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Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy

Shumei Kato  et al.[#]

Next-generation sequencing (NGS) can identify novel cancer targets. However, interpreting the molecular findings and accessing drugs/clinical trials is challenging. Furthermore, many tumors show resistance to monotherapies. To implement a precision strategy, we initiated a multidisciplinary (basic/translational/clinical investigators, bioinformaticians, geneticists, and physicians from multiple specialties) molecular tumor board (MTB), which included a project manager to facilitate obtaining clinical-grade biomarkers (blood/tissue NGS, specific immunohistochemistry/RNA expression including for immune-biomarkers, per physician discretion) and medication-acquisition specialists/clinical trial coordinators/navigators to assist with medication access. The MTB comprehensively reviewed patient characteristics to develop N-of-One treatments implemented by the treating physician's direction under the auspices of a master protocol. Overall, 265/429 therapy-evaluable patients (62%) were matched to ≥ 1 recommended drug. Eighty-six patients (20%) matched to all drugs recommended by MTB, including combinatorial approaches, while 38% received physician's choice regimen, generally with unmatched approach/low degree of matching. Our results show that patients who receive MTB-recommended regimens (versus physician choice) have significantly longer progression-free (PFS) and overall survival (OS), and are better matched to therapy. High ($\geq 50\%$) versus low ($< 50\%$) Matching Score therapy (roughly reflecting therapy matched to $\geq 50\%$ versus $< 50\%$ of alterations) independently correlates with longer PFS (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.50–0.80; $P < 0.001$) and OS (HR, 0.67; 95% CI, 0.50–0.90; $P = 0.007$) and higher stable disease ≥ 6 months/partial/complete remission rate (52.1% versus 30.4% $P < 0.001$) (all multivariate). In conclusion, patients who receive MTB-based therapy are better matched to their genomic alterations, and the degree of matching is an independent predictor of improved oncologic outcomes including survival.

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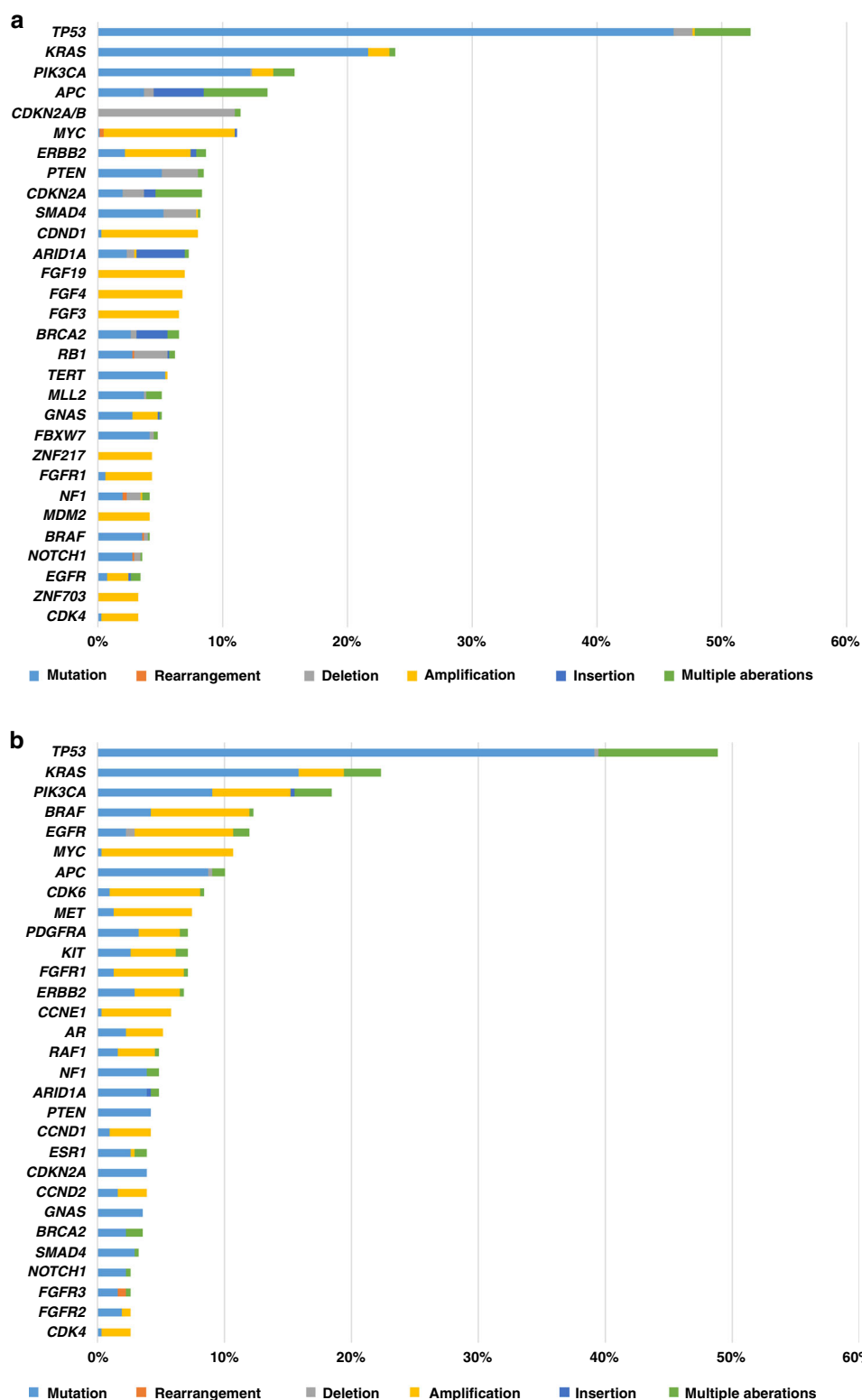


Fig. 1 Frequency of characterized genomic alteration from tissue NGS and cfDNA. a Frequency of characterized genomic alterations by tissue NGS ($N = 646$) (also see Supplementary Table 1). TP53 was the most commonly altered (52.3% [338/646]) followed by KRAS (23.8% [154/646]), PIK3CA (15.8% [102/646]), APC (13.6% [88/646]) and CDKN2A/B (11.5% [74/646]) alterations. *Percent indicates percent of the patient with alteration. Alterations seen in >3% of patients were included. **b** Frequency of characterized genomic alterations by cfDNA ($N = 309$) (See also Supplementary Table 2). The most common alterations were seen in TP53 (48.9% [151/309]) followed by KRAS (22.3% [69/309]), PIK3CA (18.4% [57/309]), BRAF (12.3% [38/309]) and EGFR (12.0% [37/309]) alterations. *Percent indicates percent of the patient with alteration. Alterations seen in >2.5% of patients were included.

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