Contra:
Molecular Profiling for Every GI Cancer Patient

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DISCLOSURE INFORMATION
GERALD PRAGER

- Advisory Board Meetings / Symposiums: Merck Serono, Roche, Amgen, Sanofi, Lilly, Servier, Taiho, Bayer, Halozyrne, BMS, Celgene, Shire

- Institutional financial interests – Clinical trials: Celgene, Array, Servier, Bayer, BostonBiomedical, Merck, BMS
- The arguments discussed here DO NOT necessarily represent my personal opinion.
BIOMARKER OUT OF DISCUSSION

Gastric: HER-2

mCRC: RAS
Targeting Tumor using different approaches:

**IMMUNOTHERAPY**

- **New Paradigm:** Targeting Immune Cells
- Lymphocyte

**TARGETED THERAPY**

- **Historical Paradigm:** Targeting Tumor Cells
- Tumor Cell
IMMUNOTHERAPY

Potential Biomarker:
PD-L1 expression
MSI/MMR
KEYNOTE-059 trial: Maximum Percentage Change From Baseline in Target Lesion Size

Patients With Reduction, %

- All patients: 42.4%
- PD-L1 positive: 47.3%
- PD-L1 negative: 36.3%

*Only patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 postbaseline assessment were included (n = 223)

Data cutoff: January 16, 2017

KEYNOTE-062: Pembrolizumab+Chemo vs Chemo

Key Eligibility Criteria
- Locally advanced, unresectable or metastatic gastric or gastroesophageal adenocarcinoma
- HER2/neu negative, PD-L1-positive disease (CPS ≥1)
- ECOG PS 0 or 1

Stratification Factors
- Region
  - Region a: EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America)
- Locally advanced or metastatic disease
- 5-FU or Capecitabine

Primary endpoints: OS and PFS
Secondary endpoints: ORR, Safety

Pembrolizumab 200 mg Q3W for up to 35 cycles
Pembrolizumab 200 mg Q3W (to 35 cycles) + Chemotherapy
Placebo + Chemotherapy

R (1:1:1)
N = 763

N = 256
N = 257
N = 250

Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

aEU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
bAdministration of pembrolizumab monotherapy was not blinded.
cChemotherapy: Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m²/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).
Overall Survival: P+C vs C (CPS ≥10)

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>76%</td>
<td>0.85</td>
<td>0.158</td>
</tr>
<tr>
<td>Chemo</td>
<td>83%</td>
<td>(0.62-1.17)</td>
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Median (95% CI)
- 12.3 mo (9.5-14.8)
- 10.8 mo (8.5-13.8)

12-mo rate
- Pembro + Chemo: 51%
- Chemo: 47%

24-mo rate
- Pembro + Chemo: 28%
- Chemo: 22%

Data cutoff: March 26, 2019.
FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed ..... 

This is the FDA’s first tissue/site-agnostic approval.
Non-randomized Phase II trials

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

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

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**Figure 1. CheckMate 142 NIVO3 + IPI1 1L cohort study design**

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

NIVO3 Q2W + IPI1 Q6W

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4 Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; 5 Patients with a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.

BICR, blinded independent central review; CRC, colorectal cancer; DCR, disease control rate; IPI1, ipilimumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
Checkmate-142: NIVO3 + IPI1, first-line
78% Disease Control Rate;
58% Response Rate (centrally assessment)

Randomized prospective Phase 3 trial results are still pending (Keynote-177)

Chemotherapy in 1st line

<table>
<thead>
<tr>
<th>Trial</th>
<th>ORR</th>
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<tr>
<td>FIRE-3 (RAS w.t.)</td>
<td>59%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
</tr>
<tr>
<td>FIRE-3(RAS w.t.)</td>
<td>65%</td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
</tr>
<tr>
<td>TRIBE-2</td>
<td>61%</td>
</tr>
<tr>
<td>VOLFI</td>
<td>87%</td>
</tr>
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1 not selected for MSI status
Summary: Biomarker for IOs in GI Cancer

• PD-L1 is a weak and likely the wrong biomarker for immunotherapy in GI cancer
  • PD-L1 negative patients might benefit from IOs
  • Not every patient with PD-L1 expression do benefit from anti-PD-1 treatment
  • PD-L1 expression is useless in colorectal cancer

• MSI-H/dMMR is a reliable and reproducible biomarker to predict a clinical benefit from IOs in mCRC
  • Results from prospective randomized trials are still pending
  • Also MSS/pMMR patients with (upper) GI cancer might have a benefit from IOs
Targeting Tumor using different approaches:

**IMMUNOTHERAPY**

**New Paradigm:** Targeting Immune Cells

- Lymphocyte

**TARGETED THERAPY**

**Historical Paradigm:** Targeting Tumor Cells

- Tumor Cell
POLO-Trial: Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

Talia Golan et al.; June 2, 2019
DOI: 10.1056/NEJMoa1903387
POLO-Trial: Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

BRCA testing in pancreatic cancer can assist clinicians in genetic counselling

• Does olaparib also work in BRCA w.t. patients?
• Do we need to test for BRCA, if overall survival is not improved?
BRAF Mutation

- 5 - 10% of mCRC
- associated with MSI
- \textit{RAS} und \textit{BRAF} mutation are widely exclusive
- \textit{BRAF} is prognostic
- Predictive role is uncertain
VOLFI-trial: Deepness of response (DpR) and molecular profile via central assessment

All Patients

BRAF mutated tumors

BRAF-mutation seems not to predict response

Modest et al., J Clin Oncol 37, 2019 (suppl; abstr 3530) – Poster Session
TRIBE - KRAS/ BRAF Status

BRAF-mutation seems not to predict response

Falcone A et al. JCO 2013; 31 (Suppl; abstr 3505)
BEACON trial design, clinical phase III in BRAF V600E

Figure 1. BEACON CRC Trial Schema

Patients with \textit{BRAF}^{V600E}-mutant mCRC

Safety Lead-in Completed

Phase 3 Currently Enrolling

Randomization 1:1:1

- Dose-determining cohort n=9

- Dose expansion cohort n=21

- Triplet Therapy
  Binimetinib + encorafenib + cetuximab n=205
  Disease progression

- Doublet Therapy
  Encorafenib + cetuximab n=205
  Disease progression

- Control Arm
  FOLFIRI + cetuximab, or irinotecan + cetuximab n=205
  Disease progression

Continued follow-up for evaluation of OS

\textit{mCRC} = metastatic colorectal cancer; \textit{FOLFIRI} = 5-fluorouracil/leucovorin/irinotecan; \textit{OS} = overall survival.
BEACON Trial: clinical phase 3 trial, safety-in phase (n=28)

FDA Grants Novel Triplet Breakthrough Designation in BRAF+ mCRC
NOT approved by EMA

mCRC=metastatic colorectal cancer
Excludes 1 patient with BRAF*V600E mutation who did not have a postbaseline measurement.
*Patients with lymph node disease in short axis dimensions consistent with RECIST version 1.1-defined complete response.
*Patients had unconfirmed partial response.
HER-2 in mCRC: The HERACLES Trial *

HER2 amplification is a driver of resistance to cetuximab in mCRC patient-derived xenografts (xenopatients)

Bertotti A. et al, Cancer Discovery 2011
HERACLES treatment and assessments

Therapy with:
- **Trastuzumab** iv 4mg/kg load and then 2mg/kg qw
- **Lapatinib** po 1000 mg/qd

**Tumor assessments**
- CE-CT scan: baseline, q8 weeks, until progression

**Translational assessments**
- HER2 ctDNA (plasma): baseline, q2 weeks, and at progression
- HER2 ECD (serum): baseline, q8 weeks, and at progression
- NGS Custom Panel (plasma, tumor tissue): baseline and at progression

PD: re-biopsy if possible
Responses by HER2 IHC Score

*3 patients are not shown: 122026 (IHC 2+), not assessed yet; 121011 (IHC 3+) and 121013 (IHC 3+) early clinical PD.
• Tumour **BRAF** mutation status should be assessed alongside the assessment of tumour **RAS** mutational status for **prognostic assessment** (and/or potential selection for clinical trials) [I, B].

• **MSI testing** in the metastatic disease setting can assist clinicians in **genetic counselling** [II, B]. MSI testing has strong **predictive value** for the use of immune check-point inhibitors (pembrolizumab) in the treatment of patients with mCRC [II, B]

• Evaluation of **HER2** amplification or HER2 activating mutations is **currently not recommended** outside clinical research.

• Evaluation of **HER3**, and **MET receptor** overexpression is **not recommended** [IV, D]

• Detection of mutations in **PIK3CA**, exon 20 is optional [II, D].

• Evaluation of **PTEN** loss by IHC is **not recommended** [V, D].

• Evaluation of the levels of the **EGFR ligands** amphiregulin, epi/regulin and transforming growth factor-α, is **not recommended** [II, D].

• Evaluation of levels of **EGFR protein** expression is **not recommended** [II, E].
Patients whose treatment was nonadherent with treatment guidelines (NCCN; n = 117) had
- A 3.55-fold increased risk of death within 1 year compared with patients who had guideline-adherent therapy (n = 560)
- The effect remained significant in years 2-5

Risk of Death for Nonadherent vs Adherent

- Year 1: 3.55-fold increased risk of death
- Year 2-5: 1.8-fold increased risk of death

Thank you!