National Cancer Institute

NCI M-PACT: Molecular Profiling Based Assignment of Cancer Therapy

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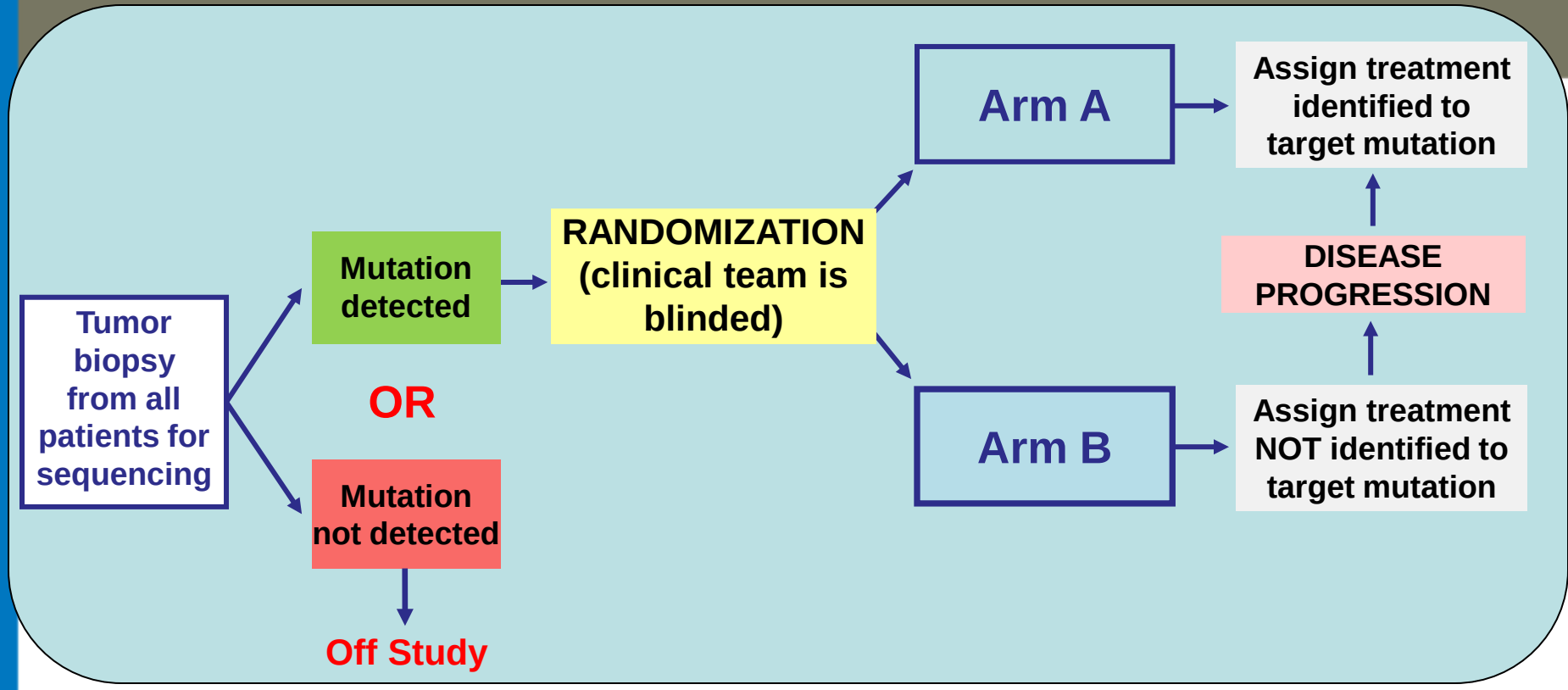
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

M-PACT Study Design

- Randomized trial
- Objective: Assess whether the response rate (CR+PR) and PFS is improved following treatment with agents chosen based on the presence of specific mutations in patient tumors.
  - Only patients with defined actionable mutations of interest (aMOIs) will be eligible
  - **Arm A**: Receive treatment based on a study agent prospectively identified to target that mutation/pathway
  - **Arm B**: Receive treatment with one of the study agents in the complementary set (not specifically targeting the detected mutations/pathways)
- Patients with advanced refractory solid tumors (phase 1 population)

Study Design



[a] Tumor biopsy (mandatory) will be performed on all patients enrolled on study; fresh tissue will be sequenced for the presence of specific mutations of interest.

[b] Only patients with specified mutations of interest will continue on study and be randomized into either Arm A (receive treatment regimen prospectively identified to target that mutation/pathway) or Arm B (receive treatment regimen assigned from the complementary set not prospectively identified to target one of their mutations). Drugs will be administered at recommended Phase II doses and schedules.

M-PACT

4 Treatment Regimens, 3 Pathways, and 20 Targeted Genes

	Gain of Function	Loss of Function
RAS pathway: GSK 1120212 MEK inhibitor	***BRAF, KRAS NRAS, HRAS***	***NF1***
PI3K pathway: Everolimus mTOR inhibitor	***AKT1, PIK3CA, MTOR***	***PTEN FBXW7***
DNA repair pathways: Veliparib (PARP inhibitor) + TMZ		***ATM, ATR, ERCC1, MLH1, MSH2, NBN, RAD51***
MK1775 (Wee1 inhibitor) + carboplatin		***PARP1, PARP2, TP53***

391 aMOIs (with COSMIC ID) selected

Rule-Based Assignment of Therapy

- Rules have been developed prospectively by a multidisciplinary tumor board
  - Will be periodically reviewed in light of study data and reports in the literature; not on an individual basis
- All aMOIs are reported with associated treatment selection(s)
- A report is sent to the oncologist which states the treatment selection; oncologist is blinded to assay results at the time of randomization and treatment assignment
- No combinations are being studied that target aMOIs in more than one pathway

Statistical Design

- Patients will be randomized 2:1 to Arm A (experimental) versus Arm B (control); 180 evaluable patients.
- Within each agent cohort of the experimental arm, up to 30 patients will be accrued, to discriminate between tumor response rates of 20% vs. 5%.
- The comparison of response rates will have 88% power to detect an over-all difference of 20% vs. 5% objective response, by means of the chi-square test, conducted at the 1-sided 0.04 significance level.

Statistical Design

- The comparison of PFS will have 90% power to detect an over-all increase of 80% in median PFS (for example, 3.6 vs. 2 months), by means of the log rank test, conducted at the 1-sided 0.01 significance level, with at least 165 PFS events observed.

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