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## Supplemental information

# Machine learning modeling of patient health signals informs long-term survival on immune checkpoint inhibitor therapy

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**Table S3, related to STAR Methods:** Clinical trial cohorts used in the present study.

| Trial name | ClinicalTrials.gov ID | Phase | *n* used in present study | Treatment arm | Randomized | Blinded | Disease indication |
|---|---|---|---|---|---|---|---|
| MYSTIC[1] | NCT02453282 | 3 | 1,092 | Durvalumab, durvalumab + tremelimumab, chemotherapy | Y | N | NSCLC |
| PACIFIC[2] | NCT02125461 | 3 | 709 | Durvalumab, placebo | Y | Y | NSCLC |
| ARCTIC[3] | NCT02453282 | 3 | 595 | Durvalumab, tremelimumab, durvalumab + tremelimumab, chemotherapy | Y | N | NSCLC |
| ATLANTIC[4] | NCT02087423 | 2 | 444 | Durvalumab | N | N | NSCLC |
| CD1108[5] | NCT01693562 | 1/2 | 690 | Durvalumab | N | N | Solid tumors |

N, no; NSCLC, non–small-cell lung cancer; Y, yes.

Supplementary References


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2. Antonia, S.J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., Yokoi, T., Chiappori, A., Lee, K.H., de Wit, M., et al. (2017). Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine *377*, 1919-1929. 10.1056/NEJMoa1709937.
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**Figure S1, related to Figure 1:** Comparison of trial-reported immune-related adverse events versus the machine learning adverse event signature in the context of different landmark analysis times. (A) Examination of trial-reported immune-related adverse events without controlling for guarantee-time bias. Point estimates and 95% confidence intervals for hazard ratios (Cox proportional hazards regression model) with machine learning adverse event signature class as the only covariate, computed per treatment arm, per trial, for overall survival. (B) Point estimates and 95% confidence intervals for hazard ratios (Cox proportional hazards regression model) with trial-reported irAE class as the only covariate, computed per treatment arm, per trial, after adverse event and overall survival data were landmarked at each of the days shown. (C) Point estimates and 95% confidence intervals for hazard ratios (Cox proportional hazards regression model) with machine learning adverse event signature class as the only covariate, computed per treatment arm, per trial, after adverse event and overall survival data were landmarked at each of the days shown. CI, confidence interval; HR, hazard ratio; irAE, immune-related adverse event; ML, machine learning.

**Figure S2, related to Figure 2:** Evaluation of AE signature in the context of progression-free survival or progressive disease. Point estimates and 95% confidence intervals for hazard ratios (Cox proportional hazards regression model) with machine learning adverse event signature class as the only covariate, computed per treatment arm, per trial, after data were landmarked at 60 days. (A) progression-free survival for patients with <1% PD-L1 tumor cells. (B) Progression-free survival in patients with >1% PD-L1 tumor cells. (C) Progression-free survival in all patients. (D) Overall survival in patients with progressive disease at their first RECIST evaluation. CI, confidence interval; HR, hazard ratio; ML, machine learning; NSCLC, non–small-cell lung cancer; PD, progressive disease; PFS, progression-free survival; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; sig, ML AE signature.

**Figure S3, related to Figure 3:** Disease control rate (the proportion of patients with a best objective response that is complete response, partial response, or stable disease) for each combination of machine learning adverse event signature class and PD-L1 negative status (PD-L1$^{-}$ = PD-L1 <1%), for each trial. Raw numbers of patients are shown near datapoints. sig, ML AE signature.

**Figure S1**

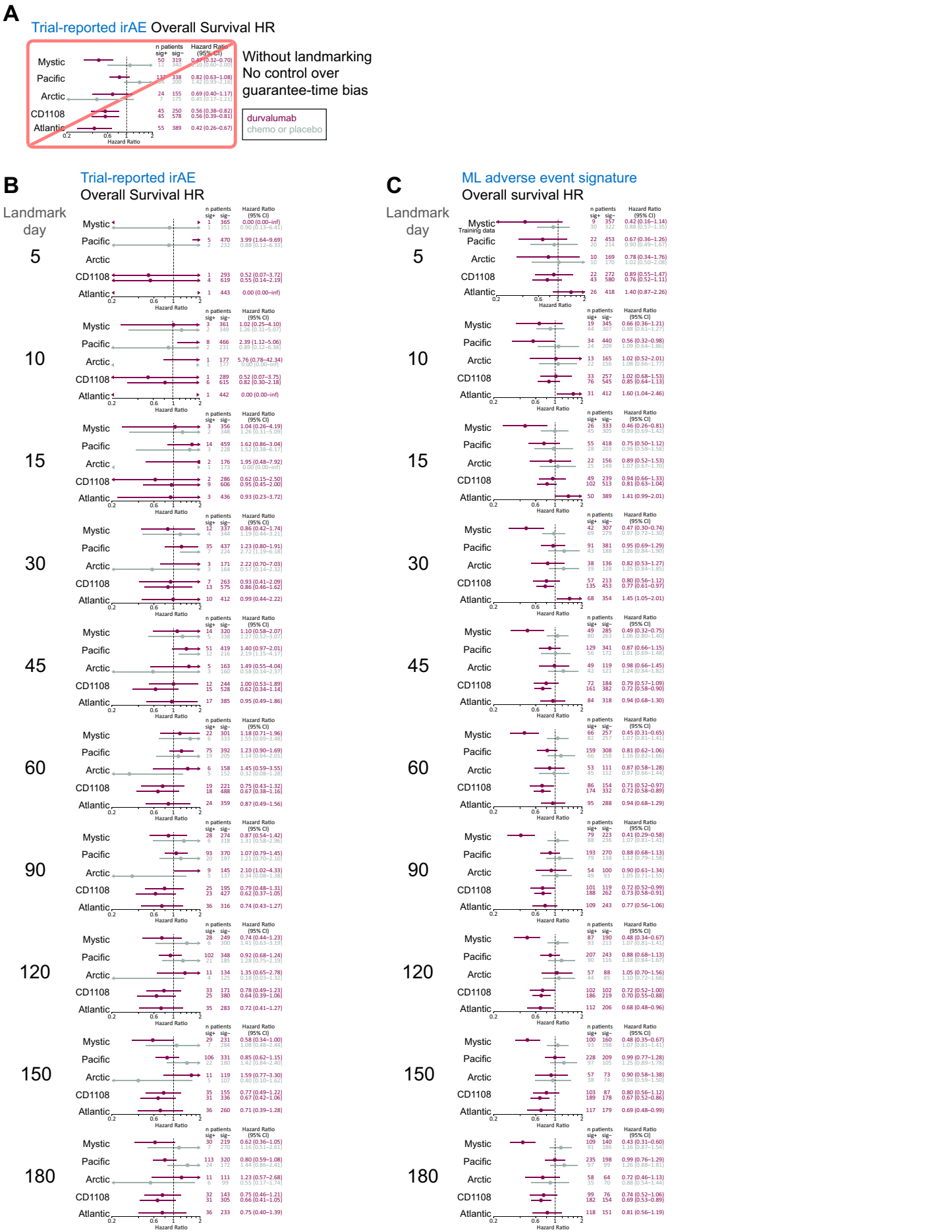

A
Trial-reported irAE Overall Survival HR
Without landmarking
No control over
guarantee-time bias
durvalumab
chemo or placebo
B
Trial-reported irAE
Overall Survival HR
C
ML adverse event signature
Overall survival HR
Landmark day
5
10
15
30
45
60
90
120
150
180
Mystic
Pacific
Arctic
CD1108
Atlantic
Hazard Ratio

**Figure S2**

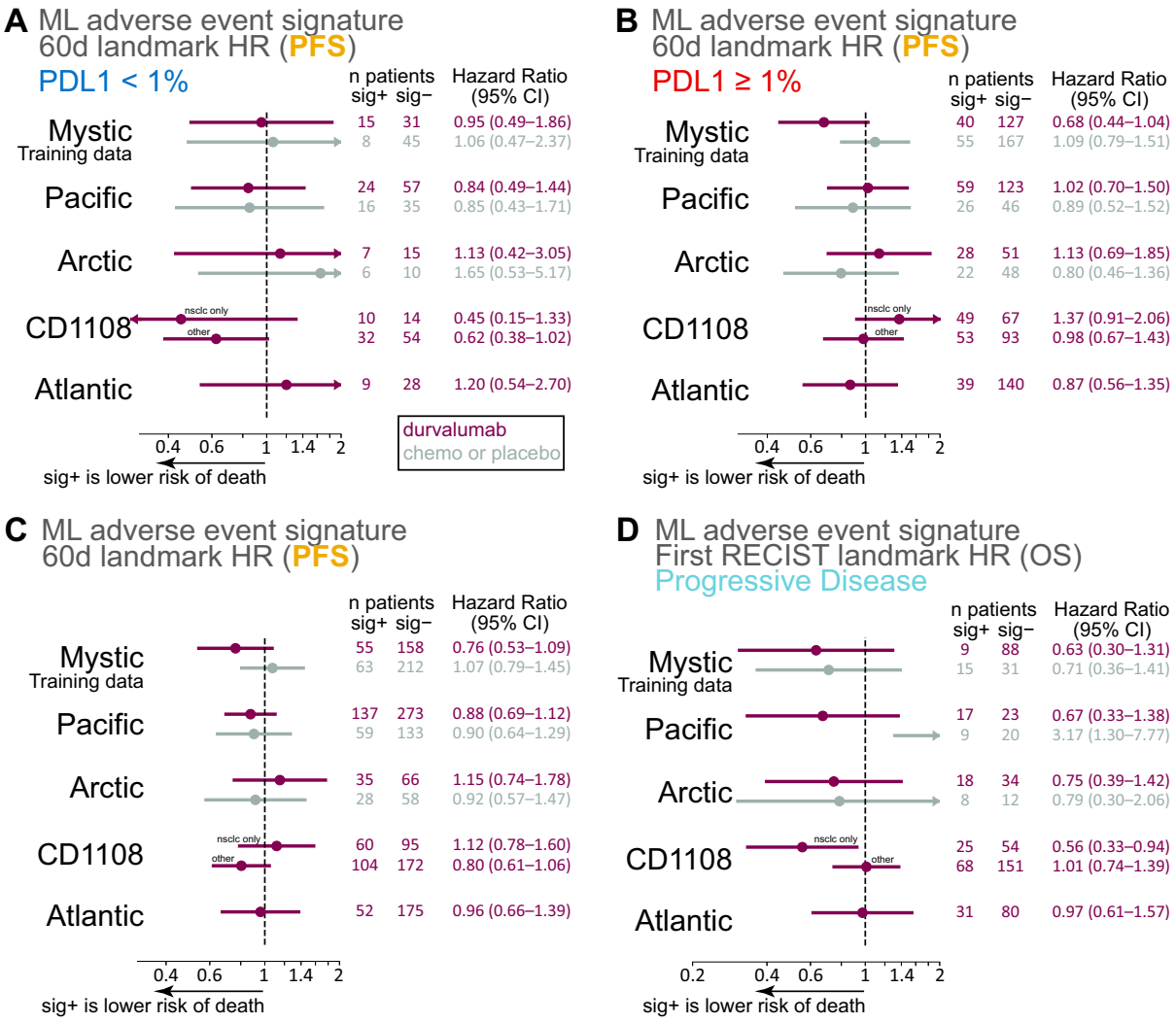
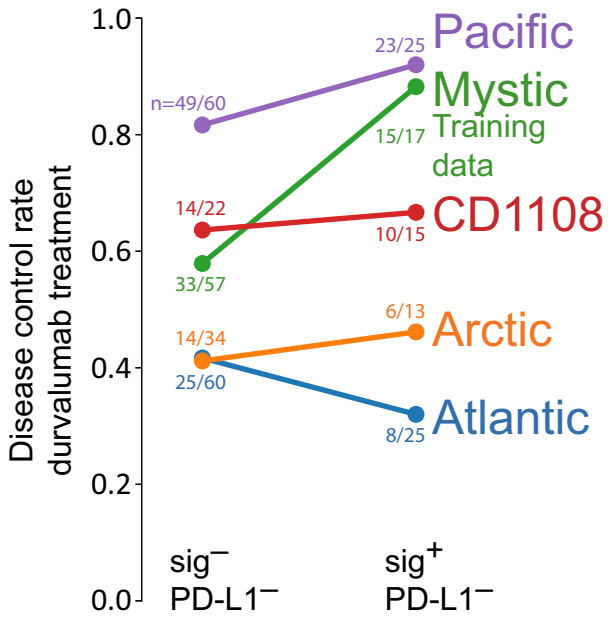

A ML adverse event signature
60d landmark HR (PFS)
PDL1 < 1%
n patients
sig+ sig−
Hazard Ratio
(95% CI)
Mystic
Training data
15 31 0.95 (0.49–1.86)
8 45 1.06 (0.47–2.37)
Pacific
24 57 0.84 (0.49–1.44)
16 35 0.85 (0.43–1.71)
Arctic
7 15 1.13 (0.42–3.05)
6 10 1.65 (0.53–5.17)
CD1108
nsclc only
10 14 0.45 (0.15–1.33)
other
32 54 0.62 (0.38–1.02)
Atlantic
9 28 1.20 (0.54–2.70)
0.4 0.6 1 1.4 2
sig+ is lower risk of death
durvalumab
chemo or placebo
B ML adverse event signature
60d landmark HR (PFS)
PDL1 ≥ 1%
n patients
sig+ sig−
Hazard Ratio
(95% CI)
Mystic
Training data
40 127 0.68 (0.44–1.04)
55 167 1.09 (0.79–1.51)
Pacific
59 123 1.02 (0.70–1.50)
26 46 0.89 (0.52–1.52)
Arctic
28 51 1.13 (0.69–1.85)
22 48 0.80 (0.46–1.36)
CD1108
nsclc only
49 67 1.37 (0.91–2.06)
other
53 93 0.98 (0.67–1.43)
Atlantic
39 140 0.87 (0.56–1.35)
0.4 0.6 1 1.4 2
sig+ is lower risk of death
C ML adverse event signature
60d landmark HR (PFS)
n patients
sig+ sig−
Hazard Ratio
(95% CI)
Mystic
Training data
55 158 0.76 (0.53–1.09)
63 212 1.07 (0.79–1.45)
Pacific
137 273 0.88 (0.69–1.12)
59 133 0.90 (0.64–1.29)
Arctic
35 66 1.15 (0.74–1.78)
28 58 0.92 (0.57–1.47)
CD1108
nsclc only
60 95 1.12 (0.78–1.60)
other
104 172 0.80 (0.61–1.06)
Atlantic
52 175 0.96 (0.66–1.39)
0.4 0.6 1 1.4 2
sig+ is lower risk of death
D ML adverse event signature
First RECIST landmark HR (OS)
Progressive Disease
n patients
sig+ sig−
Hazard Ratio
(95% CI)
Mystic
Training data
9 88 0.63 (0.30–1.31)
15 31 0.71 (0.36–1.41)
Pacific
17 23 0.67 (0.33–1.38)
9 20 3.17 (1.30–7.77)
Arctic
18 34 0.75 (0.39–1.42)
8 12 0.79 (0.30–2.06)
CD1108
nsclc only
25 54 0.56 (0.33–0.94)
other
68 151 1.01 (0.74–1.39)
Atlantic
31 80 0.97 (0.61–1.57)
0.2 0.4 0.6 1 1.4 2
sig+ is lower risk of death

**Figure S3**


1.0
0.8
0.6
0.4
0.2
0.0
Disease control rate
durvalumab treatment
n=49/60
23/25
Pacific
Mystic
15/17
Training
data
14/22
10/15
CD1108
33/57
6/13
14/34
Arctic
25/60
8/25
Atlantic
sig−
PD-L1−
sig+
PD-L1−