



DURA: Durable Response Assessment

A Multimodal AI Model Integrating Clinical and Genomic Features to Predict Durable Immune Checkpoint Inhibitor Response in Metastatic NSCLC

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0.78

DURA AUROC, pooled

5-fold cross-validated (N = 410)
PD-L1 alone 0.61

19.4 vs 6.4

Median PFS, months

Favorable vs unfavorable
log-rank $p < 0.001$

OR 4.28

Histone modifiers

52% vs 20% durable
Fisher $p = 0.002$

OR 3.60

HRD pathway

48% vs 20% durable
Fisher $p = 0.004$

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Financial relationships, past 24 months

- Advisory board — Johnson & Johnson
- Honoraria — MJH Life Sciences

FUNDING & ETHICS

- Supported by City of Hope National Medical Center. No commercial or industry funding supported this analysis.
- IRB protocols COH 25411; HIPAA Safe Harbor de-identification applied to all patient data.

DATA AVAILABILITY

- External and pre-training cohorts are public via cBioPortal (Hellmann 2018; Rizvi 2018; TCGA Pan-Lung).
- Analyses in Python (scikit-learn, lifelines, PyTorch Geometric); survival analyses cross-checked in R.

BACKGROUND

- Only 15–20% of patients with metastatic NSCLC achieve durable (>2-year) benefit from immune checkpoint inhibitors.
- PD-L1 discriminates poorly (AUROC $\approx$ 0.6); TMB alone adds little.
- Genomic context — DNA-damage repair and chromatin state — is not captured by single-marker testing.

PRIMARY ENDPOINT

Durable response: continued clinical benefit beyond 2 years from ICI initiation.

COHORTS

- Internal: 335 patients with metastatic NSCLC treated with ICI at an NCI-designated cancer centre; 205 sequenced, 147 with reportable mutations.
- External: 75 ICI-treated patients with whole-exome sequencing (Hellmann, Cancer Cell 2018).
- Pooled N = 410; NGS-evaluable N = 280.
- Tumour genomics enter the model as log-TMB and TMB-high from the NGS panel.

STATISTICS

- Kaplan–Meier with log-rank; Cox PH; OS also modelled on the continuous score.
- Fisher exact for pathways; DeLong CIs.

DURA ARCHITECTURE

Clinical + TMB model

L2-regularised logistic regression on 8 features: age, sex, ECOG PS, PD-L1, smoking history, histology, log-TMB and TMB-high (≥ 10 mut/Mb).



DURA score

Predicted probability of durable response (0–1).
Favorable >0.60 · Intermediate 0.40–0.60 · Unfavorable <0.40 .

Genomic pathway analysis

Fisher exact tests of durable response by mutated gene set (HRD, histone modifiers, chromatin) in the NGS-evaluable cohort (N = 280).

INTERNAL COHORT CHARACTERISTICS (N = 335)

66

Median age, years

54%

Male

82%

Adenocarcinoma

51 (15.2%)

Durable responders

205

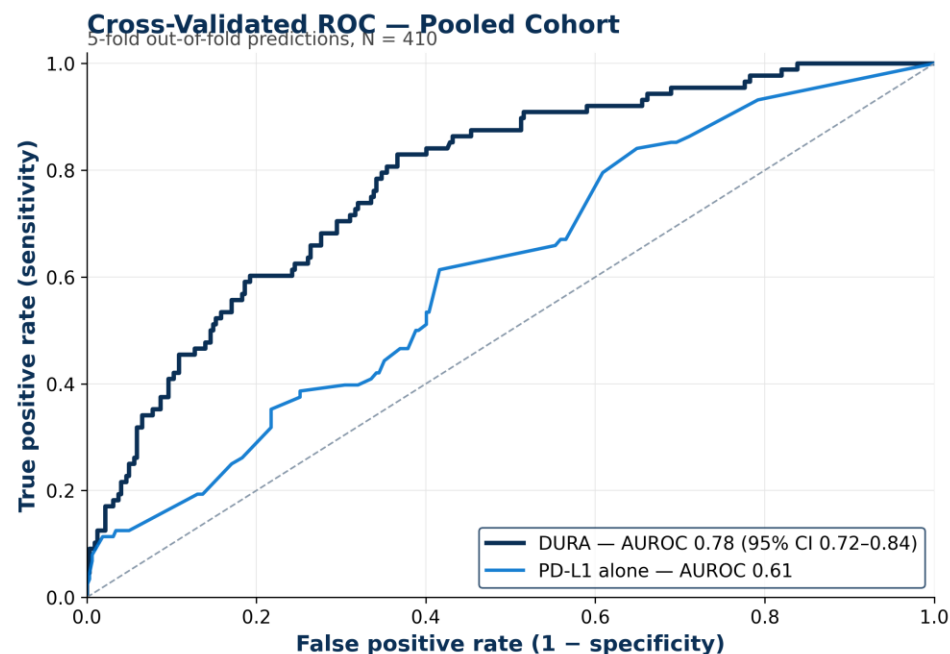
Sequenced

147

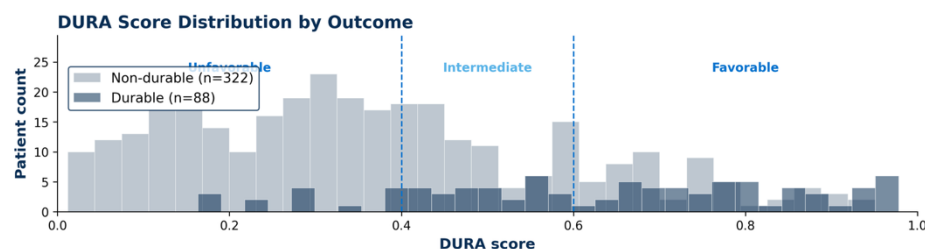
Reportable mutations

Results I — Model Performance

Discrimination of durable ICI benefit



Cross-validated ROC, pooled cohort (N = 410): 5-fold out-of-fold predictions; PD-L1 alone on the same patients.



DURA score distribution by outcome; dashed lines mark the 0.40 / 0.60 thresholds.

DISCRIMINATION — POOLED COHORT (N = 410)

0.78

cross-validated AUROC

5-fold CV · pooled N = 410 · 95% CI 0.72-0.84

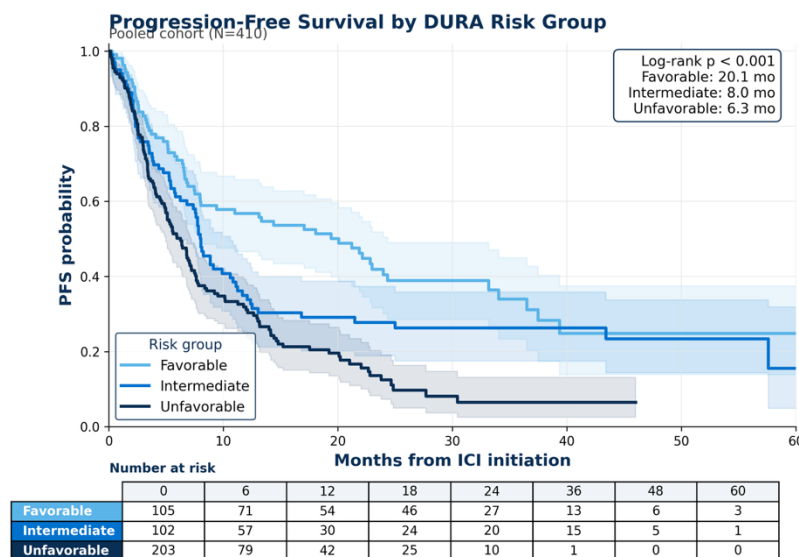
PD-L1 alone: 0.61

KEY POINTS

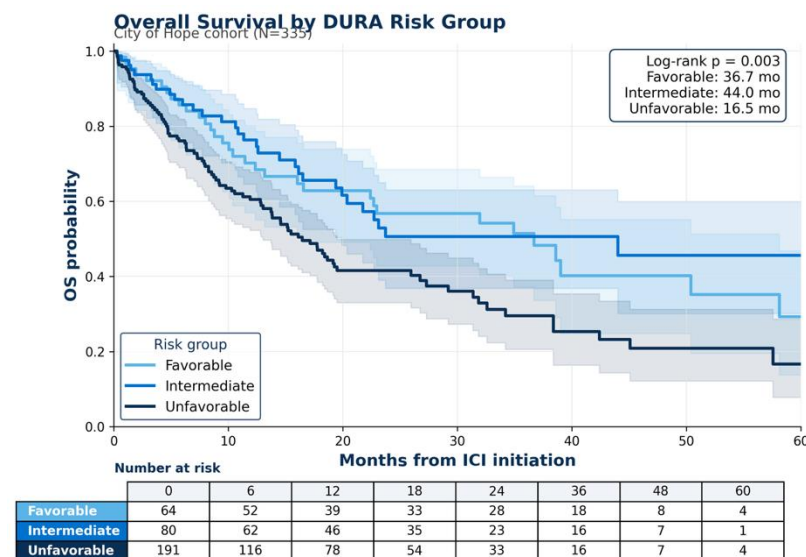
- Cross-validated AUROC 0.78 (95% CI 0.72-0.84) on the pooled cohort, versus 0.61 for PD-L1 alone in the same 410 patients.
- The DURA score is the clinical + TMB model; tumour genomics enter through log-TMB and TMB-high from the NGS panel.
- The curve is built from 5-fold out-of-fold predictions, avoiding the optimistic in-sample estimate.
- Durable responders concentrate above the 0.60 threshold, while the unfavorable band is almost entirely non-durable.

Results II — Risk Stratification & Survival

Survival by DURA risk group and by continuous score



PFS by DURA risk group, pooled cohort (N = 410).



OS by DURA risk group, internal cohort (N = 335).

Internal cohort (N = 335) by DURA risk group

Risk group	n	Durable	mPFS, mo	mOS, mo	PFS HR (95% CI)
Favorable	64	21 (32.8%)	19.4	36.7	0.48 (0.33–0.69)
Intermediate	80	19 (23.8%)	8.9	44.0	0.58 (0.42–0.81)
Unfavorable	191	11 (5.8%)	6.4	16.5	reference

— Unfavorable vs Intermediate + Favorable — median OS 16.5 vs 36.7 mo; HR 1.74 (1.26–2.39), $p = 0.0006$. Pairwise vs unfavorable: HR 0.61 favorable, 0.54 intermediate (both $p < 0.02$).

Results III — Genomic Pathways

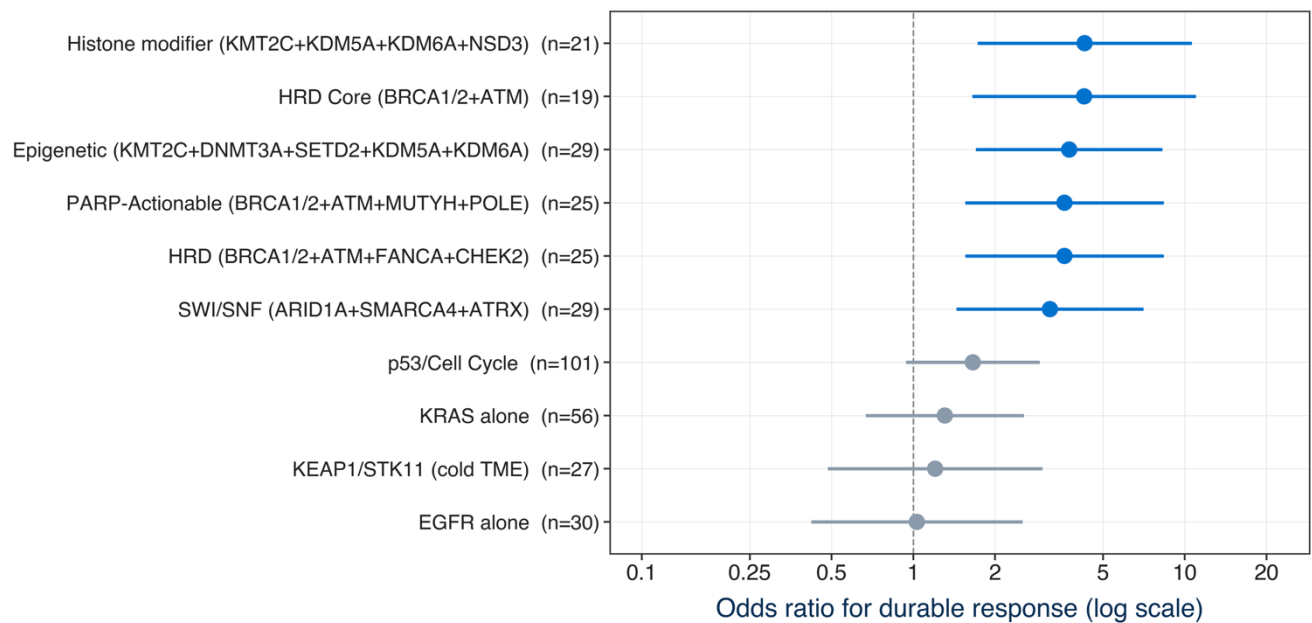
Pathway-level predictors in the NGS-evaluable cohort



Pathway-Level Predictors of Durable Response

Pooled NGS-evaluable cohort (N=280) · Fisher exact OR with 95% CI

sig n.s. p < 0.05



Odds ratios for durable response, pooled NGS-evaluable cohort (N = 280; 64 durable, 22.9%). Blue denotes Fisher p < 0.05.

PATHWAY ASSOCIATIONS · N = 280

Pathway	n	Durable vs WT	OR	p
HRD pathway	25	48% vs 20%	3.60	0.004
Histone modifiers	21	52% vs 20%	4.28	0.002
Chromatin + epigenetic	40	42% vs 20%	3.04	0.004
KEAP1 / STK11	27	26% vs 23%	1.20	0.64

HRD = BRCA1/2, ATM, FANCA, CHEK2. Histone modifiers = KMT2C, KDM5A, KDM6A, NSD3. Chromatin + epigenetic = 8 genes, SMARCA4 excluded.

INTERPRETATION

- Histone-modifier mutations showed the strongest association with durable benefit (OR 4.28; PFS log-rank p = 0.040).
- HRD mutations nearly tripled the odds of durable response (OR 3.60; PFS p = 0.001) — rationale for ICI + PARP inhibitor trials.
- KEAP1/STK11: no association pooled; 0/12 mutant patients durable internally.

MOST FREQUENTLY MUTATED GENES (NGS-evaluable, N = 280)

TP53 97 · 35%	KRAS 56 · 20%	EGFR 30 · 11%	CDKN2A 21 · 8%	STK11 20 · 7%	PIK3CA 14 · 5%	SMARCA4 14 · 5%	ALK 13 · 5%
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CONCLUSIONS

- A multimodal score integrating clinical features with tumour mutational burden predicted durable ICI benefit with a cross-validated AUROC of 0.78, versus 0.61 for PD-L1 alone in the same patients.
- DURA stratified PFS across risk groups (median 19.4 vs 6.4 months; $p < 0.001$). Unfavorable patients had shorter OS than all others (16.5 vs 36.7 months; HR 1.74, $p = 0.0006$), and the continuous score predicted OS directly (HR 0.85 per +0.1, $p < 0.0001$).
- Histone-modifier and HRD pathway mutations independently predicted durable benefit, nominating HRD-mutant NSCLC for ICI + PARP inhibitor combination trials.

LIMITATIONS

- Retrospective, single-centre derivation with a modest favorable subgroup ($n = 64$).
- Risk-group assignment is sensitive to the fixed 0.40 / 0.60 cutpoints; the continuous score is the more stable predictor.
- Prospective validation and additional genomic features are warranted.

AT A GLANCE

AUROC 0.78

cross-validated; PD-L1 alone 0.61

19.4 vs 6.4 mo

median PFS, fav vs unfav

HR 1.74

OS, unfavorable vs rest, $p = 0.0006$

OR 4.28 / 3.60

histone modifiers / HRD