Immunotherapy of Hepatocellular Carcinoma
Where are we now?

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Drug Development for HCC

The long and winding road
• 1950-2000 Chemotherapy

• 2000- Molecular targeted therapy
Results of SHARP was presented in June 2007. Sorafenib was approved by FDA in Dec. 2007.
The landscape of altered genes and pathways in HCC

Schulze K et al. Nature Genetics 2015; Published online 30 March 2015
Drug Development for HCC
The long and winding road

Up to 80 other compounds have been investigated in more than 190 trials. None has succeeded.
Baseline
(31 July 2015)

After 2 doses of nivolumab
(31 August 2015)
58 y/o man, HBV (+), Hepatocellular Carcinoma lung metastases, progression after sorafenib

Baseline (31 Jul. 2015)
AFP 2262

PR documentation (14 Sep. 2015)
AFP 21
Nivolumab (anti-PD1) plus Ipilimumab (anti-CTLA4) in Advanced Melanoma

Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Figure 2. Computed Tomographic (CT) Scans of the Chest Showing Tumor Regression in a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.
Anti-PD1 trials in clinicaltrials.gov
Data retrieved on 10 January 2016

**Keywords:** PD-1 or nivolumab or pembrolizumab
**Inclusion:** cancer intervention trials (phase 0-4), recruiting/not yet recruiting

- **Multiple** (≥3 cancer types): 46 trials
  - Phase 1: 23
  - Phase 1/2: 20
  - Phase 2: 3
- **Melanoma**: 45 trials
  - Phase 0: 1
  - Phase 1: 10
  - Phase 1/2: 4
  - Phase 2: 22
  - Phase 2/3: 1
  - Phase 3: 4
  - Phase 4: 3
- **NSCLC**: 48 trials
  - Phase 1: 10
  - Phase 1/2: 12
  - Phase 2: 18
  - Phase 3: 8
- **Lymphoma/leukemia/myeloma**: 35 trials
  - Phase 1: 6
  - Phase 1/2: 9
  - Phase 2: 18
  - Phase 3: 2
- **Others**: 2 trials
  - Brain: 12
  - Breast: 13
  - Cervical: 1
  - Colorectal: 9
  - Endometrial: 2
  - Esophageal: 4
  - Gastric: 6
  - GCT: 1
  - H&N: 14
  - Meso: 2
- **HCC**: 2 trials
  - Phase 1/2: 1
  - Phase 3: 1
- **NPC**: 2
- **Ovary**: 4
- **Pancreas**: 5
- **Prostate**: 5
- **RCC**: 11
- **Sarcoma**: 4
- **SCLC**: 7
- **Thymic**: 2
- **TCC**: 12
Tremelimumab (Anti-CTLA-4) for HCV-HCC

- 21 pts with HCV-HCC which was not amenable to locoregional therapy (* 40% were BCLC stage C; 57.5% were untreated)
- Tremelimumab 15 m/kg iv every 90 days for up to 4 cycles
- ORR: 17.6% (3 PRs, lasting for 3.6, 9.2 and 15.8 months)
- DCR: 76.4% (half of them lasting >6 months)

Sangro B, et al: J Hepatol 2013 Mar 4
## Investigator-Assessed Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>Uninfected (n=21)</th>
<th>HCV (n=11)</th>
<th>HBV (n=10)</th>
<th>Total Evaluable* (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response, n (%)</td>
<td>3 (14)</td>
<td>4 (36)</td>
<td>1 (10)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (10)</td>
<td>0</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (5)</td>
<td>4 (36)</td>
<td>1 (10)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>10 (48)</td>
<td>5 (45)†</td>
<td>5 (50)</td>
<td>20 (48)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (38)</td>
<td>2 (18)</td>
<td>4 (40)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Ongoing response, n (%)</td>
<td>3/3 (100)</td>
<td>3/4 (75)</td>
<td>0</td>
<td>6/8 (75)</td>
</tr>
</tbody>
</table>

Responses assessed by RECIST 1.1
*5 patients not evaluable: first disease assessment not yet performed in 4 patients, 1 patient died from clinical progression before disease assessment
†Patient with resolved HCV infection

Presented By Anthony El-Khoueiry at 2015 ASCO Annual Meeting
Immunotherapy for advanced HCC

( pilot trials completed )

- **2nd line**
  - Tremelimumam (anti-CTLA4) *(phase II)*
  - Nivolumab dose escalation/expansion *(phase I/II)*
  - Durvalumab (MEDI4736) (anti-PDL1) *(phase I/ II)*
At the Crossroad
Molecular Targeted Therapy at the Era of Immunotherapy

• While we are about to cash our long years of hard work on MTTs, the promise of immunotherapy has rapidly emerged ---

• How can we make the most out of the two modalities of treatment?
Immunotherapy for advanced HCC
(trials ongoing/ recruiting)

- 1st line
  - Nivolumab (anti-PD1) vs. Sorafenib (phase II)
    - Primary endpoint: ORR
  - Nivolumab vs. Sorafenib (phase III)
    - Primary endpoint: TTP and OS
Sorafenib Relieves Cell-intrinsic and Cell-extrinsic Inhibitions of Effector T Cells in Tumor Microenvironment to Augment Antitumor Immunity

Figure 6. A model illustrating the mechanisms by which sorafenib augments antitumor immunity through relieving PD-1- and Treg-mediated inhibitions in tumor microenvironment.


- 48th 2012/07/10 mice data (Sor + PD1)

- * P < 0.05, ** P < 0.01
- Treatment time: 22 days

- Vehicle
- Sor-5
- PD-1
- Sor 5 + PD-1

- anti-PD1: 200 μg/ i.p. × 5 doses (days 5, 7, 9, 14, 21)

- Body Weight (g)

- Days of Treatment

- % TUNEL (+) cells

- % CD31 (+) cells
Immunotherapy for advanced HCC
(trials under planning)

• **1st line**
  – Pembrolizumab (anti-PD1) vs. sorafenib **(phase III)**
  – PDR001 (anti-PD1) + sorafenib vs. PDR001 vs. sorafenib **(phase II)**

• **2nd line**
  – Durvalumab (anti-PDL1) + ramucirumab (anti-VEGFR) **(phase I)**
  – Pembrolizumab vs. placebo **(phase III)**
  – Pembrolizumab **(phase II)**
HCC Immune Microenvironment and HCC-specific Immunotherapy
Whole Genome Sequencing Identifies Recurrent Mutations in HCC

Wnt Pathway Genomic Alterations in 62.5% of HCC

Melanoma-intrinsic $\beta$-catenin Pathway Activation Correlates with T-cell Exclusion

T-cell exclusion is caused by impaired priming of anti-tumor T cells and reduced numbers of CD103$^+$ dermal dendritic cells.

Wnt/$\beta$-catenin signalling induces expression of ATF3, which suppresses CCL4 and thereby interferes recruitment and activation of CD103$^+$ dendritic cells.

Spranger S. et al Nature 2015;523:231-235
Small-molecules Targeting Wnt Signaling

**IWP** (Inhibitors of Wnt production)
- LGK974

**IWR** (Inhibitors of Wnt response)
- XAV939
- Other Tankyrase inhibitors

**β-ID** (β-catenin interaction disruptors)
- ICG-001
- PRI-724

Classifying Cancers Based on T-cell Infiltration and PD-L1

- Combined with anti-CTLA4.
- In situ vaccination (e.g. STING, cyclic dinucleotides, immunostimulatory RNA)
- Induction of immunogenic cell death (e.g. RT, CT, MTT)
- Adoptive T-cell transfer (e.g. CART)
- Promotion of T-cell trafficking (e.g. anti-angiogenics)
- Wnt/B-catenin inhibition

Immunotherapy for advanced HCC
(trials ongoing/ recruiting)

- **2nd line**
  - Nivolumab + ipilimumab (anti-CTLA4) *(phase I/II)*
  - Durvalumab (anti-PDL1) + tremelimumumab (anti-CTLA4)
    vs. durvalumab vs. tremelimumumab *(phase I/II)*
  - Nivolumab + galunisertib *(TGFβR1 inhibitor)* *(phase I/II)*
Immunotherapy for advanced HCC
(trials under planning)

• **1st line**
  – Pembrolizumab (anti-PD1) vs. sorafenib (phase III)
  – PDR001 (anti-PD1) + sorafenib vs. PDR001 vs. sorafenib (phase II)

• **2nd line**
  – Durvalumab (anti-PDL1) + ramucirumab (anti-VEGFR) (phase I)
  – Pembrolizumab vs. placebo (phase III)
  – Pembrolizumab (phase II)
HCC Immune Microenvironment and
HCC-specific Immunotherapy
Kupffer Cells of HBV-HCC Express High Level of Galectin-9

Li H et al. Hepatology 2012;56:1342-1351
HBV-HCC is Associated with Higher Expression of Tim-3 of Infiltrating T cells

Li H et al. Hepatology 2012;56:1342-1351
Tim-3 Expression in Tumour-associated Macrophages: a new player in HCC progression

Immunotherapy for advanced HC
(example anti-PD1 combinations to be explored)

• + Anti-TIM3
  – TIM3 mediated immune suppression in HCC microenvironment
  – Pre-clinical antitumor synergy with anti-PD-1

• + IAP inhibitor
  – Single-agent anti-tumor activity; combinations under studies
  – Anti-HBV effects in pre-clinical models
HCC Immune Microenvironment and HCC-specific Immunotherapy
Immunosuppressive and Tumor-Promoting Functions of TAMs and MDSCs in HCC

Classifying Cancers Based on T-cell Infiltration and PD-L1

- Other immune check point inhibitors. (e.g. anti-LAG3, anti-TIM3, anti-TIGIT)
- Combined with costimulator agonists (e.g. 4-1BB, OX40, GITR)
- Combined with antagonists of immune suppressors (e.g. IDO inhibitors)
- Combined with TAM/MDSC depletion (e.g. CSF-1R inhibitors)

Immunotherapy for advanced HCC
(example anti-PD1 combinations to be explored)

- **IDO inhibitor**
  - ORR 40-50% in multiple cancer types
  - AEs: fatigue, diarrhea, rash, arthralgia, nausea

- **CSF-1R inhibitor**
  - May shift macrophages polarization from M2 to M1
  - Single-agent anti-tumor activity (+); combination studies under way
Combined Immunotherapy Based on PD1/PDL1 Blockake

HCC-specific Immunotherapy

In-situ vaccination
STING (STimulator of INterferon Genes)-Dependent Innate Immune Signaling

Barber GN. Trends in Immunology, February 2014;35(2):88-93.
CXCR3(+) B cells link IL-17 inflammation to protumorigenic macrophage polarization in human HCC.

HCC-activated macrophage ↓ IL-17 producing T cells ↓ CXCL-9,10,11 of epithelial cells

CXCR3 (+) B cells ↓ M2b polarization of macrophage

Liu RX et al. Hepatol 2015;62:1779-1790
Categories of Anticancer Therapies and Their Targets

- Targeted therapies
  - AZD8055 (mTOR)
  - Cetuximab (EGFR)
  - Dabrafenib (BRAF)
  - Dasatinib (BCR-ABL, cKIT, SRC)
  - Imatinib (BCR-ABL, cKIT)
  - Lapatinib (EGFR, ERBB2/HER2)
  - PLX4720 (BRAF)
  - Rapamycin (mTOR)
  - Rituximab (CD20)
  - Ruxolitinib (JAK1 and 2)
  - Temsirolimus (mTOR)
  - Trastuzumab (ERBB2/HER2)
  - Vemurafenib (BRAF)

- Radiotherapy
  - Single high dose
  - Fractionated

- Immunomodulatory agents
  - AMD3100 (CXR4)
  - AMG820 (CSF1R)
  - AZD8309 (CXR2)
  - BLZ945 (CSF1R)
  - Carlumab (CCL2)
  - GSK1325756 (CXR2)
  - IMC-CS4 (CSF1R)
  - PLX3397 (cKIT, CSF1R, FLT3)
  - RG7155 (CSF1R)
  - SB-656933 (CXR2)
  - SCH527123 (CXR2)
  - S-265610 (CXR2)
  - Trabectedin

- Checkpoint inhibitors
  - AMP-224 (PD1)
  - Ipilimumab (CTLA4)
  - MPDL3280A (PD-L1)
  - Nivolumab (PD1)
  - Pembrolizumab (PD1)

- Vascular-targeting agents
  - Anti-angiogenic agents
    - Bevacizumab (VEGFA)
    - DC101 (mVEGFR2)
    - Nesvacumab (ANGPT2)
    - Sunitinib (VEGFRs, PDGFRs, FLT3, CSF1R)
    - Sorafenib (VEGFRs, RAF, PDGFRs, cKIT)
    - Trebananib (ANGPT1 and 2)

- Vascular damaging agents
  - Combretastatin A-4 phosphate

Coffelt S.B. et al. Trends in Immunology 2015;36:198-216
Conclusion

Immunotherapy for HCC

- Immune checkpoint inhibitors have modest, yet definite efficacy.

- Combinations of immunotherapy with molecular targeted or other modalities of treatments are under investigation.

- HCC-specific or even personalized immunotherapy is possible.
Combined Non-immune and Immunotherapy