Abstract 6262: Emergence of tumor mismatch repair deficiency and increased mutational burden in blood and tissue of metastatic colorectal cancer patients treated with temozolomide

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Emergence of tumor mismatch repair deficiency and increased mutational burden in blood and tissue of metastatic colorectal cancer patients treated with temozolomide

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The majority of metastatic colorectal cancers (mCRC) are mismatch repair (MMR) proficient (MMRp) and unresponsive to immunotherapy, while MMR deficient (MMRd) tumors often respond to immune checkpoint blockade (ICB). We previously reported that treatment of CRC preclinical models with temozolomide (TMZ) leads to MMR deficiency, increased tumor mutational burden (TMB) and, sensitization to immunotherapy. To clinically translate these findings, we designed the ARETHUSA clinical trial whereby O6-Methylguanine-DNA-methyltransferase (MGMT) deficient, MMR proficient and *KRAS* mutant mCRC patients receive priming therapy with TMZ. Analysis of solid tissue biopsies and circulating tumor DNA (ctDNA) obtained after TMZ treatment revealed the emergence of TMZ mutational signature, alterations in MMR genes and increased TMB in 14 out of 16 patients. Genetic mutations induced by TMZ were dose-dependent and multiple alterations in the nucleotide context favored by the TMZ signature emerged in MMR genes such as the *MSH6* T1219I variant which was detected in ctDNA and tissue of 13/14 (93%) of the cases. A subset of the patients whose tumors after TMZ priming displayed the *MSH6* mutation, the TMZ mutational signature and increased TMB, achieved disease stabilization upon pembrolizumab treatment. Overall, we provide *proof-of-concept* that treatment of MGMT deficient/MMR proficient *KRAS* mutant mCRCs with TMZ can be tracked by mutational signature analysis and lead to inactivation of the MMR pathway, emergence of the TMZ mutational signature, TMB increase, and, in some cases, to disease stabilization during ICB.

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G. Crisafulli: None. **A. Sartore-Bianchi:** ; A.S.B. is a member of advisory boards; Amgen. ; Amgen. ; Bayer. ; A.S.B. is a member of advisory boards; Bayer. ; A.S.B. is a member of advisory boards; Sanofi. ; Sanofi. ; Servier. ; A.S.B. is a member of advisory boards; Servier. ; A.S.B. is a member of advisory boards; Servier. ; Servier. **L. Lazzari:** None. **F. Pietrantonio:** ; F.P. received honoraria; Merck-Serono. ; Merck-Serono. ; Amgen. ; F.P. received honoraria; Amgen. ; F.P. received honoraria; Sanofi. ; Sanofi. ; Lilly. ; F.P. received honoraria; Lilly. ; F.P. received honoraria; Servier. ; Servier. ; Bayer. ; F.P. received honoraria; Bayer. ; F.P. received honoraria; Astrazeneca. ; Astrazeneca. ; BMS. ; BMS. **A. Amatu:** None. **M. Macagno:** None. **L. Barault:** ; Biocartis. ; Biocartis. **A. Cassingena:** None. **A. Bartolini:** None. **P. Luraghi:** None. **G. Mauri:** None. **P. Battuello:** None. **N. Personemi:** ; N.P. received consulting fees; Amgen. ; Amgen. ; Merck-Serono. ; N.P. received consulting fees and institutional research funding; Merck-Serono. ; N.P. received consulting fees and institutional research funding; Servier. ; Servier. ; AbbVie. ; N.P. received lectures fees; AbbVie. ; N.P. received lectures fees; Gilead. ; Gilead. ; Lilly. ; N.P. received lectures fees; Lilly. ; N.P. received lectures fees; Sanofi. ; Sanofi. ; ArQule. ; ArQule. ; N.P. received institutional research funding; Basilea. **V. Pessei:** None. **P. Vitiello:** None. **F. Tosi:** None. **L. Idotta:** None. **E. Valtorta:** None. **E. Bonoldi:** None. **G. Germano:** ; G.G. is cofounder and shareholder of NeoPhore; NeoPhore. ; NeoPhore. **F. Di Nicolantonio:** None. **S. Marsoni:** None. **S. Siena:** ; S.S. is an advisory board member; AstraZeneca. ; AstraZeneca. ; Bayer. ; S.S. is an advisory board member; Bayer. ; S.S. is an advisory board member; BMS. ; S.S. is an advisory board member; CheckmAb. ; CheckmAb. ; Daiichi-Sankyo. ; S.S. is an advisory board member; Daiichi-Sankyo. ; S.S. is an advisory board member; Menarini. ; Menarini. ; Merck. ; S.S. is an advisory board member; Merck. ; S.S. is an advisory board member; Seattle Genetics. ; Seattle Genetics. **A. Bardelli:** ; A.Bardelli served in a consulting/advisory role; Illumina. ; Illumina. ; Inivata. ; A.Bardelli served in a consulting/advisory role; Inivata. ; A.Bardelli is a member of the NeoPhore scientific advisory board. A.Bardelli is cofounder and shareholder of NeoPhore.; NeoPhore. ; NeoPhore.

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