IMMUNOTHERAPY IN METASTATIC COLORECTAL CANCER (mCRC)

SHASHANK CINGAM, MD
UNM Comprehensive Cancer Center, Albuquerque, NM

October 18th, 2019
Dr. Shashank Cingam does not have any relevant financial relationship to disclose.
WHY THE NEED FOR NEWER/INVESTIGATIONAL THERAPIES IN mCRC?

- Third leading cause of cancer related mortality in both men/women in US\(^1\)
- Approximate **51,020 deaths during 2019**\(^1\)
- Poor 5 year survival with mCRC (SEER data: -14.2% - <65 years; 7.4% - >65 years)\(^2\)
- Paucity of targetable / actionable mutations
- Limited options after failure of standard chemotherapy

---

mCRC, metastatic colorectal cancer; SEER, Surveillance, Epidemiology, and End Results;

IMMUNOTHERAPY

- Immune checkpoint inhibitors (PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, IDO1 inhibitors, anti-LAG3 antibodies)
- Immune stimulatory (anti-OX40 agonists, TLR-9 agonists)
- Vaccines
- Oncolytic viruses
- Other agents (dual A_{2a}R/A_{2b}R antagonists)

A_{2a}R, adenosine 2a receptor; A_{2b}R, adenosine 2b receptor; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; IDO1, Indoleamine-pyrrole 2,3-dioxygenase; LAG3, Lymphocyte-activation gene 3; TLR-9, Toll-like receptor 9
CHECKPOINT INHIBITORS

- Available agents for commercial use:
  - PD-1 inhibitors Nivolumab, Pembrolizumab; Cemiplimab
  - PD-L1 inhibitors Atezolizumab, Durvalumab, Avelumab
- Poor response in Nivolumab and Pembrolizumab in unselected mCRC patients in Phase 1 studies
- Better responses in patients with Microsatellite Instability–High (MSI-H) or Mismatch Repair Deficient (dMMR)

**NCT01876511: clinical responses to Pembrolizumab treatment**

# Ongoing mCRC PD-1/PD-L1 Inhibitor Trials as Monotherapy/Adjuvant Setting

<table>
<thead>
<tr>
<th>Title</th>
<th>Identifier</th>
<th>Phase</th>
<th>MMR/ MSI status</th>
<th>Therapy Line</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of Pembrolizumab (MK-3475) vs Standard Therapy in Participants With Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Stage IV Colorectal Carcinoma (KEYNOTE-177)</td>
<td>NCT02563002</td>
<td>Phase 3</td>
<td>dMMR</td>
<td>Refractory</td>
<td>Pembrol, SOC</td>
</tr>
<tr>
<td>Study of Pembrolizumab (MK-3475) as Monotherapy in Participants With Previously-Treated Locally Advanced Unresectable or Metastatic Colorectal Cancer (KEYNOTE-164)</td>
<td>NCT02460198</td>
<td>Phase 2</td>
<td>dMMR</td>
<td>Refractory</td>
<td>Pembrol, SOC</td>
</tr>
<tr>
<td>Phase II Study to Evaluate the Efficacy of MEDI4736 (Durvalumab) in Immunological Subsets of Advanced Colorectal Cancer</td>
<td>NCT02227667</td>
<td>Phase 2</td>
<td>dMMR</td>
<td>Refractory</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>Avelumab Plus 5-FU Based Chemotherapy as Adjuvant Treatment for Stage 3 MSI-High or POLE Mutant Colon Cancer (POLEM)</td>
<td>NCT03827044</td>
<td>Phase 3</td>
<td>dMMR</td>
<td>First Line/Adjuvant setting</td>
<td>Adjuvant Avelumab, No intervention</td>
</tr>
</tbody>
</table>

5-FU, Fluorouracil; dMMR, Mismatch Repair Deficient; MSI-H, Microsatellite Instability-High; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; Pembro, Pembrolizumab; SOC, standard of care
RESISTANCE MECHANISMS TO IMMUNE CHECKPOINT INHIBITORS

FORMATION OF TUMOR REACTIVE CELLS (1/2)

- Resistance
  1. Lack of suitable neoantigen
  2. Impaired intra-tumoural immune infiltration

- Promising solutions
  • promote immunogenic cell death
    - Chemotherapy and Radiotherapy
    - Targeted therapy
    - Ablative therapies
    - TRAIL-R agonists and TNFSF

REGORAFENIB + NIVOLUMAB – (PHASE IB): DESIGN AND ENDPOINTS

• **Background**: TAMs may contribute to resistance to anti-PD-1/PD-L1 inhibitors. Regorafenib, a broad spectrum tyrosine kinase inhibitor, reduced TAMs in tumor models\(^1\)

• **REGONIVO**: Open-label, dose-finding and dose-expansion Phase 1b trial

• 50 previously treated patients enrolled with advanced gastric cancer (n=25) or advanced CRC (n=25)

• Regorafenib (80 to 160 mg) was administered once daily for 3 weeks on/1 week off, with nivolumab (3 mg/kg) given every 2 weeks

• **Primary endpoint**: dose-limiting toxicity during cycle one (4 weeks) to estimate the maximum tolerated dose and the recommended dose

---

CRC, colorectal cancer; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; TAMs, tumor-associated macrophages

REGORAFENIB + NIVOLUMAB – (PHASE IB): RESULTS

- Manageable safety and encouraging anti-tumor activity
- These results warrant further investigation of this combination in a larger cohort

**Progression-free survival in all patients (A) and in patients with CRC and GC (B)**

- All patients: Median 6.3 months (95%CI 3.4-9.3)
- Colorectal: Median 6.3 months
- Gastric: Median 5.8 months

**Anti-tumor activity**

- 77-year-old mal with RAS WT metastatic rectum cancer
- Disease progression after FOLFIRI+Bevacizumab, FOLFOX, Irinotecan+cetuximab, trifluridine/tipiracil
- MSS, PD-L1 CPS 0

CRC, colorectal cancer; GC, gastric cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable; ORR, objective response rate; PD, progressive disease; PD-L1, Programmed death-ligand 1; PR, partial response; SD, stable disease; WT, wild-type

RESISTANCE MECHANISMS TO IMMUNE CHECKPOINT INHIBITORS

FORMATION OF TUMOR REACTIVE CELLS (2/2)

- Resistance
  - Impaired processing and/or presentation of tumor antigens

- Promising solutions
  - Enhance APC/APC function and adjuvanticity
    - Vaccine therapy
    - Immune adjuvants
    - Toll like receptors
    - Interferon
    - GM-CSF
    - CD-40

APC, antigen presenting cell; β2M, β2 microglobulin; CD-40, Cluster of differentiation 40; GM-CSF, Granulocyte-macrophage colony-stimulating factor; MHC, Major histocompatibility complex; TCR, T cell receptor

RESISTANCE MECHANISMS TO IMMUNE CHECKPOINT INHIBITORS

ACTIVATION OF EFFECTOR T-CELL FUNCTION

• Resistance
  4. Impaired IFNγ signaling
  5. Metabolic/Inflammatory mediators
  6. Immune suppressive cells
  7. Alternate Immune Checkpoints

• Promising solutions
  – IDO1 Inhibitors (indoximod, epacadostat)
  – Anti-LAG 3 antibodies
  – TIM3 inhibitors
  – PI3K inhibitors

Arg1, arginase 1; β2M, β2 microglobulin; CTLA4, Cytotoxic T lymphocyte antigen 4; IDO, indolamine dioxygenase; INF, interferon; JAK1, janus kinase 1; LAG-3, Lymphocyte-activation gene 3; M2 Mφ, M2 macrophage; MHC, Major histocompatibility complex; MDSC, myeloid derived suppressor cell; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PI3K, Phosphoinositide 3-kinases; PGE2, TCR; T cell receptor; TIM3, T-cell immunoglobulin and mucin-domain containing-3; Tregs, regulatory T cells

RESISTANCE MECHANISMS TO IMMUNE CHECKPOINT INHIBITORS

FORMATION OF EFFECTOR OF MEMORY T-CELLS

• Resistance
  8. Severe T Cell exhaustion
  9. T-Cell epigenetic changes

• Promising solutions
  - Hypomethylating agents
  - HDAC inhibitors

CD4+, cluster of differentiation 4 positive cell; CD8+, cluster of differentiation 8 positive T cell; HDAC, Histone deacetylases; MHC, Major histocompatibility complex; PD-1, Programmed cell death protein 1; TCR, T cell receptor;
THE CLINICAL TRIAL LANDSCAPE FOR PD1/PD-L1 IMMUNE CHECKPOINT INHIBITORS


PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1
OX40 (CD134), a co-stimulatory molecule that can be expressed by activated immune cells\(^1\)
- Several anti-OX40 agonistic monoclonal antibodies are currently tested in early phase cancer clinical trials

TLR 9 agonist (MGN1703) was evaluated in IMPACT\(^2\) (Phase II) and IMPALA\(^3\) (Phase III).

Phase II data showed improvement in PFS and OS\(^2\) but did not translate into a successful outcome in the Phase III study\(^3\)
VACCINES

• Activates a host’s immune response against cancer

• Autologous, DC, peptide, and viral vectors

• Phase II clinical trials evaluating five human leukocyte antigen (HLA)-A*2402-restricted peptides (three from onco-antigens and two from VEGF receptors)\(^1\), an autologous tumor lysate dendritic cell vaccine\(^2\) and non-replicating canary pox virus (ALVAC) expressing CEA and B lymphocyte antigen B7 (B7-1; CD80) (ALVAC-CEA/B7-1)\(^3\) vaccine showed no-limited benefit

• Currently, no approved vaccines are available for patients with mCRC

CEA, Carcinoembryonic antigen; DC, dendritic cell; mCRC, metastatic colorectal cancer; VEGF, Vascular endothelial growth factor
ONCOLYTIC VIRUSES

• Selectively infect and damage malignant cells without affecting the normal tissue

• A phase I/II - genetically engineered oncolytic herpes simplex virus, NV1020, in patients with previously treated mCRC. Approximately two thirds of patients had disease control with a 1-year survival rate of 47.2%\(^1\)

• Currently, no approved oncolytic therapies are available for patients with mCRC

CONCLUSIONS

- Immunotherapy has the potential to become the new standard of care in the management of mCRC
- Checkpoint inhibitors have clearly shown benefit in MSI-H tumors and are FDA approved in MSI-H mCRC
- Overcoming the resistance of ICI’s is the most exciting avenue of research in mCRC
- Better biomarkers are needed to predict response with ICIs
- Other immunotherapy agents are in early research. None approved in mCRC

FDA; Food and Drug Administration; ICI, immune checkpoint inhibitor; mCRC, metastatic colorectal cancer; MSI-H, Microsatellite Instability-High
ACKNOWLEDGMENTS

- Dr. Heloisa Soares MD PhD, UNM Comprehensive Cancer Center
- GI CONNECT Scientific Committee
  https://giconnect.info/masterclass/the-scientific-commitee/
## APPENDIX - COMBINATION STRATEGIES WITH PD-1/PD-L1 INHIBITORS: LIST OF CLINICAL TRIALS (1/2)

<table>
<thead>
<tr>
<th>Title</th>
<th>Identifier</th>
<th>Phase</th>
<th>MMR/MSI Status</th>
<th>Therapy Line</th>
<th>Treatment Arms</th>
</tr>
</thead>
</table>
| Nivolumab, or Nivolumab Combinations in Recurrent and Metastatic Microsatellite High (MSI-H) and Non-MSI-H Colon Cancer | NCT02060188    | Phase 2        | All mCRC       | Refractory   | Nivo+ Ipi  
Nivo+Ipi + cobimetinib  
Nivo+ anti- LAG 3 antibody  
Nivo+ daratumumab          |
| An Investigational Immunotherapy Study of Nivolumab With Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Colorectal Cancer That Has Spread (CheckMate 9X8) | NCT03414983    | Phase 2/3      | –              | First Line   | First line  
FOLFOX + bevacizumab  
FOLFOX + bevacizumab+ nivolumab |
| Combination Chemotherapy, Bevacizumab, and/or Atezolizumab in Treating Patients With Deficient DNA Mismatch Repair Metastatic Colorectal Cancer | NCT02997228    | Phase 3        | dMMR           | First Line   | mFOLFOX+ bevacizumab  
Atezolizumab  
mFOLFOX+bevacizumab |
| A Study of Atezolizumab Administered in Combination with Bevacizumab and/or With Chemotherapy in Participants With Locally Advanced or Metastatic Solid Tumors | NCT01633970    | Phase 1        | –              | Refractory   | Atezolizumab + bevacizumab  
Atezolizumab + bevacizumab + FOLFOX  
Atezolizumab + carboplatin + paclitaxel  
Atezolizumab + carboplatin + pemetrexed  
Atezolizumab + carboplatin + nab-paclitaxel  
Atezolizumab + nab-paclitaxel |
| Cetuximab and Pembrolizumab in Treating Patients With Colorectal Cancer That is Metastatic or Cannot Be Removed by Surgery | NCT02713373    | Phase Ib/II    | –              | Second Line  | Cetuximab+ pembrolizumab |
| Efficacy of the Anti-PD-L1 Antibody Atezolizumab (MPDL3280A) Administered With Stereotactic Ablative Radiotherapy (SABR) in Patients With Metastatic Tumours | NCT02992912    | Phase 2        | –              | Refractory   | Atezolizumab+ hypofractionated SABR will be delivered at a dose of 45 Gy in 3 fractions of 15 Gy |
| MEDI4736 in Combination With Olaparib and/or Cediranib for Advanced Solid Tumors and Advanced or Recurrent Ovarian, Triple Negative Breast, Lung, Prostate and Colorectal Cancers | NCT02484404    | Phase I/II     | pMMR/MSS       | Refractory   | Durvalumab + olaparib + cediranib |
| Pembrolizumab (MK-3475) and Poly-ICLC in Patients With Metastatic Mismatch Repair-proficient (MRP) Colon Cancer | NCT02834052    | Phase I/II     | pMMR/MSS       | Refractory   | Pembrolizumab + poly-ICLC |

**Abbreviations:**  
dMMR, deficient expression of DNA mismatch repair gene; Ipi, Ipilimumab; FOLFOX, folinic acid, fluorouracil and oxaliplatin; Gy, gray; LAG-3, Lymphocyte-activation gene 3; MSI-H, microsatellite instability-high; MSS, microsatellite stable; Nivo, Nivolumab; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; pMMR, Proficient expression of DNA mismatch repair gene; SABR, Stereotactic ablative radiotherapy
# APPENDIX- COMBINATION STRATEGIES WITH PD-1/PD-L1 INHIBITORS: LIST OF CLINICAL TRIALS (2/2)

<table>
<thead>
<tr>
<th>Title</th>
<th>Identifier</th>
<th>Phase</th>
<th>MMR/MSI Status</th>
<th>Therapy Line</th>
<th>Treatment Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Study of Combinations of D-CIK Immunotherapy And Anti-PD-1 In Refractory Solid Tumors</td>
<td>NCT02886897</td>
<td>Phase 1/2</td>
<td>–</td>
<td>Refractory</td>
<td>D-CIK and anti-PD-1 antibody</td>
</tr>
<tr>
<td>Immunotherapy Combined With Y-90 and Stereotactic Body Radiation Therapy (SBRT) for Colorectal Liver Metastases</td>
<td>NCT03802747</td>
<td>Phase 1</td>
<td>–</td>
<td>Durvalumab + Y-90 + SBRT Durvalumab and tremelimumab + Y-90 + SBRT</td>
<td></td>
</tr>
<tr>
<td>Ph1b/2 Dose-Escalation Study of Entinostat With Pembroliuzumab in NSCLC With Expansion Cohorts in NSCLC, Melanoma, and Colorectal Cancer</td>
<td>NCT02437136</td>
<td>Phase 1</td>
<td>–</td>
<td>Refractory</td>
<td>Pembrolizumab + entinostat</td>
</tr>
<tr>
<td>Regorafenib and Nivolumab Simultaneous Combination Therapy for Advanced and Metastatic Solid Tumors (REGONIVO)</td>
<td>NCT03406871</td>
<td>Phase 1/2</td>
<td>dMMR/MSS</td>
<td>Refractory</td>
<td>Nivolumab + regorafenib</td>
</tr>
<tr>
<td>A Study of the Safety, Tolerability, and Efficacy of Epacadostat Administered in Combination With Nivolumab in Select Advanced Cancers</td>
<td>NCT02327078</td>
<td>Phase 1/2</td>
<td>–</td>
<td>Refractory</td>
<td>Nivolumab + epacadostat Nivolumab + epacadostat + Chemo</td>
</tr>
<tr>
<td>A Dose Escalation and Cohort Expansion Study of Anti-CD27 (Varililumab) and Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors</td>
<td>NCT02335918</td>
<td>Phase 1</td>
<td>–</td>
<td>Refractory</td>
<td>varililumab + nivolumab</td>
</tr>
<tr>
<td>Pembrolizumab (MK-3475) in Combination With Azacitidine in Subjects With Chemo-refractory Metastatic Colorectal Cancer</td>
<td>NCT02260440</td>
<td>Phase 2</td>
<td>–</td>
<td>Refractory</td>
<td>Pembrolizumab + azacitidine</td>
</tr>
<tr>
<td>A Phase 2 Study With Safety Lead-in, Evaluating TAS-102 Plus Nivolumab in Patients With Microsatellite Stable Refractory Metastatic Colorectal Cancer</td>
<td>NCT02860546</td>
<td>Phase 2</td>
<td>pMMR/MSS</td>
<td>Refractory</td>
<td>TAS-102 (Lonsurf) + nivolumab</td>
</tr>
<tr>
<td>Dual Immune Checkpoint Blockade With Durvalumab Plus Tremelimumab Following Palliative Hypofractionated Radiation in Patients With Metastatic Colorectal Cancer Progressing on Chemotherapy</td>
<td>NCT03007407</td>
<td>Phase 2</td>
<td>pMMR/MSS</td>
<td>Refractory</td>
<td>Radiation + durvalumab (MEDI4736) + tremelimumab</td>
</tr>
</tbody>
</table>

Chemo, chemotherapy; D-CIK, dendritic and cytokine-induced killer cell; dMMR, deficient expression of DNA mismatch repair gene; MSS, microsatellite stable; NSCLC, Non-Small Cell Lung Cancer; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; SBRT, Stereotactic Body Radiation Therapy; Y-90, yttrium-90
IMMUNOTHERAPY IN THE TREATMENT OF METASTATIC COLORECTAL CANCER

Sakti Chakrabarti, MD
Mayo Clinic, Rochester, MN

October 18th, 2019
Dr. Sakti Chakrabarti does not have any relevant financial relationship to disclose.
CASE PRESENTATION

October, 2016:

- 40 year old Caucasian man presented with abdominal pain and anemia
- Colonoscopy- Partially obstructing ascending colon mass
- Biopsy (colon mass): Adenocarcinoma, loss of MSH6
- Family history of colon/endometrial cancer (subsequent work up confirmed Lynch syndrome)
- Staging scans: Solitary liver metastasis (5.2 cm) in segment 5/6
- CEA at baseline 3.2 ug/L

Early November, 2016

- Loop ileostomy to relieve obstructive symptoms

CEA, carcinoembryonic antigen; MHS6, MutS homolog 6
AFTER 3 MONTHS (NOVEMBER, 2016 – JANUARY, 2017) OF NEO-ADJUVANT FOLFOX

BASELINE

POST NEO-ADJUVANT CTX

5.2 CM

4.8 CM

CTX, chemotherapy; FOLFOX, folinic acid, fluorouracil and oxaliplatin
**CLINICAL COURSE**

**February 14, 2017**
- Rt. Hemicolecotomy
- Liver segment 5/6 resection
- Ileostomy reversal

**Pathology:**
\[ pT3pN1c(0/18),M1 \]

**March 16, 2017**
FOLFOX resumed – stopped after 1 cycle because of hepatic abscess

**March–June, 2017**
Hepatic abscess required catheter drainage and prolonged antibiotic therapy.

**Chemotherapy was on hold**

FOLFOX, folinic acid, fluorouracil and oxaliplatin
**CLINICAL COURSE**

**June 14, 2017**
Disease progression in the form of a new liver lesion near the dome
No other site of metastatic disease

**July 2017**
- Biopsy of the new liver lesion confirmed adenocarcinoma
- FOLFIRI initiated but poorly tolerated, stopped after 2 cycles

**August 8, 2017**
Pembrolizumab initiated

**October 10, 2017**
(after 3 doses of pembrolizumab)
CT scan: stable disease, possible recurrent liver abscess

After FOLFOX and FOLFIRI chemotherapy options, immunotherapy was initiated in August 8, 2017:

- **Pembrolizumab**: Immune Checkpoint Inhibitor (PD-1 inhibitor)

CT, computerized tomography; FOLFIRI: folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; PD-1, Programmed cell death protein 1
AFTER 3 CYCLES OF PEMBROLIZUMAB

**JULY, 2017**

**OCTOBER, 2017**

Distance:
- **2.6 cm** in July 2017
- **2.7 cm** in October 2017

**Abscess?**
October 16, 2017

- Abdominal exploration and subsegmental resection of liver segments V, VI, and VII
- **Pathology: NO VIABLE TUMOR (pCR)**

December, 2017 – February, 2018

- “Adjuvant” pembrolizumab- tolerated well
- **Post-therapy scan: no evidence of disease**

**Subsequent course**

- Observation with periodic scans.
- **In complete remission to date (May, 2019)**

pCR, pathologic complete response
TAKE HOME MESSAGES

- Radiological studies can be misleading in assessing tumor response to immunotherapy with PD-1 blockade
- PD-1 blockade should be considered early in the treatment of dMMR metastatic colorectal cancer

dMMR, deficient mismatched repair; PD-1, programmed cell death protein 1