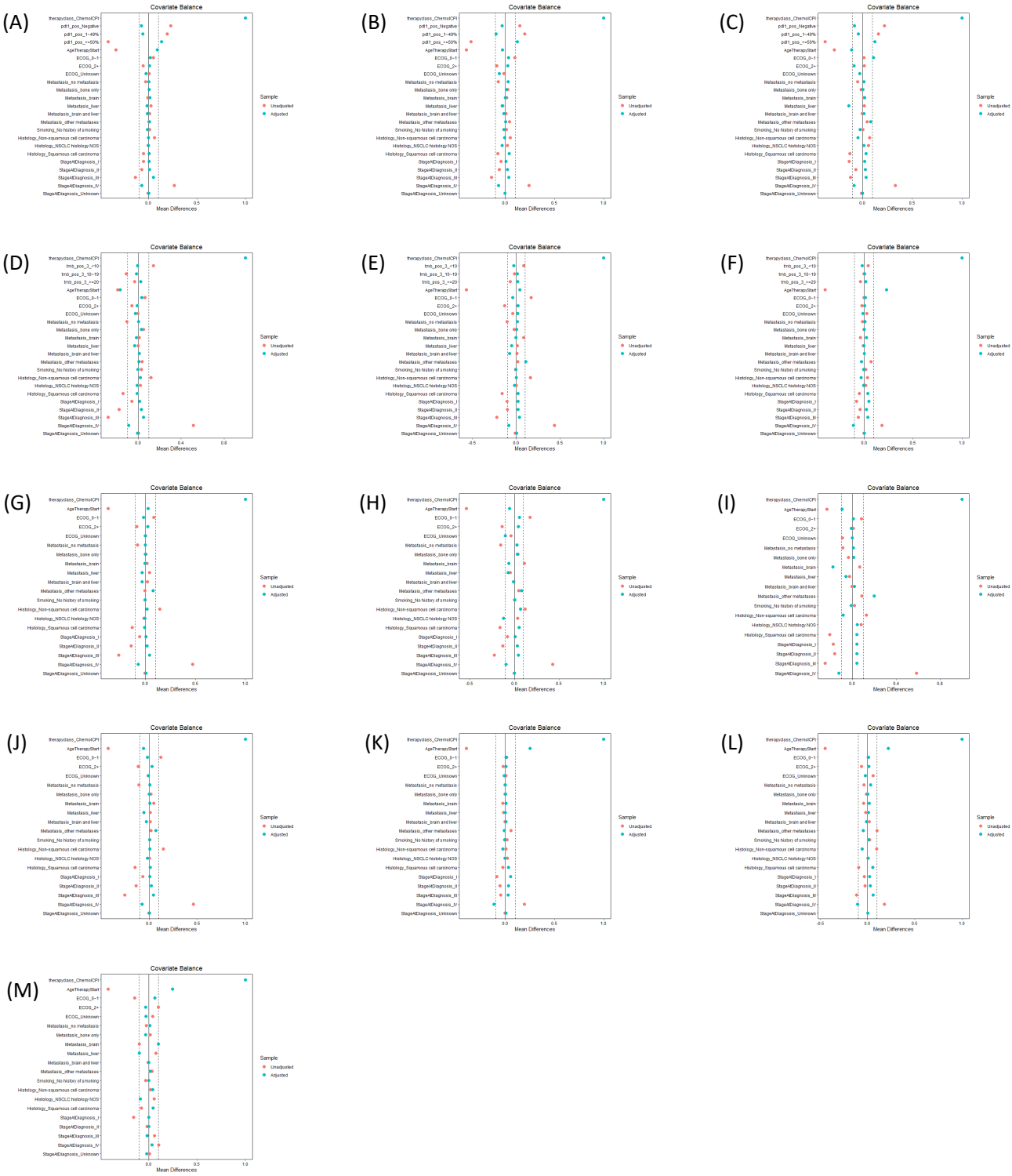
Supplemental Figure 7: Between-Treatment Subgroup analyses by PD-L1 or TMB. Here, we examined the between-treatment subgroup (1L ICPI and chemoICPI) analyses by TMB or PD-L1. (a) Estimates of the HRs when comparing rwPFS on chemoICPI vs ICPI for TMB <10, 10-19, and ≥20. (b) Estimates of the HRs when comparing rwOS on chemoICPI vs ICPI fpr different levels of TMB. (c) Estimates of the HRs when comparing rwPFS on chemoICPI vs ICPI for PD-L1 TS <1%, 1-49%, and ≥50%. (d) Estimates of the HRs when comparing rwOS on chemoICPI vs ICPI for different levels of PD-L1. Multivariable Cox proportional hazard models were fitted on rwPFS and rwOS to estimate the adjusted hazard ratio and its significance. Features included in the Cox model included PD-L1 status (trichotomized at TS 1% and 50%) or TMB status (cut-offs at 10 and 20), age at treatment start, ECOG performance score (0~1, 2+, and unknown), sites of metastasis, history of smoking, disease histology, stage at initial diagnosis, and therapy class. Covariate imbalance between patients receiving ICPI and chemo-ICPI was adjusted using inverse probability of treatment weighting (IPTW).



Supplemental Figure 8: Between-Treatment Subgroup analyses by both PD-L1 and TMB.
(a) rwPFS and (b) rwOS estimates of the HR in the PD-L1 TS <50% cohort when comparing chemoICPI vs ICPI and stratified by TMB <10, 10-19, and ≥20. (c) rwPFS and (d) rwOS estimates of the HR in the PD-L1 TS ≥ 50% cohort when comparing chemoICPI vs ICPI and stratified by TMB <10, 10-19, and ≥20. Multivariable Cox proportional hazard models were fitted on rwPFS and rwOS to estimate the adjusted hazard ratio and its significance. Features included in the Cox model included age at treatment start, ECOG performance score (0~1, 2+, and unknown), sites of metastasis, history of smoking, disease histology, stage at initial diagnosis, and therapy class. Covariate imbalance between patients receiving ICPI and chemo-ICPI was adjusted using inverse probability of treatment weighting (IPTW).



Supplemental Figure 9: When examining the outcomes for patients with both PD-L1 TS <50% and TMB ≥20, no significant difference was observed between patients receiving chemoICPI and ICPI alone. Unweighted Kaplan-Meier plots of rwPFS (A) and rwOS (B) for patients (PD-L1 TS <50% and TMB ≥20) with outcomes stratified by ICPI (black) and chemo-ICPI (orange). IPTW adjusted HR (not shown) also showed a non-significant trend (rwPFS: HR 1.5 [0.49-4.8], p =0.461; and rwOS: HR 0.86 [0.33-2.2], p = 0.75). Covariate imbalance between patients receiving ICPI and chemo-ICPI was adjusted using inverse probability of treatment weighting (IPTW).



Supplemental Figure 10: Balance plots showing covariate balance before and after IPTW. Covariate balance plots for (A) TMB <10, (B) TMB 10-19, (C) TMB ≥20, (D) PD-L1 TS <1%, (E) PD-L1 TS =1-49%, (F) PD-L1 TS ≥50%, (G) PD-L1 TS <50% and TMB <10, (H) PD-L1 TS <50% and TMB 10-19, (I) PD-L1 TS <50% and TMB ≥20, (J) PD-L1 TS <50% and TMB <20, (K) PD-L1 TS ≥50% and TMB <10, (L) PD-L1 TS ≥50% and TMB 10-19, (M) PD-L1 TS ≥50% and TMB ≥20. The dashed vertical lines indicate 10% standardized mean difference.