Gene Sequencing of Serial Tumor Biopsies from a Large Cohort of Cancer Patients Shows Longitudinal Changes in *TP53* Mutation Status Are Uncommon

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Background

The p53 pathway is one of the most important in cancer biology, with mutation of the *TP53* gene that encodes the p53 tumor suppressor protein observed in ≈50% of all cancers. For individual patients, next-generation sequencing of tumor biopsy samples is commonly used to determine *TP53* mutational status. The consistency of this measurement in repeat biopsies of individual patients is of significance to guide treatment decisions for selective p53-activating agents such as MDM2 inhibitors, as well as the use of *TP53* mutational status as a prognostic indicator.

Methods

We evaluated the frequency of changes in *TP53* mutation status in a large cohort of serial tumor biopsies. From the FoundationCORE database of >200,000 next-generation gene sequencing results we identified 16,592 samples arising from repeat biopsies from 7840 patients (pts), average 2.12 per pt, 1007 pts with ≥3, max 11; over an interval up to 234 months (mos), average 11.0 mos. *TP53* mutations with known or unknown significance in successive biopsies and changes in assignment from *TP53*-Wild-Type (WT) to Mutant (Mut), or Mut to WT, were evaluated vs. cancer type and time between biopsies.

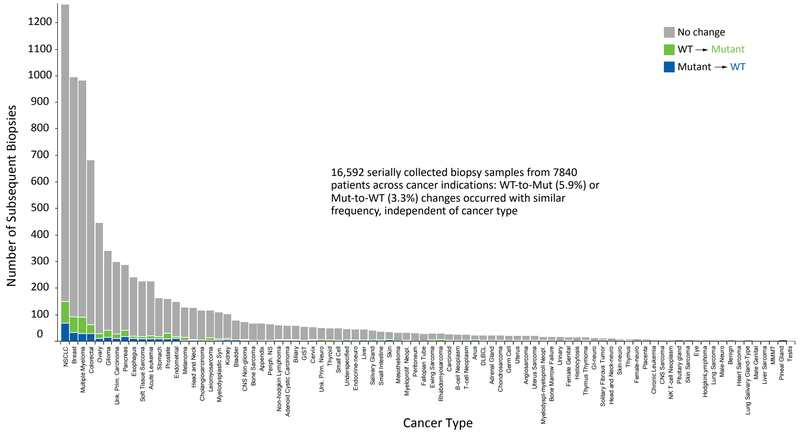
Results

Change In *TP53* Mutation Status in Serial Biopsies: All Samples Plus Three Most Highly Represented Cancer Types in Database

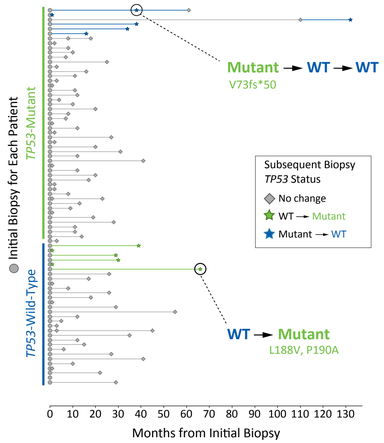
		Overall	Months 1-12	13 - 24	25 - 36	37 - 48	49 - 60	61-240
All (7840 initial, 8752 subsequent)	No Change	7950 (90.8%)	3680 (91.2%)	1974 (91.7%)	1014 (90.5%)	521 (89.7%)	298 (91.1%)	463 (86.5%)
	WT to Mut	513 (5.9%)	205 (5.1%)	121 (5.6%)	67 (6%)	42 (7.2%)	20 (6.1%)	58 (10.8%)
	Mut to WT	289 (3.3%)	151 (3.7%)	57 (2.6%)	40 (3.6%)	18 (3.1%)	9 (2.8%)	14 (2.6%)
NSCLC (1189 initial, 1268 subsequent)	No Change	1118 (88.2%)	518 (89.2%)	299 (90.3%)	145 (84.3%)	70 (82.4%)	33 (89.2%)	53 (85.5%)
	WT to Mut	83 (6.5%)	29 (5%)	16 (4.8%)	21 (12.2%)	9 (10.6%)	1 (2.7%)	7 (11.3%)
	Mut to WT	67 (5.3%)	34 (5.9%)	16 (4.8%)	6 (3.5%)	6 (7.1%)	3 (8.1%)	2 (3.2%)
Breast (947 initial, 993 subsequent)	No Change	902 (90.8%)	313 (92.1%)	209 (92.1%)	152 (93.8%)	73 (85.9%)	49 (86%)	106 (86.9%)
	WT to Mut	60 (6.0%)	14 (4.1%)	14 (6.2%)	6 (3.7%)	9 (10.6%)	6 (10.5%)	11 (9%)
	Mut to WT	31 (3.1%)	13 (3.8%)	4 (1.8%)	4 (2.5%)	3 (3.5%)	2 (3.5%)	5 (4.1%)
MM (578 initial, 981 subsequent)	No Change	892 (90.9%)	523 (90.5%)	253 (90.7%)	77 (95.1%)	25 (92.6%)	13 (86.7%)	1 (100%)
	WT to Mut	62 (6.3%)	38 (6.6%)	20 (7.2%)	2 (2.5%)	1 (3.7%)	1 (6.7%)	0 (0%)
	Mut to WT	27 (2.8%)	17 (2.9%)	6 (2.2%)	2 (2.5%)	1 (3.7%)	1 (6.7%)	0 (0%)

N (%) of samples vs. change in *TP53* status from previous biopsy vs. mos from initial biopsy in all samples (7840 initial + 8752 successive, 46% *TP53*-Mut) and the three most represented cancers: non-small cell lung cancer (NSCLC, 1189 initial + 1268 successive, 60% Mut), breast (947 initial + 993 successive, 55% Mut), multiple myeloma (MM, 578 initial + 981 successive, 18% Mut).

Number and Frequency of *TP53* Mutation Status Changes in Serial Biopsies for all Samples by Indication



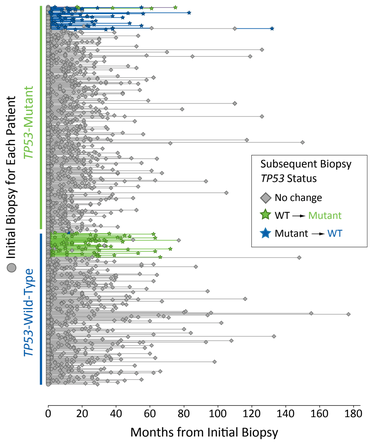
Change in *TP53* Mutation Status in Serial Biopsies: For illustration, Results Shown for 80 Randomly Selected NSCLC Patients



- 80 initial samples (unique patients)
- 84 subsequent samples
- 12/84 (14%) change status vs. prior biopsy:
- 6 (7%) WT→ Mut, 6 (7%) Mut → WT

164 serially collected tumor samples from 80 randomly selected NSCLC patients

Change in *TP53* Mutation Status in Serial Biopsies: All NSCLC Samples

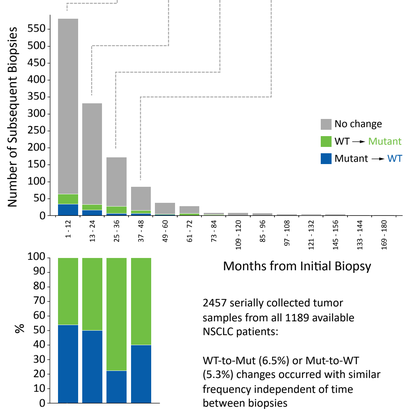


- 1189 initial samples (unique patients)
- 1268 subsequent samples
- 150/1268 (12%) change status vs. prior biopsy:
- 83 (6.5%) WT→ Mut, 67 (5.3%) Mut → WT

All 2457 serially collected tumor samples from all 1189 available NSCLC patients

Number and Frequency of *TP53* Mutation Status Changes in Serial Biopsies for All NSCLC Samples vs. Time

	Overall	Months 1-12	13 - 24	25 - 36	37 - 48	49 - 60	61-180
No Change	1118 (88.2%)	518 (89.2%)	299 (90.3%)	145 (84.3%)	70 (82.4%)	33 (89.2%)	53 (85.5%)
WT to Mut	83 (6.5%)	29 (5%)	16 (4.8%)	21 (12.2%)	9 (10.6%)	1 (2.7%)	7 (11.3%)
Mut to WT	67 (5.3%)	34 (5.9%)	16 (4.8%)	6 (3.5%)	6 (7.1%)	3 (8.1%)	2 (3.2%)

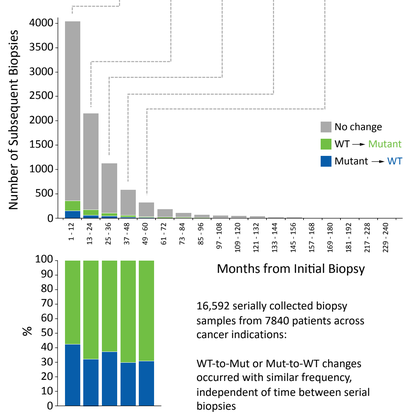


2457 serially collected tumor samples from all 1189 available NSCLC patients:

WT-to-Mut (6.5%) or Mut-to-WT (5.3%) changes occurred with similar frequency independent of time between biopsies

Number and Frequency of *TP53* Mutation Status Changes in Serial Biopsies for All Samples, All Indications vs. Time

	Overall	Months 1-12	13 - 24	25 - 36	37 - 48	49 - 60	61-240
No Change	7950 (90.8%)	3680 (91.2%)	1974 (91.7%)	1014 (90.5%)	521 (89.7%)	298 (91.1%)	463 (86.5%)
WT to Mut	513 (5.9%)	205 (5.1%)	121 (5.6%)	67 (6%)	42 (7.2%)	20 (6.1%)	58 (10.8%)
Mut to WT	289 (3.3%)	151 (3.7%)	57 (2.6%)	40 (3.6%)	18 (3.1%)	9 (2.8%)	14 (2.6%)

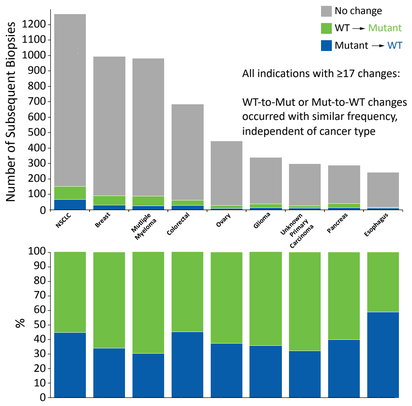


16,592 serially collected biopsy samples from 7840 patients across cancer indications:

WT-to-Mut or Mut-to-WT changes occurred with similar frequency, independent of time between serial biopsies

Number and Frequency of *TP53* Mutation Status for Cancers with Greatest Number of Serial Biopsy Results by Indication

	NSCLC	Breast	Multiple Myeloma	Colorectal	Ovary	Glioma	Unknown Primary Carcinoma	Pancreas	Esophagus
No Change	1118 (88.2%)	902 (90.8%)	892 (90.9%)	620 (90.9%)	417 (93.7%)	300 (88.5%)	273 (91.6%)	247 (86.1%)	224 (92.9%)
WT to Mut	83 (6.5%)	60 (6%)	62 (6.3%)	34 (5%)	19 (4.3%)	25 (7.4%)	15 (5%)	25 (8.7%)	7 (2.9%)
Mut to WT	67 (5.3%)	31 (3.1%)	27 (2.8%)	28 (4.1%)	9 (2%)	14 (4.1%)	10 (3.4%)	15 (5.2%)	10 (4.1%)



Conclusions

Changes in *TP53* status were rare (<10% of samples). Differences may occur in serial biopsy samples for pathophysiological reasons, e.g., a mutant clone becoming dominant and/or heterogeneity at different tumor biopsy sites, or analytical differences in biopsy tumor content or assay sensitivity between samples. WT-to-Mut changes were more frequent (5.9%) than Mut-to-WT changes (3.3%), suggesting a small selection pressure for *TP53* alterations later in oncogenesis and indicating that these alterations are truncal. Mut-to-WT changes are not readily explained by genetic drift and may suggest these infrequent changes are mostly due to sampling or analytical variability or biopsies from tumors that represent secondary malignancies, and genuine changes in *TP53* mutation status are quite rare.