Immunotherapy in Colorectal cancer

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Introduction

The Molecular and Immunologic landscape of Colorectal Cancer (CRC) had evolved the last decade.

Emphasis on precision Genomic-based medicine is able to provide a better understanding of CRC biomarkers that can be used to enhance successful treatment of patients with CRC.

Identification of mutations in CRC in The EGFR signaling pathways involving all exons of KRAS and in NRAS, BRAF, PIK3CA, and PTEN helped to understand lack of response to anti-EGFR therapy.

Mismatch Repair protein identification in CRC not only may have predictive value in certain clinical setting but also a therapeutic implication.

Recent molecular biomarker data have shown the importance of microsatellite instability (MSI) testing, a marker of deficient mismatch repair (dMMR), for the selection of patients for immunotherapy.
CRC and Mismatch Repair status

Sporadic MSI:
- 10-15% of all colon cancer
- Acquired hypermethylation of *MLH1* promoter
- More common than Lynch/HNPCC
- Leads to IHC profile: MLH1/PMS2 negative
- Lynch due to MLH1 germline mutation can have the same IHC profile

Unstable, MLH1/PMS2 (-):
- BRAF V600E mutation in about 50% of sporadic unstable tumors, only rarely
- occurs in Lynch/HNPCC (so far, minority of those with PMS2 germline mutation; Senter, Gastroenterology, 2008)
- MLH1 methylation in most sporadic
- unstable tumors, only rarely in Lynch/ HNPCC
MMR-Deficiency and CRC Immune Microenvironment

MMR system is a DNA integrity maintenance system with is the correction of single base nucleotide mismatches (insertions or deletions) generated during DNA replication and recombination, thus maintaining the genomic stability.

The mechanism of MMR involves at least three different processes:

1. Recognition of single base replication errors is performed by the MutSα (MSH2-MSH6 heteroduplex) or MutSβ (MSH2-MSH3 heteroduplex)

2. Excision of the lagging strand from the mismatch by one of the MutL complexes (mainly MutLα formed by MLH1/PMS2) recruited by MutS protein

3. Resynthesis of the excised-DNA and ligation by DNA polymerase delta and DNA ligase I

MLH1 complexes with PMS2

MSH2 complexes with MSH6

Therefore, if MLH1 is negative, PMS2 is usually negative and if MSH2 is negative, MHS6 is negative. Corollary not necessarily true (MLH1 and MSH2 bind to other proteins as well)
Mismatch Repair Deficient Tumors stimulates Immune system by Infiltration and Th1-associated environment

Several immune checkpoint ligands are upregulated in the dMMR tumor microenvironment: PD-1, PD-L1, cytotoxic T-lymphocyte associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3) and IDO.

Thus, the active immune microenvironment appears to be counterbalanced by immune inhibitory signals that prevent tumor elimination

Immune infiltration directed → Neoantigens.

PD-L1 is also upregulated on tumor cells and tumor-associated myeloid cells, and impairs T-cell-induced immune responses upon engaging its cognate co-inhibitory receptor, programmed cell death 1 (PD-1), which is always highly expressed on tumor-infiltrating lymphocytes (TILs)
Immune System: Able to Recognize and Eliminate Tumor Cells

**INNATE IMMUNE RESPONSE**
- The innate immune response is the body’s first line of defense against pathogens and cancer\(^1\)
- **Natural killer (NK)** cells are essential innate effectors of anti-tumor immunity\(^2\)

**ADAPTIVE IMMUNE RESPONSE**
- The adaptive immune response is antigen specific and able to produce a durable response\(^1\)
- **Cytotoxic T cells** are essential anti-tumor effector cells of the adaptive immune system\(^2,3\)

Tumors Use Complex, Overlapping Mechanisms to Evade and Suppress the Immune System

A. Ineffective presentation of tumor antigens (eg, downregulation of MHC I)

B. Recruitment of immunosuppressive cells (eg, Tregs, MDSCs)

C. T-cell checkpoint dysregulation (eg, CD27, 4-1BB, CTLA-4, LAG-3, OX-40, PD-1)

D. Tumor release of immunosuppressive factors (eg, TGF-β, IDO, IL-10)

CD, cluster of differentiation; CTLA-4, cytotoxic T-lymophocyte antigen-4; DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; IL, interleukin; LAG-3, lymphocyte activation gene-3; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed death receptor-1; TGF-β, transforming growth factor beta; TIM-3, T cell immunoglobulin and mucin domain-3; Treg, regulatory T cell.

Molecular markers that define high-risk stage II/III CRC

Cancer cell + Microenvironment markers: Gene expression CMS

RFS in 1,785 stage II/III CRC patients

Guinney et al, Nat Med 2015
Rationale of Immunotherapy in CRC MMR-D

Programmed death 1 (PD-1) pathway is a negative feedback system that represses Th1 cytotoxic immune responses and that, if unregulated, can damage the host.

It is up-regulated in many tumors and in their surrounding microenvironment.

Blockade of this pathway with antibodies to PD-1 or its ligands has led to remarkable clinical responses in patients with many different types of cancer:

- Melanomas, non–small-cell lung cancer, renal-cell carcinoma, bladder cancer
- GI malignancies with MMR deficiency

The expression of PD-1 ligands (PD-L1 or PD-L2) on the surface of tumor cells or immune cells is an important — but not a definitive — predictive biomarker of response to PD-1 blockade.
Anti-Tumor Immune Response
Inhibition by Tumors

1. Insufficient number of T cells are generated within the lymphoid compartment.
2. Insufficient number of T cells extravasate into the tumor.
3. T cells are inhibited in the tumor microenvironment.

Targeting Checkpoints as an Approach to Cancer Therapy

**Select Agents Targeting NK Cells (Innate Immunity)**
- Lirilumab

**Select Agents Targeting T Cells (Adaptive Immunity)**
- MOXR0916
- TRX518
- Urelumab
- Varilumab

Adapted from Pardoll et al.

Adapted from Mellman et al and Pardoll et al.

**Blocking agents**
- Tremelimumab
- Ipilimumab

**Stimulating agents**
- Nivolumab
- Pembrolizumab
- Durvalumab
- Atezolizumab
- Avelumab
- BMS-986016

*CTLA-4=cytotoxic T-lymphocyte antigen-4; GITR=glucocorticoid-induced TNFR family related gene; KIR=killer-cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene-3; NK=natural killer; PD-1=programmed death-1; PD-L1=programmed death ligand-1.

Anti-PD1/PDL1 plus Anti-CTLA.4 to Influence the Lymphoid Compartment

Early immune response:
T cell activation

Effector Phase
Tumor cells

Blood vessel

Peripheral tissues

Lymph node

APC

T Cell

Ipilimumab
Tremellimunab

1st signal
2nd signal
MHC
TCR
B7
B7
CD28
CTLA-4

Activation

Inhibition

Nivolumab
MK-3475

PD-1

MPDL3280A
MEDI4736

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

PD-1 Blockade in Cancer with MMR- Deficiency

Le et al  NEJM 2015:

- Phase II Trial for patients with MMR-D utilizing Pembrolizumab.
- 41 Patients with Metastatic Carcinoma with and Without MMR deficiency with Pembrolizumab between 2013-15
- Primary End Point: Immune Related ORR and PFS
- Pembrolizumab was administered intravenously at a dose of 10 mg per kilogram of body weight every 14 days
- The immune-related OR, PFS rate were:
  - 40% (4 of 10 patients) and 78% (7 of 9 patients), for MMR-deficient CRC
  - 0% (0 of 18 patients) and 11% (2 of 18 patients) for MMR-Proficient CRC.
- The median PFS and overall survival:
  - Not reached in the cohort with MMR-Deficient CRC
  - 2.2 and 5.0 months for MMR-Proficient (MSS) CRC
PD-1 Blockade in Cancer with MMR- Deficiency

Table 3. Objective Responses According to RECIST Criteria.

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Mismatch Repair-Deficient Colorectal Cancer (N = 10)</th>
<th>Mismatch Repair-Proficient Colorectal Cancer (N = 18)</th>
<th>Mismatch Repair-Deficient Noncolorectal Cancer (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response — no. (%)</td>
<td>0</td>
<td>0</td>
<td>1 (14)*</td>
</tr>
<tr>
<td>Partial response — no. (%)</td>
<td>4 (40)</td>
<td>0</td>
<td>4 (57)†</td>
</tr>
<tr>
<td>Stable disease at week 12 — no. (%)</td>
<td>5 (50)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (10)</td>
<td>11 (61)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Could not be evaluated — no. (%)§</td>
<td>0</td>
<td>5 (28)</td>
<td>0</td>
</tr>
<tr>
<td>Objective response rate (95% CI) — %</td>
<td>40 (12–74)</td>
<td>0 (0–19)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Disease control rate (95% CI) — %§</td>
<td>90 (55–100)</td>
<td>11 (1–35)</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>Median duration of response — wk</td>
<td>Not reached</td>
<td>NA</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median time to response (range) — wk</td>
<td>28 (13–35)</td>
<td>NA</td>
<td>12 (10–13)</td>
</tr>
</tbody>
</table>

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.

Figure 1. Clinical Responses to Pembrolizumab Treatment.
PD-1 BLOCKADE IN MISMATCH-REPAIR DEFICIENCY

A Progression-free Survival in Cohorts with Colorectal Cancer

- Probability of Progression-free Survival
- Months
- No. at Risk
  - Mismatch repair-deficient: 11 8 6 2 0 0
  - Mismatch repair-proficient: 21 2 1 0 0 0

B Overall Survival in Cohorts with Colorectal Cancer

- Probability of Overall Survival
- Months
- No. at Risk
  - Mismatch repair-deficient: 11 9 7 5 1 0
  - Mismatch repair-proficient: 21 12 5 1 1 0
Management of MCRC: An Evolving Treatment Algorithm

Diagnosis of MCRC

- Resectable
  - Neoadjuvant/preoperative therapy
    - Surgery
    - Adjuvant therapy
  - Borderline/potentially resectable
  - Surgery

- Unresectable
  - First line
  - Second line
  - Third line
  - Fourth line

Treatment continuum
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

SUBSEQUENT THERAPY

- FOLFIRO or irinotecan
- FOLFIRO + (bevacizumab [preferred] or ziv-afibercept or ramucirumab)
- Irinotecan + (bevacizumab [preferred] or ziv-afibercept or ramucirumab)
- FOLFIRO + (cetuximab or panitumumab) (KRAS/NRAS WT only)
- Irinotecan + (cetuximab or panitumumab) (KRAS/NRAS WT only)
- Irinotecan + (cetuximab or panitumumab) + vemurafenib (BRAF V600E mutation positive)
- (Nivolumab or pembrolizumab) (dMMR/MSI-H only)

- Regorafenib
- Trifluridine + tipiracil
- Regorafenib
- Trifluridine + tipiracil
- Best supportive care

*if neither previously given
**if not previously given

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2018
Colon Cancer

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

INITIAL THERAPY
- FOLFOX ± bevacizumab
- CAPEOX ± bevacizumab
- FOLFOX + (cetuximab or panitumumab)\(^3\,^5\) (KRAS/NRAS WT and left-sided tumors only)
- FOLFIRI ± bevacizumab
- FOLFIRI + (cetuximab or panitumumab)\(^2\,^3\,^5\) (KRAS/NRAS WT and left-sided tumors only)
- FOLFOXIRI ± bevacizumab
- 5-FU/leucovorin (infusional preferred) ± bevacizumab\(^2\)
- Capecitabine ± bevacizumab\(^7\)

**Patient appropriate for intensive therapy**
- Progression → See COL D 2 of 10
- Progression → See COL D 3 of 10
- Progression → See COL D 4 of 10
- Progression → See COL D 5 of 10

**Patient not appropriate for intensive therapy**

Infusional 5-FU + leucovorin ± bevacizumab
- Capecitabine ± bevacizumab
- (Cetuximab or panitumumab)\(^2\,^3\,^5\) (category 2B) (KRAS/NRAS WT and left-sided tumors only)
- (Nivolumab or pembrolizumab) (dMMR/MSI-H only)\(^3\)

- Improvement in functional status → Consider initial therapy as above\(^8\)
- No improvement in functional status → Best supportive care

See footnotes COL D 6 of 10
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

SUBSEQUENT THERAPY

FOLFOX or FOLFOX + bevacizumab or CAPOEX + bevacizumab or Irinotecan + (cetuximab or panitumumab) (KRAS/NRAS WT only) or Irinotecan + (cetuximab or panitumumab) + vemurafenib (BRAF V600E mutation positive) or (Nivolumab or pembrolizumab) (dMMR/MSI-H only)

See Subsequent therapy

Regorafenib or Trifluridine + tipiracil

Regorafenib or Trifluridine + tipiracil

FOLFOX or CAPOEX or (Nivolumab or pembrolizumab) (dMMR/MSI-H only)

See Subsequent therapy

*if neither previously given
Table 1. Key immunotherapy trials in metastatic colorectal cancer (CRC).

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Target</th>
<th>Population</th>
<th>Patients</th>
<th>Response Rate</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials for MSI-H CRC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Refractory MSI-H CRC</td>
<td>25</td>
<td>57%</td>
<td>Le et al. [30]</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Refractory MSI-H CRC</td>
<td>47</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Nivolumab + Ipilimumab</td>
<td>PD-1 + CTLA-4</td>
<td>Refractory MSI-H CRC</td>
<td>30</td>
<td>33%</td>
<td>NCT02060188 [31]</td>
</tr>
<tr>
<td><strong>Trials for MSS CRC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Refractory MSS CRC</td>
<td>28</td>
<td>0%</td>
<td>Le et al. [30]</td>
</tr>
<tr>
<td>Nivolumab + Ipilimumab</td>
<td>PD-1 + CTLA-4</td>
<td>Refractory MSS CRC</td>
<td>20</td>
<td>5%</td>
<td>NCT02060188 [31]</td>
</tr>
<tr>
<td><strong>Trials of Various CRC Sub-Types</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>CTLA-4</td>
<td>Refractory CRC</td>
<td>49</td>
<td>2%</td>
<td>Chung et al. [28]</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Refractory CRC</td>
<td>19</td>
<td>0%</td>
<td>Topalian et al. [32]</td>
</tr>
<tr>
<td>BMS-936599</td>
<td>PD-L1</td>
<td>Refractory CRC</td>
<td>18</td>
<td>0%</td>
<td>Brahmer et al. [33]</td>
</tr>
<tr>
<td>Atezolizumab + Bevacizumab</td>
<td>PD-L1</td>
<td>Refractory CRC</td>
<td>14</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab + FOLFOX/bev</td>
<td>PD-L1 MEK</td>
<td>Metastatic CRC (70% first line)</td>
<td>30</td>
<td>40% (total) (first-line)</td>
<td>NCT01633970 [34]</td>
</tr>
<tr>
<td>Atezolizumab + Cobimetinib</td>
<td>PD-L1 MEK</td>
<td>Refractory CRC (30% MSS, 70% unknown)</td>
<td>23</td>
<td>17% (3 MSS, 1 unknown)</td>
<td>NCT01988896 [35]</td>
</tr>
</tbody>
</table>
Nivolumab Mechanism of Action

PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function\textsuperscript{11}

Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function\textsuperscript{12–14}
Nivolumab in MMR-D CRC

CheckMate-142 Study Design

Phase 2 Nonrandomized Study

- Histologically confirmed metastatic or recurrent CRC
- dMMR/MSI-H per local laboratory
- ≥ 1 prior line of therapy

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

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

- Median follow-up in the combination therapy cohort (N = 119) was 13.4 months (range, 9–25)\(^c\)

- Results of the monotherapy cohort (N = 74) with a similar median follow-up of 13.4 months (range, 10–32) are also presented\(^{1,c}\)

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\(^a\)Enrollment was staggered with additional patients being enrolled if ≥ 7 of the first 15 centrally confirmed MSI-H patients had a confirmed response (CR or PR). CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison. \(^b\)Patients with a CR, PR, or SD for ≥ 12 weeks. \(^c\)Defined here as the time from first dose to data cutoff.

Presented at: 2018 Gastrointestinal Cancers Symposium | #GI18

Presented by: Prof Thierry André
Nivolumab + Ipilimumab Combination in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: First Report of the Full Cohort From CheckMate-142

Thierry André,1 Sara Lonardi,2 Ka Yeung Mark Wong,3 Heinz-Josef Lenz,4 Fabio Gelsomino,5 Massimo Aglietta,6 Michael Morse,7 Eric Van Cutsem,8 Ray McDermott,9 Andrew Graham Hill,10 Michael B. Sawyer,11 Alain Hendlisz,12 Bart Neyns,13 Magali Svrcek,1 Thalita A. Moss,14 Jean-Marie Ledeine,15 Z. Alexander Cao,14 Shital Kamble,14 Scott Kopetz,16 Michael J. Overman16

1Hôpital Saint Antoine and Sorbonne Universités, UPMC Paris 06, Paris, France; 2Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; 3The University of Sydney, Sydney Medical School, Sydney, Australia; 4University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; 5University Hospital of Modena, Italy; 6University of Turin, Turin, Italy; 7Duke University Office of Research Administration, Durham, NC; 8University Hospitals Gasthuisberg - Leuven, Leuven, Belgium; 9St Vincent’s University Hospital, Dublin, Ireland; 10Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; 11Cross Cancer Institute, Edmonton, AB, Canada; 12Institut Jules Bordet, Brussels, Belgium; 13Universitair Ziekenhuis Brussel, Brussels, Belgium; 14Bristol-Myers Squibb, Princeton, NJ; 15Bristol-Myers Squibb, Braine-l’Alleud, Belgium; 16MD Anderson Cancer Center, Houston, TX
Investigator-Assessed Response and Disease Control

- DCR\textsuperscript{b} was 80% (95% CI: 71.5, 86.8) with combination therapy and 69% (57.1, 79.2) with monotherapy\textsuperscript{1,d}
- Combination therapy provided a numerically higher ORR, including CRs, and DCR relative to monotherapy during a similar follow-up period\textsuperscript{d}

\textsuperscript{a}Median follow-up was 13.4 months (range, 9--25). \textsuperscript{b}Disease control was defined as patients with a CR, PR, or SD for ≥12 weeks. \textsuperscript{d}Median follow-up was 13.4 months (range, 10--32).

\textsuperscript{1}Overman MJ et al. Lancet Oncol 2017;18:1162--1171.
Characterization of Response

Nivolumab + ipilimumab

- Median time to response was 2.8 months (range, 1–14)
- Responses were durable:
  - Median DOR was not reached
  - 94% of responders had ongoing responses at data cutoff

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*Response per investigator assessment.
Progression-Free and Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Nivolumab + ipilimumab&lt;sup&gt;a,d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-month rate (95% CI), %</td>
<td>76 (67.0, 82.7)</td>
<td>87 (80.0, 92.2)</td>
</tr>
<tr>
<td>12-month rate (95% CI), %</td>
<td>71 (61.4, 78.7)</td>
<td>85 (77.0, 90.2)</td>
</tr>
</tbody>
</table>

With similar follow-up, combination therapy provided improved PFS and OS relative to monotherapy<sup>a,e,f</sup>

<sup>a</sup>Median follow-up was 13.4 months (range, 9–25). <sup>b</sup>Median PFS was not reached (95% CI, not estimable). <sup>c</sup>FFS per investigator assessment. <sup>d</sup>Median OS was not reached (95% CI, 18.0, not estimable).

<sup*e</sup>CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.
Conclusions

- Nivolumab + ipilimumab provided durable clinical benefit in previously treated patients with dMMR/MSI-H mCRC
  - High ORR (55%) and durable responses (median DOR not reached)
  - Median PFS and OS not reached with median follow-up of 13 months; 85% of patients alive at 1 year
- Meaningful improvements in quality of life were observed
- Safety was manageable with a low rate of discontinuation due to TRAEs
- Indirect comparisons in CheckMate-142 suggest that nivolumab + ipilimumab provides improved clinical benefit relative to nivolumab monotherapy
- Nivolumab + ipilimumab represents a promising new treatment option for patients with previously treated dMMR/MSI-H mCRC
Nivolumab in Patients With DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer: Long-Term Survival According to Prior Line of Treatment From CheckMate-142

Michael J. Gerecitano, Francesco Bergamaschi, Ray McDermott, Massimiliano Aglietta, Franklin Chen, Fabio Gelber, Eun Young Park, Michael Morse, Eric Van Cutsem, Alain Hendlisz, Scott Nauss, Rebecca A. Moss, Ruijuan Zhong, Z. Alexander Cao, Shikhal Kedar, Scott Kopolitz, Thierry André

Background
- Approximately 4% of patients with metastatic colorectal cancer (mCRC) have a deficiency in the DNA mismatch repair system (dMMR), which leads to high microsatellite instability (MSI-H).
- These patients benefit from anti-PD-1/PD-L1 therapy.

Methods
- 154 patients received nivolumab (nivolumab + ipilimumab or nivolumab alone).
- 12 months of follow-up, ORR was 37%, and PFS was 19.4 months.

Study Design
- CheckMate-142 was an ongoing, multicenter, phase II trial investigating the efficacy and safety of nivolumab monotherapy in patients with mCRC.
- Between March 10, 2014, and March 16, 2015, 94 patients with locally advanced or metastatic mCRC were enrolled.

Results
- No new safety signals were reported.
- Efficacy: ORR was 37%, and PFS was 19.4 months.
- Overall survival: Median OS was 76.7 months.

Conclusions
- Nivolumab provided durable clinical benefit in patients with mCRC, with a median OS of 34.7 months in the intention-to-treat population.
- Nivolumab was well-tolerated, and safety was consistent across subgroups.

References

Acknowledgments
The authors thank the patients, their families, and the healthcare professionals who participated in this study. This research was supported by Bristol-Myers Squibb.
Pembrolizumab  Mechanism of Action

PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function\(^{11}\)

Pembrolizumab  binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function\(^{12–14}\)
Pembrolizumab for MMR-D CRC

*KEYNOTE-016, -164, -012, -028, and -158*

Patients received pembrolizumab at 200 mg every 3 weeks or 10 mg/kg Q2 weeks for up to 24 months or until unacceptable toxicity or PD.

90 patients had colorectal cancer and 59 patients had 14 other cancer types.

Objective response rate on blinded independent central radiologist review according to Response Evaluation Criteria in Solid Tumors 1.1 was 39.6% (95% confidence interval = 31.7%–47.9%), with a complete response in 11 patients (7.4%).

The median duration of response was not reached, with durations ranging from 1.6+ to 22.7+ months.

Responses lasting ≥ 6 months in 78% of responders.

Response rates were 36% in patients with colorectal cancer and 46% in those with other cancer types.
Pembrolizumab for MMR-D CRC

Table 2. Key ongoing/planned trials in MSI-H CRC.

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Primary Endpoint</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Refractory (Cohort A); or ≥1 Prior Therapy (Cohort B)</td>
<td>Pembrolizumab Monotherapy</td>
<td>Objective Response Rate</td>
<td>Keynote 164 NCT02460198</td>
</tr>
<tr>
<td>1st Line Metastatic</td>
<td>Pembrolizumab monotherapy vs. Standard of Care Chemotherapy</td>
<td>Progression-Free Survival</td>
<td>Keynote 177 NCT02563002</td>
</tr>
<tr>
<td>1st Line Metastatic</td>
<td>Atezolizumab vs. Atezolizumab + FOLFOX + Bevacizumab</td>
<td>Progression-Free Survival</td>
<td>NRG-G1004/S1610 NCT02997228</td>
</tr>
<tr>
<td>Stage III</td>
<td>Atezolizumab + FOLFOX vs. FOLFOX alone</td>
<td>Disease-Free Survival</td>
<td>Alliance A021502 NCT02912559</td>
</tr>
</tbody>
</table>
### Table 3. Combinatorial immunotherapy trials in progress.

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>PD-1/PD-L1 Partner (Target)</th>
<th>Description</th>
<th>Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRC Specific or CRC Expansion Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Cibimetinib (MEK), Bevacizumab (VEGF-A)</td>
<td>Phase I—Metastatic CRC</td>
<td>NCT02876224</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Cetuximab (EGFR)</td>
<td>Phase Ib/II—Pre-treated CRC</td>
<td>NCT02713373</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Capecitabine, Bevacizumab (VEGF-A)</td>
<td>Randomized Phase II Refractory CRC</td>
<td>NCT02873195</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Cediranib (VEGFR, c-kit)</td>
<td>Phase I/II—Refractory CRC Expansion</td>
<td>NCT02484404</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Nintedanib (VEGFR, PDGFR, FGFR)</td>
<td>Phase I/II—CRC</td>
<td>NCT02856425</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Napabucasin (STAT3)</td>
<td>Phase I/II Refractory CRC</td>
<td>NCT02851004</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Oral azacitidine (DNMT), Romidepsin (HDAC1/2)</td>
<td>Phase I—Pre-treated MSS CRC</td>
<td>NCT02512172</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Azacitidine (DNMT), Ipacadostat (IDO-1)</td>
<td>Phase I/II Refractory MSS CRC and NSCLC</td>
<td>NCT02994437</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Ipacadostat (IDO-1)</td>
<td>Phase I/II—Solid tumors, CRC</td>
<td>NCT02327078</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Poly-ICLC (TLR-3)</td>
<td>Phase I/II—MSS CRC</td>
<td>NCT02834052</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Varilimumab (CD-27)</td>
<td>Phase I/II—Solid tumors, CRC</td>
<td>NCT02335918</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Pecidatinib (CSF-1R)</td>
<td>Phase I—Pre-treated pancreas and CRC</td>
<td>NCT02777710</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>CPI-14 (Adenosine-A2A)</td>
<td>Phase I—Solid tumors, MSI-H CRC</td>
<td>NCT02655822</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Chemoradiation</td>
<td>Phase I/II—Locally advanced rectal cancer</td>
<td>NCT02948348</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Tremelimumab (CTLA-4), Radiation</td>
<td>Phase II—NSCLC and CRC with liver metastases</td>
<td>NCT02888743</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Tumor infiltrating Lymphocytes, IL-2, cytoxan, fludarabine</td>
<td>Phase II—digestive tumors, CRC arm</td>
<td>NCT01174121</td>
</tr>
<tr>
<td><strong>Phase I Studies in Solid Tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Selumetinib (MEK)</td>
<td>Phase I—Solid Tumors</td>
<td>NCT02586987</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Afiberecept (VEGF-A/B, PIGF)</td>
<td>Phase I—solid tumors</td>
<td>NCT02298959</td>
</tr>
</tbody>
</table>
Molecular markers in CRC

Molecular markers that define high-risk stage II/III CRC

Cancer cell markers: MSI status, KRAS/BRAF$^{V600E}$ mutations

OS in stage III, ADJUVANT CHEMOTHERAPY
OS in stage II, NO ADJUVANT CHEMOTHERAPY

Train cohort (n = 3106)

0 12 24 36 48 60

Event-free survival %

N0147
PETACC-03

Clinical trials

0 12 24 36 48 60

Event-free survival %

Val3 cohort (n = 1080)

0 12 24 36 48 60

Event-free survival %

MSS/MSS-low, KRAS/BRAF wt
MSS/MSS-low, KRAS mutated
MSS/MSS-low, BRAF V600E mutated
MSS/MSS-low, KRAS/BRAF wt
MSS/MSS-low, BRAF V600E mutated

Clinical trials

N0147
PETACC-03

Observational

Oslo
CCFR

High-risk: stage II/III, MSS $BRAF^{V600E}$
~ 5%

Low-risk: stage II, MSI, KRAS/BRAF wt
~ 5%

Dienstmann et al, Annals Oncol 2017

PRESENTED AT: ASCO ANNUAL MEETING ‘17  #ASC017 Presented by: Rodrigo Dienstmann
Future of Immunotherapy in CRC MMR-Deficient

Where do we go From here?

After the FDA Approval of PD-1 Inhibitors in Metastatic CRC MMR-D
KEYNOTE-177: Randomized phase III study of pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient or microsatellite instability-high metastatic colorectal carcinoma

270 patients will be randomly assigned to 200 mg of pembrolizumab every 3 weeks or investigator’s choice of 1 of 6 chemotherapy regimens chosen prior to randomization. Treatment is to continue until disease progression, unmanageable toxicity.

Investigators are hoping to show that frontline treatment with the PD-1 inhibitor pembrolizumab can improve progression-free survival (PFS) compared with standard-of-care chemotherapy in patients with mismatch repair-deficient or microsatellite instability-high (MSI-H) colorectal cancer (CRC).
**Alliance Trial A021502**

Randomized Trial of Standard of care chemoRx Vs Combined Atezolizumab as adjuvant Therapy for Stage III Colon Cancer with MMR-Deficient

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### Schema

- **Surgery to confirm stage III colon cancer**
- **Assessment of dMMR Status**
- **Registration and Randomization**

**Arm 1***: mFOLFOX6 + atezolizumab for 12 cycles*, then atezolizumab alone for an additional 6 months

**Arm 2***: mFOLFOX6 alone for 12 cycles*

---

*up to 10 weeks*
Adjuvant Therapy Decision-Making:
General Principles

- Recurrence Risk
- Absolute Treatment Benefit
- Toxicity
- Cost
<table>
<thead>
<tr>
<th>Experimental arm</th>
<th>Active comparator regimen</th>
<th>Disease</th>
<th>Setting</th>
<th>Phase</th>
<th>Comments</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab + FOLFOX</td>
<td>FOLFOX</td>
<td>CRC</td>
<td>Adjuvant, stage III</td>
<td>3</td>
<td>CT plus ID up to 25 courses</td>
<td>NCT02912559</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>FOLFOX, Bevacizumab, Cetuximab</td>
<td>CRC</td>
<td>IV</td>
<td>3</td>
<td>KEYNOTE-477: IO for up to 35 treatments</td>
<td>NCT02563002</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Single arm</td>
<td>CRC</td>
<td>Advanced</td>
<td>2</td>
<td>MRMp</td>
<td>NCT02981524</td>
</tr>
<tr>
<td>Pembrolizumab/Cyclophosphamide</td>
<td>Single arm</td>
<td>Pancreatic, NSCLC, and MRRM CRC</td>
<td>Advanced</td>
<td>2</td>
<td>—</td>
<td>NCT02983578</td>
</tr>
<tr>
<td>AZD9150</td>
<td>Single arm</td>
<td>MMRp CRC</td>
<td>IV</td>
<td>1/2</td>
<td>IO for 1 year</td>
<td>NCT02834052</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Single arm</td>
<td>NA</td>
<td>MMRp CRC</td>
<td>IV</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Single arm</td>
<td>Hypermutated malignancies</td>
<td>Recurrent or refractory disease</td>
<td>1/2</td>
<td>Pediatric patients (12 months to 18 years of age) Biologic MMRp</td>
<td>NCT02902964</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Single arm</td>
<td>mCRPC with mutations in DNA repair defects</td>
<td>Recurrent or refractory disease</td>
<td>1/2</td>
<td>Pediatric patients (12 months to 18 years of age) Biologic MMRp</td>
<td>NCT03043701</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>FOLFOX, Bevacizumab, Cetuximab</td>
<td>CRC</td>
<td>IV</td>
<td>2</td>
<td>IO until progression or unacceptable toxicity</td>
<td>NCT03012014</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Single arm</td>
<td>High-grade gliomas, diffuse intrinsic pontine gliomas, or hypermutated brain tumors</td>
<td>NA</td>
<td>2</td>
<td>IO for 34 courses</td>
<td>NCT02559565</td>
</tr>
</tbody>
</table>

FOLFOX: Fluorouracil, Leucovorin, and Oxaliplatin combination regimen. CRC: colorectal cancer. CT: chemotherapy. ID: immunotherapy. FOLFOX: Fluorouracil, Leucovorin, and Irinotecan. MMRp: mismatch repair proficient profile. MMR: mismatch repair deficient profile. NSCLC: non-small cell lung carcinoma. mCRPC: metastatic castration-resistant prostate cancer. *GVAL: cancer vaccine composed of irradiated tumor cells genetically modified to secrete granulocyte-macrophage colony-stimulating factor.** AZD9150: histone deacetylase inhibitor of SMARCA2. **Poly-ICLC (cytovirolymphoblasite, polynosinic-polycytidylic acid, and poly-L-lysine double-stranded RNA). signal of TLR3. **DS-8201a, anti-tumor death receptor 5 (DR5) agonistic antibody. **patients must have evidence of biallelic mismatch repair deficiency either in their tumor tissue (by immunohistochemistry or sequencing) or in their germline (by sequencing) and/or evidence of hypermutant malignancy by whole genome sequencing with a mutation load > 100 per exome. **the germline and somatic DDR (BRCA1, BRCA2, ATM, PTEN, CHEK2, RAD51C, RAD51D, PALE2, MSH6, MSH3, and PMS2) will be assessed by 7-NOS of metastatic sites or by liquid biopsy.
Future of Immunotherapy in CRC
MMR-Deficient

Future of adjuvant therapy in high-risk Stage II/III CRC

Proof-of-concept trial for micrometastatic microenvironment targeting

Stage II MSS, high-risk pathology + Stage III CRC
Baseline ctDNA (+)

FOLFOX adjuvant
ctDNA (-) → Observation
ctDNA (+) → Novel immuno-targeted therapy combinations

ctDNA monitoring
ctDNA

- Stage II - Observation

- Stage III - Observation?
  - Standard chemotherapy?
  - ctDNA test
  - Personalized therapy as below?

**Tumor profiling**

- MSI
  - CMS1 or Immunoscore® high
    - 15% Standard chemotherapy + PD1/PDL1 blockade?
  - CMS2/3 Epithelial or “immune-desert” microenvironment sign.
    - 45% Standard chemotherapy + T cell attracting therapies?
  - MSS, BRAF^{V600E}
    - 5% Chemotherapy + double BRAF targeted therapies?
- CMS4 Mesenchymal or “stromal-rich” “immunosuppressive” microenvironment sign.
  - 35% Standard chemotherapy + novel targeted-immunotherapy combos?
Conclusion

CRC Immunotherapy after the approval of 2 drugs as immune checkpoints inhibitors will have a positive impact on Median survival of patients with Metastatic CRC MMR-Deficient

Need to continue to identify Predictive Biomarkers for Response to checkpoints inhibitors which may explain lack of response and resistance to Immunotherapy in CRC

Combination Chemo-Immunotherapy Trials will lead to better optimization of first Line therapy in Selected CRC

Combination of novel agents co-stimulatory CD137 with PD-1 Inhibitors is appealing