

## 1 **Supplementary Methods**

### 2 **Patient population**

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5 This multicenter retrospective analysis included all consecutive patients with documented stage III  
6 NSCLC (AJCC 8<sup>th</sup> Edition) treated with platinum-based chemotherapy concurrently with definitive  
7 radiation therapy and received at least one dose of consolidation durvalumab between November 2017 to  
8 July 2022. Clinicopathologic and genomic data were obtained from Dana-Farber Cancer Institute (DFCI)  
9 and Memorial Sloan Kettering Cancer Center (MSKCC) cohorts. Patients were included if they had  
10 consented to each institution's institutional review board-approved medical review protocols. The patient  
11 studies were conducted according to the ethical guidelines of the Declaration of Helsinki. A total of 197  
12 patients at DFCI (N=98) and MSKCC (N=99) were identified. Data analysis was performed from  
13 November 2022 to April 2023.  
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### 15 **Specific Site**

16 *Dana-Farber Cancer Institute cohort*

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19 Patients at the Dana-Farber Cancer Institute who consented to institutional review board-approved  
20 protocols DF/HCC 02-180, 11-104, 13-364, and/or 17-000 which allowed for conducting translational  
21 research and multiplexed immunofluorescence, respectively, were also included.  
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### 23 **Programmed death ligand 1 immunohistochemistry**

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26 The PD-L1 tumor proportion score (TPS) was determined by immunohistochemistry using validated anti-  
27 PD-L1 antibodies: E1L3N (Cell Signaling Technology, Danvers, MA), 22C3 (Dako North America Inc,  
28 Carpinteria, CA), and SP263 [Roche Tissue Diagnostics, Oro Valley, AZ] depending on local institutional  
29 practice. PD-L1 scores were performed on pre-treated tissue.  
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### 31 **Next Generation Sequencing (NGS)**

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33 Non-small cell lung cancers were sequenced by targeted NGS using OncoPanel<sup>1,2</sup> (DFCI) and MSK-  
34 IMPACT<sup>3</sup> (MSKCC) platforms. TMB distributions were harmonized between the two platforms as  
35 previously described<sup>4</sup>. The tumor content was determined by pathologist assessment at DFCI or by  
36 molecular assessment at MSKCC for each sample<sup>3</sup>.  
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### 38 **Quantification of aneuploidy using ASCETS**

39 To quantify aneuploidy levels, targeted sequencing data were analyzed using ASCETS (Arm-level  
40 Somatic Copy-number Events in Targeted Sequencing), as previously described<sup>5</sup>; this method utilizes  
41 segmentation files and log<sub>2</sub> copy ratios (LCRs) for all interrogated genomic loci. LCRs are used to  
42 determine the noise per segment by separating alternating LCRs within a given segment into two groups  
43 and calculating their difference in means. These differences are compiled across all segments and  
44 samples to determine a noise threshold representing one standard deviation above the mean. This  
45 threshold and its additive inverse are taken as amplification and deletion thresholds, respectively. After  
46 stratifying amplified and deleted segments, ASCETS computes the fraction of chromosome  
47 encompassed by copy-number segments of each arm corresponding to each segment class (amplified,  
48 deleted, or neutral). A chromosomal arm was considered altered if at least 70% of its territory was either  
49 amplified or deleted. Samples with >20% tumor purity and chromosomal arms with adequate coverage  
50 were included to determine arm-level events. The number of altered chromosome arms for each tumor  
51 was calculated as the sum total of altered arms, ranging from 0 (no arm alterations) to 39 (all arms  
52 altered); the chromosome arms included in this calculation included the long and short arms for

1 chromosomes 1-12 and 16-20, as well as the long arms for the acrocentric chromosomes 13-15 and 21-  
2 22<sup>6</sup>. The fraction of chromosomal arm alterations is defined as the number of altered chromosome arms  
3 divided by the number of chromosome arms assessed for each sample. Because of the relationship  
4 between fraction of chromosomal arm alterations and tumor content<sup>5</sup>, we multiplied the fraction of  
5 chromosomal arm alterations by  $[1 - (\text{Tumor content}/100)]^{7,8}$  to calculate the adjusted fraction of  
6 chromosomal arm alterations, hereafter referred to as FAA. The FAA distributions were harmonized  
7 across the different NGS versions and the two different platforms (DFCI OncoPanel and MSK-IMPACT)  
8 by applying a normal transformation followed by standardization to FAA Z-scores, as previously described  
9 for TMB harmonization across different platforms<sup>4</sup>. We designated aneuploidy as high and low,  
10 considering the median FAA value as a boundary.

### 11 **Specific Site**

12 *Memorial Sloan Kettering Cancer Center*

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14 The copy number profile for each tumor in the MSKCC cohort found using FACETS (Fraction and Allele-  
15 Specific Copy Number Estimates from Tumor Sequencing) v0.5.14<sup>9</sup> compared to its matched normal. The  
16 segmentation profile was compiled with FACETS-suite and used to determine aneuploidy with ASCETS,  
17 as described above.

### 18 **Tumor mutational burden assessment and harmonization**

19 Tumor mutational burden (TMB), defined as the number of somatic, coding, base substitution, and indel  
20 mutations per megabase (Mb) of genome examined, was determined using the OncoPanel and MSK-  
21 IMPACT NGS platforms. DFCI mutation counts were divided by the number of bases covered in each  
22 OncoPanel version: v1, 0.753334 Mb; v2, 0.826167 Mb; and v3, 1.315078 Mb. For MSKCC samples, the  
23 mutation count was divided by 0.896665, 1.016478, and 1.139322 Mb for the 341-, 410-, and 468-gene  
24 panels, respectively. Because TMB was determined using two different platforms, TMB distributions were  
25 harmonized across institutions by applying a normal transformation followed by standardization to Z-  
26 scores, as previously described<sup>4</sup>. Power transformations were used to normalize cohort-specific TMB  
27 distributions, and Tukey's ladder of powers in the rcompanion package was used to identify the optimal  
28 transformation coefficient. Normalized distributions were then standardized into Z-scores by subtracting  
29 the transformed distribution mean and dividing by the standard deviation.

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### 31 **Multiplexed immunofluorescence (ImmunoProfile)**

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33 Multiplexed immunofluorescence (mIF) was performed on a separate cohort of NSCLCs from the DFCI to  
34 determine the immunophenotype-associated subgroups by staining 5-micron formalin-fixed, paraffin-  
35 embedded (FFPE) whole tissue sections with standard, primary antibodies sequentially and paired with a  
36 unique fluorochrome followed by staining with nuclear counterstain/4',6-diamidino-2-phenylindole  
37 (DAPI)<sup>10,11</sup>. All samples were stained for PD-L1 (clone E1L3N), PD-1 (clone EPR4877[2]), CD8 (clone  
38 4B11), and FOXP3 (clone D608R). Each sample had a single slide stained and scanned at 20x resolution  
39 by a Vectra Polaris imaging platform. Regions of Interest (ROIs) were defined for each image, and only  
40 these regions were used for quantitative image analysis. Within each ROI, InForm Image Analysis  
41 software (Perkin Elmer/ Akoya) was run to phenotype and score cells based on biomarker expression. A  
42 custom script quantified the number/ percentage of positive cells for relevant biomarkers in the intra-  
43 tumoral region, defined as the region of the slide consisting of tumors beyond the tumor-stroma interface.  
44 Cell count was calculated per ROI and averaged (unweighted) across ROIs, reported as count per  
45 millimeter squared +/- standard error. Statistical significance of differential cell type enrichment between  
46 groups was estimated with the Wilcoxon/Kruskal Rank Sum test.

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### 48 **Statistical Analysis**

1           Categorical and continuous variables were summarized descriptively using percentages and  
2 medians. The Wilcoxon-Rank Sum test and Kruskal-Wallis test were used to test for differences between  
3 continuous variables, and Fisher's exact test was used to test for associations between categorical  
4 variables. The clinical follow-up schedule followed standard treatment and included history, physical, and  
5 chest CT every 3-4 months for the first 2 years. Event-time distributions were estimated using Kaplan-  
6 Meier methodology. Log-rank tests were used to test for differences in event-time distributions, and Cox  
7 proportional hazards models were used to estimate hazard ratios in univariable and multivariable models  
8 for PFS and OS. We first discovered the effect of baseline clinicopathological factors of tumor stage, age,  
9 sex, smoking status, histology, Eastern Cooperative Oncology Group performance status (ECOG PS),  
10 aneuploidy level (low vs high), TMB (lower vs middle vs upper tertile), and PD-L1 TPS levels (<90% vs  
11 ≥90%) on clinical outcomes in univariable analyses. Multivariable models included factors found to be  
12 predictive from a complementary study using this patient population<sup>12</sup> and included the variables with P-  
13 value <0.1 into the multivariable analysis to control for the potential confounding effects. All P-values are  
14 2-sided and confidence intervals are at the 95% level, with significance pre-defined to be at the two-sided  
15 0.05-level. Relevant co-variants were analyzed for interaction. All statistical analyses were performed  
16 using R version 3.6.3.

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