Immunotherapy Is Coming For HCC

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Saronic Biotechnology Inc.

Hepdart 2017, Kona, HI
Global Age-Standardized Rate of Cancer (Both Sexes)
### Worldwide Cancer Incidence (Both Sexes) vs. Mortality

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lung</td>
<td>13.0%</td>
</tr>
<tr>
<td>2. Breast</td>
<td>11.9%</td>
</tr>
<tr>
<td>3. Colorectal</td>
<td>9.7%</td>
</tr>
<tr>
<td>4. Prostate</td>
<td>7.8%</td>
</tr>
<tr>
<td>5. Stomach</td>
<td>6.8%</td>
</tr>
<tr>
<td><strong>6. Liver</strong></td>
<td><strong>5.6%</strong></td>
</tr>
<tr>
<td>7. Cervix</td>
<td>3.8%</td>
</tr>
<tr>
<td>8. Esophagus</td>
<td>3.2%</td>
</tr>
<tr>
<td>9. Lymphoma</td>
<td>3.2%</td>
</tr>
<tr>
<td>10. Bladder</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

Number of US FDA Approved Systemic Therapies by Cancer Type

1. Lung        31
2. Breast      34
3. Colorectal  14
4. Prostate    13
5. Stomach     9
6. Liver       2*
7. Cervix      8
8. Esophagus   7
9. Lymphoma    34
(+10 drug combinations)
10. Bladder    10
November 2007, 1st FDA Approved Systemic Therapy for HCC

- Sorafenib Tosylate (Nexavar, Bayer Pharmaceuticals)
- Small Molecule Raf kinase and VEGF receptor kinase
- SHARP trial; randomized double blind placebo-controlled trial
- 602 randomized to 800mg/day (299 patients) vs. placebo (303 patients)
- Advanced disease, extensive pre-treatment (20% surgical resection, 40% local regional therapy, 5% radiation, 4% chemotherapy)
- Primary outcome measure median survival: 10.7 months (sorafenib) vs. 7.9 months (placebo)
- US Cost of drug: $62,000 per year
- Toxicity profile: diarrhea (55%), hand foot syndrome (21%), rash (19%), hypertension, headache, nausea, abdominal pain
US FDA approved drugs for HCC

sorafenib 2007

regorafenib 2017
April 2017, 2\textsuperscript{nd} FDA Approved Systemic Therapy for HCC

- Regorafenib (Stivarga, Bayer Pharmaceuticals)
- Small Molecule Raf kinase and VEGF receptor kinase
- Resorce trial; randomized, placebo-controlled trial
- 573 patients randomized to 160mg/day regorafenib (379 patients) vs. placebo (194 patients)
- Advanced disease, progressed on sorafenib, extensive pre-treatment
- Primary outcome measure median survival: 10.6 months (sorafenib) vs. 7.8 months (placebo)
- Toxicity profile: hypertension (15%), hand foot reaction (13%), fatigue (9%)
Sorafenib vs. Regorafenib (fluoro-sorafenib) Chemical Structure

A  Regorafenib

B  Sorafenib

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Manufacturer</th>
<th>Median Survival (treated)</th>
<th>Median Survival (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHARP</td>
<td>Sorafenib</td>
<td>Bayer</td>
<td>10.7 months</td>
<td>7.9 months</td>
</tr>
<tr>
<td>RESORCE</td>
<td>Regorafenib</td>
<td>Bayer</td>
<td>10.6 months</td>
<td>7.8 months</td>
</tr>
</tbody>
</table>
US FDA approved drugs for HCC

- sorafenib
- regorafenib

2007 - 2017

US FDA approved drugs for Colorectal Cancer

- panitumumab
- cetuximab
- regorafenib
- bevacisumab
- lonsurf
- ziv-aflibercept
- ramucirumab
- nivolumab

2007 - 2017
US FDA approved drugs for HCC

sorafenib (2007)

regorafenib (2017)
nivolumab (2017)
Checkmate 040 Trial (nivolumab, Bristol-Myers Squibb)

- Published in Lancet June 2017. Accelerated FDA approval September 2017.
- Advanced HCC, **Phase I/II**
- Initiated 2012, estimated completion 2018

- Multiple cohorts:
  - nivolumab alone
  - nivolumab+sorafenib
  - nivolumab+ipilimumab
  - nivolumab+ipilimumab+cabozantinib

- Primary outcomes: safety, tolerability, objective response rate
- Secondary outcomes: time to response, time to progression, progression free survival, overall survival, duration of response, PD-L1 expression
Checkmate 040 Trial (nivolumab, Bristol-Myers Squibb)

- 262 patients enrolled
- Accelerated FDA approval based on results in 154 patients with progression or toxicity to sorafenib (31%HBV, 21%HCV)
- 3 complete responses (1 patient with HBV HCC)
- 19 partial responses
- 40% stable disease for 6 months
HCC is an Immunogenic Tumor in Humans: CD4 and CD8 Cell Infiltration

H&E  CD20 (B cells)  TIA (NK cells)

CD3  CD4  CD8
Number of HCC studies currently indexed on clinicaltrials.gov

- Enrolling in the United States, interventional (therapeutic), phase 2, phase 3
- Immunotherapy (15)
- Local regional therapy (11)
- Small molecule tyrosine kinase inhibitors (3)
- Other (9)
- Chemotherapy (1)
Categories of Most Common Cancer Immunotherapies

- Checkpoint inhibitors
  - CTLA-4
  - PD-1/PD-L1
- Autologous Cell Therapy
  - CAR-T Cells
  - Adoptive (effector cell) immunotherapy
  - Dendritic Cell immunotherapy
- Vaccines
- Other
Checkpoint inhibitors

Ipilimumab (Yervoy®, Melanoma, Bristol-Myers Squibb)
CTLA4 (Inhibition Blocked)
Pembrolizumab (Keytruda®, Melanoma, Merck)
PD1 (Inhibition Blocked)

CD8+ Cytotoxic T Cell (CTL, Effector Cell)

Tumor Cell Killing

Tumor Cells
CAR T cell and TCR Tcell Therapy
CAR T Cell Therapy

• One time systemic dosing

• Requires an identified overexpressed target cancer antigen

• Unlikely to become feasible in HCC due to cancer antigen diversity
HCC Immuno-Oncology Drugs/Biologics/Cell Therapies Currently in Human Testing

- Nivolumab (PD-1)
- Pembrolizumab (PD-1)
- Durvalumab (PD-1)
- PDR001 (PD-1)
- Tremelimumab (CTLA-4)
- Ipilimumab (CTLA-4)
- Vaccinia Virus
- Tumor Infiltrating Lymphocytes
- CC-122 (immunomodulator)
- Mogamulizumab (CCCR4 chemokine targeting ab)
**SBI1997: Dendritic Cell Immunotherapy**

- **SBI1997** is a cell-based immunotherapy where a patient’s tumor cells are loaded onto dendritic cells (antigen-presenting immune cells) and reinserted into the patient.
- This leads to selective reduction of inhibitory immune cells (regulatory T cells), tumor regression and a dramatic increase in survival.
- No Grade III or IV toxicities have ever been reported in any dendritic cell immunotherapy clinical trials.
- Manufactured in vitro from autologous tumor and immune cells.
- Administered intravenously (not injected directly into tumor).
- Stable in cryostorage over prolonged time.
- The role and function of the target cell population is well validated in human studies.
SBI1997: Method of Manufacture

Liver Resection → Autologous Tumor Cells → Tumor Lysates → Load, Activate → Mature Loaded Dendritic Cells → Aliquot, Store → SBI1997 Delivered Intravenously

Leukapheresis → Autologous Peripheral Blood Mononuclear Cells (PBMC)
Improved Overall Survival

- 100% of control animals died in 60 days vs. 90% survival of SBI1997-treated animals

Inhibited Tumor Progression

- Spiros Hiotis is a leading expert in this and has perfected these animal models for HCC immunotherapeutics
- SBI1997 is the first immunotherapy to show efficacy and far precedes other immunotherapeutics in this space

Increased serum levels of alpha-fetoprotein (AFP), a HCC tumor biomarker, correlate with cancer progression. AFP levels in SBI1997 vaccinated animals were observed to decrease over time to reach undetectable levels. Hence, showing that SBI1997 effectively reduced tumor progression in animal models.
SBI1997 Mechanism of Action vs Checkpoint Inhibitors

SBI1997 Dendritic Cell Immunotherapy

CD4⁺ Treg

Foxp3 (Selective Reduction of Treg)

CD8⁺ Cytotoxic T Cell (CTL, Effector Cell)

Tumor Cells

Ipilimumab (Yervoy®, Melanoma, Bristol-Myers Squibb)

CTLA4 (Inhibition Blocked)

Tumor Cell Killing

Pembrolizumab (Keytruda®, Melanoma, Merck)

PD1 (Inhibition Blocked)

Tumor Cells
Mechanism of Action: Selective Reduction of Treg cell Accumulation in Tumor Microenvironment

- Tregulatory (Treg) cells inhibit immune response to cancer cells.
- Foxp3 is a specific cell surface marker for Treg cells.
- SBI1997 immune cell therapy demonstrated significantly reduced Foxp3 levels in tumor, indicating decreased Treg cell accumulation in the liver tumor.

TGF-β, which plays an important role in the thymus in regulatory T cell development, is depleted from the HCC tumor microenvironment following Dendritic cell Immunotherapy.
Intrahepatic Hepa-1-6 tumor model represents a clinically relevant model for HCC.

This model is established in immunocompetent mice, and is therefore very useful for preclinical testing of immunotherapy.

Results of tumor lysate-loaded dendritic cell vaccine in murine model:
- Improved survival
- Inhibited tumor progression
- Decreased serum AFP (tumor marker)
- Prevention of Treg cell accumulation in tumor

Vaccine inhibits tumor progression and immunosuppression within the tumor microenvironment.
High Foxp3 in tumor microenvironment associated with high rate of mortality

• Foxp3 is a molecular marker for regulatory T cells, the cell population targeted by SBI1997
• High occurrence of regulatory T cells corresponds to a high rate of mortality from HCC
• Hence, regulatory T cells are a determining factor with HCC mortality
• SBI1997 selectively removes regulatory T cells from the tumor microenvironment

Human HCC Prognostic Associations: Foxp3+ Cells in Tumor Microenvironment

Validation Data: Human HCC

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Foxp3 low (n=32)</th>
<th>Foxp3 high (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.03</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>0.10</td>
<td>0.10</td>
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<tr>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
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<tr>
<td>0.30</td>
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<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
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<tr>
<td>0.50</td>
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<td>0.50</td>
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<td>0.60</td>
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<td>0.60</td>
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<tr>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
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<tr>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
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<tr>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>1.00</td>
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</tr>
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Number of US FDA Approved Systemic Therapies by Cancer Type; HCC is Alone Among Top 10 Most Common Cancers Without a Single FDA Approved Adjuvant Systemic Therapy

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Approvals</th>
</tr>
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<tr>
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<td>31</td>
</tr>
<tr>
<td>Breast</td>
<td>34</td>
</tr>
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(+10 drug combinations)
Measure of Vaccine Efficacy: Two-Year Recurrence-Free Survival

MSSM Historical Controls

2-year recurrence-free survival: 35%

80-patient enrollment will provide statistical power to detect a 20% increase in recurrence-free survival.
**AUDIT HCC (Phase I/II) Clinical Trial**

**AUDIT HCC Trial: Adjuvant Use Dendritic Cell ImmunoTherapy for HCC**

<table>
<thead>
<tr>
<th>Phase I: Safety</th>
<th>Phase II: Efficacy</th>
</tr>
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<tbody>
<tr>
<td><strong>Objective:</strong> Safety</td>
<td><strong>Objective:</strong> Improving two-year recurrence-free survival</td>
</tr>
<tr>
<td>6 patients</td>
<td>74 patients</td>
</tr>
<tr>
<td>• Staggered Enrollment Design</td>
<td></td>
</tr>
<tr>
<td>‒ 1+2+3</td>
<td>• Randomized Enrollment Design</td>
</tr>
<tr>
<td>• Toxicity assessment after two vaccine infusions</td>
<td></td>
</tr>
<tr>
<td>‒ Safety clearance must be obtained before treatment initiation in subsequent group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>‒ Vaccine: 34 patients</td>
</tr>
<tr>
<td></td>
<td>‒ Reference: 40 patients</td>
</tr>
<tr>
<td></td>
<td>• Treatment group will undergo a series of nine vaccine infusions.</td>
</tr>
</tbody>
</table>
**Objective:** Evaluate safety and efficacy of SBI1997 among patients with liver cancer (hepatocellular carcinoma) with high risk of recurrence.

**Targeted Enrollment:** 80 patients over 18-36 months

**Primary Endpoints:**
- Safety
- Two-year recurrence-free survival

**Secondary Endpoints:**
- Overall Survival
- Serum alpha-fetoprotein (AFP)
- Immune Monitoring