Targeting Critical Immune Drivers of Cancer and Inflammation

37th Annual J.P. Morgan Healthcare Conference
January 2019
FLX Bio: Unique Approach to Targeting Critical Immune Drivers of Cancer and Inflammation

- Robust pipeline of first-in-class oral small molecule agents
  - FLX475 (Cancer): Selectively targeting tumor T_{reg} in Phase 1/2 oncology study mono/combo with Keytruda®
  - FLX193 (Allergy): Targeting validated Th2 pathway
  - GCN2 Program (Cancer)
  - HPK1 Program (Cancer)

- Growing pipeline driven by big data and machine learning

- Predictive biomarker approach to patient selection

- Supported by top tier investors, strong management team and a world-class SAB
# FLX Bio Pipeline: Best-in-Class Compounds Targeting Critical Immune Drivers

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
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<tbody>
<tr>
<td>FLX475 (CCR4) Cancer</td>
<td>Monotherapy</td>
<td>PD1 Combination</td>
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<tr>
<td>FLX193 (CCR4) Inflammation</td>
<td>Atopic Dermatitis</td>
<td>Asthma</td>
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<tr>
<td>GCN2 Cancer</td>
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<tr>
<td>Discovery Targets</td>
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<tr>
<td>(HPK1 &amp; other undisclosed)</td>
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FLX475: CCR4 Antagonist for Cancer

Best-in-Class Oral CCR4 Antagonist That Selectively Blocks Tumor $T_{reg}$ with Phase 2 Readout in 2019
CCR4 Protein on T_{reg} Cells Drives Tumor Progression

- Regulatory T cells (T_{reg}) are critical drivers of immune suppression in tumor
- T_{reg} recruited into tumor by CCR4; suppress beneficial CD8 T cells
- CCR4 antagonism blocks T_{reg} recruitment and enhances tumor immunity
- Highly selective approach to target tumor T_{reg} without resorting to cell depletion
FLX475: Most Selective Approach to Targeting Tumor T<sub>reg</sub>

- Potently binds to CCR4
- Blocks interaction with ligands CCL22 and CCL17
- **Selectively inhibits T<sub>reg</sub> recruitment** in tumor microenvironment
  - Decreases tumor T<sub>reg</sub> without affecting T<sub>reg</sub> in healthy tissues
  - No impact on beneficial immune cells needed for anti-tumor response
- Potential both as **single-agent** and **in combination**
FLX475: Excellent Exposure & Safety in Healthy Volunteer Study

High Trough Exposures

Excellent Safety Profile

- No autoimmunity or immune-related AEs
- No changes in peripheral immune cell populations
- No significant clinical AEs or laboratory changes
- No significant QTc prolongation at projected efficacious exposures

- 75 mg QD exceeded target exposure corresponding to 90% inhibition of T\textsubscript{reg} recruitment and preclinical efficacy
FLX475: Strong Single Agent Activity in Preclinical Models

- Single agent efficacy in tumor model with high CCR4 ligand expression at baseline (Pan02)

**Single Agent Efficacy**

![Graph showing single agent efficacy](image)

**CD8: T_{reg} Ratio**

![Bar chart showing CD8: T_{reg} Ratio](image)
FLX475: Robust Combination Activity in Preclinical Models

- Robust combination activity in tumor models with checkpoint inhibitor-induced CCR4 ligand expression (CT26)

**CCR4 Ligand Expression in CT26 Tumors**

**Activity in Combo with Checkpoint Inhibitor**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Median Tumor Volume (mm$^3$)</th>
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</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
</tr>
<tr>
<td>Checkpoint Inhibitor</td>
<td>5</td>
</tr>
<tr>
<td>Checkpoint + CCR4 Antag. 1/10 Tumor-Free</td>
<td>30</td>
</tr>
<tr>
<td>Checkpoint + CCR4 Antag. 5/10 Tumor-Free</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Graph Details**

- X-axis: Days Post Inoculation
- Y-axis: Median Tumor Volume (mm$^3$)
- Treatment initiation marked by red arrow (Day 0)
- Statistical significance indicated by asterisks:
  - **: p < 0.001
  - ***: p < 0.0001

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FLX475: Big Data Analysis Identified “Charged” Tumors Most Likely to Respond

- “Charged” tumors: Tumors expressing high levels of CCR4 ligands and $T_{\text{reg}}$
  - Non-Small Cell Lung Cancer
  - Triple Negative Breast Cancer
  - Head and Neck

- “Charged” tumors tend to be “hot” with high levels of $T_{\text{reg}}$ likely holding back the anti-tumor immune response

**Data from in-house analysis of TCGA database; Confirmed in > 400 tumor microarrays**
Prospectively-Selected “Charged” Tumors Include EBV and HPV-Associated Tumors

- High concordance of EBV and CCL22
- Similar pattern for CCL17

- Prospectively-selected “charged” tumors identified using big data and confirmed using in situ hybridization
- EBV and HPV directly drive CCR4 pathway to recruit T\textsubscript{reg}
  - Nasopharyngeal (EBV+)
  - Hodgkin Lymphoma (EBV+)
  - Cervical, Oropharyngeal cancers (HPV+)
- Potential for accelerated approval in tissue-agnostic cancers
Addressable Opportunity: “Charged” Cancers

Addressable Opportunity: Charged Tumors
Metastatic, second-line+ patients in NSCLC, H&N, TNBC

<table>
<thead>
<tr>
<th>Region</th>
<th>NSCLC</th>
<th>H&amp;N</th>
<th>TNBC</th>
<th>Total</th>
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<tbody>
<tr>
<td>EU5</td>
<td>34,393</td>
<td>15,306</td>
<td>14,852</td>
<td>77,740</td>
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<tr>
<td>US</td>
<td>43,347</td>
<td>14,349</td>
<td>12,333</td>
<td>70,029</td>
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</table>

Addressable Opportunity: EBV/HPV Tumors
Metastatic, second-line+ patients in NPC, GC, cHL, Cervical

<table>
<thead>
<tr>
<th>Region</th>
<th>US/EU5</th>
<th>Japan</th>
<th>China</th>
<th>Rest of Asia</th>
<th>Total</th>
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<tr>
<td>US/EU5</td>
<td>13,271</td>
<td>13,816</td>
<td>51,335</td>
<td>34,926</td>
<td>113,348</td>
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</tbody>
</table>

Additional Upside in 1st Line Patients
FLX475 Phase 1/2 Trial: Seamless, Rapid Path to PoC in 2019

- **Phase 1:** Safety, PK/PD, biomarkers, overall response rate (ORR)

  - FLX475 Monotherapy
  - Escalating Dose
  - Charged tumors
  - EBV+/HPV+ tumors
  - ~18-24 patients

- **Phase 2:** Gated 2-stage design, PoC in 2019, biomarkers, ORR

  - FLX475 + Keytruda®
  - Escalating Dose
  - Charged tumors
  - EBV+/HPV+ tumors
  - 80 patients

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FLX475: Best-in-Class CCR4 Inhibitor with Phase 2 PoC in 2019

- Highly specific tumor T_{reg} inhibitor spares normal tissues and beneficial immune cells
- Excellent PK/PD and safety with oral dosing
- Phase 1/2 study with prospective patient selection and efficacy readout in 2019
- Data supports development as single agent and in combination therapy with multiple IO agents
- Wholly-owned IP, long patent life
FLX193: CCR4 Antagonist for Allergic Disorders

Best-in-Class Oral CCR4 Inhibitor In Highly Validated Pathway for Allergic Disorders with Phase 2 Readout 1Q20
CCR4 Protein on Th2 Drives Allergic Inflammation

- CCR4 recruits Th2 cells into tissues and drives allergic inflammation
- CCR4 antagonist suppresses allergic inflammation
- Pathway highly validated with approved biologics
FLX193: Second CCR4 Molecule Advancing in Allergic Disorders

- Highly potent oral CCR4 antagonist targeting allergic disorders: atopic dermatitis, asthma, others
- Oral convenience provides substantial competitive advantage to injectables and topical agents
- Rapid path to clinical proof of concept
FLX193: Efficacious in Th2-Driven Inflammation Preclinical Model

**Allergic Airway Inflammation Model**

- Sensitisation Day 1
- Boost Day 14
- OVA Challenge Days 20-23
- 24 Hrs After Day 23 Challenge BALF Collection and Cell Count
- p.o. compound Days 19 - 23

**Eosinophils**

<table>
<thead>
<tr>
<th>Group</th>
<th>Eosinophils (x10⁶)</th>
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<tr>
<td>sham</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>OVA</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>FLX193 Low Dose</td>
<td>2 ± 0.5</td>
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<tr>
<td>FLX193 High Dose</td>
<td>1 ± 0.3</td>
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**IL-5**

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-5 pg/ml</th>
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<tbody>
<tr>
<td>sham</td>
<td>150 ± 10</td>
</tr>
<tr>
<td>OVA</td>
<td>200 ± 20</td>
</tr>
<tr>
<td>FLX193 Low Dose</td>
<td>100 ± 15</td>
</tr>
<tr>
<td>FLX193 High Dose</td>
<td>50 ± 5</td>
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**IL-13**

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-13 pg/ml</th>
</tr>
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<tbody>
<tr>
<td>sham</td>
<td>500 ± 50</td>
</tr>
<tr>
<td>OVA</td>
<td>600 ± 60</td>
</tr>
<tr>
<td>FLX193 Low Dose</td>
<td>300 ± 30</td>
</tr>
<tr>
<td>FLX193 High Dose</td>
<td>150 ± 15</td>
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FLX193: Clinical Plan

**Phase 1a/1b Healthy Volunteer/Atopic Dermatitis Study**
- FLX193 SAD (Escalating Dose)
  - ~40-50 HV
- FLX193 MAD (Escalating Dose)
  - Mod-Severe AD
  - Readout 4 weeks
- FLX193 AD
  - ~20-30 AD Patients

**Phase 2a/2b Studies**
- Phase 2 Atopic Dermatitis
- Phase 2 Allergic Asthma
- Other Allergic Disorders

**Phase 1a/1b**: Safety, PK/PD, PoC in small atopic dermatitis (AD) cohort

**Phase 2**: Studies in AD, asthma, and other allergic disorders
FLX193: Potentially Disruptive Convenience and Safety Profile

Atopic Dermatitis (AD) US Prevalence**

- Total US AD Prevalence (~19 M)
  - 48%
  - US Diagnosed Prevalence (~9 M)
    - Mild AD ~40%
    - Moderate AD ~36%
    - Severe AD ~24%

FLX193 Target Population

**2018 Data, Decision Resources
GCN2

Targeting Key Metabolic Pressure Point in Tumor Microenvironment
GCN2: Key Driver of Immunosuppression in TME

- TME harbors significant metabolic stress
- GCN2: key target driving immunosuppression caused by metabolic stress
- GCN2 inhibitors have potential to:
  - Reactivate the immune response
  - Increase tumor cell death
  - Act in the TME resulting in better therapeutic index
  - Generate greater efficacy
- Preclinical candidate 2Q19

Tumor Microenvironment

- ↓ Arginine
- ↓ Tryptophan
- ↓ Asparagine
- ↓ Glucose

- CD8
  - Decrease Survival and Tumor Killing

- MDSC
  - Increase Immune Suppression
  - Increase Tumor Survival

Mellor and Munn, 2008; Ye et al, 2010; Wang et al, 2013
FLX GCN2 Inhibitor: Restores Human CD8 T Cell Proliferation and Effector Function in Presence of MDSCs

Tolerogenic MDSC + Human CD8 cells

Assess T cell proliferation and effector functions

GCN2 Inhibitor Restores CD8 T Cell Proliferation

GCN2 Inhibitor Restores CD8 T Cell IFNγ Expression
# Key Upcoming Milestones

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<thead>
<tr>
<th>TIMING</th>
<th>MILESTONES</th>
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<tr>
<td></td>
<td>FLX475</td>
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<tr>
<td>2019</td>
<td></td>
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<tr>
<td>1H</td>
<td>Ph 2 dose selection (monotherapy &amp; combo)</td>
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<tr>
<td>2H</td>
<td>Ph 2 PoC</td>
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<tr>
<td>2020</td>
<td></td>
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<tr>
<td>1H</td>
<td>Additional expansion cohorts</td>
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<tr>
<td>2H</td>
<td>Initiate registrational studies</td>
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Management, Board, Advisors, & Investors
## World Class Scientific and Clinical Advisors

### Leading Clinicians and Scientific Researchers

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Institution</th>
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<tbody>
<tr>
<td><strong>Alexander Rudensky, Ph.D.</strong></td>
<td>Chairman, FLX Scientific Advisory Board; Chairman, Immunology Program, Sloan-Kettering Institute, Director, Ludwig Center at MSKCC; Member Natl. Acad. Sci.</td>
</tr>
<tr>
<td><strong>Antoni Ribas, M.D., Ph.D.</strong></td>
<td>Professor, Medicine, Hematology/Oncology &amp; Director, JCCC Tumor Immunology, UCLA</td>
</tr>
<tr>
<td><strong>Scott J. Antonia, M.D., Ph.D.</strong></td>
<td>Chair, Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute; Professor of Oncologic Sciences, University of South Florida College of Medicine</td>
</tr>
<tr>
<td><strong>Drew Pardoll, M.D. Ph.D.</strong></td>
<td>Professor, Johns Hopkins University, Director; Bloomberg-Kimmel Institute for Cancer Immunotherapy</td>
</tr>
<tr>
<td><strong>Philip Greenberg, M.D.</strong></td>
<td>Professor, Medicine (Oncology) &amp; Immunology, University of Washington; Head of Immunology, Fred Hutchinson Cancer Research Center</td>
</tr>
<tr>
<td><strong>Robert Zamboni, Ph.D.</strong></td>
<td>Adjunct Professor of Chemistry, McGill University; Former VP of Research at Merck &amp; Co.</td>
</tr>
<tr>
<td><strong>David V. Goeddel, Ph.D.</strong></td>
<td>Founder &amp; CEO Tularik; Founder &amp; Partner The Column Group; Member Natl. Acad. Sci.</td>
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Experienced Board of Directors & Strong Investor Base

**BOARD OF DIRECTORS**

- **David V. Goeddel, Ph.D.**  Managing Partner, The Column Group
- **Beth Seidenberg, M.D.**  General Partner, Kleiner Perkins
- **Linda Kozick**  Former VP and Head of Immuno-Oncology/Oncology Product & Portfolio Strategy, Bristol-Myers Squibb
- **Michael F. Giordano, M.D.**  Former SVP and Head of Development, Oncology & Immuno-Oncology, Bristol-Myers Squibb
- **William Rieflin, J.D.**  CEO, NGM Biopharmaceuticals Inc.
- **Brian Wong, M.D., Ph.D.**  CEO, FLX Bio

**MAJOR INVESTORS**
# Proven Management Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Affiliations</th>
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<tbody>
<tr>
<td>Brian Wong, M.D., Ph.D.</td>
<td>Chief Executive Officer</td>
<td>FivePrime, Roche, rigel</td>
</tr>
<tr>
<td>Rekha Hemrajani</td>
<td>Chief Operating Officer</td>
<td>Onyx Pharmaceuticals, EXELIXIS, Credit Suisse, First Boston, G-V Biosciences, Lehman Brothers</td>
</tr>
<tr>
<td>William Ho, M.D., Ph.D.</td>
<td>Chief Medical Officer</td>
<td>IGENICA Biotherapeutics, Genentech</td>
</tr>
<tr>
<td>Dirk Brockstedt, Ph.D.</td>
<td>Senior Vice President of Biology</td>
<td>Aduro Biotech, Aventis</td>
</tr>
<tr>
<td>Paul Kassner, Ph.D.</td>
<td>Vice President, Quantitative and Computational Biology</td>
<td>AMGEN, Tularik, Cleave Biosciences, Pfizer, XenonPort</td>
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<tr>
<td>David Wustrow, Ph.D.</td>
<td>Vice President, Drug Discovery</td>
<td>FLX Bio, BIO, Pfizer, XenonPort</td>
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