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Pembrolizumab in MMR-proficient metastatic colorectal cancer pharmacologically primed to trigger dynamic hypermutation status: The ARETHUSA trial.

Authors: Salvatore Siena, Andrea Sartore-Bianchi, Nicola Personeni, Filippo Pietrantonio, Giovanni Germano, Alessio Amatu, Emanuela Bonoldi, Emanuele Valtorta, Ludovic Barault, Federica Di Nicolantonio, Giulia Siravegna, Giovanni Crisafulli, Lorenza Rimassa, Filippo G. De Braud, Armando Santoro, Luca Lazzari, Paolo Luraghi, Nabil Amirouchene-Angelozzi, Alberto Bardelli, and Silvia Marsoni SHOW FEWER | AUTHORS INFO & AFFILIATIONS

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Abstract

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Background: Metastatic colorectal cancer (CRC) harbouring genetic defects in the mismatch-repair pathway (MMRd) presents with a high tumor mutational burden (TMB), and is highly sensitive to anti–programmed cell death protein 1 (PD-1) immune checkpoint inhibitors. We recently showed in preclinical models that the pharmacological treatment with temozolomide (TMZ) can induce the inactivation of MMR genes, and consequently the increase of TMB and immunogenic neoantigens, thus suggesting that TMZ could be used to prime MMR proficient (MMRp) tumors for response to checkpoint inhibitors. Accordingly, mCRC patients recruited in previous clinical trials where TMZ was administered, acquired alterations of MMR genes upon treatment and showed remarkable increase in TMB at disease progression (PD). We thus designed the ARETHUSA clinical trial to test whether a priming course with TMZ in patients can sensitize mCRC to the anti-PD1 inhibitor pembrolizumab. **Methods:** Arethusa (NCT03519412) is a 2-cohorts, phase II trial consisting of three different phases. In the *SCREENING*, 348 mCRC *RAS*-mutated patients will be tested for MMR status. MMRd patients will proceed directly to *TRIAL* for immediate pembrolizumab treatment (expected 14). MMR-proficient (MMRp) patients will be further tested for expression of O^6-methylguanine-DNA methyltransferase (MGMT) by immunohistochemistry and by promoter methylation analysis. IHC-negative, promoter methylation-positive MMRp patients (expected 67) will enter in the *PRIMING* phase and will be treated with TMZ until PD. TMB will then be assessed on tumor biopsies at resistance. Those patients that will have > 20 mutations/megabase will proceed to *TRIAL* (expected 20) and will be treated with pembrolizumab. Overall response rate (primary outcome), Progression Free, and Overall Survival, and treatment related toxicities (secondary outcomes) in MMRp pembrolizumab-treated patients will be estimated., while the MMRd cohort will be used for comparison. Tissue biopsies, longitudinal blood and stool collection will be used for discovery of predictive molecular biomarkers and assessment of tumor evolution. Clinical trial information: NCT03519412.

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2318 Mill Road, Suite 800, Alexandria, VA 22314