TO: Disease Site Chairs

FROM: Roisin O’Cearbhaill, MD
Chair, DT committee, NRG Oncology
NRG Oncology Representative to NCI ComboMatch

DATE: January 14, 2020

RE: Solicitations for suggestions/concepts for NCI ComboMATCH trial

Summary
NRG Oncology is soliciting concepts for the NCI ComboMatch study. This trial will focus on rational combinations of agents supported by preclinical in vivo evidence. Please note that IO combinations are NOT permitted for the ComboMatch study.

NRG Oncology will propose a cassette that includes subprotocols. Projects are to be implemented by July 2020.

Background
The hypothesis behind this trial is that in vivo evidence, in particular PDX and cell line derived xenograft data, can be used to predict the benefit of drug combination therapy in multiple specified patient subgroups. Like MATCH, ComboMATCH is conceived as a signal-seeking study. To distinguish this trial from the original MATCH trial, this trial will focus on rational combinations of agents supported by preclinical in vivo evidence.

The trial is envisioned as having an overall Master Control document managed by ECOG-ACRIN that will coordinate separate NCTN group-specific treatment “cassettes” and each cassette will have 4-6 subprotocols. Therefore, each cassette and up to 4-6 subprotocols will be administratively managed by each of the lead protocol organizations in coordination with EA. Like with NCI-MATCH we hope to have multiple investigators involved in each arm with junior and senior investigators and translational researchers.

The ComboMATCH Agents and Genes Working Group (C-AGWG) will review subprotocol proposals. This will consist of members from each Lead Protocol Organization (LPO) group along with additional members with Developmental Therapeutics and Precision Oncology expertise. This working group in coordination with each of the LPOs will assemble accepted sub protocols into the different cassettes.

Brief scientific principles:
• Both a strong scientific rationale and in vivo evidence of efficacy as well as synergism of the combination must support subprotocol proposals.
Combination therapy proposals are desired. There should be evidence that both agents in the combination are required for efficacy. The proposed need to have safety data available or justification of why a short run-in design may be considered.

- Single arm, sequential or randomized designs can be considered.
- **Combinations involving immunotherapy agents will not be permitted.** A separate NCI initiative is being planned that will provide relevant immune-oncology diagnostic support for signal-seeking studies involving immune-oncology agents (iMATCH).

Combinations with strong preclinical data but lacking safety data can be considered for future arms after safety data is obtained. NRG Oncology will review on a case-by-case basis to obtain this safety data or alternatively this could be done with the ETCTN.

*In vivo* preclinical data should demonstrate enhancement of tumor growth inhibition with a combination compared to either agent alone with tumor regression and stabilization with increased time to tumor progression. Statistical slowing of tumor growth is not sufficient. Studies require at least two xenograft models in the disease under study or clinical data.

Funda Meric-Bernstam, Jim Ford, Lyndsay Harris, and Jeff Moscow lead the ComboMATCH committee.

**Instructions for second round of Applications**

Please submit the attached NCI ComboMatch form to ocearbhr@mskcc.org by 5pm EST, Tuesday, February 18, 2020.

Proposals should include:
- Brief description of the proposed concept, including summary of preclinical data, safety data and rationale for the combination
- **Ideally, all subprotocols will have a junior investigator and senior mentor.**