LATER-LINE MANAGEMENT OF MCRC: INDIVIDUALIZING TREATMENT AND CARE OF PATIENTS IN THE LATER-LINE SETTING

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October 19th, 2019
DISCLOSURE

Dr. Daniel Ahn does not have any relevant financial relationships to disclose.

Dr. Tanios Bekaii-Saab has the following relevant financial relationships to disclose:

• Research Funding (to institution): Boston Biomedical, Bayer, Amgen, Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Array Biopharma, Genentech, Abgenomics, Incyte, BMS
• Consulting (to institution): Ipsen, Array Biopharma, Bayer, Genentech, Incyte and Merck
• IDMC/DSMB (to self): Astra Zeneca, Exelixis, Lilly, PanCan and 1Globe
WHAT INFLUENCES TREATMENT CHOICES IN mCRC?

- Patient characteristics
  - Comorbidities
  - Age
  - Prior adjuvant treatment
  - Performance status

- Tumor characteristics
  - Tumor burden
  - Resectability
  - Tumor location

- Molecular characteristics
  - RAS
  - BRAF
  - MSI-high
  - HER2

- Therapy tailored according to individual patient needs
  - 1L
  - 2L
  - 3L
  - 4L

- Patient preference
  - Quality of life
  - Toxicity profile

MSI-high, Microsatellite instability- high

Slide credit: clinicaloptions.com
MANY OPTIONS: HOW DO WE PERSONALIZE THERAPY?

5-FU, fluorouracil; TAS-102, trifluridine+tipiracil; BSC, best supportive care
PROPORTIONAL IMPACT ON MAGNITUDE OF OS BENEFIT ACHIEVED ACROSS LINES OF THERAPY

1 L

- **FOLFIRI ± cetuximab**
  - Median OS improvement: 0.8 months
  - Not for RAS MT

- **FOLFOX4 ± panitumumab**
  - Median OS improvement: 0.83 months

- **FOLFIRI or FOLFOX/XELOX ± bevacizumab**
  - Median OS improvement: 0.89 months

2 L

- **FOLFOX ± bevacizumab**
  - Median OS improvement: 0.75 months

- **FOLFIRI ± panitumumab**
  - Median OS improvement: 0.85 months
  - Not for RAS MT

- **CT ± continued bevacizumab**
  - Median OS improvement: 0.81 months

- **FOLFIRI ± aflibercept**
  - Median OS improvement: 0.82 months

3/4 L

- **Regorafenib vs placebo**
  - Median OS improvement: 0.77 months

- **TAS102 vs placebo**
  - Median OS improvement: 0.68 months

**HR for OS**

- **FOLFIRI or FOLFOX/XELOX ± bevacizumab**
  - HR for OS: 0.81

**References**


**Median OS improvement, months**

- **FOLFIRI or FOLFOX/XELOX ± bevacizumab**
  - Median OS improvement: 0.81 months

- **TAS102 vs placebo**
  - Median OS improvement: 0.77 months

**HR for OS**

- **FOLFIRI or FOLFOX/XELOX ± bevacizumab**
  - HR for OS: 0.81

**CT, chemotherapy; HR, hazard ratio; OS, overall survival; L, line of therapy; MT, mutation; TAS-102, trifluridine+tipiracil; WT, wild type.**

**a** KRAS WT subset; P value = significant.

**b** KRAS WT subset; P value = not significant.
RAS WT MSS MCRC : DOES ANATOMICAL SIDE MATTER?
MSI, microsatellite instability; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phoshatase and tensin homolog; APC, adenomatous polyposis coli; TP53, tumor protein 53

Source: © 2017 The Ruesch Center for the Cure of GI Cancers

MSI, microsatellite instability; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; APC, adenomatous polyposis coli; TP53, tumor protein 53
CALGB/SWOG 80405: CHEMO + BEV OR CETUX - OS BY TUMOR LOCATION (RAS WT)

<table>
<thead>
<tr>
<th></th>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>Cetux (n=173 vs 71)</td>
<td>39.3</td>
<td>13.6</td>
<td>1.82 (1.27-2.56)</td>
</tr>
<tr>
<td>Bev (n=152 vs 78)</td>
<td>32.6 (28.3-36.2)</td>
<td>29.2 (22.4-36.9)</td>
<td>1.14 (0.80-1.61)</td>
</tr>
</tbody>
</table>

BEV, bevacizumab; CETUX, cetuximab; CHEMO, chemotherapy; OS, overall survival; HR, hazard ratio; WT, wild type

*Adjusted for treatment arm, protocol chemotherapy, prior adjuvant therapy, prior radiotherapy, age, sex, synchronous disease, in place primary, liver metastases
PRIMARY TUMOR LOCATION AND POTENTIAL TREATMENTS

**Right-sided**
- Anti-PD1
- MSI-H
- Bev + Triplet CT
- ↑ KRAS MT
- Bevacizumab + CT
- Anti-EGFRs + CT

**Left-sided**
- HER2+
- HER2-targeted agents
- ↑ KRAS WT
- ↑ AREG/EREG

AREG/EREG, Amphiregulin/Epiregulin; Bev, bevacizumab; CT, chemotherapy; EGFR, Epidermal growth factor receptor; MSI-H, microsatellite instability high; MT, mutation; PD1, Programmed cell death 1; WT, wild type
GENOTYPE-SPECIFIC COLORECTAL CANCER SUBPOPULATION
HERACLES: TRASTUZUMAB + LAPATINIB

- Proof of concept, open-label phase 2 trial aimed to assess the activity of trastuzumab+lapatinib in patients with HER2-positive, KRAS exon 2 WT mCRC after failure of standard therapies

- Primary endpoint: proportion of patients achieving an objective response (complete or partial response)
  - 30% patients achieved an objective response

- Trastuzumab + lapatinib= active and well tolerated in treatment refractory patients with HER2-positive mCRC

mCRC, metastatic colorectal cancer; WT, wild type
HERACLES: TRASTUZUMAB + LAPATINIB

- Best tumor response of patients treated with trastuzumab+lapatinib (A) and dynamics of response in 25 patients with HER2-positive tumours assessed with CT scans until disease progression (B)

CT, computerized tomography
## ANTI-HER2 CLINICAL TRIALS IN PATIENTS WITH REFRACTORY HER2+ mCRC

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Therapies</th>
<th>Patients HER2-positive mCRC (N)</th>
<th>Response Rate</th>
<th>TTP/PFS (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERACLES</td>
<td>Lapatinib + Trastuzumab</td>
<td>27</td>
<td>30%</td>
<td>4.9 months</td>
</tr>
<tr>
<td>MyPathway</td>
<td>Pertuzumab + Trastuzumab</td>
<td>37</td>
<td>38%</td>
<td>2.9 months</td>
</tr>
</tbody>
</table>

mCRC, metastatic colorectal cancer; PFS, progression-free survival; TTP, time to progression;
HERACLES-B (open-label phase II trial in RAS/BRAF wild-type HER2+ mCRCs) Cohort-B initiated following the results from HERACLES-A study

- **Endpoints**: ORR and Progression-Free Survival (PFS)
- **Main inclusion criteria**: ECOG PS 0-1, progression after 5FU, oxaliplatin, irinotecan, and anti-EGFR containing regimens.
- **Results**:
  - ORR = 10% [95% CI: 0-28]
  - Median PFS = 4.8 months. [95% CI: 3.6-5.8].
  - Higher HER2 IHC score (3+ vs 2+) associated with objective response ≥4 months. [p = 0.03]
- **Conclusion**:
  - HERACLES-B did not reach its primary endpoint
  - Disease control was achieved in 80% of patients with a median PFS of 4.8 months that is superimposable to the 4.2 months achieved in the positive HERACLES-A trial

5-FU, fluorouracil; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group - performance Status; mCRC, metastatic colorectal cancer; ORR, objective response rate; PFS, progression-free survival; TTP, time to progression

MOUNTAINEER study (a multicenter open-label single-arm phase II trial): Patients with RAS WT HER2+ mCRCs

Pts received tucatinib 300mg PO bid and standard doses of trastuzumab (IV, Q3 weeks).

- **Endpoints:** ORR

- **Main criteria:** Prior treatment with 5FU, oxaliplatin, irinotecan, and an anti-VEGF antibody was required. Prior anti-HER2 therapy was excluded.

- **Results:** (22 evaluable patients)
  - ORR= 55% (CR/PR= 12; SD = 5; PD = 5).
  - Clinical benefit rate (CR+PR+SD≥4 months) = 64%.
  - At a median follow-up of 10.6 months, median PFS= 6.2 months (95% CI 3.5-NE).
  - Median OS = 17.3 months (95% CI 12.3-NE).
  - There were 2 (9%) grade 3 TRAEs and no grade 4/5 TRAEs.

- **Conclusion:**
  - The combination of tucatinib and trastuzumab is well tolerated and has met its primary efficacy endpoint.
TRIUMPH study (Phase II trial)/GOZILA sub-study: Patients with central tissue and/or ctDNA confirmed wild-type RAS and HER2+ mCRC.

Patients received trastuzumab and pertuzumab

- **Endpoints:** Confirmed ORR by investigator assessment, analyzed for two primary populations: tissue-positive and ctDNA-positive

- **Results:** (median follow up : 5.4 months)
  - 6 confirmed responders in the tissue-positive group (ORR = 35%, 95% CI 14-62%; 1 CR and 5 PR) and 5 in the ctDNA positive group (ORR = 33%, 95% CI 12-62%; 1 CR and 4 PR).
  - Median progression-free survival for both groups was 4.0 months (95% CI = 1.4-5.6 months and 1.3-5.6 months, respectively).

- **Conclusion:**
  - The combination of tucatinib and trastuzumab is well tolerated and has met its primary efficacy endpoint.
**COLOMATE TRIAL (ACCRU)**

- **Metastatic CRC**
- **Prior treatment with a fluoropyrimidine, oxaliplatin, irinotecan, and anti-VEGF monoclonal antibody (bevacizumab, ramucirumab, or ziv-aflibercept)**

Note: this is a preliminary list of targets
- Targets to change based on available science and drug development opportunities

- Tucatinib + Trastuzumab

**ctDNA/ tissue screening**
- **ctDNA/ tissue screening** (n~ 1000)

- Absence of acquired KRAS, NRAS, BRAF, EGFR mutation or ERRB2/MET amplification**
  - EGFR rechallenge
  - N= 75 (15%)

- HER2 amplified
  - Anti-HER2
  - N= 25 (5%)

- MET amplified
  - Anti-MET
  - N= 75 (15%)

- EGFR mutation
  - Anti-EGFR
  - N= 50 (10%)

- FGFR
  - Anti-FGFR
  - N= 30 (?) (5%)

- No actionable change
  - SOC
  - N= 320 (65%)

**Primary endpoint:** ORR by RECIST v1.1

**Secondary endpoints:** PFS, duration of response, OS, QOL, safety and tolerability

- Other cohorts/ arms encouraged
- Each arm to have a junior/senior investigator leadership team
- Flexible design: arms open and close with best available science

**Tucatinib + Trastuzumab**

ACCRU, Academic and Community Cancer Research United; COLOMATE, Colorectal and Liquid Biopsy Molecularly Assigned Therapy; ctDNA, Circulating tumor DNA; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life; RECIST, Response evaluation criteria in solid tumors

ClinicalTrials.gov, NCT03043313

* Patients may be eligible for assignment to a treatment arm based on FFPE tumor tissue testing or blood-based testing.

** In patients who have received prior anti-EGFR therapy.
HER2 AMPLIFICATION AS A NEGATIVE PREDICTIVE BIOMARKER FOR ANTI-EGFRS: OUTCOMES

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HER2 Amp</th>
<th>HER2NA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS – Cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-EGFR based therapy in 2L/3L</td>
<td>2.9</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non anti-EGFR based therapy in 1L</td>
<td>9.7</td>
<td>10.1</td>
<td>0.848</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS – Cohort 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-EGFR based therapy in 2L/3L</td>
<td>2.8</td>
<td>9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non anti-EGFR based therapy in 1L</td>
<td>13.7</td>
<td>11.3</td>
<td>&lt;0.616</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS - Cohort 1 and 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>1.13 (0.5-2.3)</td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>median OS, HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>1.09 (0.4-2.7)</td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>median OS, HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1L/2L/3L, first line/second line/third line treatment; CI; confidence intervals; EGFRS, anti-epidermal growth factor receptors; HER2 Amp, HER2 amplification: HER2NA, HER2 non-amplified; HR, hazard ratio; PFS, progression-free survival; OS; overall survival

Raghav KPS, et al. Poster. ASCO. 2016 (abstr 3517)
## PFS AND OS IN BRAF MUT CRC PATIENTS TREATED WITH EGFR mABS

### OS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bokemeyer 2012</td>
<td>-0.478</td>
<td>0.275</td>
<td>20.7%</td>
<td>0.62 [0.36, 1.06] 2012</td>
</tr>
<tr>
<td>Douillard 2013</td>
<td>-0.105</td>
<td>0.342</td>
<td>17.0%</td>
<td>0.90 [0.46, 1.76] 2013</td>
</tr>
<tr>
<td>Karapetis 2013</td>
<td>-0.174</td>
<td>0.736</td>
<td>6.0%</td>
<td>0.84 [0.20, 3.56] 2013</td>
</tr>
<tr>
<td>Seymour 2013</td>
<td>0.61</td>
<td>0.263</td>
<td>21.5%</td>
<td>1.84 [1.10, 3.08] 2013</td>
</tr>
<tr>
<td>Peeters 2014</td>
<td>-0.446</td>
<td>0.354</td>
<td>16.4%</td>
<td>0.64 [0.32, 1.28] 2014</td>
</tr>
<tr>
<td>Stintzing 2014</td>
<td>-0.139</td>
<td>0.314</td>
<td>18.5%</td>
<td>0.87 [0.47, 1.61] 2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.91 [0.62, 1.34] 2014</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.11; \chi^2 = 10.09, df = 5 (P = 0.07); I^2 = 50\%$

Test for overall effect: $Z = 0.48 (P = 0.63)$

### PFS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bokemeyer 2012</td>
<td>-0.4</td>
<td>0.34</td>
<td>12.6%</td>
<td>0.67 [0.34, 1.31] 2012</td>
</tr>
<tr>
<td>Peeters 2013</td>
<td>-1.079</td>
<td>0.669</td>
<td>3.8%</td>
<td>0.34 [0.09, 1.26] 2013</td>
</tr>
<tr>
<td>Seymour 2013</td>
<td>0.336</td>
<td>0.273</td>
<td>17.5%</td>
<td>1.40 [0.82, 2.39] 2013</td>
</tr>
<tr>
<td>Douillard 2013</td>
<td>-0.545</td>
<td>0.351</td>
<td>12.0%</td>
<td>0.58 [0.29, 1.15] 2013</td>
</tr>
<tr>
<td>Smith 2013</td>
<td>0.131</td>
<td>0.207</td>
<td>25.1%</td>
<td>1.14 [0.76, 1.71] 2013</td>
</tr>
<tr>
<td>Karapetis 2013</td>
<td>-0.274</td>
<td>0.711</td>
<td>3.4%</td>
<td>0.76 [0.19, 3.06] 2013</td>
</tr>
<tr>
<td>Peeters 2014</td>
<td>-0.371</td>
<td>0.392</td>
<td>10.0%</td>
<td>0.69 [0.32, 1.49] 2014</td>
</tr>
<tr>
<td>Stintzing 2014</td>
<td>-0.139</td>
<td>0.297</td>
<td>15.5%</td>
<td>0.87 [0.49, 1.56] 2014</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.88 [0.67, 1.14] 2014</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.03; \chi^2 = 8.88, df = 7 (P = 0.26); I^2 = 21\%$

Test for overall effect: $Z = 0.98 (P = 0.33)$

EGFR mABs did not increase the benefit of standard therapy or BSC in BRAF-mut CRC patients.

9 Phase III trials
1 Phase II trial
→ 463 patients

BSC, best supportive care; CRC, colorectal cancer; mABs, monoclonal antibodies; MUT, mutant; OS; overall survival; PFS, progression-free survival

PATIENTS WITH BRAF-MUTANT COLORECTAL CANCER: FUTURE TREATMENT PATHWAYS

Current therapeutic approaches

- Good performance status
  - FOLFOXIRI + bevacizumab
  - FOLFOX/XELOX or FOLFIRI + bevacizumab
  - Irinotecan + cetuximab + vemurafenib
  - Consideration of clinical trial

- Advanced age or impaired performance status
  - Capecitabine or fluorouracil/LV + bevacizumab
  - FOLFOX/XELOX or FOLFIRI + bevacizumab
  - Irinotecan + cetuximab + vemurafenib
  - Consider dose modification for combination therapy
  - Consideration of clinical trial

Future Approaches

- Targeted therapy combinations
  - EGFR + BRAF inhibition?
  - Triplet BRAF + MEK + EGFR inhibition?
  - Triplet BRAF + EGFR + PI3K inhibition?

EGFR, Epidermal growth factor receptor; FOLFOX, 5-fluorouracil+leucovorin+oxaliplatin; FOLFIRI, 5-fluorouracil+leucovorin+irinotecan; FOLFOXIRI, 5-fluorouracil+leucovorin+irinotecan+oxaliplatin; LV, leucovorin; MEK, mitogen-activated kinase; PI3K, Phosphoinositide 3-kinase; XELOX, capecitabine+leucovorin+oxaliplatin

BEACON CRC: SAFETY LEAD-IN

EFFICACY RESULTS IN 29* PATIENTS WITH BRAF\textsuperscript{V600E} mCRC

• Median time on study treatment was 7.9 months (range, 1.0–11.9 months)

<table>
<thead>
<tr>
<th>Best Overall Response, n (%) (per local assessment)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=29)</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (10)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (38)</td>
</tr>
<tr>
<td>SD</td>
<td>13 (45)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable for response</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

• Preliminary estimate of median PFS is 8.0 months (95% CI, 5.6–9.3 months), with 6 of 30 patients (20%) still in follow-up and progression-free (as of Sep 2, 2018)
  – mPFS similar between patients who had 1 vs 2 previous regimens:
    8.0 months (95% CI, 5.6–9.6) vs 7.7 months (95% CI, 4.1–10.8) respectively

CI, confidence intervals; CR, complete response; mCRC, metastatic colorectal; mPFS, median progression-free survival; ORR, objective response rate; PFS, progression-free survival; PD, progression disease; PR, partial response; SD, stable disease;

*Thirty patients were enrolled in the safety lead-in BEACON study. One patient had a non-V600 mutation of BRAF (kept in safety analysis but excluded in efficacy analysis)

EFFICACY RESULTS IN 29* PATIENTS WITH BRAF\textsuperscript{V600E} mCRC

- Kaplan-Meier plots of (A) PFS (local assessment) and (B) OS.

CI, confidence intervals; NR, not reached; OS, overall survival; PFS, progression-free survival;

*Thirty patients were enrolled in the safety lead-in BEACON study. One patient had a non-V600 mutation of BRAF (kept in safety analysis but excluded in efficacy analysis). Van Cutsem E, et al. J Clin Oncol, 2019;37(17):1460-1469
A combination of encorafenib, cetuximab, and binimetinib resulted in significantly longer overall survival and a higher response rate than standard therapy in patients with mCRC with the *BRAF* V600E mutation.

CI, confidence interval; mCRC, metastatic colorectal cancer; OS, overall survival
### BEACON CRC: SECONDARY ENDPOINTS

**TRIPLET VS DOUBLET: RESULTS AND CONCLUSIONS**

<table>
<thead>
<tr>
<th></th>
<th>Triplet therapy (n=224)</th>
<th>Doublet therapy (n=220)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>9.0 (8.0-11.4)</td>
<td>8.4 (7.5-11.0)</td>
<td>0.79 (0.59-1.06)</td>
</tr>
<tr>
<td>Overall response rate, % (95% CI)</td>
<td>26 (18-35)</td>
<td>20 (13-29)</td>
<td>–</td>
</tr>
<tr>
<td>Patients with one prior therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>34 (23-47)</td>
<td>22 (14-33)</td>
<td>–</td>
</tr>
<tr>
<td>Grade ≥3 adverse events, %</td>
<td>58</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>Rate of discontinuation, %</td>
<td>7</td>
<td>8</td>
<td>–</td>
</tr>
</tbody>
</table>

There were no differences in QoL across all used instruments

Median follow up: 7.8 months

→ Triplet therapy compared to doublet therapy has some improved efficacy with a modest increase in toxicities and no detrimental effect in QoL

CI, confidence interval; HR, hazard ratio; OS, overall survival; ORR, objective response rate; QoL, quality of life
EFFICACY OF LAROTRECTINIB IN TRK FUSION–POSITIVE CANCERS

Expanded cohort with 98 new NTRK gene fusions positive patients treated with larotrectinib

**Primary endpoint**
Best objective response rate (ORR)
RECIST v1.1 per investigator assessment

**Secondary endpoints:**
Duration of response
Progression-free survival
Safety

**Dosing:**
Larotrectinib 100mg BID predominantly

**Data cut-off:** 19 February 2019

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**NCT02122913:** Phase I dose escalation study in adult with advanced solid tumours

**SCOUT: NCT02637687:**
Phase I/II dose escalation study in paediatric with advanced solid tumours

**NAVIGATE: NCT02576431:**
Phase II, open-label, basket study in adult/adolescent with advanced solid tumours and TRK fusion positive

---

BID, twice a day; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; TRK, tropomyosin receptor kinase

One patient (asterisk) had a tropomyosin receptor kinase (TRK) solvent front resistance mutation (NTRK3 G623R) at baseline owing to previous therapy.
One patient (dagger) had a pathological complete response.
Note: Data for 1 patient are not shown; the patient had clinical deterioration and no tumor measurements after baseline were recorded.
One patient (double dagger) had a missing restaging scan after the confirmed response was established, and progression-free survival was censored at 3.7 months.

mo, months; TRK, tropomyosin receptor kinase

EFFICACY OF LAROTRECTORINIB IN TRK FUSION-POSITIVE CANCERS

In the primary cohort of 55 patients
- Median follow-up = 26 months (Data cut-off: 19 February 2019)
- The median DOR in 44 patients with complete or partial responses was 35.2 months (95% CI 21.2–NE), with 17 progression events and 27 responses ongoing (range 1.6–44 months).
- The median PFS in the primary cohort was 25.8 months (95% CI 9.9–NE), with 27 patients having progressed

In the expanded combined dataset of 153 patients
- The most common tumor types= soft tissue sarcoma (n = 36), infantile fibrosarcoma (n = 29), thyroid carcinoma (n = 26), salivary gland carcinoma (n = 21), and lung cancer (n = 12).
- The overall ORR = 79% (95% CI 72–85), with complete responses in 16%
- Adverse events were primarily grade 1-2, with 13% of patients having had a grade 3-4 event related to larotrectinib.
- Only one patient discontinued due to an AE related to larotrectinib.

AE, adverse event; CI, confidence interval; DOR, duration of response; NE, not estimated; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall survival rate; PFS, progression-free survival

REGORAFENIB DOSE-OPTIMISATION IN PATIENTS WITH REFRACTORY METASTATIC COLORECTAL CANCER (ReDOS): A RANDOMISED, MULTICENTRE, OPEN-LABEL, PHASE 2 STUDY

**ReDOS DESIGN**

**Randomization**: Two distinct regorafenib dosing strategies: dose escalation (**arm A**) vs standard dose (**arm B**) + clobetasol usage (pre-emptive (1*) vs reactive (2*))

**Primary endpoint**: Proportion of patients who completed 2 cycles of treatment and initiated cycle 3 in arm A and arm B

**Secondary endpoints**: OS, PFS, TTP, cumulative dose and dose intensity received within the first 2 cycles, proportion who exhibited grade 3 PPES or fatigue, and QoL

---

**Dose escalation strategy**

<table>
<thead>
<tr>
<th>WEEK</th>
<th>C1 schedule</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>w1</td>
<td>Starting dose C1</td>
<td>80 mg</td>
</tr>
<tr>
<td>w2</td>
<td>↓</td>
<td>120 mg</td>
</tr>
<tr>
<td>w3</td>
<td>End dose C1</td>
<td>160 mg</td>
</tr>
<tr>
<td>w4</td>
<td></td>
<td>off</td>
</tr>
</tbody>
</table>

**DOSE WEEK of C2+**

| w1   | Dose from C1 |

*See the dose escalation strategy table for dosing regimen*

---

**Randomization**

1:1:1:1

(Progression on previous standard therapy, including EGFRi if KRAS WT; ECOG PS 0-1)

---

**Arm A**

- **Arm A 1**: Regorafenib
  - Start low dose*
  - + pre-emptive strategy for PPES

**Arm A 2**: Regorafenib
- Start low dose*
- + reactive strategy for PPES

---

**Arm B**

- **Arm B 1**: Regorafenib 160 mg
  - PO daily for 21 days of 28-day cycle
  - + pre-emptive strategy for PPES

**Arm B 2**: Regorafenib 160 mg
- PO daily for 21 days of 28-day cycle
- + reactive strategy for PPES

---

C1, cycle 1; C2+, cycle 2 and more; ECOG PS, Eastern Cooperative Oncology Group - performance Status; EGFRi; Epidermal growth factor receptor inhibitor; OS, overall survival; QoL, quality of life; PFS, progression-free survival; PO, oral administration (per os); PPES, Palmar-plantar erythrodysesthesia syndrome; TTP, time to progression, w1, week 1

ReDOS: PATIENT SELECTION CRITERIA

ReDOS main eligibility criteria
- ECOG ≤1
- Acceptable organ and none marrow function
- Failure of all standard intravenous regimens, including appropriate biologics

ReDOS relevant exclusion criteria
- Prior treatment with regorafenib
- History of contact dermatitis with:
  - clobetasol propionate or similarly fluorinated steroids
  - steroids with the propionate ester

Patients ≥18 years with histologically or cytologically confirmed advanced or metastatic CRC that was refractory to previous standard therapy

ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer
Primary endpoint: proportion of patients who completed 2 cycles of treatment and who initiated Cycle 3

Assuming an 8-week planned continuation rate of 45% in the standard dose (Arm B) group, and desiring an improvement to 63% (+18%) in the dose escalation (Arm A) group, a one-sided test with alpha = 0.20 and power of 80% would require a sample size of 110 patients (55 patients per group)

The primary endpoint was calculated with asymptotic Wald 95% CIs, with a one-sided Fisher’s exact test used to detect a difference between groups

Cis, confidence intervals; Bekaii-Saab TS, et.al. Lancet Oncol 2019; 20(8):1070-1082
# PATIENT DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Dose escalation group - Arm A (n=54)</th>
<th>Standard dose group - Arm B (n=62)</th>
<th>Total (n=116)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median (IQR)</td>
<td>62 (53-68)</td>
<td>61 (53-68)</td>
<td>61 (53-68)</td>
<td>0.9010</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.2601</td>
</tr>
<tr>
<td>Female</td>
<td>18 (33%)</td>
<td>27 (44%)</td>
<td>45 (39%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (67%)</td>
<td>35 (56%)</td>
<td>71 (61%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td>0.9947</td>
</tr>
<tr>
<td>0</td>
<td>20 (37%)</td>
<td>23 (37%)</td>
<td>43 (37%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34 (63%)</td>
<td>39 (63%)</td>
<td>73 (63%)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor status</td>
<td></td>
<td></td>
<td></td>
<td>0.3015</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>Resected</td>
<td>37 (69%)</td>
<td>44 (71%)</td>
<td>81 (70%)</td>
<td></td>
</tr>
<tr>
<td>Unresected</td>
<td>13 (24%)</td>
<td>17 (27%)</td>
<td>30 (26%)</td>
<td></td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td></td>
<td></td>
<td></td>
<td>0.2096</td>
</tr>
<tr>
<td>1</td>
<td>6 (11%)</td>
<td>2 (3%)</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12 (22%)</td>
<td>18 (29%)</td>
<td>30 (26%)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>36 (67%)</td>
<td>42 (68%)</td>
<td>78 (67%)</td>
<td></td>
</tr>
<tr>
<td>BRAF mutation status</td>
<td></td>
<td></td>
<td></td>
<td>0.7485</td>
</tr>
<tr>
<td>Mutated</td>
<td>0</td>
<td>2 (3%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Wild Type</td>
<td>17 (31%)</td>
<td>20 (32%)</td>
<td>37 (32%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (69%)</td>
<td>40 (65%)</td>
<td>77 (66%)</td>
<td></td>
</tr>
<tr>
<td>KRAS mutation status</td>
<td></td>
<td></td>
<td></td>
<td>0.1486</td>
</tr>
<tr>
<td>Mutated</td>
<td>21 (39%)</td>
<td>34 (55%)</td>
<td>55 (47%)</td>
<td></td>
</tr>
<tr>
<td>Wild Type</td>
<td>31 (57%)</td>
<td>27 (44%)</td>
<td>58 (50%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>3 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group – performance status; IQR, interquartile range
PHASE II ReDOS STUDY: PERCENTAGE OF PATIENTS STARTING CYCLE 3 (PRIMARY ENDPOINT)

PRIMARY ENDPOINT MET

**Fisher's exact test (1-sided)**


- **Arm A (Escalating dose)**: 37% PD, P = 0.043
- **Arm B (Standard dose)**: 47% PD

PD, progressive disease

*Fisher’s exact test (1-sided)*
PHASE II ReDOS STUDY: OS (SECONDARY ENDPOINT)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS</th>
<th>HR &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (dose escalation)</td>
<td>9.8 months</td>
<td>0.72, 95% CI 0.47-1.10 p=0.12</td>
</tr>
<tr>
<td>Arm B (standard dose)</td>
<td>6.0 months</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; OS, overall survival.
## OS IN ReDOS AND CORRECT

<table>
<thead>
<tr>
<th>ReDOS study</th>
<th>Median OS (95% CI)</th>
<th>HR &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekaii-Saab TS, et al. 2019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A (dose escalation group, n=54)</td>
<td>9.8 months (7.5-11.9)</td>
<td>0.72, 95% CI 0.47-1.10</td>
</tr>
<tr>
<td>Arm B (standard dose group, n=62)</td>
<td>6.0 months (4.9-10.2)</td>
<td>p=0.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CORRECT study</th>
<th>Median OS (IQR)</th>
<th>HR &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose group (regorafenib 160 mg, n=505)</td>
<td>6.4 months (3.6-11.8)</td>
<td>0.77, 95% CI 0.64-0.94 p=0.0052</td>
</tr>
<tr>
<td>Placebo group (n=255)</td>
<td>5.0 months (2.8-10.4)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OS, overall survival.

OS in patients who initiated cycle 3:

- 17 events in 23 patients in the dose-escalation group vs
- 5 events in 16 patients in the standard-dose group

→ No significant differences observed in overall survival

OS, overall survival.
SENSITIVITY ANALYSIS FOR EFFECT OF KRAS MUTATION STATUS ON OS

• The proportion of patients with a KRAS-mutant tumor was lower in escalating dose group; arm A (39%) compared with standard dose group: arm B (55%). There was a concern whether it impacted OS.

• A proportional hazard model was used to perform an adjusted post-hoc analysis. The time-to-event variable was OS and the variables included in the model were arms (arm A vs B) and KRAS mutation status (wild-type vs mutant). The adjusted hazard ratio of OS for arm A vs arm B was 0.742 (95% CI 0.478–1.151; p=0.18). The KRAS variable was not a significant covariate (p=0.95).

→ KRAS mutation did not appear to affect overall survival
PHASE II ReDOS STUDY: PFS (SECONDARY ENDPOINT)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS</th>
<th>HR &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (dose escalation)</td>
<td>2.8 months</td>
<td>0.84, 95% CI 0.57-1.24, p=0.38</td>
</tr>
<tr>
<td>Arm B (standard dose)</td>
<td>2.0 months</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; PFS, progression-free survival.
PHASE II ReDOS STUDY: OVERALL QoL (SECONDARY ENDPOINT)

LASA=Linear Analogue Self-Assessment; QoL, quality of life.
<table>
<thead>
<tr>
<th>n (%)</th>
<th>Dose escalation group (n=54)</th>
<th>Standard dose group (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>8 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms: benign, malignant, unspecified, other (specified)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Colonic obstruction</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

AEs, adverse events


Note: in bold grade 3 adverse events commonly associated with regorafenib treatment
PHASE II ReDOS STUDY: SWIMMER PLOT OF DOSING HISTORY

Regorafenib dose escalation group (n=54)

PHASE II ReDOS STUDY: SWIMMER PLOT OF DOSING HISTORY

Regorafenib standard dose group (n=62)

A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF REGORAFENIB AND TAS-102 IN REFRACTORY mCRC

Regorafenib 160 mg and TAS-102 appear to have similar efficacy in refractory metastatic colorectal cancer

A dose escalation strategy of regorafenib (Rego 80 mg) is superior to BSC

A trend for improved OS was observed with dose escalation strategy (Rego 80 mg) vs. Rego 160 mg or TAS 102

<table>
<thead>
<tr>
<th>Network meta-analysis for OS and PFS</th>
<th>HR, 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rego 80 mg vs. BSC</td>
<td>OS: 0.44, 0.23-0.84 PFS: 0.37, 0.21-0.65</td>
<td>0.01 0.001</td>
</tr>
<tr>
<td>Rego 80 mg vs. Rego 160 mg</td>
<td>OS: 0.65, 0.36-1.15 PFS: 0.89, 0.54-1.45</td>
<td>0.14 0.71</td>
</tr>
<tr>
<td>Rego 80 mg vs. TAS-102</td>
<td>OS: 0.65, 0.33-1.27 PFS: 0.83, 0.45-1.52</td>
<td>0.21 0.55</td>
</tr>
<tr>
<td>Rego 160 mg vs. TAS-102</td>
<td>OS: 1.00, 0.72-1.41 PFS: 0.93, 0.66-1.32</td>
<td>0.95 0.71</td>
</tr>
<tr>
<td>Rego 160 mg vs. BSC</td>
<td>OS: 0.67, 0.48-0.93 PFS: 0.40, 0.26-0.63</td>
<td>0.02 &lt;0.0001</td>
</tr>
<tr>
<td>TAS-102 vs. BSC</td>
<td>OS: 0.67, 0.57-0.80 PFS: 0.46, 0.40-0.52</td>
<td>&lt;0.00001 &lt;0.001</td>
</tr>
</tbody>
</table>

BSC, best supportive care; CI, confidence interval; mCRC, metastatic colorectal cancer OS, overall survival; PFS, progression-free survival; rego, regorafenib

Treatment is predicated on therapies the patient received or is intolerant to in prior lines. NCCN has recently incorporated tumor location ("sidedness") into the guidelines for first-line therapy options and recommends anti-EGFR therapy in patients with RAS WT mCRC with left-sided tumors only.

Regorafenib should be considered as soon as the patient has been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy (if RAS WT).

*Biologic = bevacizumab, or cetuximab or panitumumab (RAS WT only).
**Single agent panitumumab or cetuximab in patients intolerant to irinotecan.
***if no previous treatment with a checkpoint inhibitor
PHASE II ReDOS STUDY: CONCLUSIONS

• A strategy with weekly dose escalation of regorafenib from 80 mg/day to 160 mg/day was found to be superior to a starting dose of 160 mg/day

• A trend for improved OS was seen in the dose escalation group (the difference for OS between the two groups was not statistically significance)

• At 2-weeks from initiation of therapy, the dose escalation strategy did not appear to compromise QOL unlike the standard dose administration

• These results potentially establish a new standard for optimizing regorafenib dosing through a dose escalation strategy

• A preemptive strategy with CL may decrease the risk of HFSR warranting further investigation

• Further data on PK analysis will be presented at a later meeting

CL, clobetasol; HFSR, hand-foot skin reaction; OS, overall survival; PK, pharmacokinetic; QOL, quality of life
MISMATCH REPAIR STATUS IN CRC
PEMBROLIZUMAB (ANTI–PD-1) IN MMRD CRC

• Eligibility for cohorts A and B:
  – Metastatic or locally advanced CRC, with or without dMMR (defined as: deficiency in MLH1, MSH2, MSH6 or PMS2 by IHC, or MSI in ≥ 2 loci by PCR)
  – ≥ 2 previous cancer therapy regimens
  – ECOG PS ≤ 1
  – No previous checkpoint inhibitor therapy

• Treatment: pembrolizumab 10 mg/kg Q2W

• MMR testing using standard PCR-based assay for detection of MSI

• Coprimary endpoints: immune-related ORR and the 20-week immune-related PFS

Cohort A (n=11) MMRD CRC
Cohort B (n=21) MMRP CRC
Cohort C (n=9) MMRD non-CRC

CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group - performance status; ICH, Immunohistochemistry; MLH, MutL homolog 1; MMR, mismatch repair; MMRD, Mismatch repair deficient; MMRP, mismatch repair-proficient; MSH, MutS protein homolog; MSI, microsatellite instability; ORR, objective response rate; PCR, polymerase chain reaction; PFS, progression-free survival; PMS2, postmeiotic segregation increased 2 (Mismatch repair endonuclease); Q2W, every 2 weeks

# PEMBROLIZUMAB IN MMRD/P CRC: EFFICACY

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MMRD CRC (n=10)</th>
<th>MMRP CRC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, months</td>
<td>9.3</td>
<td>6</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>40 (12-74)</td>
<td>0 (0-19)</td>
</tr>
<tr>
<td>Response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• PR</td>
<td>40 (0-100)</td>
<td>0</td>
</tr>
<tr>
<td>• SD (Wk 12)</td>
<td>50 (0-100)</td>
<td>11 (0-100)</td>
</tr>
<tr>
<td>• PD</td>
<td>10 (0-100)</td>
<td>61 (0-100)</td>
</tr>
<tr>
<td>• NE (no 12-wk scan)</td>
<td>0</td>
<td>28 (0-100)</td>
</tr>
<tr>
<td>Disease control rate, % (95% CI)</td>
<td>90 (55-100)</td>
<td>11 (1-35)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>NR</td>
<td>2.2 (1.4-2.8)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR</td>
<td>5.0 (3.0-not estimable)</td>
</tr>
</tbody>
</table>

- MMRR status predicted clinical benefit of immune checkpoint blockade with pembrolizumab

CI, confidence intervals; CR, complete response; CRC, colorectal cancer; MMRD, Mismatch repair deficient; MMRP, mismatch repair-proficient; NE, not evaluated; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progression disease; PR, partial response; SD, stable disease

PEMBROLIZUMAB IN 12 DIFFERENT TUMOR TYPES: SURVIVAL AND CLINICAL RESPONSE

86 patients enrolled

SLD, sum of longest diameters
PEmbrolizumab in 12 Different Tumor Types: PFS and OS

- Neither median PFS nor median OS has yet been reached
- Estimates of PFS at 1- and 2-years = 64% and 53%
- Estimates of OS at 1- and 2-years = 76% and 64%

→ MMRD cancer = sensitive to immune checkpoint blockade regardless of the cancers tissue of origin

MMRD, Mismatch repair deficient; OS, overall survival; PFS, progression-free survival
PHASE II CHECKMATE-142: NIVOLUMAB ± IPILIMUMAB IN MMRD/MSI-H mCRC: DESIGN AND ENDPOINTS

- 119 patients with MMRD/MSI-H mCRC treated with the following main eligibility criteria: ECOG PS= 0-1; disease progression after ≥1 prior systemic treatment including a fluoropyrimidine and oxaliplatin or irinotecan

- Primary endpoint: ORR per investigator (RECIST v1.1)
- Secondary endpoint: ORR per BIRC
- Exploratory endpoints: safety, tolerability, PFS, OS, biomarkers

BIRC, Blinded Independent Review Committee; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group - performance status; Ipi, Ipilimumab; mCRC, metastatic colorectal cancer; MMRD, mismatch repair deficiency; MSI-H, microsatellite instability high; Nivo, nivolumab; ORR, objective response rate; OS, overall survival;
PFS, progression-free survival: Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST, Response evaluation criteria in solid tumors

# PHASE II CHECKMATE-142: NIVOLUMAB ± IPILIMUMAB IN MMRD/MSI-H mCRC:
RESPONSE AND TREATMENT EXPOSURE

<table>
<thead>
<tr>
<th>Response</th>
<th>Nivo 3 mg/kg + Ipi 1 mg/kg (n=119)</th>
<th>Parameter</th>
<th>Nivo 3 mg/kg + Ipi 1 mg/kg (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>55 (45.2-63.8)</td>
<td>Mean no. doses received</td>
<td>24 of Nivo 4 of Ipi</td>
</tr>
<tr>
<td>• CR, %</td>
<td>3</td>
<td>Continuing treatment, %</td>
<td>63</td>
</tr>
<tr>
<td>• PR, %</td>
<td>51</td>
<td>Discontinued treatment, %</td>
<td>37</td>
</tr>
<tr>
<td>• Stable disease, %</td>
<td>31</td>
<td>Reasons for discontinuation</td>
<td></td>
</tr>
<tr>
<td>• PD, %</td>
<td>12</td>
<td>• PD, %</td>
<td>19</td>
</tr>
<tr>
<td>• Not determined/reported, %</td>
<td>3</td>
<td>• TRAE, %</td>
<td>13</td>
</tr>
<tr>
<td>Median TTR, months (range)</td>
<td>2.8 (1-14)</td>
<td>• AE, unrelated to study drug, %</td>
<td>2</td>
</tr>
<tr>
<td>Median duration of response, months (range)</td>
<td>NR (NE-NE)</td>
<td>• Death, %</td>
<td>1</td>
</tr>
<tr>
<td>DCR for ≥ 12 wks, % (95% CI)</td>
<td>80 (71.5-86.6)</td>
<td>• Patient withdrawal, %</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Loss to follow-up, %</td>
<td>1</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence intervals; CR, complete response; CRC, colorectal cancer; DCR, disease control rate; Ipi, ipilimumab; MMRD, Mismatch repair deficient; MSI-H, microsatellite instability high; NE, not estimable; Nivo, nivolumab; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; TRAE, treatment-related adverse event; TTR, time to response

NIVOLUMAB ± IPILIMUMAB IN MSI-H COLON CANCER: BEST REDUCTION IN TARGET LESION SIZE

Investigator-Assessed Response With Nivo Monotherapy (n = 74)
- ORR: 31%
- 62% of pts had a reduction in tumor burden from baseline
- Median TTR: 2.8 mos
- Median DoR: not reached; 83% (19/23) responses ongoing

Best Reduction in Target Lesion Size With Nivo + Ipi
- 80% of pts had a reduction in tumor burden from baseline

* Confirmed CR or PR per investigator

% Change truncated at 100

OPEN QUESTIONS IN MSI-H CRC

• Optimal pt selection?
  – PD-L1 expression levels?
  – Gene expression profile (TML)
• Monotherapy or combination with CTLA4 inhibitors?
• Duration of immunotherapy?
• Role of checkpoint inhibitors in the adjuvant setting?
• Enhancing role in MSS tumors

CRC, colorectal cancer; CTLA4, cytotoxic T-lymphocyte-associated protein 4; MSI-H, microsatellite instability high; MSS, microsatellite stable; PD-L1, Programmed death-ligand 1; TML, tumor mutational load
CRC: TREATMENT PARADIGM 2019

**R SIDE:** CHEMO + BEV

**L SIDE:** CHEMO + BEV OR ANTI-EGFR

**MSI-H:** IO TRIAL

**BRAF-mut:** FOLFOXIRI + Bev

**CHEMO:**
Plus BIOLOGIC
Anti-VEGF or Anti-EGFR

**BRAF-mut:**
Eco+Bin+Cet

Test HER-2 NTRK fusions

**If BBP then:**
FOLFIRI + anti-EGFR

**HER-2 overexpressed:**

➔ TRIAL

*May exclude EGFRi

**TAS-102**
Regorafenib as administrated in ReDOS

**Phase 1**
Other actionable mutation

BBP, bevacizumab beyond first progression; Bev, bevacizumab; Bin, binimetinib; Cet, cetuximab; CHEMO, chemotherapy; CRC, colorectal cancer; CTLA4, L side, Left side; Eco, encorafenib; EGFR, epidermal growth factor receptor; EGFRi, epidermal growth factor receptor inhibitor; FOLFIRI, 5-fluorouracil+leucovorin+irinotecan; FOLFOXIRI, 5-fluorouracil+leucovorin+irinotecan+oxaliplatin; MSI-H, microsatellite instability high; MSS, microsatellite stable; mut, mutant; NTRK, neutrophil tropomyosin receptor kinase; R side, right side; TAS-102, Trifluridine/tipiracil; VEGF, vascular endothelial growth factor
CONCLUSION

- Survival of patients with mCRC has significantly improved in the last decade
- Survival gains are not driven by advances in first-line therapy, but by incremental additions of effects of subsequent treatment lines
- In order to maximize outcomes, patients should receive all active agents
- Based on their tumor genomic profile, biomarker based therapies may result in improved patient outcomes
THANK YOU