Novel Drugs In Early Development

Rana R. McKay
Associate Professor of Medicine
University of California San Diego
Disclosures

• Consulting/Advisory Board – Aveo, AstraZeneca, Bayer, Bristol Myers Squib, Calithera, Caris, Denderon, Exelixis, Janssen, Merck, Myovant, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Tempus.

• Institutional Research Funding – Bayer, Tempus.
Approaches to Target RCC
Novel Targets

- **Anti-Angiogenics**
  - Belzutifan
  - ARO-HIF2
  - NKT2152
  - XL-092

- **Immunomodulators**
  - Botensilimab + Balstilimab
  - Relatlimab
  - Linrodostat
  - SRF-388
  - Ciforadenant
  - ALLO-316

- **Direct Tumor Cell Killing**
  - DS-6000a
  - $^{177}$Lu-Girentuximab
  - Palbociclib
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kcrs.kidneycon.org
Targeting the HIF Pathway

Normoxia

Hypoxia

Prolyl hydroxylation

pVHL

HIF-α

HIF-α

HIF-α

HIF-β

HRE

Proteasomal degradation

UB

UB

UB

UB

UB

UB
Belzutifan

**LITESPARK-001 – Phase 1 Belzutifan in RCC**

**Key Eligibility Criteria**
- Locally advanced/metastatic solid sporadic ccRCC
- Received ≥1 prior treatment for ccRCC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

**Median number of prior lines 3**

**Primary end point: Safety**

**Secondary end point: PFS, ORR, DOR per RECIST v1.1 by investigator**

**Belzutifan**
120 mg orally QD
Up to 1 year

**Objective Response Rate 25%**

**Progression Free Survival**
14.5 months

**MK-6482-005 – Phase 3 Belzutifan in RCC**

**Key Eligibility Criteria**
- Age ≥18 years
- Unresectable locally advanced/metastatic ccRCC
- Previously received ≥3 systemic regimens
- Measurable disease per RECIST v1.1

**Key End Points**
- Primary: PFS and OS
- Key secondary: DOR, ORR, and PRO
- Other secondary: safety and tolerability

**Belzutifan – Small molecule inhibitor of hypoxia-inducible factor 2α**

Jonasch et al, ASCO Annual Meeting, 2022

RCC=Renal cell carcinoma.
Belzutifan + Cabozantinib

LITESPARK-003 – Phase 2 Belzutifan + Cabozantinib in RCC

Objective Response Rate 57%

Objective Response Rate 31%

RCC: Renal cell carcinoma.
Belzutifan Combination Studies

MK-6482-012 – Phase 3
Combination Belzutifan in Front Line

- **Arm A**: Belzutifan 120 mg PO QD + Pembrolizumab 400 mg IV Q6W + Lenvatinib 26 mg PO QD

- **Arm B**: Quavolimab 25 mg/Pembrolizumab 400 mg IV Q6W coformulation + Lenvatinib 26 mg PO QD

- **Arm C**: Pembrolizumab 400 mg IV Q6W + Lenvatinib 26 mg PO QD

**Key Eligibility Criteria**
- Advanced or metastatic ccRCC
- No prior systemic therapy
- Measurable disease per RECIST v1.1
- KPS score ≥70%

**Key Assessments**
- Tumor imaging at week 12 then Q6W up to week 78 and Q12W thereafter

**End Points**
- Primary: PFS per RECIST v1.1 by BICR, OS
- Secondary: ORR per RECIST v1.1 by BICR, DCR per RECIST v1.1 by BICR, safety, and tolerability

MK-6482-011 – Phase 3
Belzutifan + Lenvatinib in Second Line

- **Arm A**: Belzutifan 120 mg PO QD + Lenvatinib 20 mg QD

- **Arm B**: Cabozantinib 60 mg QD

**Key Eligibility Criteria**
- Advanced or metastatic RCC with clear cell component
- Disease progression after first- or second-line anti-PD-1/PD-L1 therapy
- Immediately preceding therapy must be anti-PD-1/PD-L1
- Received ≥2 prior systemic therapies
- Measurable disease per RECIST v1.1
- KPS score ≥70%

**Key Assessments**
- Q8W imaging follow-up through week 60, then Q12W thereafter
- Q12W survival follow-up status for patients with documented progression

**End Points**
- Primary: PFS, OS
- Secondary: ORR, DOR, safety, and tolerability

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Choueiri et al, GU ASCO, 2022; Motzer et al, GU ASCO, 2022
ARO-HIF2 – Synthetic double-stranded RNA interference trigger designed to silence HIF-2α expression

Phase 1 Study

Cohort 1: 225 mg, weekly
Cohort 2: 525 mg, weekly
Cohort 3: 1050 mg, weekly

Treatment Duration and Response

- 8% Objective response rate
- 39% Disease control rate

Brugarolas et al, GU ASCO, 2022
NKT2152 – Small molecule inhibitor of hypoxia-inducible factor 2α

Phase 1/2 NTK2152 in Treatment Refractory Disease

Eligibility
- Clear Cell RCC
- Prior treatment (1-4 including ICB)
- Measurable disease
- ECOG 0-2

Primary Endpoints: Safety, Recommended Phase 2 dose, Objective response rate

NiKang Therapeutics and AVEO Oncology Announce a Clinical Trial Collaboration and Supply Agreement to Evaluate the Combination of NKT2152, a HIF2α Inhibitor, and FOTIVDA® (tivozanib) for the Treatment of Advanced Clear Cell Renal Cell Carcinoma

- Phase 2 Clinical Trial Targeted to Commence in 2022 -
XL-092

Similar target profile to cabozantinib with a shorter clinical half-life and pharmacokinetic properties suitable for once daily oral dosing

**XL092 – Multi-targeted inhibitor of receptor tyrosine kinases MET, VEGFR2, and TAM kinases**

**XL092 Targets Pathways Associated with Tumor Immunosuppression**

**STELLAR-001** – Phase 1 XL-092 alone or in combination with atezolizumab or avelumab in solid tumors

**STELLAR-002** – Phase 1 XL-092 in combination with nivolumab or nivolumab + ipilimumab in solid tumors

Hsu et al, Eur J Cancer, 2020; Sharma et al GU ASCO, 2022; Choueiri et al, ASCO, 2022
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Targeting the RCC Immune Microenvironment

Stimulatory and inhibitory immune checkpoints

Novel cytokine based therapies to activate T cell responses

Targeting immune metabolic pathways
Botensilimab + Balstilimab

Botensilimab – Fc-enhanced CTLA-4 inhibitor
Botensilimab – PD-1 inhibitor

C-800 Study Design: MSS CRC
NCT03980272: First-in-human trial of botensilimab + balstilimab in patients with advanced cancer

Key Eligibility
- Dose Escalation
  - Advanced solid tumors refractory to standard treatment
  - Prior IO therapy allowed

TREATMENT (up to 2 years)

ENDPOINTS
- Efficacy
  - ORR
  - DCR (SD, CR or PR)
  - PFS
  - OS
- Safety
  - AEs
  - TRAEs
  - IARs

Overall MSS CRC (N=41)

Change in Target Lesions (%)
Relatlimab

Relativity-047 – Phase 2–3, double-blind, randomized trial in previously untreated metastatic or unresectable melanoma
Primary Endpoint – PFS by BICR

FRACTION RCC – Phase 2, open-label, randomized trial (Fast Real-Time Assessment of Combination Therapies in Immuno-Oncology)
Primary Endpoint – Objective Response Rate

Linrodostat – IDO Inhibitor
BMS-813160 – Chemokine receptor (CCR2/5) dual antagonist
Linrodostat

Linrodostat – Indoleamine 2,3-dioxygenase 1 (IDO-1) inhibitor which reduces kynurenine production

FRACTION RCC – Phase 2, open-label, randomized trial (Fast Real-Time Assessment of Combination Therapies in Immuno-Oncology)
Primary Endpoint – Objective Response Rate

ECHO-202/KEYNOTE-037 – Phase 1/2 Open-Label study of Epacadostat Plus Pembrolizumab in Patients With Advanced Solid Tumors

KEYNOTE-679/ECHO-302

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Terminated given negative phase 3 melanoma study

SOC=Standard of care; TKI=Tyrosine kinase inhibitor.

Mitchell et al, JCO, 2018
SRF-388

IL-27 is an immunoregulatory cytokine which upregulates inhibitory immune checkpoint receptors (e.g., PD-L1, TIGIT) and downregulates pro-inflammatory cytokines (e.g., IFNγ, TNFα).

SRF388 – First-in-class anti-IL-27 antibody

SRF388-101 – Phase 1 First-in-Human Study

ccRCC Dose Expansion
100% with prior IO and VEGF targeted therapy

RP2D 10 mg/kg IV every 4 weeks as monotherapy and 3 weeks with pembrolizumab
Ciforadenant

Adenosine blocks T-cell activation and promotes myeloid suppression

Ciforadenant – Small molecule inhibitor targeting adenosine-2A receptors

Fong et al, Cancer Discovery, 2020

cccRCC=Clear cell renal cell carcinoma; IO=Immuno-oncology; VEGF=Vascular endothelial growth factor; RP2D=Recommended phase 2 dose.

Phase 1B (N=8)
Ipilimumab + Nivolumab + Ciforadenant

-ccRCC-No prior systemic therapy

Phase 2 (N=42)
Ipilimumab + Nivolumab + Ciforadenant

Primary Endpoint – Safety (P1); Depth of response (P2)
PI – K. Beckerman

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cccRCC=Clear cell renal cell carcinoma; IO=Immuno-oncology; VEGF=Vascular endothelial growth factor; RP2D=Recommended phase 2 dose.

Fong et al, Cancer Discovery, 2020
ALLO-316 CAR-T

ALLO-316 – Allogeneic anti-CD70 AlloCAR T™

CD70 is expressed in RCC with limited normal tissue expression

A: CD70 expression in RCC (Tumor vs. Normal)
B: CD70 expression in RCC (Primary Tumor vs. Cell Lines)
C: CD70 expression in Tumor and Tumor Tumors
D: CD70 expression in Activated T cells

CD70 CARs with optimal off-switch showed anti-tumor efficacy in multiple in vivo models

C: Tumor Volume
D: Tumor Growth

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DS-6000a

- Cadherin 6 is involved in cell-cell adhesion and epithelia-mesenchymal transition
- Cadherin 6 is overexpressed in RCC
- Preclinical studies demonstrated inhibited tumor groups and tumor regression
- DS-6000a is a cadherin 6 directed ADC with three components

RCC = Renal cell carcinoma; ADC = Antibody drug conjugate.
**177Lu-Girentuximab**

- **177Lu-Girentuximab – 177Lu-labeled anti-carbonic anhydrase IX monoclonal antibody**

- CAIX is a cell surface glycoprotein expression in >90% of clear cell RCC and rarely expressed in normal tissue

- Radiolabeling anti-CAIX monoclonal antibody girentuximab with 177Lu has promise a therapeutic agent

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**STARLITE 2 Trial – Now Enrolling**

<table>
<thead>
<tr>
<th>Safety lead-in Phase (3+3 design)</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Level 1</strong> 177Lu-girentuximab 1804 MBq/m²</td>
<td><strong>177Lu-girentuximab MTD + Nivolumab 240mg q2 weeks</strong></td>
</tr>
<tr>
<td>0/3 or 1/6 DLTs 177Lu-girentuximab 2405 MBq/m²</td>
<td>Simon Stage 1 N=10*</td>
</tr>
<tr>
<td>≥ 2/6 DLTs 177Lu-girentuximab 1353 MBq/m²</td>
<td>Simon Stage 2 N=15</td>
</tr>
</tbody>
</table>

Nivolumab 240mg q2 weeks

*includes patients treated at the MTD during the safety lead-in phase

Abbreviations: DLT, dose-limiting toxicity; MTD, maximal tolerated dose
Palbociclib

CDK4 and CDK6 are canonically involved in cell cycle checkpoint control; dysregulation plays a role in RCC and may be a good therapeutic target.

HIF-Independent synthetic lethality between CDK4/6 inhibition and VHL loss

Phase 2 Multi-Center, Single-arm Study

Treatment Naïve Advanced Clear Cell RCC

N=25

Primary Endpoint – ORR

PI – B. McGregor

Avelumab, Axitinib + Palbociclib
Novel Therapeutic Agents in RCC

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Questions?

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