Immunotherapy in Colorectal Cancer

Claus-Henning Köhne
University Clinic Oncology and Haematology
North West German Cancer Center (NWTZ)
DISCLOSURE INFORMATION
CLAUS-HENNING KÖHNE

Personal honoraria:
Amgen, Bayer, Merck, Roche, Servier, BMS, Lilly

Advisory role:
EMA, haliodx, BMS, Amgen, Merck
Survival according to molecular subgroups

- Her2/neu: ~5%
- RAS wt MSI: 8%
- RAS mut MSI: 8%
- BRAF mut: 8%
- RAS mut: 38%
- RAS wt: 38%

Cremolini et al. Lancet Oncol 2015
Survival according to molecular subgroups

Cremolini et al. Lancet Oncol 2015

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RASwt L</td>
<td>Doublet + EGFR / Triplet + EGFR</td>
</tr>
<tr>
<td>RASwt R</td>
<td>Doublet +/- Bev</td>
</tr>
<tr>
<td>RASmut</td>
<td>Doublet / Triplet (+/- Bev)</td>
</tr>
<tr>
<td>BRAFmut</td>
<td>Triplet / Doublet</td>
</tr>
<tr>
<td></td>
<td>+ EGFR?</td>
</tr>
<tr>
<td></td>
<td>+ VEGF?</td>
</tr>
<tr>
<td></td>
<td>BRAF/MEK/Chemo</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>Trastuzumab / Lapatinib</td>
</tr>
<tr>
<td>&gt;3rd Line</td>
<td></td>
</tr>
</tbody>
</table>
Different pathways of Colon Cancer development

Chromosomal instability (CIN):
- Proficient Mismatch Repair (pMMR)
- Microsatellite stable (MSS) [85%]

Microsatellite instability (MSI):
- Deficient Mismatch Repair (dMMR)
- Microsatellite unstable (MSI) [15%]

Familial cases
- Lynch syndrome
  - Germline mutation: (MLH1, MSH2, MSH6, PMS2)
  - BRafV600E mutation ≈50%

Sporadic cases
- Epigenetic MLH1 inactivation
  - (MLH1 promoter methylation)
  - No BRafV600E mutation

≈50% 15% 2/3 1/3

Sinicrope ASCO 2015
Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer

Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:
• MMR-D is synonymous with MSI-H
• MMR-P is synonymous with MSI-L/MSS

Mutations per tumor

Mismatch-repair proficient colon cancers

Mismatch-repair deficient colon cancers

Melanoma and Lung Cancers

Sporadic Adult Solid Tumors

Mutagen Associated tumors

Mismatch repair tumors

Liquid Tumors

Pediatric Tumors

Mutations per tumor

0 500 1000 1500 2000
metastatic colorectal cancer

95%

5%
Prognosis in early CRC by MMR and Immunoscore

DFS by MMR status

Untreated 5Y DFS; p=.009
  dMMR 80%
  pMMR 56%

Sargent D J et al. JCO 2010;28:3219
Randomized Trial of Standard Chemotherapy Alone or Combined With Atezolizumab as Adjuvant Therapy for Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair

STAGE III colon cancer dMMR

12x FOLFOX

12x FOLFOX atezolizumab IV over 30-60 minutes starting on day 1 of course 1 or 2. q14 days up to 25 courses in the absence of disease progression or unacceptable toxicity.
Influence of MMR/MSI and BRAF on OS in mCRC

Data from CAIRO, CAIRO2, COIN and FOKUS Studies

KRASwt CALGB 80405


Innocenti-F et al ASCO 2017
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

B Radiographic Response

- Mismatch repair–proficient colorectal cancer
- Mismatch repair–deficient colorectal cancer
- Mismatch repair–deficient noncolorectal cancer

Change from Baseline in the Sum of Longest Diameters (%)

- 20% increase (progressive disease)
- 30% decrease (partial response)

Pembrolizumab

Le et al. NEJM 2015
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade.

Le et al. Science 2017

<table>
<thead>
<tr>
<th></th>
<th>Colorectal N=40</th>
<th>Non-colorectal N=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>ORR</td>
<td>52%</td>
<td>54%</td>
</tr>
<tr>
<td>DCR</td>
<td>82%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Le et al Science 2017
Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade.

Le et al Science 2017
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)

- Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19)\(^c\)

\(a\)Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; \(b\)Patients with a CR, PR, or SD for \(\geq 12\) weeks divided by the number of treated patients; \(c\)Time from first dose to data cutoff

BICR = blinded independent central review; CR = complete response; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; PFS = progression-free survival; PR = partial response; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q6W = once every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease
Ipilimumab + Nivolumab in pretreated MSI-H mCRC

**ORR 55%, DCR 79%**

Ipi + Nivo

**Ref: NIVO monotherapy**

ORR 31.1%, DCR 68.9%

Nivo alone

\[
\text{PFS (\%)}
\begin{array}{c|cccccccccc}
\hline
\text{Time (months)} & 0 & 3 & 6 & 9 & 12 & 15 & 18 & 21 & 24 & 27 & 30 \\
\hline
\text{Nivolumab} & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 \\
\text{Nivolumab + ipilimumab} & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 \\
\hline
\end{array}
\]

\[
\text{OS (\%)}
\begin{array}{c|cccccccccc}
\hline
\text{Time (months)} & 0 & 3 & 6 & 9 & 12 & 15 & 18 & 21 & 24 & 27 & 30 \\
\hline
\text{Nivolumab} & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 \\
\text{Nivolumab + ipilimumab} & 100 & 90 & 80 & 70 & 60 & 50 & 40 & 30 & 20 & 10 & 0 \\
\hline
\end{array}
\]

No. at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>74</th>
<th>48</th>
<th>41</th>
<th>32</th>
<th>17</th>
<th>12</th>
<th>12</th>
<th>11</th>
<th>6</th>
<th>3</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>119</td>
<td>95</td>
<td>86</td>
<td>78</td>
<td>39</td>
<td>12</td>
<td>11</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>74</th>
<th>64</th>
<th>59</th>
<th>55</th>
<th>37</th>
<th>21</th>
<th>19</th>
<th>17</th>
<th>11</th>
<th>6</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>119</td>
<td>113</td>
<td>107</td>
<td>104</td>
<td>78</td>
<td>33</td>
<td>19</td>
<td>17</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Overman et al. JCO 2018
NCCN Guidelines Version 2.2017: Colon Cancer

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:1 (PAGE 2 of 10)

Subsequent Therapy

Previous oxaliplatin-based therapy without irinotecan

- FOLFIRI \(10 \pm \text{(bevacizumab}^{15} \text{[preferred]}^{5,6} \text{or ziv-aflibercept}^{15,16} \text{or ramucirumab}^{15,16}) \text{or irinotecan}^{10} \pm \text{(bevacizumab}^{15} \text{[preferred]}^{5,6} \text{or ziv-aflibercept}^{15,16} \text{or ramucirumab}^{15,16})

- FOLFIRI\(10 + \text{(cetuximab or panitumumab)}^{6,8,17-19} \text{(KRAS/NRAS WT only)} \text{or irinotecan}^{10} + \text{(cetuximab or panitumumab)}^{6,8,17-19} \text{(KRAS/NRAS WT only)}

- (Nivolumab or pembrolizumab)* \text{(dMMR/MSI-H only)}

Irinotecan\(10 + \text{(cetuximab or panitumumab)}^{6,8,17-19} \text{(KRAS/NRAS WT only)} \text{or Regorafenib}^{20} \text{or Trifluridine + tipiracil}^{20} \text{or (Nivolumab or pembrolizumab)* (dMMR/MSI-H only)}

Regorafenib\(^{20}\) or Trifluridine + tipiracil\(^{20}\)

See Subsequent therapy

Regorafenib\(^{20}\) or Trifluridine + tipiracil\(^{20}\)

See Subsequent therapy

Regorafenib\(^{20}\) or Trifluridine + tipiracil\(^{20}\)

Clinical trial or Best supportive care\(^{21}\)

See Subsequent therapy

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

Regorafenib\(^{20}\) or Trifluridine + tipiracil\(^{20}\)

See Subsequent therapy

(Nivolumab or pembrolizumab)* (dMMR/MSI-H only)

*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.
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)

**CheckMate-142**

a

• Histologically confirmed metastatic or recurrent CRC

• MSI-H/dMMR per local laboratory

• Median follow-up for the 1L nivolumab plus low-dose ipilimumab cohort was 13.8 months (range, 9–19)\(^c\)

\(^a\)Previously treated

Nivolumab 3 mg/kg Q2W

Nivolumab 3 mg/kg +

ipilimumab 1 mg/kg Q3W

(4 doses and then

nivolumab 3 mg/kg Q2W)\(^a\)

Nivolumab 3 mg/kg Q2W +

ipilimumab 1 mg/kg Q6W\(^a\)

Primary endpoint:

• ORR per investigator assessment (RECIST v1.1)

Other key endpoints:

• ORR per BICR, DCR\(^b\),

DOR, PFS, OS, and safety

\(^b\)Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end;

\(^c\)Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients;

\(^d\)Time from first dose to data cutoff

BICR = blinded independent central review; CR = complete response; CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; PFS = progression-free survival; PR = partial response; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q6W = once every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

*Lenz et al. ESMO 2018*
**1st Line Nivo/IPI in MSI-H mCRC**

**Best Reduction in Target Lesions**

- ORR 60%, CR 7%
- 84% of patients had a reduction in tumor burden from baseline

*Confirmed response per investigator assessment

**CheckMate-142**

- Median time to response was 2.6 months (range, 1.2–13.8 months)
- Responses were durable:

  *Lenz et al. ESMO 2018*
Are these results incredible?

Nivo+ Ipi in MSI-H L1 mCRC

FOLFIRINOX in all comers L1
Metastatic rectal cancer

Bachet et al. EJC 2018 (in press)
Progression-Free and Overall Survival

<table>
<thead>
<tr>
<th>PFS</th>
<th>Nivolumab + ipilimumab n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR (14.1–NE)</td>
</tr>
<tr>
<td>9-mo rate, % (95% CI)</td>
<td>77 (62.0–87.2)</td>
</tr>
<tr>
<td>12-mo rate, % (95% CI)</td>
<td>77 (62.0–87.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OS</th>
<th>Nivolumab + ipilimumab n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NE)</td>
</tr>
<tr>
<td>9-mo rate, % (95% CI)</td>
<td>89 (74.9–95.1)</td>
</tr>
<tr>
<td>12-mo rate, % (95% CI)</td>
<td>83 (67.6–91.7)</td>
</tr>
</tbody>
</table>

No. at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>45</td>
<td>37</td>
<td>34</td>
<td>24</td>
<td>15</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>OS</td>
<td>45</td>
<td>42</td>
<td>40</td>
<td>38</td>
<td>24</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

*Per investigator assessment.
mo = month; NE = not estimable; NR = not reached

*Lenz et al. ESMO 2018*
Metastatic mCRC
Survival according to molecular subgroups

Cremolini et al. Lancet Oncol 2015
Lenz et al. ESMO Congress 2018

Pembrolizumab vs. Paclitaxel in 2nd Line Gastric Cancer

Overall Survival, CPS ≥1

Shitara et al. Lancet 2018
NON-response of dMMR/MSI mCRC may be due to misdiagnosis of MSI/dMMR

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Primary resistance to CPI</th>
<th>MMS on re-evaluation</th>
<th>PPV local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>38</td>
<td>5/38</td>
<td>3/5</td>
<td>92% (75-98%)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>93</td>
<td>n.a.</td>
<td>10/93</td>
<td>90% (82-95%)</td>
</tr>
</tbody>
</table>

Re-assessment MLH1, MSH2; MSH6, PMS2; PCR HT17 assey

Cohen et al. JAMA Oncol Nov 15 2018
metastatic colorectal cancer

95%

5%
### Summary of Efficacy in Patients With MSS

**Nivolumab ± Ipilimumab in Metastatic CRC**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg (n = 10)</th>
<th>Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>2.28 (0.62, 4.40)</td>
<td>1.31 (0.89, 1.71)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>11.53 (0.62, NE)</td>
<td>3.73 (1.22, 5.62)</td>
</tr>
</tbody>
</table>

...vs 17 OS and 5.3 PFS in MSI-H pts treated with nivolumab alone...vs median not reached in MSI-H pts treated with the combo

NE = not estimable
Phase Ib: Atezolizumab + cobimetinib in MSS pretreated mCRC

**Tolerability:** No DLT, Diarrhea: 70%, rash: 40%, Fatigue: 52%, Grade 3-4 toxicities: 34% incl. diarrhea: 9%

**Efficacy:** Response 17% (4 OR, 5 SD) : 3 MSS/1 statut MSI ukn, 4 to 7 mo

Tumor Biopsy: no correlation with PDL1 at D0

Bendell JVC. et al., ASCO 2016, OS 3502
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**\(^1\)

---

**MHC**, major histocompatibility complex; **ND**, no drug (vehicle alone).

\(^1\) CT26 (KRASmt) CRC models. Ebert et al. *Immunity* 2016.
**IMblaze370: randomised, Phase III, multicentre, open-label study in mCRC**

- Unresectable locally advanced or metastatic CRC
- Received ≥ 2 prior regimens of cytotoxic chemotherapy for metastatic disease
- ECOG PS 0-1
- MSI-H capped at 5%

R 2:1:1 N=363

- Atezolizumab 840 mg IV q2w + cobimetinib 60 mg oral 21/7 days
- Atezolizumab 1200 mg IV q3w
- Regorafenib 160 mg oral 21/7 days

**Stratification**
- Extended RAS mutation status (≥ 50% patients in each arm)
- Time since diagnosis of first metastasis (< 18 months vs ≥ 18 months)

**Primary endpoint**
- OS
  - Atezo + cobi vs rego
  - Atezo vs rego

**INV-assessed key secondary endpoints**
- PFS
- ORR
- DOR

- Data cutoff date: March 9, 2018

Atezo, atezolizumab; cobi, cobimetinib; INV, investigator; rego, regorafenib.

a Two-sided type I error rate of 0.05 was controlled by hierarchical testing (testing atezo vs rego only if atezo + cobi vs rego was positive). NCT02788279.

*Bendell et al., ESMO-GI 2018*
IMblaze370: randomised, Phase III, multicentre, open-label study in mCRC

<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>

N/A, not applicable. HRs are from stratified log-rank tests.
Data cutoff: March 9, 2018. \(^a\) For descriptive purposes only.

Bendell et al., ESMO-GI 2018
Fluoropyrimidine (FP) and bevacizumab ± atezolizumab as first-line treatment for BRAF wt metastatic colorectal cancer: findings from the MODUL trial of biomarker-driven maintenance

**MODUL: Cohort 2 (1L BRAF wt)**

**Induction treatment**
- FOLFOX + bevacizumab 8 cycles (16w)
- or
- FOLFOX + bevacizumab 6 cycles (12w)
  - then 5-FU/LV + bevacizumab 2 cycles (4w)

**Biomarker-driven maintenance treatment**
- Cohort 1: BRAF wt
  - 5-FU/LV + cetuximab + vemurafenib
  - FP + bevacizumab
- Cohort 2: BRAF wt
  - FP + bevacizumab + atezolizumab
  - FP + bevacizumab
- Cohort 3: HER2+
  - Capecitabine + trastuzumab + pertuzumab
  - FP + bevacizumab
- Cohort 4: HER2- BRAF wt
  - Cobimetinib + atezolizumab
  - FP + bevacizumab

**Follow-up**

**Primary objective:** Progression-free survival (PFS; RECIST v1.1) measured from randomization in each maintenance treatment cohort

**Secondary objectives:**
- Overall survival (OS)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to treatment response (TTR)
- Duration of response (DoR)
- Change in ECOG performance status
- Safety

*Key eligibility criteria: histologically confirmed mCRC; measurable, unresectable disease (RECIST 1.1); no prior chemotherapy for mCRC; age ≥ 18 years; ECOG PS ≤ 2
*Patients with disease progression following induction treatment can receive further treatment at the discretion of their physician

*Grothey et al. ESMO 2018*
Rationale combining anti-VEGF and anti-PD1

**Immunogenic cell death**

Treatment efficacy is decreased in immunodeficient mice

- Gemcitabine (Nowak AK, Cancer Res, 2003)
- Cyclophosphamide (Van der Most RG, Plos One, 2009)
- Radiation (Lee Y, Blood, 2009)
- Anthracyclins (Casares N, JEM, 2005)
- Oxaliplatin (Ghiringhelli F, Nat Med, 2009)

**anti-VEGF immuno-modulation**

Ghiringelli et al. Nat med 2009

Ghiringelli et al. Nat med 2009
Fluoropyrimidine (FP) and bevacizumab ± atezolozumab as first-line treatment for BRAF\textsuperscript{wt} metastatic colorectal cancer: findings from the MODUL trial of biomarker-driven maintenance

Median follow-up 18.7 months

Grothey et al. ESMO 2018
• MSI-H, Mutation per Mb and PD-L1 expression all predict response to checkpoint inhibitors
• MSI / MMR status appears to be predictive for response in mCRC and other tumors
• ICI may be considered at least for 2nd line in MSI-H / dMMR GI tumors
• PD-L1 plus CTLA-4 is promising in 1st line mCRC
• Combination of PD-L1 plus conventional need to be investigated
• Validation of microsatellite testing may be necessary
Thank you for your attention