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 Gelsonimo,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 Svrcék,¹ Rebecca A. Moss,¹⁴ Jean-Marie Ledeine,¹⁵ Z. Alexander Cao,¹⁴ Shital Kopetz,¹⁶ Michael J. Overman¹⁶

¹Hôpital Saint Antoine and Sorbonne Universités, UMPC 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 Torino, 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
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

Combination cohort

Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses and then nivolumab 3 mg/kg Q2W)

Monotherapy cohort

Nivolumab 3 mg/kg Q2W


• 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\(^1,c\)

\(a\)Enrollment was staggered with additional patients being enrolled if ≥ 7 of the first 19 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.
Investigator-Assessed Response and Disease Control

- DCR\textsuperscript{b} was 80\% (95\% CI: 71.5, 86.6) 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}

\*Median follow-up was 13.4 months (range, 9-25). \textsuperscript{b}Disease control 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{d}CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.

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

*Response per investigator assessment.*
### Response and Disease Control in Patient Subsets

<table>
<thead>
<tr>
<th>Tumor PD-L1 expression, n(%)</th>
<th>Nivolumab + ipilimumab (N = 119)(^a)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>ORR</td>
<td>DCR(^b)</td>
</tr>
<tr>
<td>≥ 1%</td>
<td>26</td>
<td>14 (54)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>65</td>
<td>34 (52)</td>
<td>51 (78)</td>
</tr>
<tr>
<td><strong>BRAF/KRAS mutation status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>31</td>
<td>17 (55)</td>
<td>24 (77)</td>
</tr>
<tr>
<td><strong>BRAF</strong> mutant</td>
<td>29</td>
<td>16 (55)</td>
<td>23 (79)</td>
</tr>
<tr>
<td><strong>KRAS</strong> mutant</td>
<td>44</td>
<td>25 (57)</td>
<td>37 (84)</td>
</tr>
<tr>
<td>Clinical history of Lynch syndrome, n (%)(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
<td>25 (71)</td>
<td>30 (86)</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>15 (48)</td>
<td>25 (81)</td>
</tr>
</tbody>
</table>

- Responses were observed irrespective of tumor PD-L1 expression, **BRAF** or **KRAS** mutational status, or clinical history of Lynch syndrome

\(^a\)Per investigator assessment. \(^b\)Patients with a CR, PR, or SD for ≥ 12 weeks. \(^c\)Based on the clinical records of the patients at sites in countries where this reporting was permitted (excluded Italy).
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,b&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</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>PFS per investigator assessment.  
<sup>d</sup>Median OS was not reached (95% CI, 18.0, not estimable).  
<sup>e</sup>Median follow-up was 13.4 months (range, 10-32).  
<sup>f</sup>CheckMate-142 monotherapy and combination therapy cohorts were not randomized or designed for a formal comparison.  
Quality of live
Nivolumab + ipilimumab

- Statistically significant and clinically meaningful improvements were achieved in key quality of life measures, with improvements maintained for extended periods while on treatment.

EORTC = European Organisation for Research and Treatment of Cancer; QoL = Quality of Life; VAS = visual analog scale.

*aChanges in mean scores over time were analyzed using linear mixed models adjusted for baseline score. Changes from baseline of ≥ 10 points (EORTC QLQ-C30) and ≥ 7 points (EQ-5D VAS) were regarded as clinically meaningful.1,2

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 DNAMismatch Repair-Deficient / Microsatellite Instability-HighMetastatic Colorectal Cancer: Long-Term SurvivalAccording to Prior Line of Treatment From CheckMate-142

Michel J. Overman,1 Francesca Bergamo,2 Ray McDermott,3 Massimo Aglietta,4 Franklin Chen,5 Fabio Gelsomino,6 Ka Yeung Mark Wong,7 Michael Morse,8 Eric Van Cutsem,9 Alain Hendlisz,10 Bart Neyns,11 Rebecca A. Moss,12 Huanyu Zhao,12 Z. Alexander Cao,12 Shital Kamble,12 Scott Kopetz,1 Thierry André13

1MD Anderson Cancer Center, Houston, TX; 2Istituto Oncologico Veneto – IRCSS, Padova, Italy; 3St. Vincent’s University Hospital, Dublin, Ireland; 4University of Torino, Turin, Italy; 5Novant Health Oncology Specialists, Winston-Salem, NC; 6University Hospital of Modena, Modena, Italy; 7The University of Sydney, Sydney Medical School, Sydney, Australia; 8Duke University Office of Research Administration, Durham, NC; 9University Hospitals Gasthuisberg – Leuven, Leuven, Belgium; 10Institut Jules Bordet, Brussels, Belgium; 11Universitair Ziekenhuis Brussel, Brussels, Belgium; 12Bristol-Myers Squibb, Princeton, NJ; 13Hôpital Saint Antoine and Sorbonne Universités, UMPC Paris 06, Paris, France
CheckMate-142 Monotherapy Cohort Study Design

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Monotherapy cohort

Nivolumab 3 mg/kg Q2W

Primary endpoint:
- ORR per investigator assessment

Other key endpoints:
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Primary analysis (N = 74): efficacy per BICR and safety; median follow-up, 21 months (range, 17-40)\(^c\)

Subset analysis:
- Group A (n = 53): received ≥ 3 prior chemotherapies, including a fluoropyrimidine, oxaliplatin, and irinotecan
- Group B (n = 21): did not receive prior treatment with all 3 of these chemotherapies (fluoropyrimidine, oxaliplatin, and irinotecan)

DCR = disease control rate
\(a\)Enrolment was staggered with additional patients being enrolled if ≥ 7 of the first 19 centrally confirmed MSI-H patients had a confirmed response (CR or PR).
\(b\)Patients with a CR, PR, or SD for ≥ 12 weeks.
\(c\)Time from first dose to data cutoff.
### Response, Disease Control, and Durability

<table>
<thead>
<tr>
<th>ORR, n (%)</th>
<th>All patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>N = 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>[95% CI]</td>
<td>25 (34)</td>
<td>[23.2, 45.7]</td>
</tr>
</tbody>
</table>

| Best overall response, n (%) | | |
| CR | 7 (9) |
| PR | 18 (24) |
| SD | 23 (31) |
| PD | 22 (30) |
| Unable to determine | 4 (5) |

| Disease control, n (%)<sup>d</sup> | 46 (62) |
| [95% CI] | [50.1, 73.2] |

| Median DOR (range), months | NR (1.4+ to 31.6+) |

| Median duration of SD (range), months | 8.3 (4.2, NE) |

- Median time to response was approximately 2.8 months across all groups
- Clinical benefit was observed across all groups

NE= non estimable; NR – not reached

<sup>a</sup>BICR data with a median follow-up of 21 months (range, 17-40).<sup>b</sup>Group A patients received ≥3 prior chemotherapies including a fluoropyrimidine, oxaliplatin, and irinotecan. Group B patients did not receive prior treatment with all 3 of these chemotherapies (fluoropyrimidine, oxaliplatin and irinotecan). <sup>c</sup>Patients with a CR, PR, or SD for ≥ 12 weeks.
Characterization of Response: All Patients

Responders with Nivolumab

- Nivolumab continued to provide clinically meaningful and durable responses
  - 80% of responders had ongoing responses at data cutoff
  - 64% had responses lasting ≥ 12 months

*BICR data with a median follow-up of 21 months (range, 17-40).*
Progression-Free Survival: All Patients

- Median PFS was 4.2 months and not reached in groups A and B, respectively.
- 12- and 18-month PFS rates were 41% (group A) and 52% (group B).

**N = 74**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (95% CI), months</th>
<th>PFS rate (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.6 (3.0, NE)</td>
<td>44 (32.6, 55.3)</td>
</tr>
</tbody>
</table>

NE, not estimable. BICR data with a median follow-up of 21 months. Group A patients received ≥ 3 prior chemotherapies, including a fluoropyrimidine, oxaliplatin, and irinotecan. Group B patients did not receive prior treatment with all 3 of these chemotherapies (fluoropyrimidine, oxaliplatin, and irinotecan).
Overall Survival: All Patients

- Median OS was not reached in groups A or B\(^a\)
- 12-month OS rate was 68% (group A) and 81% (group B)\(^a\)
- 18-month OS rate was 66% (group A) and 70% (group B)\(^a\)

**Table:**

<table>
<thead>
<tr>
<th>All patients</th>
<th>N = 74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), months</td>
<td>NR (19.6, NE)</td>
</tr>
<tr>
<td>OS rate (95% CI), %</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>72 (60.0, 80.9)</td>
</tr>
<tr>
<td>18 months</td>
<td>67 (54.9, 76.9)</td>
</tr>
</tbody>
</table>

\(^a\)Group A patients received ≥ 3 prior chemotherapies, including a fluoropyrimidine, oxaliplatin, and irinotecan. Group B patients did not receive prior treatment with all 3 of these chemotherapies (fluoropyrimidine, oxaliplatin and irinotecan).
Overall Survival by Best Overall Response

- Best overall response to nivolumab treatment correlated with overall survival.

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>CR + PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>NR (NE)</td>
<td>NR (14.3, NE)</td>
<td>10.3 (3.0, NE)</td>
</tr>
</tbody>
</table>

**CR + PR**

- n = 25
- Median OS: NR (NE)

**SD**

- n = 23
- Median OS: NR (14.3, NE)

**PD**

- n = 22
- Median OS: 10.3 (3.0, NE)

NE = not estimable, NR – not reached.
Conclusions:

• Nivolumab continued to provide durable clinical benefit with long-term follow-up (21 months) in previously treated patients with dMMR/MSI-H mCRC
  - PFS and OS rates demonstrated continued stability
  - CR rate increased with longer follow-up
  - Median DOR and OS were not reached

• Durable clinical benefit with deepening of response was observed regardless of prior chemotherapy with a fluoropyrimidine, oxaliplatin, and irinotecan

• No new safety signals were reported with long-term follow-up

• Results support ongoing evaluation of nivolumab-based therapy in the first-line setting