Quality Control Efforts in a Large-scale, Preclinical Trial of Rare Cancer PDXs by The National Cancer Institute's Patient-Derived Models Repository (PDMR)

The National Cancer Institute's Patient-Derived Models Repository (NCI PDMR) is performing a large-scale multi-year preclinical study with 3D PDX models of rare cancers (see below) treated with 5x novel therapeutic combinations in an effort to identify novel therapeutic combinations for these underdiagnosed cancers. Combinations that show regression or durable inhibition of tumor growth are repeated along with the single agents to determine if the response is driven by the combination or one of the agents. To do this in a timely manner, the PDXs are tested as a single agent and each passage is treated with a set of 8 combinations plus relevant vehicle control(s), in parallel on murine content and have been restarted from early passage. DNA and RNA are retained from all passages so a full NGS evaluation can be performed.

As seen below in the first bookend studies to be completed, most therapeutic combinations have a very consistent response across passages and genomic characteristics, though a couple of models have a more than additive effect compared to the single agents. Promising drug studies with bookends and NGS of tumor material from the single-agent follow-up studies will be performed to identify any underlying factors.

In addition to genomic and histopathologic QC assessments, a QC metric for response across passages was also implemented. Once all drug combinations have been tested, the first set of high impact is a response metric across all passages to determine if there is a pattern between altered response across passages and genomic characteristics, mechanism of action, or synergistic effect. A full efficacy study with planned sampling for biomarker studies will be needed to determine if there is a pattern between the altered response across passages and genomic characteristics, mechanism of action, or synergistic effect.

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Due to the large study size, a visual assessment of depth and duration of response was used to fast-track drug combinations for single-agent follow-up studies. Bookend studies indicate some variability in consistency of response across passages. Further analysis including in vivo drug studies with bookends and NGS of tumor material from the study will be performed to identify any underlying factors.

Overall, the data support the feasibility of the study design, which is consistent with the intra-model heterogeneity observed at baseline by low-pass whole genome sequence assessment.

Selection of drug sets to begin are being identified, and will be followed up by early-stage drug combinations with increased efficacy over single agents. Combinations where the hold is in a larger percentage of all models, or within a specific rare disease type, will be moved forward to full efficacy and biomarker studies.

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