RAFAEL
Pharmaceuticals, Inc.

520 Broad Street, Newark, New Jersey 07102
Tel: (973) 438-2000; Fax: (973) 438-2001

CPI-613:

A First-in-Class Therapeutic Agent Targeting Cancer Cell Metabolism

WHAT IS CPI-613

- CPI-613 is a first-in-class investigational small-molecule (lipoate analog), developed by Rafael, based on the **Altered Energy Metabolism Directed (AEMD) platform**
- CPI-613 targets the altered energy metabolism that is unique to many cancer cells
- In **nonclinical studies**, CPI-613 exhibited **excellent sensitivity and specificity** to cancer cells
- CPI-613 was investigated in **multiple hematological malignancies and solid tumors**, and exhibited **very good signal of efficacy**
- **FDA has approved initiation of pivotal trials of CPI-613 for Acute Myeloid Leukemia and Pancreatic Cancer, and Rafael is planning to initiate these trials by second half of 2017**
- CPI-613 was granted **'Orphan Designation'** by U.S. FDA for Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS) and Pancreatic Cancer

CPI-613: CLINICAL TRIALS

- Currently being evaluated in **15 Phase I to Phase II trials** as a single agent, as well as in combination with standard drug therapy for hematological malignancies and solid tumors
- To date, over **290 subjects have received** one or more doses of CPI-613 and the drug exhibited **signals of efficacy** with excellent response rate and **extended duration of response** in several tumor types
- **In pancreatic cancer, CPI-613 in combination with modified FOLFIRINOX exhibited 61% Objective Response Rate and 78% Clinical Benefit Rate**
- **In acute myeloid leukemia patients with poor cytogenetic risk, CPI-613 in combination with high dose cytarabine and mitoxantrone exhibited 38% Complete Response Rate**
- In both these trials, the efficacy of CPI-613 combinations were substantially higher than standard therapy
- **In peripheral T-cell lymphoma, CPI-613 in combination with Bendamustine exhibited signal of efficacy**

CPI-613: MECHANISM OF ACTION

- **Both Pyruvate dehydrogenase (PDH) and alpha-ketoglutarate dehydrogenase (KGDH)** of **TCA cycle** use **lipoate as a catalytic co-factor**
- Lipoate transiently forms several chemically distinct intermediates during catalysis and these intermediates allow monitoring of **carbon flux** in mitochondria specific necrosis
- **To fulfill the altered metabolic requirement, many tumor cells over-express a different set of lipoate-sensitive regulators than normal cells**
- **CPI-613 is a lipoate analog designed to mimic the catalytic intermediates to which the regulatory components that are over-expressed in tumor cells respond to**
- **Thus, tumor cell PDH and KGDH regulators respond robustly to CPI-613, allowing tumor-specific regulatory inactivation of these two indispensable enzymes**