ORIC Pharmaceuticals: Dedicated to Overcoming Resistance in Cancer

Lead program targeting primary resistance pathway for multiple cancers

- Potent and selective glucocorticoid receptor antagonist entering multiple phase 1b studies in 2019

Additional pipeline candidates focused on key resistance mechanisms

- Potential best-in-class and first-in-class programs targeting resistance to multiple therapeutic classes

Internal drug discovery capabilities support further pipeline expansion

- Expertise in nuclear hormone receptors and in identifying novel targets involved in therapy resistance

Leadership team with significant oncology experience

- Distinguished founders, investors and management with proven track records of success
Founders and Investors with Significant Oncology Experience

Distinguished Founders and Scientific Advisors

Charles Sawyers, MD  
Founder, SAB  
- MSKCC and HHMI Investigator  
- Key role in discovery and development of Gleevec, Sprycel, Xtandi and Erleada  
- National Academy of Sciences  
- Institute of Medicine

Scott Lowe, PhD  
Founder, Consultant  
- MSKCC and HHMI Investigator  
- Chair, Cancer Biology & Genetics and Cancer Research  
- Expert in tumor networks, and molecular determinants of treatment response

Rich Heyman, PhD  
Founder, BOD Chair  
- CEO-founder Aragon (sold to Johnson & Johnson)  
- CEO-founder Seragon (sold to Roche)  
- Board member at Gritstone, Vividion, Metacrine

Richard Scheller, PhD  
BOD Member, SAB  
- CSO and Head of Therapeutics 23andMe  
- Previously CSO Genentech  
- National Academy of Sciences

Over $120 Million Raised in Series A/B/C

THE COLUMN GROUP  
Fidelity Investments  
Trinitas Capital Management  
Memorial Sloan Kettering Cancer Center  
City Hill Ventures

Topspin  
OrbiMed  
Kravis Investment Partners  
EcoR1 Capital  
NS Investment  
Taiho Ventures, LLC  
Foresite Capital
### Executive Team with Expertise in Building Leading Oncology Companies

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jacob Chacko, MD</strong></td>
<td>Chief Executive Officer</td>
<td>• Previously CFO of Ignyta (acquired by Roche), raised over $500mm in capital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TPG Capital (completed $10bn of aggregate acquisitions) and McKinsey</td>
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<tr>
<td></td>
<td></td>
<td>• Board member of Turning Point Therapeutics and 4D Molecular Therapeutics; previously Bonti, RentPath, EnvisionRx, Par Pharma, IMS, Quintiles</td>
</tr>
<tr>
<td><strong>Pratik Multani, MD</strong></td>
<td>Chief Medical Officer</td>
<td>• Previously CMO of Ignyta, led development and regulatory for entrectinib &amp; other clinical assets</td>
</tr>
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<td></td>
<td></td>
<td>• CMO of Fate Therapeutics; development leadership at Salmedix, Kanisa and Kalypsys</td>
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<tr>
<td></td>
<td></td>
<td>• Contributed to development of Rituxan and Zevalin at Idec; earlier at Dana Farber and Mass General</td>
</tr>
<tr>
<td><strong>Matt Panuwat</strong></td>
<td>Chief Business Officer</td>
<td>• Previously SVP of BD at Prothena, established R&amp;D collaboration with Celgene for up to $2.2bn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Head of BD at Medivation (acquired by Pfizer), led M&amp;A including the acquisition of talazoparib</td>
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<td></td>
<td></td>
<td>• Global Healthcare Investment Banking at Merrill Lynch</td>
</tr>
<tr>
<td><strong>Edna Chow Maneval, PhD</strong></td>
<td>SVP Clinical Development</td>
<td>• Previously SVP of CD at Ignyta; clinical lead for entrectinib, led transition team through global filings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• VP of CD at Seragon and Aragon, clinical lead for apalutamide</td>
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<tr>
<td></td>
<td></td>
<td>• Led pivotal phase 3 study in RCC for Sutent at Pfizer</td>
</tr>
</tbody>
</table>
ORIC Strategy Focuses on Resistance to Multiple Treatment Modalities

- Chemotherapy
- Immune Therapy
- Targeted Therapy
- Hormone Therapy
**Pipeline of Assets Focused on Resistance in Oncology**

<table>
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<tr>
<th>Exploratory / Hit ID</th>
<th>Lead ID / Optimization</th>
<th>Preclinical / IND Enabling</th>
<th>Phase 1</th>
<th>Potential to Overcome Resistance to:</th>
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<tbody>
<tr>
<td>ORIC-101 (GR Antagonist)</td>
<td>Phase 1a Complete Phase 1b Initiated 2Q19</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
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<tr>
<td>CD73</td>
<td></td>
<td>✅</td>
<td>✅</td>
<td></td>
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<tr>
<td>Target 3</td>
<td></td>
<td>✅</td>
<td></td>
<td>✅</td>
</tr>
</tbody>
</table>

**Potential to Overcome Resistance to:**

- Chemotherapy
- Immune Therapy
- Hormone Therapy
- Targeted Therapy

**Additional programs generated from research platform and in-licensing**
Glucocorticoid Receptor (GR) Overview
Glucocorticoids Act Via the Glucocorticoid Receptor and Regulate Multiple Physiological Processes

1. Glucocorticoids regulate metabolism, cell growth, inflammation, apoptosis and differentiation

2. Glucocorticoids signal through the glucocorticoid receptor (GR), a nuclear receptor expressed across a variety of tissues

3. Upon ligand binding, GR translocates to nucleus & triggers transcription of a spectrum of genes


Note: HSP: heat shock protein, GRE: glucocorticoid response element.
GR is Overexpressed in Many Solid Tumors and Associated with Therapy Resistance

GR Overexpressed in Many Solid Tumors (1)

Tumors with High GR Expression Associated with Worse Clinical Outcomes (Chemotherapy Treated ER- Breast Cancer Patients) (2)

- Elevated GR expression also correlated with poor prognosis in:
  - Endometrial cancer (3)
  - CRPC treated with enzalutamide (4)


(3) Tangen et al. Gynecol Oncol (2017).
GR Expression is Associated with Clinical Resistance to Enzalutamide in the Treatment of Prostate Cancer

Elevated GR Expression Seen in Tumors of Patients Responding Poorly to Enzalutamide Treatment

- All 3 patients with high GR expression at baseline had a poor clinical response to enzalutamide

Elevated GR Expression Associated with a Limited PSA Response in Enzalutamide-Treated Patients

* p = < 0.05, ** p = < 0.01.

Initial observations from Sawyers’ lab established a correlation between increased GR expression and poor clinical response to enzalutamide, and raised the possibility that AR inhibition may induce GR expression in some patients.


Note: Patients who continued to benefit from enzalutamide therapy for greater than 6 months were defined as good responders, whereas those in whom therapy was discontinued earlier than 6 months due to a lack of clinical benefit were classified as poor responders.

*: p < 0.05, **: p < 0.01.
In Addition to Direct Action on Tumor, GR May Also Modulate Therapy Response by Acting on the Immune System

**GR Acts as a Pro-Survival Mechanism in Tumors**

- Glucocorticoids
  - ↓ Apoptosis
  - ↓ Adhesion
  - ↓ Inflammation
  - ↑ "Stemness"
  - Metabolic changes

**GR Inhibits Immune Function in the Tumor Microenvironment**

- ↑ Tregs
- ↑ MDSCs
- ↓ CD8+ T cells

Note: Treg: T regulatory cell, MDSC: myeloid-derived suppressor cell.

- Counteracting GR is expected to block the transcriptional program driving tumor cell survival and therapy escape
- Counteracting GR is expected to stimulate the immune system and overcome resistance to therapy
ORIC-101 Overview
ORIC-101 is a Potent and Selective GR Antagonist that was Specifically Designed for Development in Oncology

ORIC-101 is a potent and selective GR antagonist without CYP liabilities of other molecules (CYP2C8 plays a critical role in metabolism of taxanes and enzalutamide)

Source: ORIC data.
Note: GR: glucocorticoid receptor, AR: androgen receptor, PR: progesterone receptor. GR antagonism, AR antagonism and PR antagonism measured by luciferase assay.
ORIC-101 Overcomes GR-Driven Chemotherapy Resistance Across a Wide Range of Human Cancer Cell Lines

Source: Jahchan et al. AACR NCI EORTC Poster (2017) and additional ORIC data.

Note: Chemotherapeutic agent is gemcitabine for ovarian cancer and paclitaxel for TNBC and NSCLC. GR ligand is dexamethasone.
Comparable activity demonstrated in xenograft models of ovarian cancer, other TNBC and in combination with other classes of chemotherapy.

Source: ORIC data.

Note: HCC-1806 xenograft model. Paclitaxel dosed 15 mg/kg, Q3Dx5, IP. ORIC-101 dosed 150 mg/kg, QD, PO. Cortisol added to drinking water throughout study. Cortisol supplementation required for xenograft models to activate human GR since primary glucocorticoid utilized by rodents is corticosterone. Cortisol levels intended to simulate physiological corticosteroid levels in humans.
GR activation by glucocorticoid treatment (e.g. dexamethasone) drives enzalutamide resistance in vitro; ORIC-101 resensitizes these prostate cancer cells to enzalutamide

Source: ORIC data.
Recently Completed Phase 1a Study Supports Broad Clinical Development Strategy for ORIC-101

**Phase 1a: Single Agent PK, PD, and Safety**  
(Complete)

- **Phase 1a**  
  NHV Single Ascending Dose

**Phase 1b: Multiple Indications and Combinations**

- **Phase 1b**  
  Solid tumors  
  ORIC-101 + Abraxane  
  - Start: 2Q19  
  - Data:  
    - Initial Safety / PK (4Q19)
    - RP2D (1Q20)
    - Initial Translational / Efficacy (1H20)

- **Phase 1b**  
  Prostate cancer  
  ORIC-101 + AR modulator  
  - Start: 3Q19  
  - Data:  
    - Initial Safety / PK (1H20)
    - Initial Translational / Efficacy (2H20)

- **Phase 1b**  
  Solid tumors  
  ORIC-101 + PD-1 / PD-L1  
  - Start: 4Q19  
  - Data:  
    - Initial Safety / PK (1H20)
    - Initial Translational / Efficacy (2H20)

Note: NHV: normal healthy volunteer.
**ORIC-101 Demonstrated a Favorable Safety and Tolerability Profile in Phase 1a**

<table>
<thead>
<tr>
<th>Treatment-Emergent AEs</th>
<th>All doses (n=56)</th>
<th>200 mg (n=6)</th>
<th>350 mg (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade &gt;2</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Catheter site swelling</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Proctalgia</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

All adverse events observed across phase 1a studies were limited to grade 1; higher rate of GI events at 350 mg attributed, at least in part, to pill burden of the early clinical formulation (7 capsules)

Source: ORIC data.
Exposure of ORIC-101 from the Phase 1a Multiple-Ascending Dose Study Supports Once-Daily Dosing

Steady-state Cmax and AUC increased in a dose dependent manner

Half Life (t_{1/2}) = 14-15 hours

Source: ORIC data.
Mean Plasma Cortisol Levels Increased with ORIC-101 GR Inhibition in the Phase 1a Multiple-Ascending Dose Study

Mean waking plasma cortisol concentrations increased over time with once-daily ORIC-101 (44% increase on day 8 in 200 mg cohort and 78% increase on day 10 in 350 mg cohort); plasma cortisol concentrations decreased after ORIC-101 was discontinued.

Source: ORIC data.
ORIC-101 was associated with downregulation of key pharmacodynamic biomarkers of GR activity in the Phase 1a multiple-ascending dose study.

**FKBP5 Expression**

- **Day 1**: 0hr, 12hr
- **Day 8**: 0hr, 12hr
- **Day 10**: 0hr, 12hr

**DDIT4 Expression**

- **Day 1**: 0hr, 12hr
- **Day 8**: 0hr, 12hr
- **Day 10**: 0hr, 12hr

**Rapid and sustained functional GR inhibition were demonstrated in PBMCs of healthy volunteers with once-daily ORIC-101**

Source: ORIC data.

Note: ORIC-101 was dosed once daily for 10 days. PBMC: peripheral blood mononuclear cell, FKBP5: FK506 binding protein, DDIT4: DNA-damage-inducible transcript 4 protein.
ORIC Will Broadly Explore PD Activity and Predictive Biomarkers to Determine Patient Selection and Confirm Target Engagement in Phase 1b

- PD biomarker modulation will be measured to assess target engagement and pathway modulation similar to phase 1a
  - Cortisol levels in plasma
  - GR target genes in PBMCs (e.g. FKBP5, DDIT4, GILZ)

- Proprietary CLIA IHC test developed by ORIC will be used for patient stratification

- Proprietary GR gene activation signature developed by ORIC will be used for patient stratification and monitoring PD modulation
  - Developed using NGS and NanoString technologies

Note: CLIA: clinical laboratory improvement amendments, NGS: next-generation sequencing.
## Phase 1b Study of ORIC-101 in Combination with Abraxane in Patients with Solid Tumors Initiated in 2Q19

<table>
<thead>
<tr>
<th>Phase 1b: Dose Identification (n = 3-6 per dose level)</th>
<th>Phase 1b: Dose Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Level 1</strong>&lt;br&gt;ORIC-101: 240 mg QD D1-21 + Nab-paclitaxel: 100 mg/m² D1/8/15</td>
<td><strong>Cohort 1+</strong>&lt;br&gt;ORIC-101: RP2D QD D1-21 + Nab-paclitaxel: 100 mg/m² D1/8/15</td>
</tr>
<tr>
<td><strong>Dose Level 2</strong>&lt;br&gt;ORIC-101: 320 mg QD D1-21 + Nab-paclitaxel: 100 mg/m² D1/8/15</td>
<td><strong>Indications Under Consideration:</strong> TNBC, pancreatic, ovarian and endometrial</td>
</tr>
<tr>
<td><strong>Dose Level 3</strong>&lt;br&gt;ORIC-101: 400 mg QD D1-21 + Nab-paclitaxel: 100 mg/m² D1/8/15</td>
<td><strong>Dose Level 4</strong>&lt;br&gt;ORIC-101: 480 mg QD D1-21 + Nab-paclitaxel: 100 mg/m² D1/8/15</td>
</tr>
</tbody>
</table>

Initial ORIC-101 dose expected to be active based on phase 1a data

- Dose identification: Standard schedule of Abraxane (nab-paclitaxel) with escalating doses of ORIC-101 in patients with solid tumors
  - Enrollment not limited by GR status
- Dose expansion: Patients with certain solid tumors based upon baseline GR status
- Data will be generated from collection of archival tumor tissue, pre and on-treatment biopsies, and PBMCs

*Initial combination safety data expected in 4Q19 followed by preliminary efficacy / translational data in 1H20*

Note: 28-day cycles.
Phase 1b Study of ORIC-101 in Combination with an AR Modulator in Patients with Castration-Resistant Prostate Cancer Progressing on an AR Modulator

**Phase 1b: Dose Identification (n = 3-6 per dose level)**

- **Dose Level 1**
  - ORIC-101: 320 mg QD + AR modulator

- **Dose Level 3**
  - ORIC-101: 400 mg QD + AR modulator

- **Cohort 1+**
  - ORIC-101: RP2D QD + AR modulator

**Phase 1b: Dose Expansion**

- **Dose Level 3**
  - ORIC-101: 480 mg QD + AR modulator

- **Initial ORIC-101 dose expected to be active based on phase 1a data**

- Patients with chemotherapy-naïve metastatic CRPC with evidence of disease progression while on treatment with an AR modulator
  - Exclude patients who progress within 3 months of starting AR modulator treatment to exclude primary refractory patients
  - Dose identification: Continued standard dose of an AR modulator with escalating doses of ORIC-101
    - Enrollment not limited by GR status
  - Dose expansion: Additional patients treated with ORIC-101 at RP2D in combination with an AR modulator
  - Assess safety, PK, PD and initial evidence for clinical activity (PSA decline, imaging, CTC conversion)

**Initial combination safety data expected in 1H20 followed by preliminary efficacy / translational data in 2H20**

Note: AR modulators under consideration include enzalutamide and apalutamide.
ORIC-101 Commencing Three Phase 1b Studies in 2019 Across Multiple Indications In Combination with Various Treatment Regimens

<table>
<thead>
<tr>
<th></th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1b Solid tumors + Abraxane</td>
<td>Initial Efficacy / Translational Data</td>
<td>Initial Efficacy / Translational Data</td>
<td>Initial Efficacy / Translational Data</td>
</tr>
<tr>
<td>Phase 1b Prostate cancer + AR modulator</td>
<td>Initial Efficacy / Translational Data</td>
<td>Initial Efficacy / Translational Data</td>
<td>Initial Efficacy / Translational Data</td>
</tr>
<tr>
<td>Phase 1b Solid tumors + PD-1 / PD-L1</td>
<td>Initial Efficacy / Translational Data</td>
<td>Initial Efficacy / Translational Data</td>
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Pipeline
## Pipeline of Assets in Addition to ORIC-101 Focused on Resistance in Oncology

<table>
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<tr>
<th>Exploratory / Hit ID</th>
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<td>Phase 1a Complete Phase 1b Initiated 2Q19</td>
<td></td>
<td></td>
<td>• Phase 1b initiated in 2Q19</td>
</tr>
<tr>
<td><strong>CD73</strong></td>
<td>Potential best-in-class oral small molecule targeting the adenosine pathway</td>
<td></td>
<td></td>
<td>• Candidate selection in 2H19</td>
</tr>
<tr>
<td><strong>Target 3</strong></td>
<td>Potential first-in-class candidate targeting an oncogenic driver and mechanism of resistance in squamous cancers</td>
<td></td>
<td></td>
<td>• Antibody discovery initiated</td>
</tr>
</tbody>
</table>

*Additional programs generated from research platform and in-licensing*
CD73, a Broadly Expressed Ecto-nucleotidase in the Adenosine Pathway, Has Been Linked to Therapy Resistance

- CD73 coordinately converts AMP to adenosine
  - Overexpressed across cancer types driving local elevation of adenosine
  - Expression correlated with poor prognosis
  - Mediates immunosuppression and chemoresistance via adenosine production
  - Upregulated in response to PD-1 / PD-L1 and CTLA-4 inhibition

**Therapeutic Hypothesis**
- CD73 inhibition may enhance activity of chemotherapy and immunotherapy
- Small molecule approach may differentiate in safety profile, dosing regimen and tumor penetration

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Several Value-Inflection Points Across the ORIC Portfolio Expected Over the Coming Years

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
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<tr>
<td><strong>Biology</strong></td>
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<td>Cell Line / Scale Up / IND Enabling</td>
<td>IND Filing</td>
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<tr>
<td><strong>Lead Generation</strong></td>
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<td>IND Enabling</td>
<td>IND Filing</td>
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<td><strong>Cell Line / Scale Up / IND Enabling</strong></td>
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<td>IND Filing</td>
<td>IND Filing</td>
</tr>
<tr>
<td><strong>Clinical Candidate</strong></td>
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<tr>
<td><strong>IND Filing</strong></td>
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</tbody>
</table>

- **Phase 1b Solid tumors + Abraxane**
  - Initial PK / Safety Data
  - Initial Efficacy / Translational Data

- **Phase 1b Prostate cancer + AR modulator**
  - Initial PK / Safety Data
  - Initial Efficacy / Translational Data

- **Phase 1b Solid tumors + PD-1 / PD-L1**
  - Initial PK / Safety Data
  - Initial Efficacy / Translational Data
ORIC Vision: Become a Leading Oncology Company at the Forefront of Overcoming Resistance in Cancer

2015 – 2018
- Advance lead GR program from concept to clinic
- Build pipeline of resistance targets

2019 – 2020
- Progress ORIC-101 through multiple clinical studies
- Advance second program into clinical development

2021 – 2023
- Conduct ORIC-101 registrational studies
- Expand clinical and preclinical pipeline

2024+
- Commercialize ORIC-101
- Progress second program through registrational studies

Upcoming Milestones and Clinical Updates
- Phase 1b: ORIC-101 + Abraxane in solid tumors
  - Study start: 2Q19
  - Preliminary efficacy / translational data: 1H20
- Phase 1b: ORIC-101 + AR modulator in castration-resistant prostate cancer
  - Study start: 3Q19
  - Preliminary efficacy / translational data: 2H20
- Phase 1b: ORIC-101 + PD-1 / PD-L1 in solid tumors
  - Study start: 4Q19
  - Preliminary efficacy / translational data: 2H20
- CD73 candidate selection: 2H19