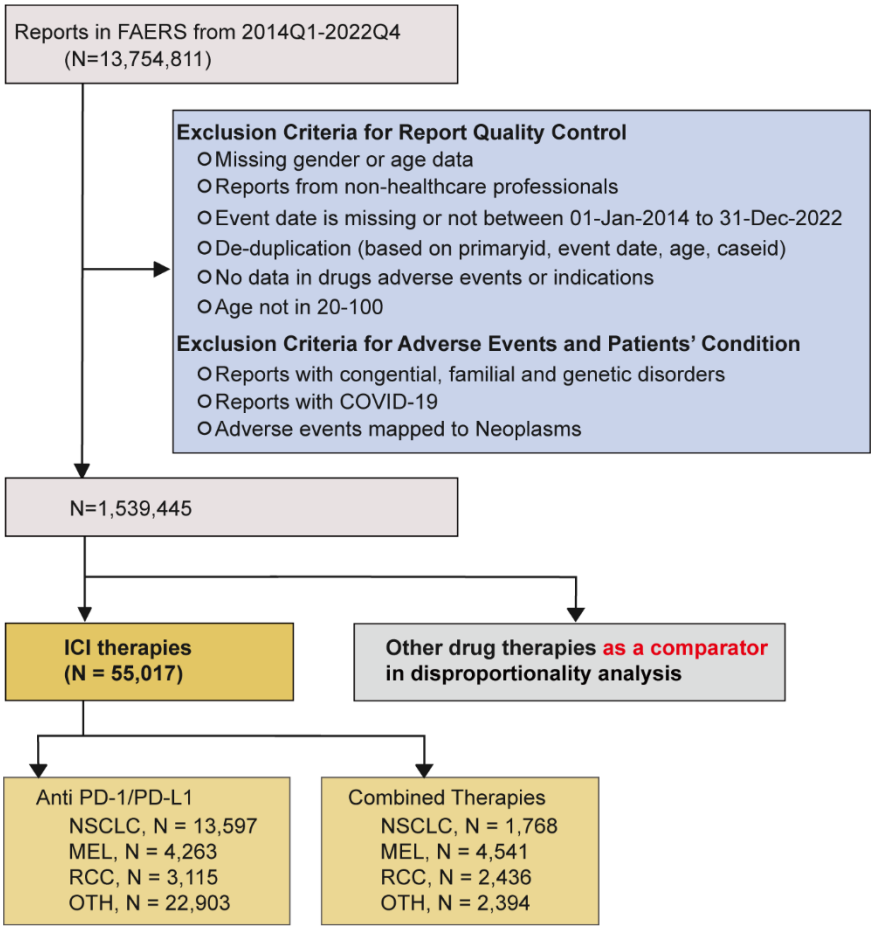
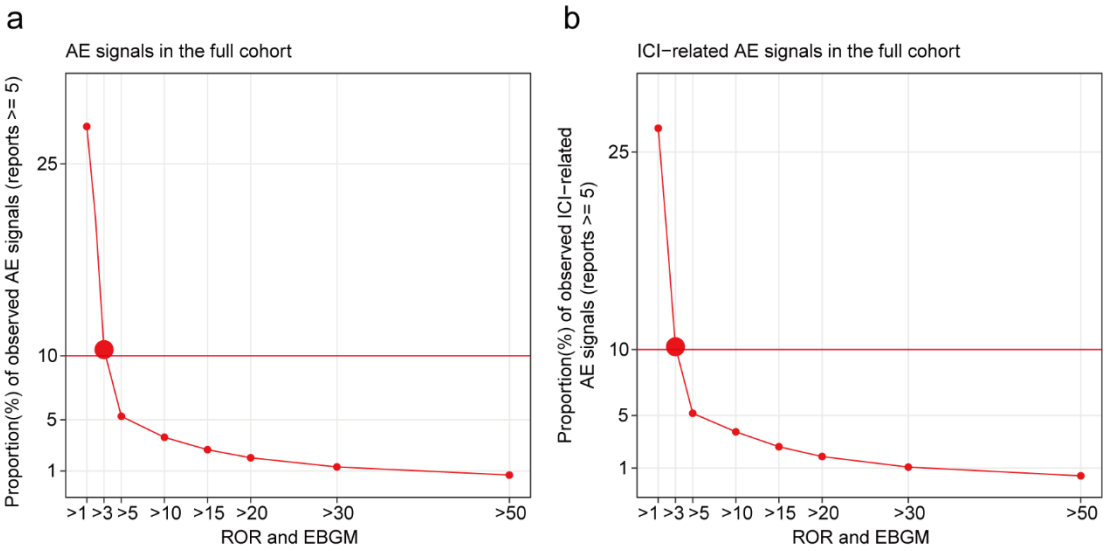
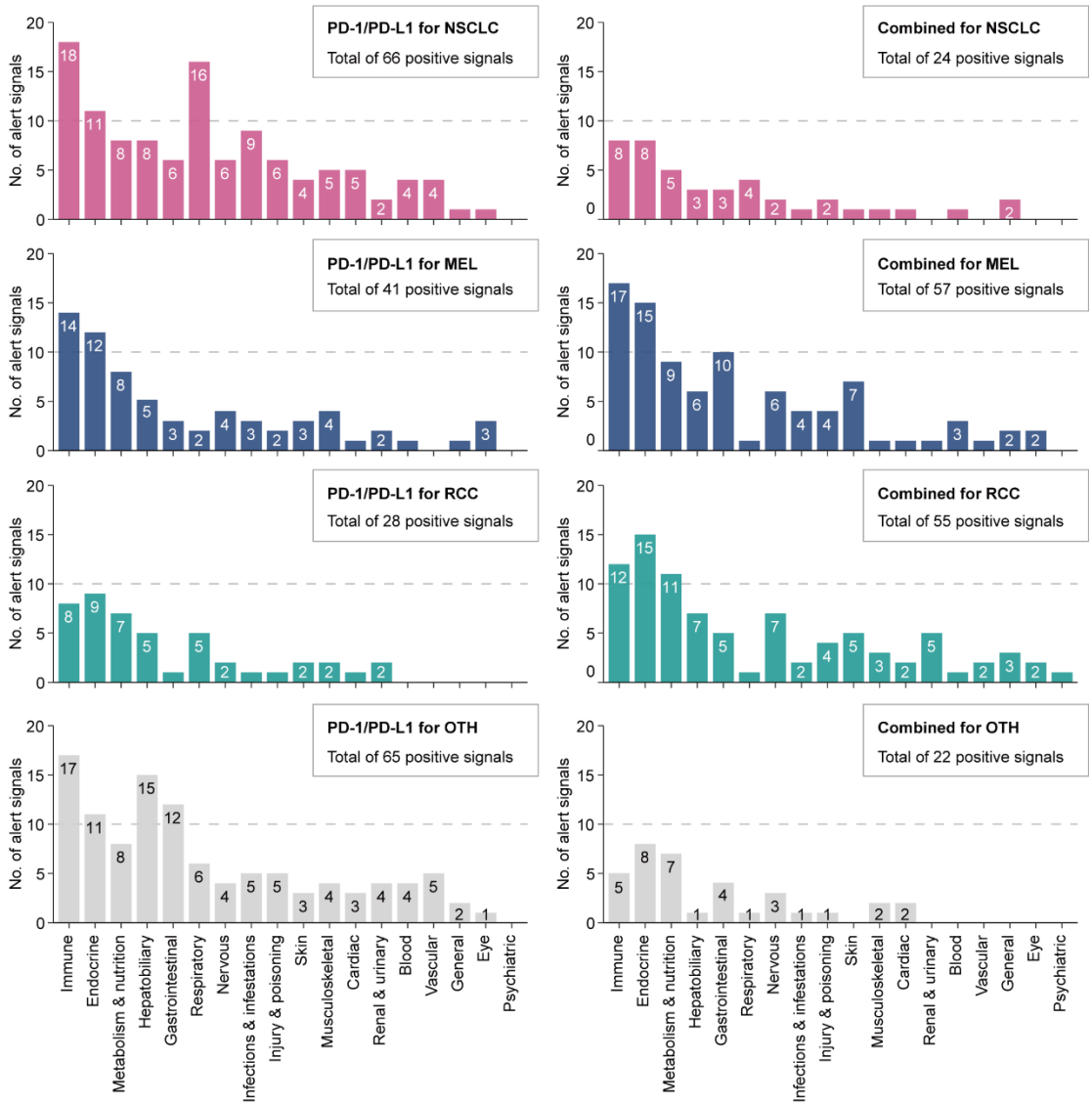
Supplementary Information of Figures



Supplementary Figure 1. Flowchart showing the preprocessing process of the AE reports in FAERS.

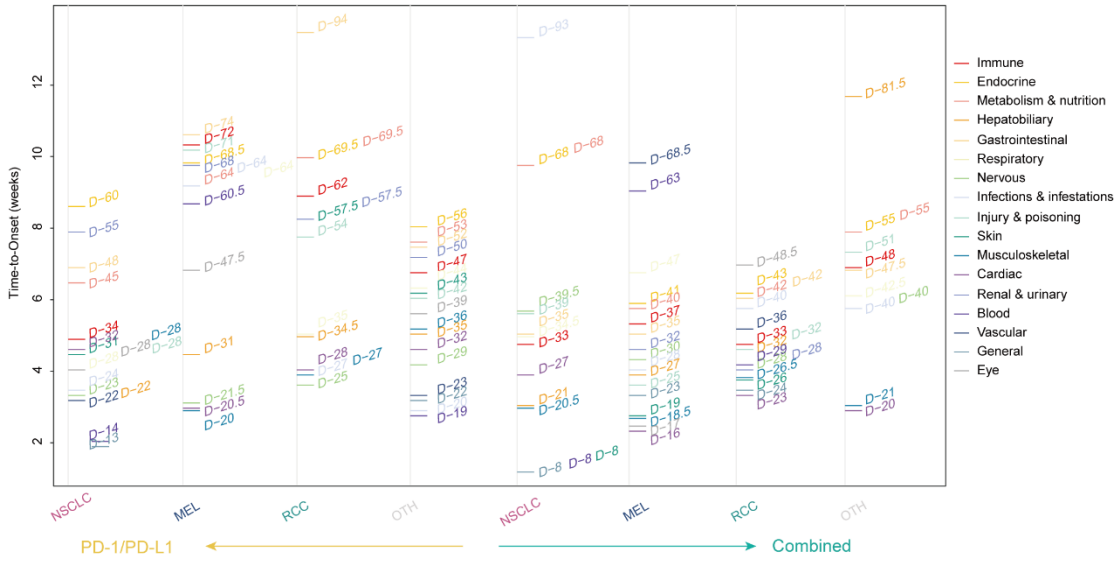


Supplementary Figure 2. Cut-off selection for positive therapy-related AE signals. Proportion of AE signals at each threshold for all therapy-related signals (**a**) and ICI therapy-related AE signals (**b**) in the cohort.

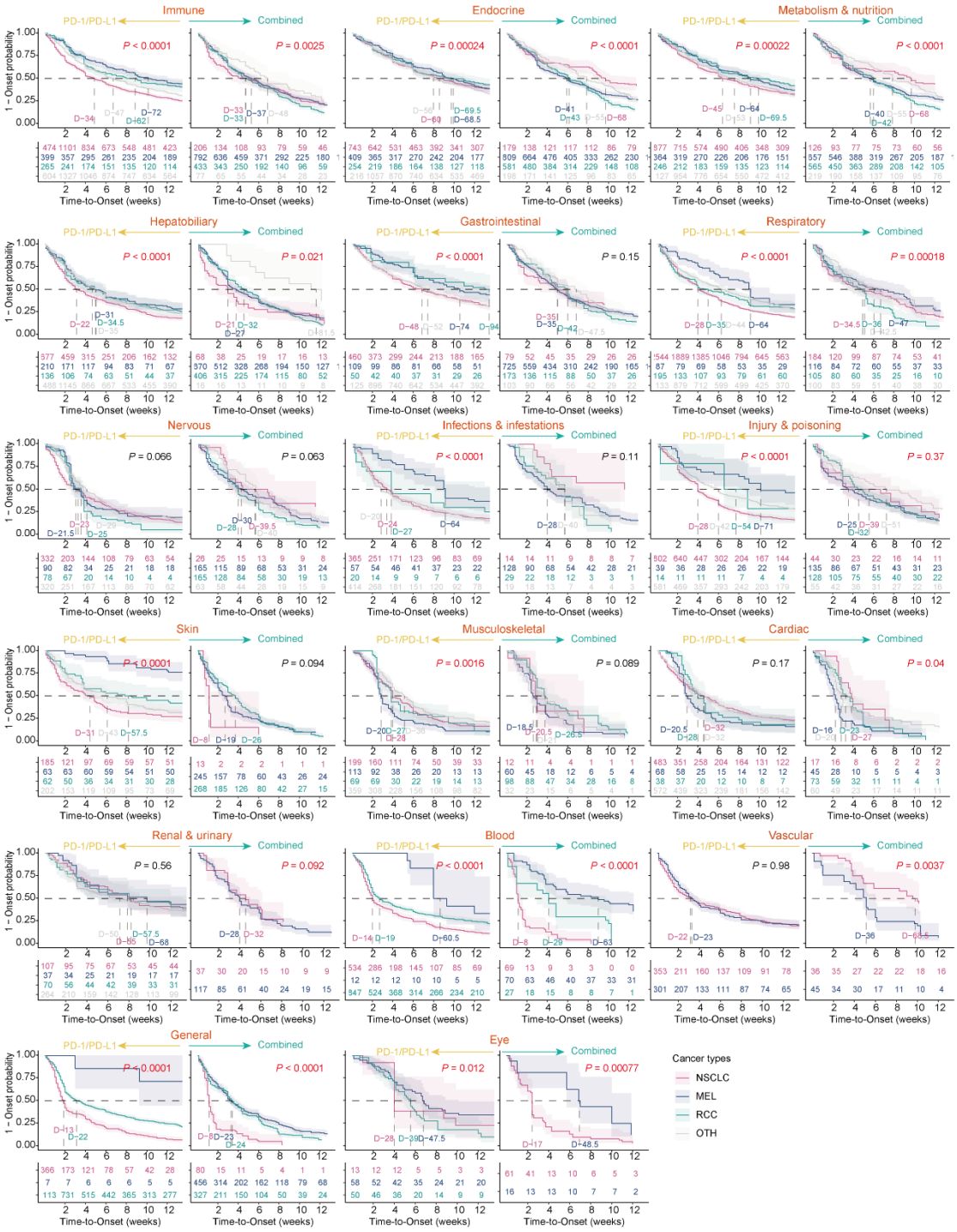


Supplementary Figure 3. SOC distribution map of ICI therapy-related AE signals. Significant signals were defined as those where both the ROR and EBGM exceeded 3. Patients with NSCLC receiving PD-1/PD-L1 therapy showed increased susceptibility to AEs affecting the respiratory system, with 16 (24.2%) AE signals, representing a 1.45-fold increase compared to those on combined therapy. Patients categorized under OTH receiving PD-1/PD-L1 therapy exhibited a high proportion of AE signals in the hepatobiliary system, with 15 (23.1%) AE signals, indicating a 5.08-fold increase compared to combined therapy. For patients on combined therapy, AE signals in MEL patients were nearly double those observed in patients on

PD-1/PD-L1 therapy (55 vs. 28 reports), despite the comparable number of reports for both therapies (4,263 vs. 4,541).

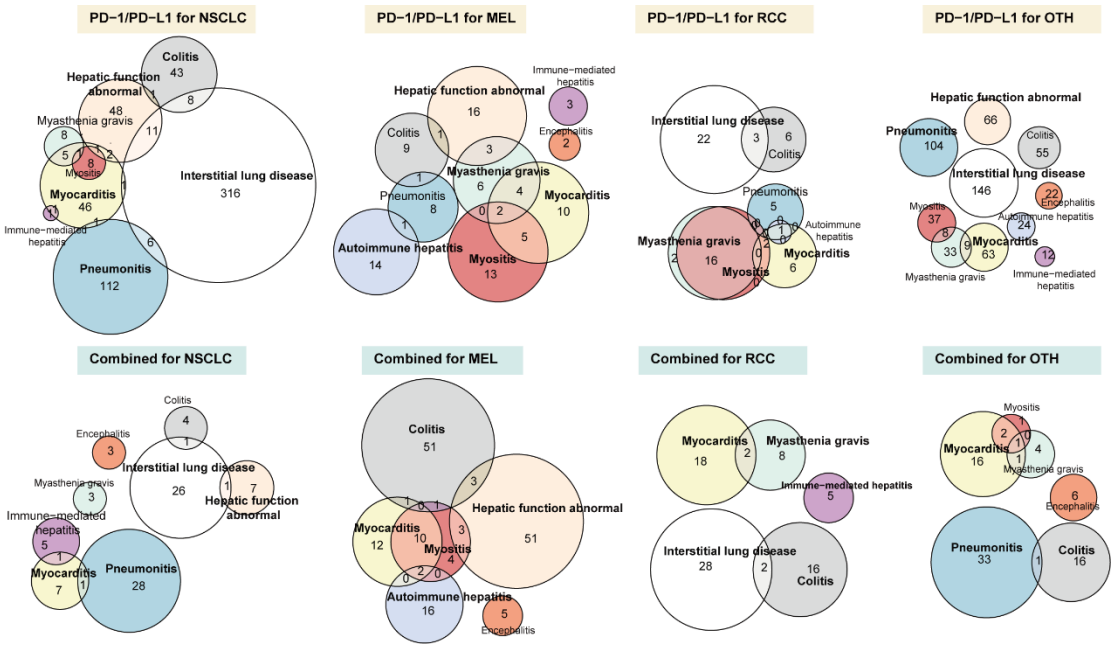


Supplementary Figure 4. Midian time-to-onset map of ICI therapy-related AE signals in different SOCs.



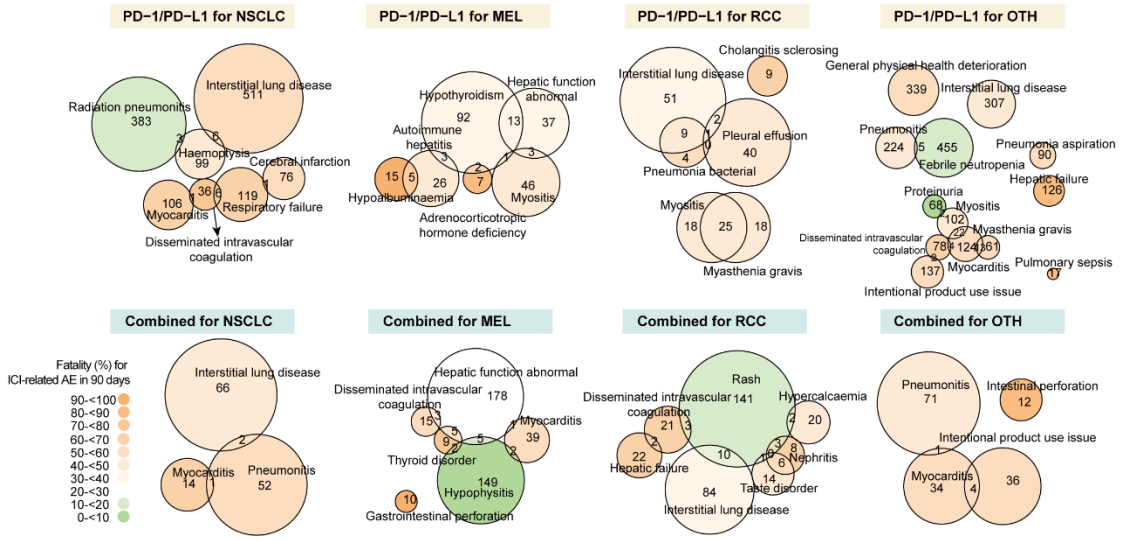
Supplementary Figure 5. Comparison of time-to-onset of ICI therapy-related AEs in different SOCs. Log-rank tests were used to analyze the tumor heterogeneity of ICI therapies across different 17 SOCs. Among these, nine SOCs showed significant differences in median time-to-onset between PD-1/PD-L1 therapies and

combined therapies, highlighting distinct focal points in their mechanisms of AE onset. Excluding general AEs, the differences in median time-to-onset for PD-1/PD-L1 therapies, from largest to smallest, were as follows: blood (46.5 days), injury & poisoning (44 days), immune (38 days), respiratory (36 days), metabolic (24.5 days), eye (19.5 days), endocrine (13.5 days), and hepatic (13 days). For combined therapies, the differences in median time-to-onset, from largest to smallest, were: hepatic (60.5 days), blood (55 days), eye (31.5 days), metabolic (28 days), endocrine (27 days), injury & poisoning (26 days), immune (15 days), and respiratory (12.5 days). Additionally, seven SOCs showed significant differences in median time-to-onset in only one therapy type. Four SOCs showed significant differences only in PD-1/PD-L1 therapies, with median time-to-onset differences from largest to smallest: skin (241 days), gastrointestinal (46 days), infections & infestations (44 days), and musculoskeletal (16 days). Three SOCs showed significant differences only in combined therapies, with median time-to-onset differences from largest to smallest: vascular (32.5 days), cardiac (11 days), and renal & urinary (4 days). Nervous system AEs did not show significant heterogeneity in time-to-onset between the two therapies, but the median time-to-onset for PD-1/PD-L1 therapies (21.5-29 days) was generally 1-2 weeks earlier than that for combined therapies (28-40 days).



Supplementary Figure 6. Venn diagram of overlapping death outcomes in ICI-related reports. Reports with fatality outcome exceeding 20%, and AE occurring within 90 days, across at least five ICI therapy categories were selected for display. In NSCLC patients, fatal cases were frequently associated with interstitial lung disease or pneumonia. Additionally, colitis, liver dysfunction, and myocarditis were reported, with interstitial lung disease-related deaths being more prevalent in PD-1/PD-L1 therapies. Among RCC patients, fatal cases commonly involved interstitial lung disease, colitis, myocarditis, and myasthenia gravis. Unlike combined therapies, fatal cases under PD-1/PD-L1 therapy often involved myositis alongside myasthenia gravis, with these myositis cases generally not overlapping with myocarditis. For MEL patients, fatal cases rarely involved interstitial lung disease, and pneumonia was also less common. Instead, many fatal cases were associated with colitis, liver dysfunction, autoimmune hepatitis, and myocarditis. In combined therapies, higher fatality rates were observed for colitis and liver dysfunction. For OTH patients, fatalities in PD-1/PD-L1 treatment were more often associated with interstitial lung disease and

pneumonia, while combined therapies reported more cases of pneumonia and myocarditis.



Supplementary Figure 7. Reporting overlaps of ICI-related with fatal-related AEs in Figure. 3. For NSCLC and OTH patients, only fatal-related AE signals with FDR-adjusted p-values < 0.001 in Figure 3 are displayed to control the number of Venn plots.