

Prognostic Impact of TP53-STK11 Co-Mutation in Stage II-III NSCLC Treated With Chemoradiotherapy and Durvalumab

Simran^{1,2}, Kayeong Shin³, Kolade O. Olabode⁴, Levi B. Martinka⁴, Joshua Kim⁵, James K. Hicks¹, Sonam Puri¹, Andreas N. Saltos¹, Tawee Tanvetyanon¹, Ben Creelan¹, Stephen A. Rosenberg¹, Salma K. Jabbour⁶, Jhanelle Gray¹, Thomas J. Dilling¹, Jongmyung Kim¹

¹Moffitt Cancer Centre, Tampa/FL/USA, ²All India Institute of Medical Sciences(AIIMS) New Delhi, New Delhi/IN, ³The University of Texas MD Anderson Cancer Center, Houston/TX/USA, ⁴Morsani College of Medicine, University of South Florida, Tampa/FL/USA, ⁵Zucker School of Medicine at Hofstra/Northwell, New York/NY/USA, ⁶Rutgers Cancer Institute, New Brunswick/NB/USA

Introduction & Rationale

- **Genomic Context:** Outcomes in locally advanced non-small cell lung cancer (NSCLC) are heavily driven by tumor genomics.
- **The Biological Paradox:**
 - *TP53* mutations typically drive higher tumor mutational burden (TMB).
 - *STK11* loss creates an "immune-cold" microenvironment, inducing resistance to immune checkpoint inhibitors (ICIs).
- **Knowledge Gap:** The clinical impact of *TP53-STK11* co-mutations in Stage II–III NSCLC treated with definitive chemoradiotherapy (CRT) + consolidation durvalumab remains poorly understood.
- **Study Objective:** Evaluate survival and recurrence patterns in *TP53-STK11* co-mutated Stage II–III NSCLC patients undergoing definitive CRT + durvalumab.

Methods & Study Design

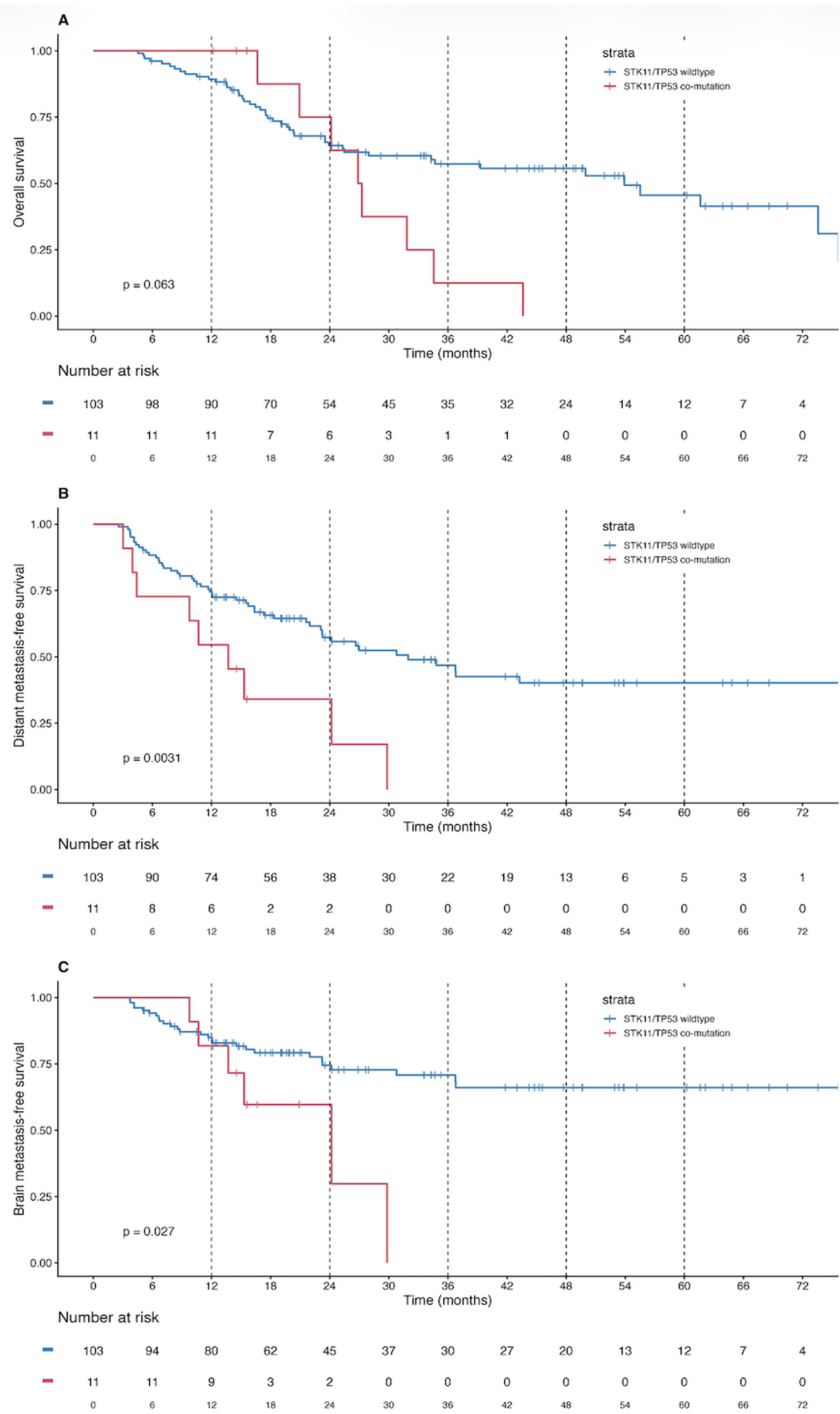
- **Study Population:** Retrospective analysis of **263 patients** with Stage II–III NSCLC treated with definitive CRT followed by durvalumab (2015–2024).
- **Inclusion Criteria:** Required baseline Next-Generation Sequencing (NGS). Final analytic cohort = **114 patients**.
- **Endpoints Evaluated:**
 - **Primary:** Overall Survival (OS)
 - **Secondary:** Distant Metastasis-Free Survival (DMFS), Brain Metastasis-Free Survival (BMFS), Locoregional Recurrence-Free Survival (LRFS), and In-Field Recurrence-Free Survival (IRFS).
- **Statistical Analysis:** Kaplan-Meier survival curves and Cox proportional hazards regression models. Median follow-up: **43.0 months** (range, 4.5–85.4)

Baseline Characteristics

	Mutant (N=11)	Wildtype (N=103)	
Age			0.367
Median (IQR)	65.8 (60.9, 70.8)	68.5 (62.3, 75.5)	
Gender			1
Female	6 (54.5%)	56 (54.4%)	
Male	5 (45.5%)	47 (45.6%)	
Race			0.211
Black /African American	2 (18.2%)	4 (3.9%)	
White	9 (81.8%)	95 (92.2%)	
American Indian or Alaska Native	0 (0%)	1 (1.0%)	
Asian	0 (0%)	3 (2.9%)	
Smoking Status			0.258
Current	2 (18.2%)	32 (31.1%)	
Former	8 (72.7%)	45 (43.7%)	
Never	1 (9.1%)	9 (8.7%)	
Unknown	0 (0%)	17 (16.5%)	
Stage (AJCC 8th ed)			0.571
IIIA	3 (27.3%)	40 (38.8%)	
IIIB	6 (54.5%)	40 (38.8%)	
IIIC	2 (18.2%)	11 (10.7%)	
IIA	0 (0%)	1 (1.0%)	
IIB	0 (0%)	11 (10.7%)	
PDL1_class			<0.001
≥1%	1 (9.1%)	41 (39.8%)	
<1%	10 (90.9%)	22 (21.4%)	
Unknown	0 (0%)	40 (38.8%)	
Chemo Regimen			0.235
Platinum, etoposide	1 (9.1%)	6 (5.8%)	
Platinum, PACLitaxel	6 (54.5%)	79 (76.7%)	
Platinum, PEMEtrexed	4 (36.4%)	18 (17.5%)	
Dose Prescribed			0.222
Median (Range)	6000 (6000, 6600)	6000 (6000, 7000)	

- ✓ Co-Mutation Frequency: *TP53-STK11* co-mutations were identified in 9.6% (11/114) of patients.
- ✓ PD-L1 Suppression: Co-mutated tumors had a significantly higher rate of PD-L1 negative (< 1%) expression compared to wildtype (90.9% vs. 21.4%, *p* < 0.001).
- ✓ Demographic Parity: No statistically significant differences were observed between groups in age, sex, race, stage distribution, or chemotherapy regimen

Overall survival (OS), distant metastasis-free survival (DMFS), and brain metastasis-free survival (BMFS)



Metric	Co-Mutated (N=11)	Wildtype (N=103)	Hazard Ratio (95% CI)	p-value
Median OS	27.1 mos.	53.9 mos.	2.03 (0.95–4.35)	p = 0.063
Median DMFS	13.7 mos.	32.0 mos.	2.85 (1.38–5.89)	p = 0.003
Median BMFS	24.2 mos	Not Reached	2.67 (1.08–6.60)	p = 0.027

- **IRFS:** no significant difference (HR 1.85, 95% CI 0.40–8.42; *p*=0.42)
- **LRFS:** trend toward worse outcome (HR 2.63, 95% CI 0.88–7.92; *p*=0.073)
- **Distant failure risk:** >2.8-fold increase in co-mutant cohort
- **CNS/brain metastasis:** significantly elevated (median 24.2 mo. vs. not reached in wildtype)

Discussion & Conclusion

- **Key Takeaway:** *TP53-STK11* co-mutation defines a high-risk subgroup of Stage II–III NSCLC with poor long-term outcomes despite standard definitive CRT and durvalumab consolidation.
- **Systemic Failure Pattern:** High rate of distant and brain progression highlights that local control (IRFS) is maintained, but systemic/micro-metastatic control fails.
- **Clinical Implications:**
 - Routine baseline NGS profiling should be integrated into stage II–III NSCLC staging workups.
 - Co-mutated patients may require **treatment intensification** (e.g., novel immunotherapeutic combinations, targeted agents, or proactive CNS surveillance).
- **Future Directions:** Further research is needed to define how the prognostic and predictive impact of *TP53-STK11* co-mutation differs from either mutation alone, to clarify whether the observed risk is additive or synergistic.

References and Acknowledgements

- An LN, Rodriguez A, Yendamuri S, et al. Outcomes of patients with stage III non-small cell lung cancer (NSCLC) that harbor a *STK11* mutation. *Transl Lung Cancer Res.* 2021;10(8):3459-3471.
- Skoulidis F, Goldberg ME, Greenawalt DM, et al. *STK11/LKB1* mutations and PD-1 inhibitor resistance in *KRAS*-mutant lung adenocarcinoma. *Cancer Discov.* 2018;8(7):822-835.