Developmental Therapeutics for HCC, Colorectal Cancer, and Pancreatic Cancer

Manish Sharma, MD
Developmental Therapeutics Symposium
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Disclosure Information
23rd Annual Developmental Therapeutics Symposium
Manish Sharma, MD

• I have the following financial relationships to disclose:
  Consultant for: Ipsen, Bayer, AbbVie, Taiho, Eisai

• I will discuss non-approved therapies and investigational uses of therapies in my presentation (these will be pointed out explicitly).
Overview

- Unresectable hepatocellular carcinoma
- Metastatic colorectal cancer
- Metastatic pancreatic cancer
Overview

- Unresectable hepatocellular carcinoma
- Metastatic colorectal cancer
- Metastatic pancreatic cancer
Current standard of care for systemic therapy of hepatocellular carcinoma (HCC)

• First line (previously untreated)
  • FDA approved: sorafenib
  • Not yet FDA-approved
    • lenvatinib non-inferior to sorafenib
    • nivolumab vs. sorafenib results expected in 2019

• Second line (previously treated with sorafenib)
  • FDA-approved (2017): regorafenib, nivolumab
  • Not yet FDA-approved
    • cabozantinib superior to placebo
    • ramucirumab superior to placebo for AFP>400 ng/mL
**Checkmate 040 study: Nivolumab in advanced HCC**

<table>
<thead>
<tr>
<th></th>
<th>Without viral hepatitis</th>
<th>HCV infected</th>
<th>HBV infected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose escalation (n=48) 3+3 design</strong></td>
<td>n=6</td>
<td>n=9</td>
<td>n=10</td>
</tr>
<tr>
<td>0.1 mg/kg (n=1)</td>
<td>0.3 mg/kg (n=3)</td>
<td>1.0 mg/kg (n=3)</td>
<td>3.0 mg/kg (n=3)</td>
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<table>
<thead>
<tr>
<th><strong>Dose expansion (n=214) 3 mg/kg</strong></th>
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<tbody>
<tr>
<td>Sorafenib untreated or intolerant (n=56)</td>
</tr>
<tr>
<td>Sorafenib progressor (n=57)</td>
</tr>
<tr>
<td>HCV infected (n=50)</td>
</tr>
<tr>
<td>HBV infected (n=51)</td>
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El-Khoueiry et al. Lancet Oncology 2017
A significant minority of HCC patients have responses to PD-1 blockade

El-Khoueiry et al. Lancet Oncology 2017
Responses to PD-1 blockade are durable in HCC patients

El-Khoueiry et al. Lancet Oncology 2017
Current trials for HCC previously untreated with systemic therapy

- Phase 1: SBRT followed by nivolumab or nivolumab/ipilimumab (investigator-initiated)
- Phase 3: Pexa-vec (intratumoral injection of attenuated vaccinia virus) + sorafenib vs. sorafenib
- Phase 3: atezolizumab + bevacizumab vs. sorafenib
Current trials for HCC previously treated with systemic therapy

- Phase 1: SBRT followed by nivolumab or nivolumab/ipilimumab (investigator-initiated)
- Phase 1b/2: PDR001 (anti-PD1) ± INC280 (cMET inhibitor)
- Phase 1: INCB024360 (IDO1 inhibitor) + pembrolizumab (expansion cohort in HCC)
Phase I study of stereotactic body radiotherapy (SBRT) followed by nivolumab or ipilimumab with nivolumab in unresectable hepatocellular carcinoma

Co-PIs: Manish Sharma, MD and Stanley Liauw, MD

Nivolumab 240 mg IV q2weeks

N = 50 (25 per arm)

3 sites:
UChicago Medicine
Medical College of Wisconsin/Froedtert
Roswell Park Cancer institute

Biopsies and blood before/after SBRT for correlative studies

Nivolumab 240 mg IV q2weeks + Ipilimumab 1 mg/kg q6weeks
Phase I study of stereotactic body radiotherapy (SBRT) followed by nivolumab or ipilimumab with nivolumab in unresectable hepatocellular carcinoma

Patient 2: cholangiolocellular carcinoma
Phase I study of stereotactic body radiotherapy (SBRT) followed by nivolumab or ipilimumab with nivolumab in unresectable hepatocellular carcinoma

Patient 3
Baseline

After SBRT and 4 cycles of nivolumab + ipilimumab
PHOCUS: Sorafenib ± Pexa-Vec in Advanced HCC

- Multicenter, open-label, randomized phase III trial in Australia, New Zealand, South Korea, Taiwan, Thailand, and United States

Wk 6

Pts with advanced HCC (BCLC B or C, C-P A, ECOG PS 0-1), ≥ 1 measurable/injectable tumor, and no prior systemic therapy (planned N = 600)

Sorafenib 400 mg PO BID

Pexastimogene Devacirepvec* Sorafenib 400 mg PO BID

*Dosed intratumorally on Day 1, Wk 2, and Wk 4.

All pts treated until PD or unacceptable toxicity

- Primary endpoint: OS
- Secondary endpoints: TTP, PFS, ORR, DCR, safety, TSP, DOR, TIR

PHOCUS: Sorafenib ± Peva-Vec in Advanced HCC
**IMbrave150 (YO40245) Phase III atezolizumab + bevacizumab vs sorafenib in metastatic HCC: study design**

**Patient Population:**
- 1L unresectable or metastatic HCC
- Measurable disease
- ECOG 0-1
- Child-Pugh A
- Varices treated per local SOC prior to enrollment

**Randomization:**
- Atezolizumab 1200 mg q3w + Bevacizumab 15 mg/kg q3w
- Sorafenib 400mg BID
- n=480

**Treatment:**
- Treat until loss of clinical benefit or unacceptable tox

**Survival Follow-up**

**Stratification:**
- Region (Asia excluding Japan / RoW)
- Macro-vascular invasion (MVI) and/or extrahepatic spread (EHS) (Presence / Absence)
- Baseline AFP (<400 / ≥400 ng/ml)
- ECOG (0 / 1)

**Open label**
- No cross-over allowed
- Treatment beyond progression, both arms
- Tumor assessments q6w
Overview

- Unresectable hepatocellular carcinoma
- Metastatic colorectal cancer
- Metastatic pancreatic cancer
Nivolumab in MMR deficient/MSI-H mCRC

Best Reduction in Target Lesion: All Patients

- 60% of patients had a reduction in tumor burden from baseline with nivolumab monotherapy

*Confirmed response per BICR assessment; □ % Change truncated to 100. † Patient from Group A with 0% best reduction in target lesion

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)

*BIKR data with a median follow-up of 21 months (range: 17-40).
Nivolumab + ipilimumab in MMR deficient/MSI-H mCRC

Best Reduction in Target Lesions

Nivolumab + ipilimumab

- 78% of patients had a reduction in tumor burden from baseline with combination therapy

*Evaluable patients per investigator assessment.*
What about immunotherapy for MMR proficient/MSS mCRC?

- Monotherapy with PD-1 blockade has essentially no response rate
- Combination immunotherapy approaches are being investigated
- MEKi + PD-1/PD-L1 blockade is the most promising at this point
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\(^1\)

- To examine the possible benefits of MEK inhibition with an anti-PDL1 agent, we evaluated cobimetinib + atezolizumab in patients with advanced solid tumors

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models. 1. Ebert et al. *Immunity* 2016.
Cobimetinib (MEKi) + atezolizumab in MMR proficient/MSS mCRC

Best Overall Response

<table>
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<tr>
<th>BOR (n = 84)</th>
<th>n (%)</th>
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<tr>
<td>ORR</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>SD</td>
<td>19 (23%)</td>
</tr>
<tr>
<td>DCR</td>
<td>26 (31%)</td>
</tr>
<tr>
<td>PD</td>
<td>51 (61%)</td>
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- 7 patients (8% [95% CI: 3, 16]) experienced PR (confirmed per RECIST v1.1)
  - 4 patients had MSS and 1 patient had MSI-low mCRC; the remaining 2 had unknown MSI status
- The DCR was 31% (DCR defined as PR + SD ≥ 6 weeks)

BOR, best overall response; DCR, disease control rate; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SLD, sum of longest diameters.
Data cutoff: September 4, 2017. Cobimetinib dose and schedule varied based on cohort and phase of the study.
* 7 patients (8%) had missing or unevaluable BOR. † Based on combined local or centralized testing results. ‡ Unlabeled bars represent patients with unknown MSI status.

Presented at 2018 Gastrointestinal Cancers Symposium | #GI18
Presented by: Bendell J, et al. Atezolizumab + cobimetinib in mCRC
Slides are the property of the author. Permission required for reuse.
KEYNOTE-651: A phase 1b trial in MMR proficient/MSS mCRC

- Cohort A: Pembrolizumab + binimetinib (MEKi) in patients previously treated with fluoropyrimidine, irinotecan, and oxaliplatin
- Cohort B: Pembrolizumab + mFOLFOX7 in previously untreated patients
- Cohort C: Pembrolizumab + mFOLFOX7 + binimetinib in previously untreated patients
- Cohort D: Pembrolizumab + FOLFIRI in patients previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen
- Cohort E: Pembrolizumab + FOLFIRI + binimetinib in patients previously treated with one line of a fluoropyrimidine plus oxaliplatin-based regimen
KEYNOTE-651: A phase 1b trial in MMR proficient/MSS mCRC

Cohort A
Pembrolizumab + Binimetinib
(Participants previously treated with fluoropyrimidine, irinotecan, and oxaliplatin)

Part 1
N=3-28
Preliminary RP2D

Dose Finding

Part 2
N=16
Cohort A

Dose Confirmation

Cohort B
Pembrolizumab + mFOLFOX7
(Previously untreated participants)

Preliminary RP2D

Cohort C
Pembrolizumab + mFOLFOX7 + Binimetinib
(Previously untreated participants)

Preliminary RP2D

Cohort D
Pembrolizumab + FOLFIRI
(Previously untreated participants)

Preliminary RP2D

Cohort E
Pembrolizumab + FOLFIRI + Binimetinib
(Previously untreated participants)

Preliminary RP2D
Overview

- Unresectable hepatocellular carcinoma
- Metastatic colorectal cancer
- Metastatic pancreatic cancer
BRCA mutations in pancreatic cancer

- Carriers of deleterious germline mutations of BRCA1 and BRCA2 have increased risk of developing pancreatic cancer

- The prevalence of germline BRCA mutations is:
  - Higher in select populations (e.g. Ashkenazi Jewish descent) and in patients with family history of pancreatic cancer

- Patients with germline BRCA mutations have defects in DNA repair mechanisms (homologous recombination)
  - BRCA defective tumors are intrinsically sensitive to platinum-based chemotherapy and to PARP inhibitors (olaparib, veliparib)
POLO: A phase III, randomized, double-blind, placebo-controlled multicenter study of maintenance olaparib monotherapy in patients with gBRCA mutated metastatic pancreatic cancer whose disease has not progressed on first-line platinum based chemotherapy

**Primary endpoint:**
- PFS

**N = 145 patients**

**Eligibility:**
- Metastatic PC
- ≥16 weeks of front-line platinum based chemo
- No disease progression

Screen for germline BRCA mutation while on chemo

**Randomize 3:2**

- **Olaparib**
  - 300 mg PO BID
  - Primary endpoint: PFS
- Placebo

PI: Hedy Kindler, MD
TNF-Related Apoptosis Inducing Ligand (TRAIL)

Amarante-Mendes GP, Griffith TS. Pharmacol Ther. 2015
Abstract DDT01-03: ABBV-621: A best-in-class TRAIL-receptor agonist fusion protein that enhances optimal clustering for the treatment of solid and hematologic tumors

Susan E. Morgan-Lappe

DOI: 10.1158/1538-7445.AM2017-DDT01-03 Published July 2017

Proceedings: AACR Annual Meeting 2017; April 1-5, 2017; Washington, DC
An Open Label Phase I, First-in-Human Study of TRAIL Receptor Agonist ABBV-621 in Subjects with Previously-Treated Solid Tumors and Hematologic Malignancies

PI: Mark Ratain, MD

- IV, weekly dosing, dose-ranging
- patients with metastatic pancreatic cancer and KRAS mutated mCRC
What about immunotherapy for metastatic pancreatic cancer?

- Monotherapy with PD-1 blockade (unless MMR deficient/MSI-H) has essentially no response rate
- Combination immunotherapy approaches are being investigated
- Dual blockade of CSF-1R and PD-1 is most promising at this point
First-in-Human Phase 1 Dose Escalation and Expansion of a Novel Combination, Anti–CSF-1 Receptor (cabiralizumab) Plus Anti–PD-1 (nivolumab), in Patients With Advanced Solid Tumors


1UCLA Medical Center, Los Angeles, CA; 2The University of Texas MD Anderson Cancer Center, Houston, TX; 3University of Chicago Medical Center, Chicago, IL; 4UC Davis Cancer Center, Sacramento, CA; 5University of Washington, Seattle Cancer Center, Seattle, WA; 6Medical University of South Carolina, Charleston, SC; 7Sidney Kimmel Cancer Center, Jefferson University, Philadelphia, PA; 8Rush University Medical Center, Chicago, IL; 9Honor Health Research Institute, Scottsdale, AZ; 10South Texas Accelerated Research Therapeutics, San Antonio, TX; 11Dana-Farber Cancer Institute, Boston, MA; 12Barbara Ann Karmanos Cancer Institute, Detroit, MI; 13FivePrime Therapeutics, South San Francisco, CA; 14Bristol-Myers Squibb, Princeton, NJ; 15University of Pittsburgh Cancer Institute, Pittsburgh, PA
Rationale for Cabiralizumab in Combination With Nivolumab

- TAMs inhibit antitumor T-cell activity in the tumor microenvironment\(^1\,\,^2\)
  - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis\(^3\,\,^5\)
  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs\(^1\,\,^2\)
- Cabiralizumab is a humanized IgG4 mAb that blocks CSF-1R\(^6\) and depletes TAMs
d- Preclinical data suggest that CSF-1R inhibition synergizes with PD-1 blockade to enhance antitumor activity\(^7\)

CSF-1 = colony stimulating factor 1; TAM = tumor-associated macrophage; IgG = immunoglobulin G; mAb = monoclonal antibody; PD-1 = programmed death-1

Oral abstract O42, SITC 2017 Annual Meeting
Deep and Durable Responses Observed in Patients With Pancreatic Cancer

Best change in tumor burden over time in efficacy-evaluable patients treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg (n = 31)*

- In this heavily pretreated population, durable clinical benefit was observed in 5 patients (16%)
  - Confirmed ORR = 10% (Updated confirmed ORR = 13%)
  - Duration of treatment for responders = 275+, 168+, 258, and 247+ days
- All 4 confirmed responses were observed in patients with MSS disease, who historically have not shown benefit with anti–PD-1/L1 therapy¹,²
- Responses were accompanied by steep declines in levels of the pancreatic tumor marker CA19-9 over baseline

C4-MOSART: Multi-Organ Site Ablative RT

Co-PIs: Jason Luke, MD and Steve Chmura, MD, PhD

Study Design Schema

- Advanced/metastatic cancer
- no active immunosuppression
- 1-4 metastases that can be safely treated with SBRT

TREATMENT

SBRT to 1-4 metastases in combination with
1. Urelumab + Nivolumab
   OR
2. Cabiralizumab + Nivolumab

FOLLOW UP

- Evaluate toxicity
- Repeat CT scan 12 weeks after SBRT
- Recollect biospecimens
- Repeat biopsy of treated lesion
- Continue immunotherapy until toxicity/progression

choice of regimen is discretion of co-PIs
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Jason Luke, MD
Mark Ratain, MD

**Personalized Cancer Care Consortium**
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Mary Sherrell, MA