Direction of the Field: The Future of Cancer Immunotherapy

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SITC Winter School

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Disclosures

• Nektar Therapeutics – Advisory Board/Honorarium
• By virtue of discussing the future, I will be discussing non-FDA approved indications during my presentation.
Improvements in Staging and Immunotherapy Biomarkers

• **Immunoscore**
  - CD3, CD8, T cell memory
  - PD-L1, TMB, GEP and others

• **Next generation sequencing**
  - MSI-high, MMR defects, etc.

• **Gut microbiome**

• **Tumor microenvironment/metabolomics**
Current standard diagnostics

- Histopathology
- Flow cytometry
- Immunohistochemistry
- Cytogenetics
- Molecular studies: RT-PCR/FISH

- Next generation sequencing (NGS) panels
  - Identify fusions without having to know fusion partners
  - Identify pathways for targeting by FDA-approved drugs, on- or off-label
Immunoscore will become part of standard pathologic reports for all tumors, used as a biomarker for responses and correlate with survival.

**Cancers where immunoscore correlates with outcome**

<table>
<thead>
<tr>
<th>Adult tumors</th>
<th>Pediatric tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Spinal chordoma</td>
<td>CD3⁺, CD8⁺Combi*</td>
</tr>
</tbody>
</table>

*Galon et al. 2006 Science*
Using assays together increases positive predictive value of responding to anti-PD(L)1 therapy

- PD-L1 immunohistochemistry
- Tumor mutation burden (TMB)
- Gene expression profiling (GEP)
- Multiplex immunohistochemistry/immunofluorescence (mIHC/IF)

Individual association of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts

Pan-tumor

HNSCC

Melanoma

Razvan Cristescu et al. Science 2018;362:eaar3593
Relationship between MSI status and immunologic response.


©2016 by American Association for Cancer Research
Better intersection of NGS with predicting immunotherapy responses

Tumor mutational burden

Mismatch repair defects

Rizvi et al. 2016 Science

Le et al. 2015 New Engl J Med
Query and modulate the gut microbiome to improve responses to immunotherapy

Zitvogel et al. 2018 Science

Routy et al. 2018 Science
Tumor microenvironment is immuno-suppressive due to multiple cells and cytokines

Gotwals et al. 2017

Nature Reviews | Cancer
Gotwals et al. 2017
Manipulate the tumor metabolic environment to enhance immunotherapy responses

Cascone et al. 2018 Cell Metab
Will also change T cell metabolism to enhance immunotherapy responses

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Target</th>
<th>Metabolic outcome</th>
<th>Clinical (C), pre-clinical (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-DG</td>
<td>Hexokinase</td>
<td>↓Glycolysis</td>
<td>P</td>
</tr>
<tr>
<td>Mdivi-1</td>
<td>Drp-1</td>
<td>↓Mitochondrial fission</td>
<td>P</td>
</tr>
<tr>
<td>JQ1</td>
<td>c-Myc</td>
<td>↓Glycolysis</td>
<td>P</td>
</tr>
<tr>
<td>STF-31</td>
<td>GLUT1</td>
<td>↓Glycolysis</td>
<td>P</td>
</tr>
<tr>
<td>WZB117</td>
<td>GLUT1</td>
<td>↓Glycolysis</td>
<td>P</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>mTOR</td>
<td>↓Glutamine metabolism</td>
<td>C</td>
</tr>
<tr>
<td>Metformin</td>
<td>AMPK, ETC</td>
<td>↑FAO, others</td>
<td>C</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>PPARα</td>
<td>↑Fatty acid catabolism</td>
<td>P</td>
</tr>
</tbody>
</table>

Dugnani et al. 2017 Cancer Lett

Kishton et al. 2017 Cell Metab
Will see improvements in use of imaging modalities to track immune response

18F-FHBG-CTL

A Pre-CTL  B Post-CTL

C SUV

$^{89}$Zr-Anti-CD8 minibody


Khun Visith Keu et al., Sci Transl Med 2017;9:eaag2196

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Expansion of immunotherapy therapeutics

- Antibody therapy
  - Checkpoint agonists/inhibitors
  - Antibody-drug conjugates
  - Bispecifics

- Oncolytic viral therapy

- Radiotherapy/Immunotherapy

- Cytokine therapy
  - Bempegaldesleukin
  - N-803

- Cellular therapy
  - Vaccines
    - +/- anti-PD1
  - CAR T, CAR NK
    - CAR NKT, CAR CIK cells emerging
  - TCR transduced T cells
The number of checkpoint agonists and antagonists will expand and be used in combination.
More development and potential approvals of antibody-drug conjugates

<table>
<thead>
<tr>
<th>Emerging antibody-drug conjugates</th>
<th>Target cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirvetuximab canavanine</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Oportuzumab monatox</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td>Denintuzumab mafodotin</td>
<td>B cell malignancies</td>
</tr>
<tr>
<td>Indatuximab ravtansine</td>
<td>Multiple myeloma</td>
</tr>
</tbody>
</table>

Carter and Lazar 2018 Nat Rev Drug Discovery
Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors

<table>
<thead>
<tr>
<th></th>
<th>Adenovirus a</th>
<th>Herpes simplex virus b</th>
<th>Pox virus</th>
<th>Coxsackie virus</th>
<th>Maraba virus</th>
<th>Poliovirus</th>
<th>Measles virus</th>
<th>Newcastle Disease virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>dsDNA</td>
<td>dsDNA</td>
<td>dsDNA</td>
<td>ssRNA</td>
<td>ss (−) RNA</td>
<td>ss (+) RNA</td>
<td>ss (−) RNA</td>
<td>ss (−) RNA</td>
</tr>
<tr>
<td>Genome size</td>
<td>Moderate (32 kb)</td>
<td>Large (152 kb)</td>
<td>Large (130–375 kb)</td>
<td>Small (~8 kb)</td>
<td>Small (11–15 kb)</td>
<td>Small (7.5 kb)</td>
<td>Small (~16 kb)</td>
<td>Small (~15 Kb)</td>
</tr>
<tr>
<td>Cell entry mechanism</td>
<td>Endocytosis</td>
<td>Endocytosis; penetration</td>
<td>Membrane penetration and fusion</td>
<td>Micropinocytosis via epithelial tight junctions</td>
<td>Endocytosis; pH-dependent fusion activation</td>
<td>Receptor-mediated endocytosis</td>
<td>Membrane fusion</td>
<td>Endocytosis; pH-independent direct fusion</td>
</tr>
<tr>
<td>Cell entry receptors</td>
<td>hCAR; VCAM1; CD46</td>
<td>HVEM; nectin 1; nectin 2</td>
<td>GAGs; EFC</td>
<td>CAR; DAF</td>
<td>Unknown</td>
<td>CD155</td>
<td>CD46; SLAM</td>
<td>Neuraminidase receptor; sialoglycoconjugates</td>
</tr>
</tbody>
</table>

aE1B-55 K/E3B-deleted adenovirus in combination with chemotherapy was approved for the treatment of late-stage refractory nasopharyngeal cancer by the Chinese State Food and Drug Administration in 2005. bHerpes simplex virus type 1 (HSV-1) with ICP34.5 deletion and encoding granulocyte–macrophage colony-stimulating factor (GM-CSF) was approved for stage III–IV melanoma treatment by the US Food and Drug Administration in 2015 and by Australia and the European Medicines Agency (EMA) in 2016.

Adapted from Bommareddy et al. 2018 Nat Rev Immunol
Oncolytic viral therapy will continue to expand viral agents, biologics, and target tumors

Guillem Pascual-Pasto et al., Sci Transl Med 2019;11:eaat9321

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Radiation therapy is immunogenic and can be safely combined with checkpoint inhibitor
Radiation therapy will be increasingly used as a means of enhancing immunotherapy

<table>
<thead>
<tr>
<th>Population</th>
<th>Reference</th>
<th>Phase</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced NSCLC</td>
<td>[31]</td>
<td>I</td>
<td>Pembrolizumab + chemoradiotherapy</td>
<td>6-mo PFS rate = 81% 12-mo PFS rate = 69.7% Median PFS = 18.7 mo</td>
</tr>
<tr>
<td>Locally advanced NSCLC</td>
<td>PACIFIC [32–34]</td>
<td>III</td>
<td>Durvalumab (12 mo) as consolidation therapy vs. placebo (12 mo)</td>
<td>ORR = 28.4% vs. 16.0% (p &lt; 0.001) Median PFS = 16.8 mo vs. 5.6 (p &lt; 0.001) 36 months OS = 35.3% vs. 43.5%</td>
</tr>
<tr>
<td>Locally advanced NSCLC</td>
<td>[35]</td>
<td>II</td>
<td>Chemoradiation + pembrolizumab (12 mo) as consolidation therapy</td>
<td>Time to metastatic disease = 30.7 mo PFS = 18.7 mo OS = 35.8 mo</td>
</tr>
<tr>
<td>1–4 metastatic sites NSCLC</td>
<td>[36]</td>
<td>II</td>
<td>Pembrolizumab within 4–12 weeks after locally ablative therapy</td>
<td>Median PFS from the start of locally ablative therapy = 19.1 mo</td>
</tr>
<tr>
<td>Locally advanced HNSCC</td>
<td>[37]</td>
<td>I</td>
<td>Cisplatin-based chemoradiotherapy + pembrolizumab (concurrently + as maintenance)</td>
<td>CR (HPV+) = 85.3% CR (HPV−) = 78%</td>
</tr>
<tr>
<td>Locally advanced HNSCC</td>
<td>JAVELIN H&amp;N 100 [38]</td>
<td>III</td>
<td>Avelumab + chemoradiotherapy + avelumab maintenance vs. Placebo + chemoradiotherapy + placebo maintenance</td>
<td>At the time of the interim analysis: no significant improvement in PFS or OS</td>
</tr>
<tr>
<td>Locally advanced HNSCC (cisplatin-unfit patients)</td>
<td>PembroRad [39]</td>
<td>II</td>
<td>Once-daily RT up to 69.9 Gy associated with Cetuximab vs. pembrolizumab</td>
<td>Loco-regional-control at 15 mo = 59% vs. 50% (p = 0.91) 24-mo PFS = 40% vs. 42% (p = 0.41) 24-mo OS = 55% vs. 62% (p = 0.5)</td>
</tr>
<tr>
<td>Stage III/IV RCC</td>
<td>RADVAX RCC [40]</td>
<td>II</td>
<td>Nivolumab + ipilimumab + SBRT (40-50 Gy in 5 fractions)</td>
<td>PR = 56% SD = 24% PD = 16% 12-mo PFS rate = 36%</td>
</tr>
<tr>
<td>2nd or 3rd line RCC</td>
<td>NIVIS [41]</td>
<td>II</td>
<td>Nivolumab + SBRT (10 Gy x 3 fractions 7 days after the 1st infusion of nivolumab)</td>
<td>ORR = 17.4% 12-mo median OS = 73.4%</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>[42]</td>
<td>I</td>
<td>RT (6-8 Gy, 2-3 times) followed by ipilimumab injections</td>
<td>PR = 18% SD = 18%</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>[43]</td>
<td>I</td>
<td>Ipilimumab + RT (between 18–50 Gy, in 1–15 fractions)</td>
<td>Clinical benefit = 50% PR = 15% CR = 15%</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>[44]</td>
<td>I</td>
<td>Nivolumab + ipilimumab + extracranial RT (30 Gy in 10 fractions or 27 Gy in 3 fractions)</td>
<td>PR outside of the irradiated volume: 6/19 No progression of irradiated metastases</td>
</tr>
</tbody>
</table>

Procureur et al 2021 Cancers
Emerging strategies for combination checkpoint modulators in cancer immunotherapy

Popovic et al. 2019 J Clin Invest
Cytokine “superagonists” will emerge as adjuvants for combination immunotherapy.
Tumor vaccines will re-emerge and become part of standard of care

Table 3 Select ongoing phase 3 studies evaluating cancer vaccines

<table>
<thead>
<tr>
<th>Vaccine platform type</th>
<th>Product name</th>
<th>Antigen(s)</th>
<th>Identifier (phase, name)</th>
<th>Patient population</th>
<th>Enrollment</th>
<th>Regimens</th>
<th>Primary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-based (trivalent DC)</td>
<td>–</td>
<td>Autologous tumor stem cells, survivin, and hTERT</td>
<td>NCT03548571 (phase 2/3, DEN-STEM)</td>
<td>Glioblastoma IDH wild-type, with unmethylated MGMT-gene promoter</td>
<td>60</td>
<td>Trivalent DC immunization vs. radiotherapy with concomitant and adjuvant temozolomide</td>
<td>PFS</td>
</tr>
<tr>
<td>Peptide</td>
<td>GP96 heat shock protein-peptide complex</td>
<td>–</td>
<td>NCT04206254 (phase 2/3)</td>
<td>Liver cancer</td>
<td>80</td>
<td>GP96 vaccination after surgery vs. no treatment after surgery</td>
<td>2-year recurrence-free survival rate</td>
</tr>
<tr>
<td>Adenoviral vector containing the herpes simplex virus thymidine kinase gene</td>
<td>ProstAtak® (AdV-tk) + valacyclovir</td>
<td>–</td>
<td>NCT01436968 (phase 3)</td>
<td>Localized prostate cancer (intermediate risk or one NCCN high-risk feature) due to undergo standard prostate-only EBRT</td>
<td>711</td>
<td>ProstAtak® (AdV-tk) + valacyclovir + radiation therapy vs. androgen deprivation therapy vs. placebo + valacyclovir + radiation therapy vs. androgen deprivation therapy</td>
<td>DFS</td>
</tr>
<tr>
<td>Cell-based (bacterial)</td>
<td>BCG Tokyo-172 strain solution</td>
<td>–</td>
<td>NCT03091660 (phase 3)</td>
<td>Stage 0/0is/1 urothelial carcinoma</td>
<td>969</td>
<td>Tokyo-172 strain BCG (arm 2) vs. Tokyo-172 strain BCG solution with priming (arm 3) vs. TICIB® BCG (arm 1)</td>
<td>Time to high-grade recurrence for arm 1 vs. arm 2, and arm 2 vs. arm 3</td>
</tr>
<tr>
<td>Cell-based (DCs)</td>
<td>DCs plus autologous tumor RNA</td>
<td>–</td>
<td>NCT01983748 (phase 3)</td>
<td>Stage T2, T3, or T4 melanomas of the uvea</td>
<td>200</td>
<td>Autologous DCs loaded with autologous tumor RNA vs. SOC</td>
<td>Prolongation of OS</td>
</tr>
<tr>
<td>Cell-based (tumor cell)</td>
<td>OncoVAX®</td>
<td>–</td>
<td>NCT02448173 (phase 3)</td>
<td>Stage II colon cancer</td>
<td>550</td>
<td>OncoVAX® and surgery vs. surgery</td>
<td>DFS</td>
</tr>
<tr>
<td>Oral vaccine (tablet) derived from pooled blood</td>
<td>Hepcortespenilisum-L (Hepko-V5)</td>
<td>–</td>
<td>NCT02232490 (phase 3, Hepko-V5)</td>
<td>Advanced hepatocellular carcinoma</td>
<td>120</td>
<td>Hepcortespenilisum-L vs. placebo</td>
<td>Changes in plasma AFP</td>
</tr>
<tr>
<td>Cell-based (bacterial)</td>
<td>BCG</td>
<td>–</td>
<td>NCT04165317 (phase 3)</td>
<td>High-risk non-muscle-invasive transitional cell carcinoma of the urethelium and complete resection of all Ta/T1 papillary disease</td>
<td>999</td>
<td>PF-06801591 + BCG induction and maintenance (arm A) vs. PF-06801591 + BCG induction only (arm B) vs. BCG induction and maintenance (arm C)</td>
<td>EFS (arm A vs. arm C and arm B vs. arm C)</td>
</tr>
</tbody>
</table>

Morse et al. 2021 Target Oncol
Immune Effector Cell Therapy Landscape

Genetically modified

TCR (allogeneic)

CAR–T (allogeneic)

Genetically modified

TCR (autologous)

CAR–T (autologous)

Genetically modified

CTL

NK

CAR–NK

Genetically modified

CAR–NKT

Genetically modified

CAR–Macrophage

Genetically modified

CAR–CIK

Genetically modified

Adjunct T cell

TIL

Kauchon et al. 2019 J Pharm Sciences
Enhanced engineering of CAR T and CAR NK will help reduce side effects while improving efficacy.

Jaspers and Brentjens 2017 Pharmacol Ther

Daher et al Blood 2021

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CRISPR-based editing of immune effector cells
CARs in development for hematologic malignancies

- **CD20** (B cell cancers)
- **CD22** (B cell cancers)
- **CD23** (B cell cancers)
- **CD30** (B cell cancers)
- **CD37** (B and T cell cancers)
- **ROR1** (lymphoid cancers)
- **CD133** (lymphoid and myeloid cancers)
- **TSLPR** (lymphoid cancers)
- **BCMA** (multiple myeloma)
- **CS1** (multiple myeloma)
- **CD138** (multiple myeloma)
- **CD5** (T cell cancers)
- **CCR4** (T cell cancers)
- **CD7** (T cell and myeloid cancers)
- **CD33** (myeloid cancers)
- **CD123** (myeloid cancers)
- **Lewis-Y** (myeloid cancers)
- **CD44v6** (myeloid cancers)
- **CLL-1** (myeloid cancers)
- **Folate receptor beta** (myeloid cancers)
- **FLT3** (myeloid cancers)
- **NKG2D** (myeloid cancers)
CARs in development for solid tumors

- **AFP** (liver cancer)
- **ALK** (neuroblastoma)
- **Carbonic anhydrase IX** (kidney cancer)
- **CD24** (ovarian cancer)
- **CD70** (kidney cancer)
- **CD133** (liver, brain, breast cancer)
- **CD171** (neuroblastoma)
- **CD276** (multiple histologies)
- **CEA** (lung, colorectal, gastric, pancreatic cancers and liver metastases)
- **cMet** (breast cancer)
- **CSFR1** (tumor-associated macrophages)
- **EGFR** (lung, colorectal, ovary, pancreatic cancer)
- **EGFRvIII** (gliomas, glioblastoma)
- **EpCAM** (liver, stomach and colon cancer)
- **EphA2** (glioma)
- **Fibroblast activation protein** (mesothelioma)
- **Folate receptor alpha** (breast, ovarian cancer)
- **GD2** (neuroblastoma, sarcomas and melanoma)
- **Glypican-3** (liver, lung cancer)
- **HER2** (breast cancer, glioblastoma, ovarian, lung, pancreatic, sarcoma and medulloblastoma)
- **IL-13Rα** (gliomas)
- **Lewis-Y** (breast cancer)
- **Mesothelin** (pancreatic, ovarian, mesothelioma, breast cancer)
- **MG7** (liver metastases)
- **MUC-1** (breast, liver, lung, pancreatic, glioma, colorectal, gastric cancer)
- **NKG2D** (multiple histologies)
- **PSCA** (pancreatic cancer)
- **PSMA** (prostate cancer)
- **TEM8/ANTRX1** (breast cancer)
- **VEGFR2** (multiple histologies)
Combination strategies to improve CAR efficacy will be used for solid tumors

Scarfo and Maus 2017 J Immunother Cancer
TCR transduced T cells will provide durable responses in solid tumors

NY-ESO-1

D’Angelo et al. 2018 Cancer Discov

MAGE-A3

Lu et al. 2017 J Clin Oncol

29 months

18 months

4 months
Conclusions

• The future of cancer immunotherapy is bright, with advances occurring in both diagnostics and therapeutics at a rapid pace

• We will see improvements in our ability to distinguish immunologically “hot” vs. “cold” tumors, and potentially be able to convert “cold” into “hot” tumors

• Advances in genetic engineering and biomanufacturing will permit development of “next generation” antibodies, viruses, targeted radiotherapies and cellular therapies for cancer.