IMMUNOTHERAPY IN GI CANCERS: FOCUS ON COLORECTAL CANCER

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IMMUNOTHERAPY FOR COLORECTAL CANCER: CHALLENGES FOR CLINICAL EFFICACY

- Colorectal cancer is a highly heterogenous disease.
- The presence of a potential active immune response is limited to subgroup(s) of patients.
- Currently, the only effective immunotherapies are obtained in molecularly selected MSI-H or dMMR tumours.
- Is it possible to activate immune competence in MSS tumours?
CMS subtypes – clinical and molecular correlates

CMS1 - MSI – Immune 14%
- Microsatellite instability
- CIMP high
- Hypermutation, BRAF mutations
- Immune activation

CMS2 – Canonical 37%
- Microsatellite stable
- CIMP negative
- WNT and MYC activation

CMS3 – Metabolic 13%
- microsatellite status
- KRAS mutations
- Metabolic reprogramming

CMS4 – Mesenchymal 23%
- TGFβ activation
- Invasion, matrix remodeling
- Angiogenesis

Immune vs Transcriptomic subtypes of CRC

Supervised immune infiltration analysis

Becht E et al, Clin Cancer Res 2016
Immune vs Transcriptomic subtypes of CRC

Immune-activated

- dMMR – MSI
- Hypermutation

Immune-activated

Th1 cells

IFNγ

PDL1

CXCL9/10/13

Cytotoxic T cells

Macrophages

NK cells

Immune-activated

Immunne-activated

Cancer cell

Phenotype

Inflammation

TGFβ

Complement

Stromal cells

Monocytes

MDSC

Th17 cells

CCL2

IL-17

CCL2

IL-23

Immune-tolerant

Inflamed

Th1 cells

IFNγ

Cancer cell

Phenotype

Inflammation

TGFβ

Complement

Stromal cells

Monocytes

MDSC

Th17 cells

CCL2

IL-17

CCL2

IL-23

Immune-ignorant

Cancer cell

Phenotype
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency


ABSTRACT

BACKGROUND Somatic mutations have the potential to encode "non-self" immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.

METHODS We conducted a phase 2 study to evaluate the clinical activity of pembrolizumab, an anti–programmed death 1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinomas with or without mismatch-repair deficiency. Pembrolizumab was administered intravenously at a dose of 20 mg per kilogram of body weight every 14 days in patients with mismatch-repair-deficient colorectal cancers, patients with mismatch-repair-proficient colorectal cancers, and patients with mismatch-repair-deficient cancers that were not colorectal. The coprimary end points were the immune-related objective response rate and the 20-week immune-related progression-free survival rate.

RESULTS The immune-related objective response rate and immune-related progression-free survival rate were 40% (6 of 15 patients) and 78% (7 of 9 patients), respectively, for mismatch-repair-deficient colorectal cancers, and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch-repair-proficient colorectal cancers. The median progression-free survival and overall survival were not reached in the cohort with mismatch-repair-deficient colorectal cancer but were 2.2 and 5.0 months, respectively, in the cohort with mismatch-repair-proficient colorectal cancer (hazard ratio for disease progression or death, 0.10 [P=0.0011], and hazard ratio for death, 0.22 [P=0.05]). Patients with mismatch-repair–deficient noncolorectal cancer had responses similar to those of patients with mismatch repair–deficient colorectal cancer (immune-related objective response rate, 72% [5 of 7 patients]; immune-related progression-free survival rate, 67% [4 of 6 patients]). Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in mismatch repair–deficient tumors, as compared with 73 in mismatch repair–proficient tumors (P=0.007), and high somatic mutation loads were associated with prolonged progression-free survival (P=0.02).

CONCLUSIONS This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab. (Funded by Johns Hopkins University and others. ClinicalTrials.gov number, NCT03876511.)

The New England Journal of Medicine

ORIGINAL ARTICLE

CANCER MARKERS

Mismatches repair deficiency predicts response of solid tumors to PD-1 blockade


Background Somatic mutations have the potential to encode "non-self" immunogenic antigens. We hypothesized that tumors with a large number of somatic mutations due to mismatch-repair defects may be susceptible to immune checkpoint blockade.

Methods We conducted a phase 2 study to evaluate the clinical activity of pembrolizumab, an anti–programmed death 1 immune checkpoint inhibitor, in 41 patients with progressive metastatic carcinomas with or without mismatch-repair deficiency. Pembrolizumab was administered intravenously at a dose of 20 mg per kilogram of body weight every 14 days in patients with mismatch-repair-deficient colorectal cancers, patients with mismatch-repair-proficient colorectal cancers, and patients with mismatch-repair-deficient cancers that were not colorectal. The coprimary end points were the immune-related objective response rate and the 20-week immune-related progression-free survival rate.

Results The immune-related objective response rate and immune-related progression-free survival rate were 40% (6 of 15 patients) and 78% (7 of 9 patients), respectively, for mismatch-repair-deficient colorectal cancers and 0% (0 of 18 patients) and 11% (2 of 18 patients) for mismatch-repair-proficient colorectal cancers. The median progression-free survival and overall survival were not reached in the cohort with mismatch-repair-deficient colorectal cancer but were 2.2 and 5.0 months, respectively, in the cohort with mismatch-repair-proficient colorectal cancer (hazard ratio for disease progression or death, 0.10 [P=0.0011], and hazard ratio for death, 0.22 [P=0.05]). Patients with mismatch-repair–deficient noncolorectal cancer had responses similar to those of patients with mismatch repair–deficient colorectal cancer (immune-related objective response rate, 72% [5 of 7 patients]; immune-related progression-free survival rate, 67% [4 of 6 patients]). Whole-exome sequencing revealed a mean of 1782 somatic mutations per tumor in mismatch repair–deficient tumors, as compared with 73 in mismatch repair–proficient tumors (P=0.007), and high somatic mutation loads were associated with prolonged progression-free survival (P=0.02).

Conclusions This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab. (Funded by Johns Hopkins University and others. ClinicalTrials.gov number, NCT03876511.)
Figure 1. Clinical Responses to Pembrolizumab Treatment.

The biochemical responses to pembrolizumab treatment are shown in Panel A. Serum levels of protein biomarkers were measured at the start of each treatment cycle, and the values represent percentage changes from baseline. Each line represents one patient; patients were included if their baseline tumor marker values were higher than the upper limit of normal. CA-125 was used as the biomarker for one patient with endometrial cancer, CA19-9 was used for one patient with cholangiocarcinoma and one patient with ampullary cancer, and carcinoembryonic antigen (CEA) was used for all other patients. Radiographic responses to treatment with pembrolizumab, evaluated on the basis of Response Evaluation Criteria in Solid Tumors (RECIST), are shown in Panel B. Tumor responses were measured at regular intervals, and the values shown are the largest percentage change in the sum of longest diameters from the baseline measurements of each measurable tumor. Each bar represents one patient.

Figure 2. Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status.

Kaplan-Meier curves are shown for progression-free survival in the cohorts with colorectal cancer (Panel A), overall survival in the cohorts with colorectal cancer (Panel B), progression-free survival among patients with mismatch repair-deficient noncolorectal cancers (Panel C), and overall survival among patients with mismatch repair-deficient noncolorectal cancers (Panel D). In both cohorts with mismatch repair-deficient tumors, median overall survival was not reached. Patients in the cohort with mismatch repair-proficient cancers had a median progression-free survival of 2.2 months (95% CI, 1.4 to 2.8) and a median overall survival of 5.0 months (95% CI, 3.0 to not estimable). Patients with mismatch repair-deficient noncolorectal cancers had a median progression-free survival of 1.4 months (95% CI, 3 to not estimable).
Fig. 1. Patient survival and clinical response to pembrolizumab across 12 different tumor types with mismatch repair deficiency. (A) Tumor types across 98 patients. (B) Waterfall plot of all radiographic responses across 12 different tumor types at 20 weeks. Tumor responses were measured at regular intervals; values show the best fractional change in the sum of longest diameters (SLD) from the baseline measurements of each measurable tumor. (C) Confirmed radiographic objective responses at 20 weeks (blue) compared to the best radiographic responses in the same patients (red). The mean time to the best radiographic response was 28 weeks. (D) Swimmer plot showing survival for each patient with mismatch repair-deficient tumors, indicating death, progression, and time off therapy. (E and F) Kaplan-Meier estimates of progression-free survival (E) and overall patient survival (F).
Fig. 3. Mismatch repair deficiency across ~715 tumors. The proportion of mismatch repair-deficient tumors in each cancer subtype is expressed as a percentage. Mismatch repair-deficient tumors were identified in 24 of 32 tumor subtypes tested, more often in early-stage disease (defined as stage I-II).
Durable Clinical Benefit With Nivolumab Plus Low-Dose Ipilimumab as First-Line Therapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer

Heinz-Josef Lenz,1 Eric Van Cutsem,2 Maria Luisa Limon,3 Ka Yeung Mark Wong,4 Alain Hendlisz,5 Massimo Aglietta,6 Pilar García-Alfonso,7 Bart Neyns,8 Gabriele Luppi,9 Dana B. Cardin,10 Tomislav Dragovich,11 Usman Shah,12 Ajlan Atasoy,13 Roelien Postema,13 Zachary Boyd,13 Jean-Marie Ledeine,13 Michael James Overman,14 Sara Lonardi15

1USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; 2University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; 3Hospital Universitario Virgen del Rocio, Sevilla, Spain; 4Westmead Hospital, Sydney, Australia; 5Institut Jules Bordet, Brussels, Belgium; 6Candiolo Cancer Institute and University of Torino Medical School, Candiolo, Italy; 7Hospital Gral Universitario Gregorio Marañon, Madrid, Spain, 8University Hospital Brussels, Brussels, Belgium; 9University Hospital of Modena, Modena, Italy; 10Vanderbilt – Ingram Cancer Center, Nashville, TN, USA; 11Banner MD Anderson Cancer Center, Gilbert, AZ, USA; 12Lehigh Valley Hospital, Allentown, PA, USA; 13Bristol Myers Squibb, Princeton, NJ, USA; 14The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 15Istituto Oncologico Veneto IVC-IRCSS, Padova, Italy

Presentation number: LBA18 PR
Introduction: CheckMate 142

- In CheckMate 142, nivolumab plus low-dose (1 mg/kg) ipilimumab provided improved clinical benefit relative to nivolumab monotherapy, with a favorable benefit-risk profile, in previously treated patients with MSI-H/dMMR mCRC\(^1\)
  - ORR, 55% vs. 31%; 12-month OS rate, 85% vs. 73%, respectively
  - Grade 3–4 TRAEs, 32% vs. 20%; discontinuation due to any grade TRAEs, 13% vs. 7%, respectively
- Based on these results, nivolumab received accelerated FDA approval as a single agent or in combination with ipilimumab in patients with MSI-H/dMMR mCRC who progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan\(^2\)
- Here we report the first results of the efficacy and safety of nivolumab plus low-dose ipilimumab as a 1L therapy for patients with MSI-H/dMMR mCRC from CheckMate 142

CheckMate 142 Study Design

CheckMate 142 is an ongoing, multi-cohort, nonrandomized phase 2 study evaluating the efficacy and safety of nivolumab-based therapies in patients with mCRC (NCT02060188)

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory

Previously treated → NIVO3 Q2W

NIVO3 Q2W + IPI1 Q3W (4 doses and then NIVO3 Q2W)

Previously treated → NIVO3 Q2W + IPI1 Q6W

Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
- ORR per BICR, DCR, DOR, PFS, OS, and safety

Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9.4−9.9)
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NIVO3 (Q2W) + IP11 (Q6W) N = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>68 [21-84]</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>23 (51)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25 (56)</td>
</tr>
<tr>
<td>1</td>
<td>20 (44)</td>
</tr>
<tr>
<td><strong>Disease stage at diagnosis, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>I (II)</td>
<td>28 (62)</td>
</tr>
<tr>
<td>IV</td>
<td>17 (38)</td>
</tr>
<tr>
<td><strong>Tumor PD-L1 expression at baseline, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>12 (27)</td>
</tr>
<tr>
<td>≥ 1%</td>
<td>26 (58)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (16)</td>
</tr>
<tr>
<td><strong>Mutation status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>BRAF/KRAS wild type</td>
<td>13 (29)</td>
</tr>
<tr>
<td>NRAS mutation</td>
<td>1 (3)</td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (11)</td>
</tr>
<tr>
<td><strong>Lynch syndrome, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (18)</td>
</tr>
<tr>
<td>No</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>26 (58)</td>
</tr>
</tbody>
</table>

*Percentages may not add up to 100% because of rounding.

*All patients had stage IV disease at study entry. Based on clinical records of patients at sites in countries where this reporting was permitted (excluded Italy).

BRAF = Vsngr v, 13/13 harbors constitutional BRAF mutations. ECOG = Eastern Cooperative Oncology Group. NRAS = Mutation for NRAS or KRAS in codon 61 or 12. KRAS = Mutation in codon 12 or 13 or 61.
## Response and Disease Control

<table>
<thead>
<tr>
<th>Investigator-assessed</th>
<th>NIVO3 (Q2W) + IPI1 (Q6W)</th>
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<tbody>
<tr>
<td></td>
<td>N = 45</td>
</tr>
<tr>
<td><strong>ORR(^a), n (%)</strong></td>
<td>27 (60)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[44.3(\text{-}74.3])</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)(^a)</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3 (7)</td>
</tr>
<tr>
<td>PR</td>
<td>24 (53)</td>
</tr>
<tr>
<td>SD</td>
<td>11 (24)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Not determined</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>DCR(^b), n (%)</strong></td>
<td>38 (84)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[70.5(\text{-}83.5])</td>
</tr>
</tbody>
</table>

Responses were observed regardless of tumor PD-L1 expression, *BRAF* or *KRAS* mutation status, or diagnosis of Lynch syndrome.

\(^a\) The ORR and DCR in patients with a *BRAF* mutation (n = 17) were 71% and 88%, respectively.

\(^b\) Percentages may not add up to 100% because of rounding.

\(^c\) Patients with CR or PR divided by the number of treated patients.

\(*\) Patients + confident interval.

CI = confidence interval; PD = progressive disease.
Best Reduction in Target Lesions

- 84% of patients had a reduction in tumor burden from baseline
Progression-Free and Overall Survival

**PF8**
- **NIVO (Q2W) + IFI1 (Q6W)**
  - Median PF8, months (95% CI): NR (14.9–NF)
  - 9-mo rate (95% CI), %: 77 (92.0–87.2)
  - 12-mo rate (95% CI), %: 47 (82.0–87.2)
- **OS**
  - Median OS, months (95% CI): NR (NF)
  - 9-mo rate (95% CI), %: 86 (74.6–95.1)
  - 12-mo rate (95% CI), %: 83 (90.8–91.7)

**Graphs**
- **Progression-Free Survival**
  - X-axis: Months
  - Y-axis: Progression-free survival (%)
  - No. at risk: 40, 37, 34, 24, 19, 16, 13, 10, 7, 4

- **Overall Survival**
  - X-axis: Months
  - Y-axis: Overall survival (%)
  - No. at risk: 40, 42, 40, 38, 24, 13, 1, 0
Summary and Conclusions

Nivolumab (Q2W) plus low-dose ipilimumab (Q6W) demonstrated robust and durable clinical benefit as a 1L treatment for MSI-H/dMMR mCRC

- High ORR (60%, with 7% CR)
- Durable responses (median DOR not reached)
- Most patients had a reduction in tumor burden from baseline (84%)
- Median PFS and OS not reached with a median follow-up of 14 months
- 12-month PFS and OS rates were 77% and 83%, respectively

Nivolumab plus low-dose ipilimumab was well-tolerated (grade 3-4 TRAEs, 16%) with a low rate of discontinuation due to TRAEs (7%)

Nivolumab plus low-dose ipilimumab may represent a new 1L treatment option for patients with MSI-H/dMMR mCRC

But wait for the results of: “KEYNOTE-177, a phase 3, open-label, randomized study of first-line pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC)”.
Cobimetinib + Atezolizumab

PD-L1 and MEK inhibition: a rational combination

- MEK inhibition alone can result in intratumoral T-cell accumulation and MHC I upregulation, and synergizes with an anti-PDL1 agent to promote durable tumor regression\(^1\)

\[\text{CD8}^+\text{T cell per tumor cell}\]
\[\text{Class I MHC}\]
\[\text{Tumor volume (mm}^3\text{)}\]

- To examine the possible benefits of MEK inhibition with an anti-PDL1 agent, we evaluated cobimetinib + atezolizumab in patients with advanced solid tumors

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models. 1: Ebert et al. *Immunity* 2016.

Bendell J et al. Proc ASCO 2016
<table>
<thead>
<tr>
<th></th>
<th>KRAS MT CRC</th>
<th>All CRC pts</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>N=20</td>
<td>N=23</td>
</tr>
<tr>
<td>ORR</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>SD</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>PD</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>NE</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>mPFS (m)</td>
<td>2.3 (1.8-9.5)</td>
<td>2.3 (1.8-9.5)</td>
</tr>
<tr>
<td>mOS (m)</td>
<td>NE (6.5-NE)</td>
<td>NE (6.5-NE)</td>
</tr>
</tbody>
</table>

Bendell J et al. Proc ASCO 2016
Efficacy and safety results from IMblaze370, a randomised Phase III study comparing atezolizumab + cobimetinib and atezolizumab monotherapy vs regorafenib in chemotherapy-refractory metastatic colorectal cancer

Johanna Bendell, Fortunato Ciardiello, Josep Tabernero, Niall Tebbutt, Cathy Eng, Maria Di Bartolomeo, Alfredo Falcone, Marwan Fakih, Mark Kozloff, Neil H Segal, Alberto Sobrero, Yi Shi, Louise Roberts, Yibing Yan, Ilsung Chang, Anne Uyei, Tae Won Kim

1 Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; 2 Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy; 3 Vall d’Hebron Institute of Oncology, VHIO, Barcelona, Spain; 4 Medical Oncology, Austin Health, Heidelberg, VIC, Australia; 5 M. D. Anderson Cancer Center, Houston, TX, USA; 6 Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 7 University Hospital of Pisa, Pisa, Italy; 8 City of Hope, Duarte, CA, USA; 9 University of Chicago, Chicago, IL, USA; 10 Memorial Sloan Kettering Cancer Center, New York, NY, USA; 11 IRCCS Ospedale San Martino IST, Genova, Italy; 12 Genentech, Inc., South San Francisco, CA, USA; 13 Asan Medical Center, University of Ulsan, Seoul, South Korea
Unresectable mCRC patients

Received at least 2 regimens in metastatic setting (not including maintenance)

ARM A: Cobimetinib + atezolizumab, n=180

ARM B: Atezolizumab, n=90

ARM C: Regorafenib, n=90

Treatment to continue until loss of clinical benefit

Stratified by tumor extended RAS status and time since diagnosis of first metastasis

MSI-H capped at approximately 5%

At least 180 patients with extended RAS-mutant tumors to be enrolled

Eng C. et al., Lancet Oncology, 2019, in press
### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Atezo + cobi (n = 183)</th>
<th>Atezo (n = 90)</th>
<th>Rego (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>8.9 (7.00, 10.61)</td>
<td>7.1 (6.05, 10.05)</td>
<td>8.5 (6.41, 10.71)</td>
</tr>
<tr>
<td>HR vs rego (95% CI)</td>
<td>1.00 (0.73, 1.38)</td>
<td>1.19 (0.83, 1.71)</td>
<td>N/A</td>
</tr>
<tr>
<td>(P) value</td>
<td>0.9871</td>
<td>0.3360(^a)</td>
<td>N/A</td>
</tr>
<tr>
<td>12-mo OS, %</td>
<td>38.5%</td>
<td>27.2%</td>
<td>36.6%</td>
</tr>
</tbody>
</table>

\(^a\) Statistically significant at \(p < 0.05\).
Conclusions

• IMblaze370 did not meet its primary objective of improvement in OS with atezolizumab + cobimetinib and atezolizumab monotherapy vs regorafenib
  – There were no statistically significant differences in OS by clinical or biomarker subgroups, including patients with MSS or extended RAS mutation disease
  – PFS, ORR, DOR were not improved between the arms
  – Efficacy in MSI high disease was not estimable due to limited patient number
    • Responses were observed in 2 of 3 patients with atezolizumab + cobimetinib and 1 of 3 with atezolizumab monotherapy

• Lack of clinical activity may be due to the immune-excluded phenotype of mCRC
  – Simultaneous inhibition of the PD-L1 immune checkpoint and MAPK-mediated immune suppression may not be sufficient to generate anti-tumour immune responses in immune-excluded tumours, such as mCRC
Non-profit phase II, open-label, single-arm study of cetuximab plus avelumab as rechallenge in patients with RAS WT mCRC treated in first line with chemotherapy in combination with an anti-EGFR drug that have had a clinical benefit (complete or partial response) from previous treatment.

Sponsor: Department of Precision Medicine, Università degli Studi della Campania “L. Vanvitelli”

P.I.: Fortunato Ciardiello
A biological rationale supports anti-EGFR rechallenge strategies in mCRC


*Cetuximab is approved in patients with EGFR-expressing, RAS wt mCRC: in combination with irinotecan-based CT, or in 1st line in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.2

Primary endpoint met: 21% (95% CI: 10–40) achieved response to cetuximab + irinotecan rechallenge

- DCR: 54%
- PR n=6 (2 unconfirmed)
- SD n=9
Background

In patients with RAS WT mCRC the combination of cetuximab and avelumab could be a promising rechallenge strategy based on the hypothesis of a synergistic effect able to boost immune response and increase clinical outcome.

Hot Topic

Rationale for combination of therapeutic antibodies targeting tumor cells and immune checkpoint receptors: Harnessing innate and adaptive immunity through IgG1 isotype immune effector stimulation

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mmed death-ligand 1; TGFβ, transforming growth factor β; Treg, regulatory T cells.
Study plan

75 Patients with RAS WT mCRC, regardless of MSI status:

treated in first line with CT + anti-EGFR drugs

achieved in first line a complete or partial response

received a second line therapy

Subjects will be treated with Avelumab (10 mg/kg q14 in a 1-hour i.v. infusion) plus Cetuximab (400 mg/m² over 2-hour and subsequently 250 mg/m² weekly as 1-hour i.v. infusion) until disease progression, unacceptable toxicity, or other discontinuation criterion is met. Treatment may continue beyond progressive disease according to RECIST 1.1 in case of subject’s clinical benefit, upon opinion of the Investigator (i.e subject’s performance status has remained stable and no new symptoms or worsening of existing symptoms and no decrease in performance score has occurred).

Number of Italian centers involved in the trial: 12 (5 open for recruitment as of March 22, 2019).

First patient enrolled on August 20, 2018 at Università degli Studi della Campania “L. Vanvitelli” in Napoli.

Patients enrolled in the trial: 29 (as of March 22, 2019).
Primary endpoint:
Overall survival (OS)

Secondary endpoints:
Overall Response Rate (ORR), Progression free survival (PFS), Safety Profile

Other objectives:
Biomarker correlative studies

The current study aims to demonstrate a median OS of 11.0 months (alternative hypothesis) by experimental combination for comparison with historical median OS 8.0 (null hypothesis CORRECT, REcourse) with standard third line treatment, which correspond to an improvement of OS at 6 months from 35% to 46%. It was estimated that we would need to enrol 66 patients to achieve with a 1-sided 5% level test in this single stage, single arm trial. The accrual period will be of 18 months and the total duration of the study will be of 36 months. Considering a potential drop-out of approximately 15% of patients a total of 75 patients will be recruited.
Main Inclusion Criteria

• RAS (NRAS and KRAS exon 2, 3 and 4) wild-type in tissue at initial diagnosis.

• Efficacy of a first line therapy containing an anti-EGFR agent (panitumumab or cetuximab) with an objective response achieved (complete or partial response).

• A second line therapy.

• More than 4 months from last dose of anti-EGFR agent administered in first line treatment before randomization.

• Measurable disease according to RECIST criteria v1.1

• Adequate bone marrow, liver and renal function.

• Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1.
## Liquid biopsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>RAS/BRAF status on tissue (archival)</th>
<th>RAS/BRAF status on ctDNA (baseline)</th>
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<tbody>
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<td>#14</td>
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</tbody>
</table>

Every 8 weeks at disease progression
Thanks for your attention

*Mosaic on the floor at the entrance of “La Casa del Poeta Tragico”, Pompei*