



# Transforming the Treatment of Cancer and Inflammation

January 2021  
Corporate Presentation

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# Oral Drugs Targeting Critical Immune Drivers of Disease

- Proprietary discovery engine
- Diversified pipeline
- Large market opportunities
- Multiple near-term clinical readouts
- Strategic collaborations

CLINICAL

**FLX475** (Oncology):  **MERCK** 

- Selectively targets immunosuppressive tumor  $T_{reg}$
- PoC in Phase 2 with multiple expansions underway
- Monotherapy and combo clinical activity observed
- **Next Phase 2 update 2H 2021**

**RPT193** (Allergic Disease):

- Oral agent targets inflammatory Th2 cells
- Robust PK/PD with excellent safety in Ph1 study
- **Phase 1b PoC in atopic dermatitis ongoing – data readout in 1H 2021**

DISCOVERY

**HPK1** (Oncology)

**GCN2** (Oncology)

# Proprietary Drug Discovery and Development Engine

R

Rapid

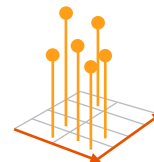
- Drug discovery
- Clinical development to POC



A

Analytics

- Interrogating clinically-relevant big datasets to identify targets and biomarkers



P

Patient selection

- Driven by data to improve chances of clinical success



T

Targeting

- Critical immune drivers of cancer and inflammation

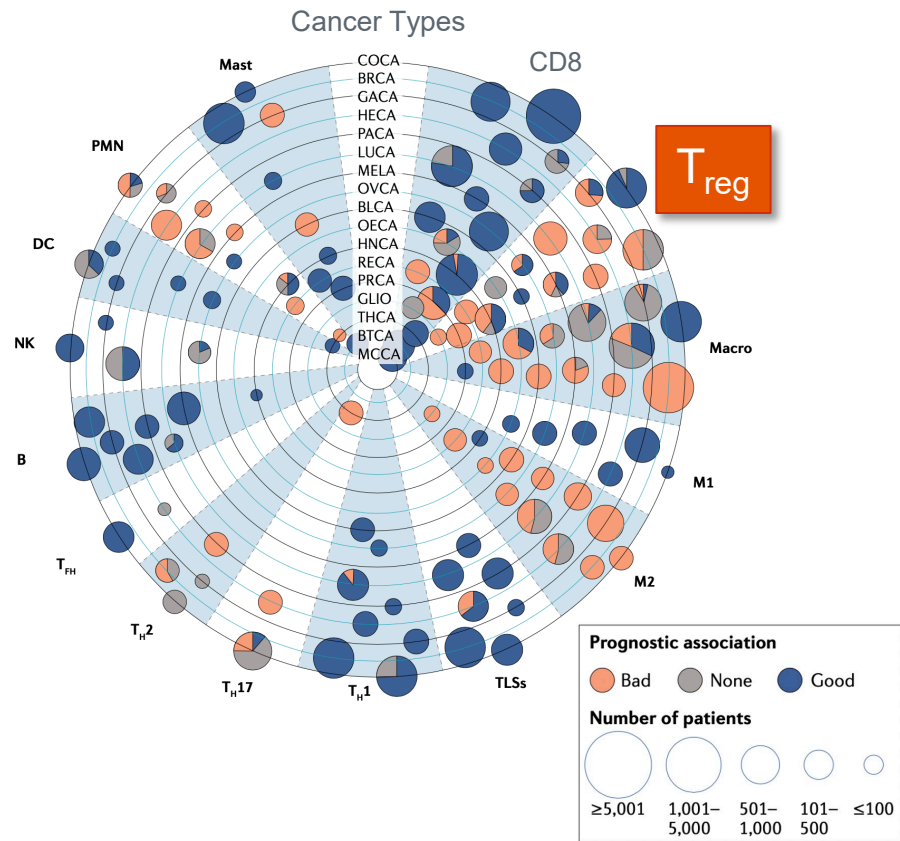




# FLX475: CCR4 Antagonist for Oncology

# $T_{reg}$ Are Key Targets in the Tumor Microenvironment (TME)

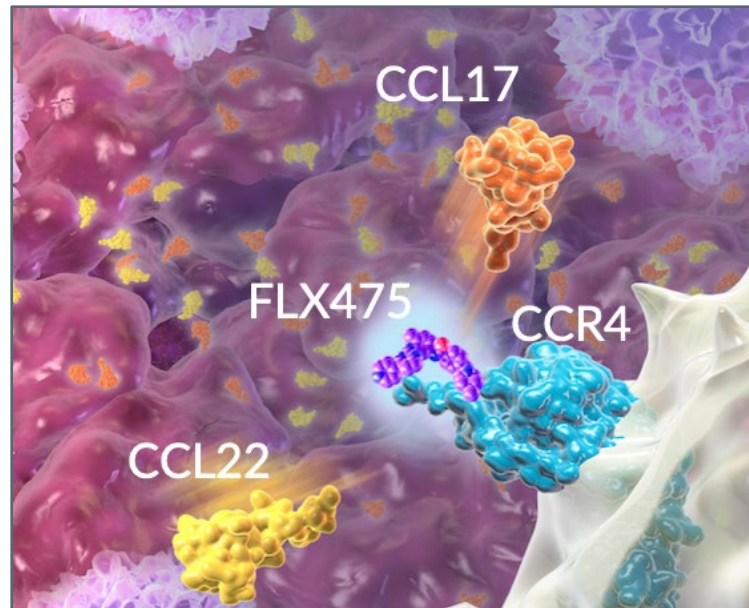
- Correlate with poor prognosis across most cancers
- Mechanism for immune evasion by viruses and tumors
- Barrier to checkpoint inhibitor efficacy
- Challenge: selective inhibition of  $T_{reg}$  in the TME
  - Depleting antibodies targeting CD25, CCR4, etc. do not appear to have adequate selectivity





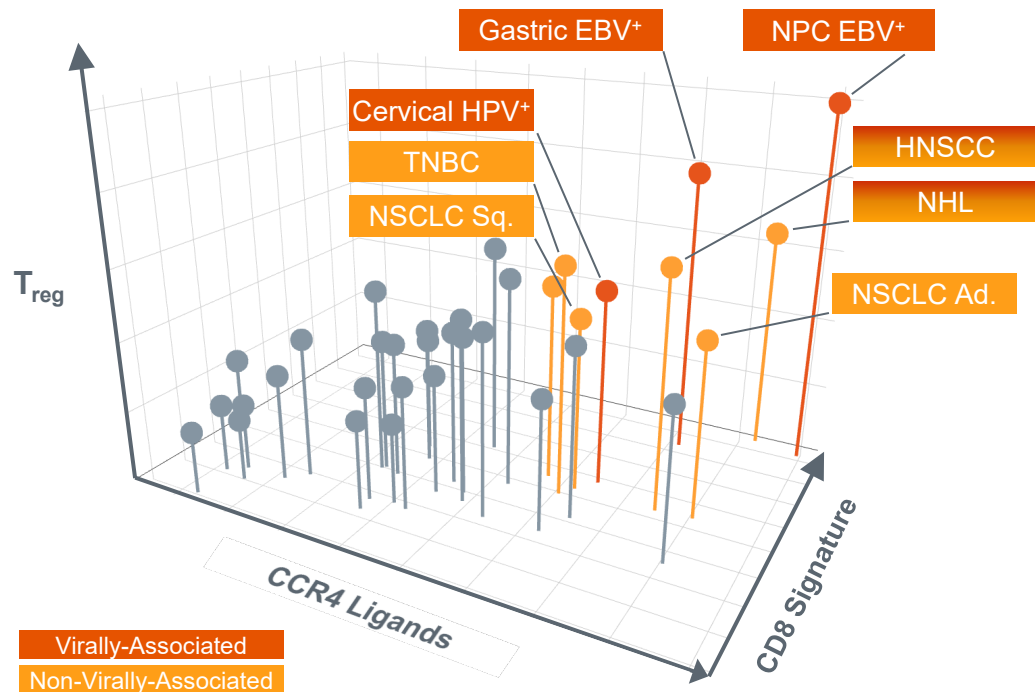
# FLX475: Oral CCR4 Antagonist in Phase 2

- Highly potent and selective CCR4 small molecule antagonist
- Selectively blocks tumor  $T_{reg}$  while sparing normal tissues and beneficial cells
- Potential for superior safety and efficacy compared to depleting antibodies
- Issued U.S. composition of matter patent with coverage through 2037
- Monotherapy and combination antitumor activity in charged cancers



Blocks interaction with CCR4 ligands  
CCL22 and CCL17 on  $T_{reg}$

# Identification and Characterization of Charged Tumors



Data from in-house analysis of TCGA database combined with other data sets;  
Confirmed in > 400 tumor microarrays

The graph above reflects a logarithmic scale on each axis

NPC Nasopharyngeal; HNSCC Head & Neck Squamous Cell Carcinoma; NHL Non-Hodgkin

Lymphoma; NSCLC Non-Small Cell Lung Cancer; TNBC Triple Negative Breast Cancer

- “Charged” tumors: high levels of CCR4 ligands,  $T_{reg}$  and CD8 T cells
- Potential for both monotherapy and combination activity
- Represent cancers with high unmet need and large markets
- Potential for tissue-agnostic accelerated approval in virally-associated tumors



# A Large Proportion of Multiple Tumor Types Are Charged

Tumor Type	Prevalence* (U.S.)	Virally Associated	Percent Viral	Estimated Percent Charged**
Non-Small Cell Lung Cancer	268,600	N/A	N/A	60-80%
Triple Negative Breast Cancer	145,500	N/A	N/A	
Head and Neck Squamous Cell Carcinoma	143,000	✓	25%-60%	
Nasopharyngeal Cancer	105,000***	✓	>95%	>90% of virally associated tumors
Cervical Cancer	46,800	✓	>95%	
EBV+ Lymphoma	28,700****	✓	100%	> 90%

\* Based on 2012 Globocan registries 5-year prevalence (2008-2012 estimates)

\*\* Data from in-house analysis

\*\*\* World-wide prevalence

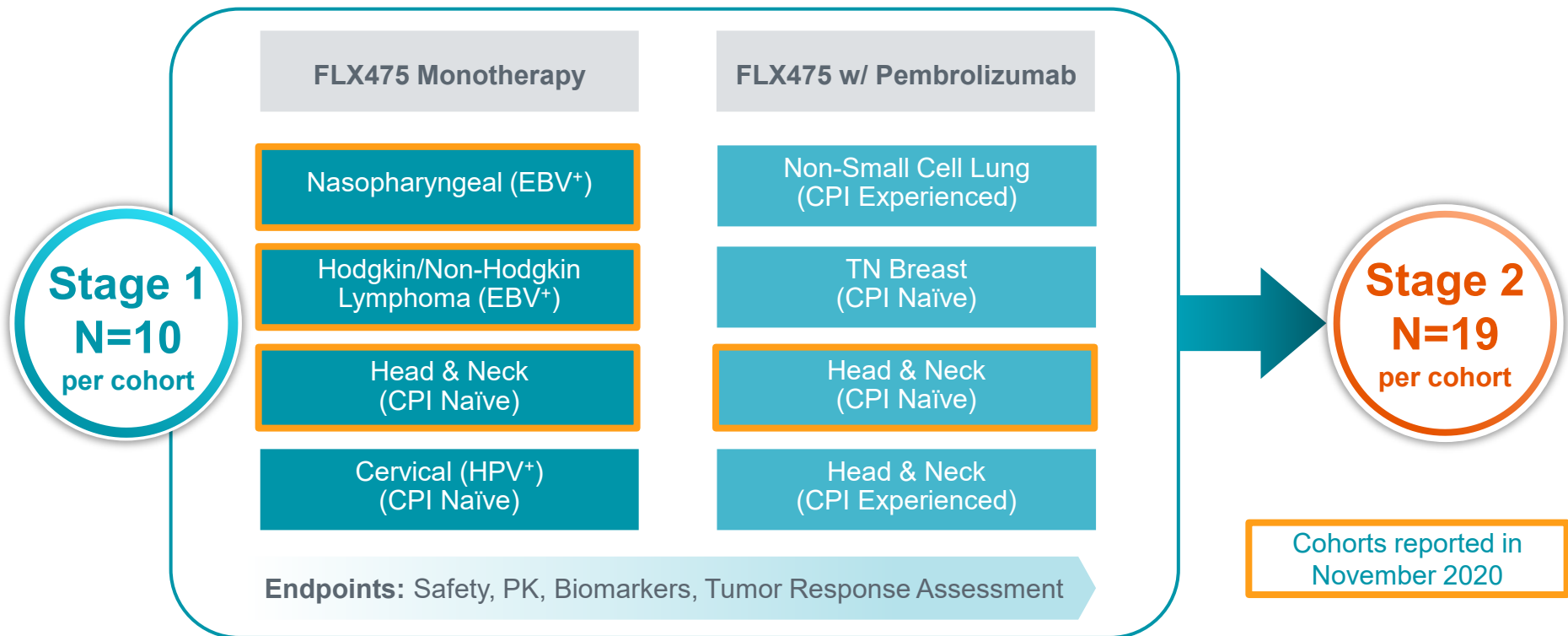
\*\*\*\* Estimated based on 2018 Globocan registries 5-year prevalence (2013-2018 estimates and Heslop, H., American Society of Hematology 2005, 260-266)

# Phase 1 Dose Escalation Summary

- Standard 3+3 dose escalation of monotherapy and in combination in non-charged and charged cancers
- 37 patients enrolled, 4 remain on study (12-18 months)
- Favorable safety with no overlapping toxicities with pembrolizumab
- Tumor biomarker changes supportive of  $T_{reg}$  mechanism
- 100 mg QD selected as the Phase 2 dose
- Preliminary evidence of monotherapy and combination clinical activity in heavily pretreated charged tumor types
  - 1 unconfirmed partial response in monotherapy (cervical)
  - 2 partial responses in combination (1 in PD-L1 refractory NSCLC, 1 in CPI-naïve bladder)

## Phase 2: Gated Simon 2-Stage Design

- To evaluate the antitumor activity of FLX475 as monotherapy and in combination with pembrolizumab in charged cancers that progressed after  $\geq 1$  line of therapy



CPI = Checkpoint Inhibitor

# Predefined Success Criteria for Phase 2 Stage 1

## Monotherapy

- Any monotherapy activity would be considered highly encouraging in this small trial
  - Most IO agents have failed to clearly demonstrate monotherapy activity
  - Demonstrates activity: important to interpret combination data
- Robust monotherapy activity could permit a single agent path in some indications and settings

## Combination

- Activity above expected from checkpoint inhibition alone
  - Checkpoint naïve - varies
  - Checkpoint experienced – less than 5-10%

Overlay clinical judgement based on depth and durability of responses

# Phase 2 Trial Update: Key Findings

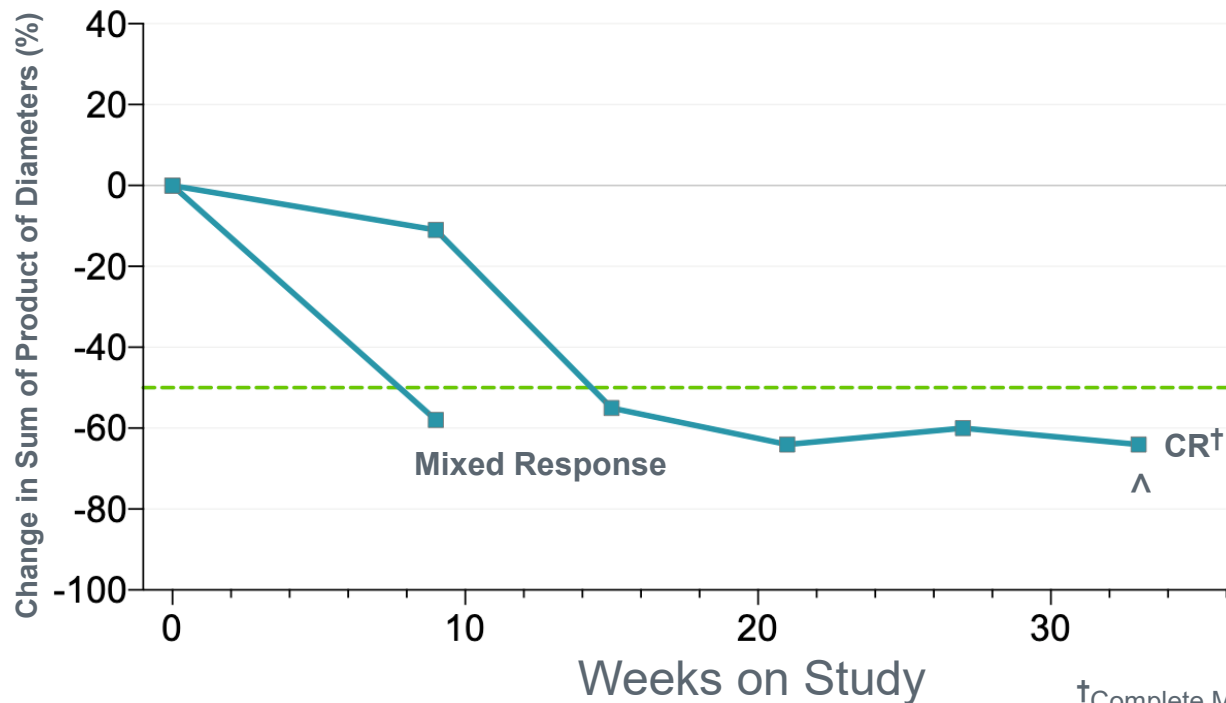
Tumor Type	Observations	Decision
EBV <sup>+</sup> Hodgkin/Non-Hodgkin Lymphoma	Deep and durable response to FLX475 monotherapy	<ul style="list-style-type: none"><li>Expand monotherapy cohort</li><li>Expand a combination cohort</li></ul>
Nasopharyngeal Carcinoma (NPC)	Frequent and deep responses in CPI-naïve patients in combination	<ul style="list-style-type: none"><li>Expand a combination cohort</li></ul>
Head & Neck Squamous Cell Carcinoma (HNSCC)	Multiple responses in CPI-naïve patients in combination including a confirmed CR	<ul style="list-style-type: none"><li>Expand combination cohort</li></ul>

- Favorable safety profile with once-daily oral dosing both as monotherapy and in combination with pembrolizumab

This combined Phase 1/2 study is ongoing. Data are as of 11/10/2020 and findings and conclusions subject to change as more data accumulate and the study is completed.

# EBV<sup>+</sup> Lymphoma: Monotherapy Activity Observed

First 2 of 2 EBV<sup>+</sup> lymphoma patients enrolled experienced significant reduction in size of target lesions, including one with durable complete metabolic response (PET)



- Both are EBV<sup>+</sup> NHL subtypes and are charged
- Compelling monotherapy activity observed supports enrollment of full Stage 2 cohort
- Plan to explore combination activity in parallel

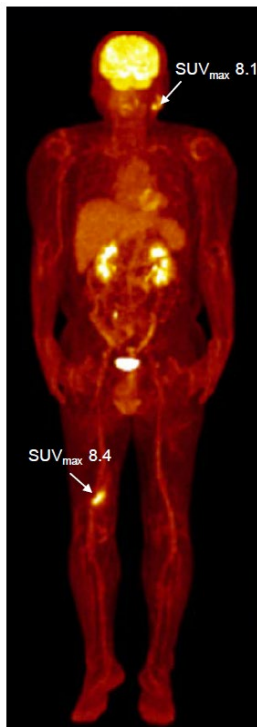
<sup>†</sup>Complete Metabolic Response

<sup>^</sup>Remains on study

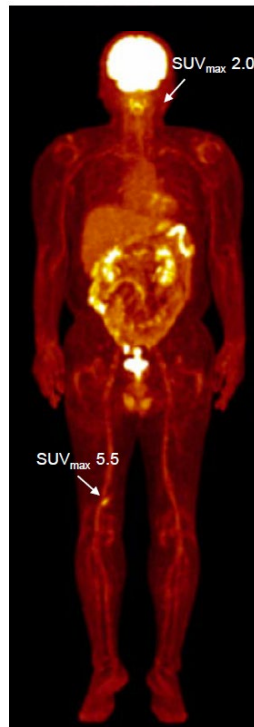
# EBV<sup>+</sup> NHL Case: Complete Metabolic Response to FLX475 Monotherapy

- EBV<sup>+</sup> NK/T NHL
  - 53 y/o, 2L with prior chemotherapy 1H 2019
  - 2 primary lesions
    - L posterior auricular (target), R distal anterior thigh (non target)
- Deep Durable Response
  - 8-week scan with complete metabolic response (Deauville score of 5 reduced to 2) and target lesion visibly improving by 12 weeks
  - Patient remains in complete metabolic response and on study > 9 months

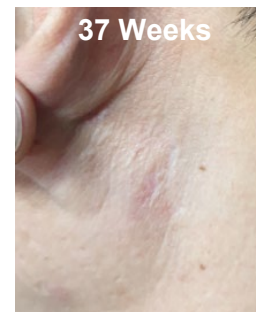
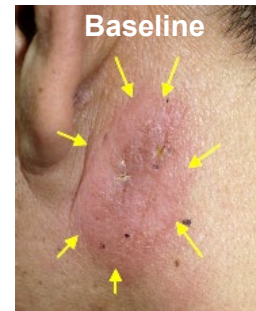
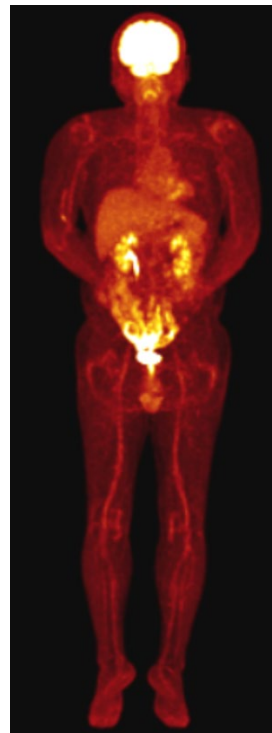
Baseline PET



8 Weeks

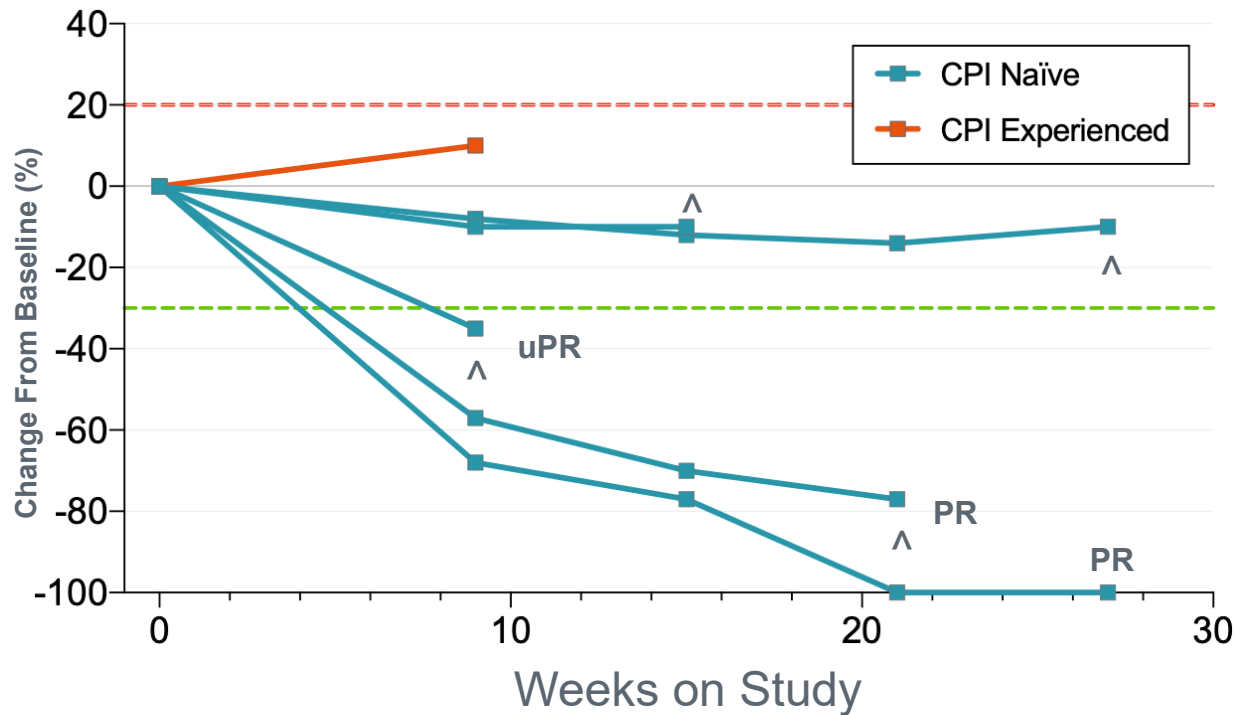


33 Weeks





# NPC Crossover: 5/5 CPI-naïve Patients with Tumor Shrinkage, 3/5 with Unconfirmed or Deep PR

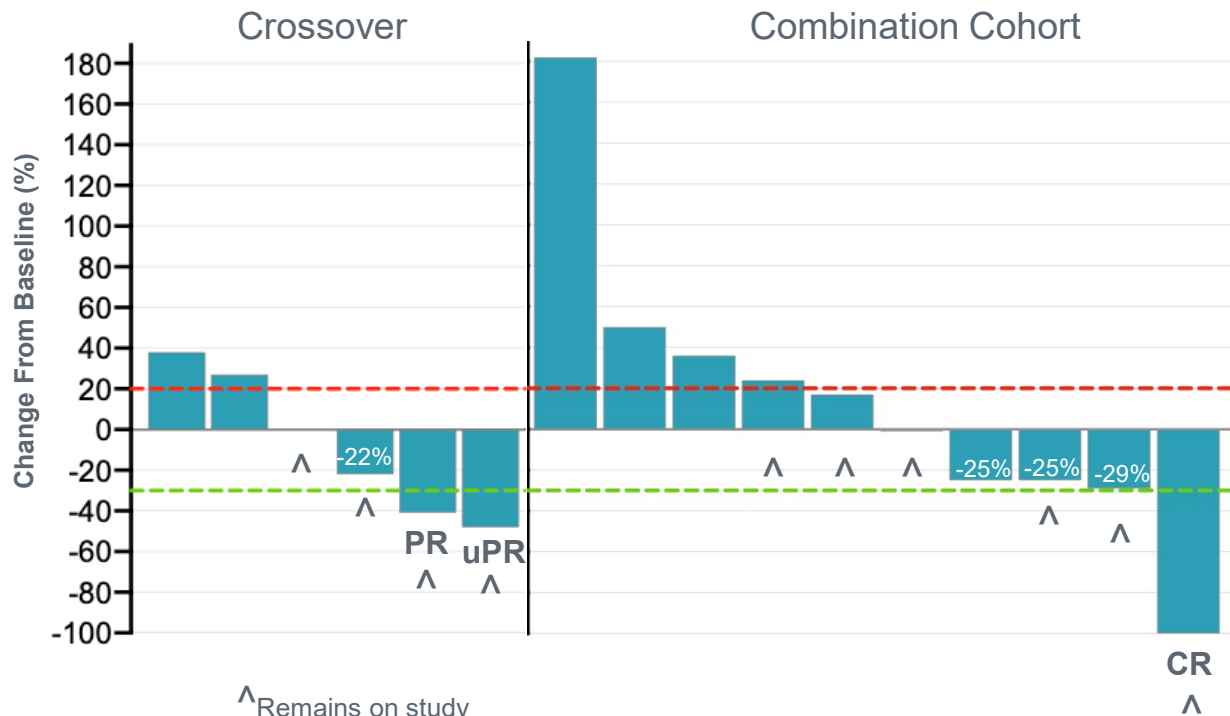


- 6 evaluable crossover patients, 5 CPI-naïve
  - 5/5 tumor shrinkage, including 1 uPR and 2 deep PRs
- ORR of pembrolizumab alone in CPI-naïve NPC is 26% (all PRs)<sup>1</sup>
- Data support further exploration of combination in patients with CPI-naïve NPC

^ Remains on study

<sup>1</sup>Hsu et al. (2017) J Clin Oncol 35:4050-4056 (KEYNOTE-028)

# HNSCC CPI-Naïve: Promising Combination Activity (Best Response on Study)

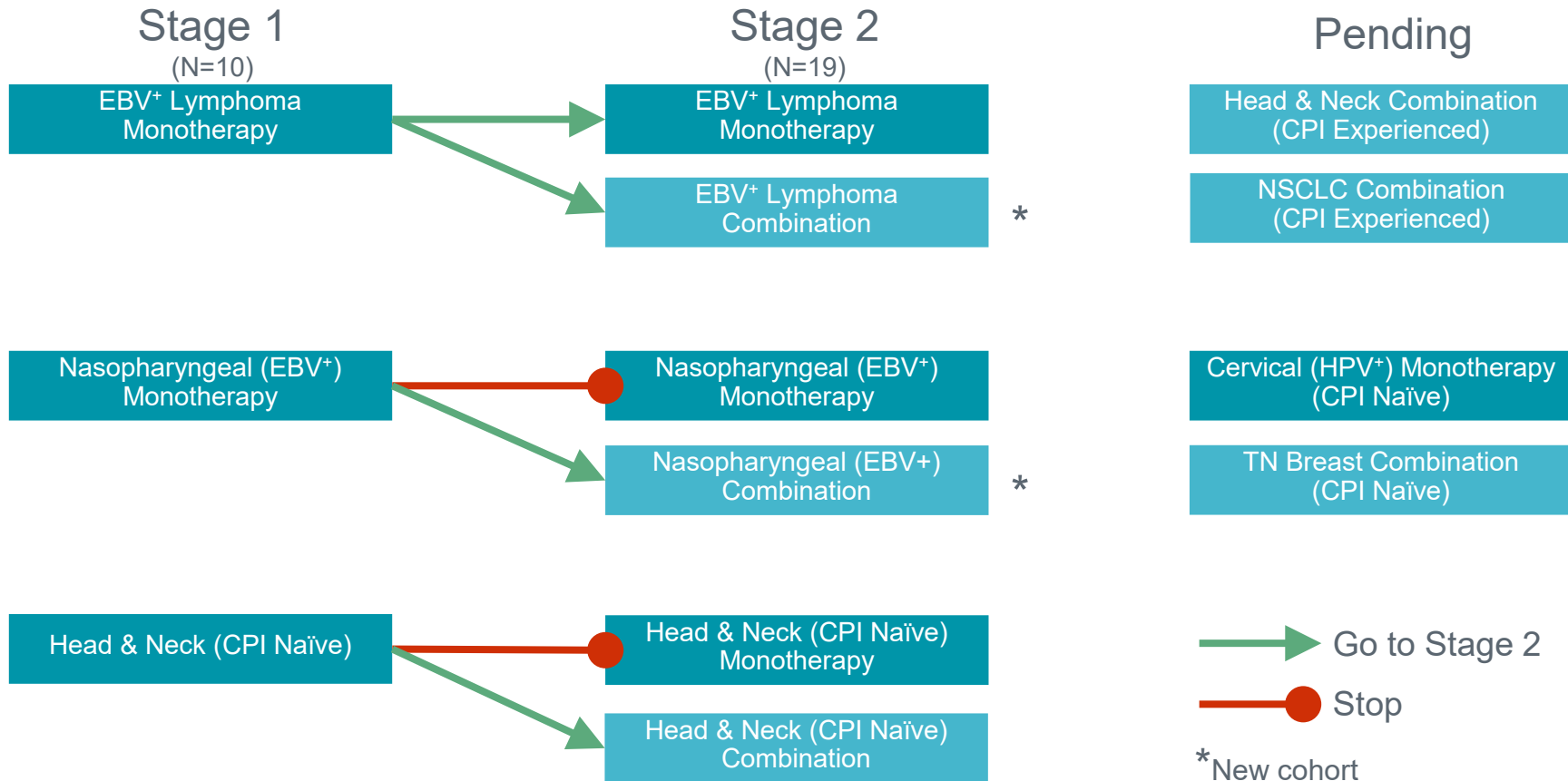


- Crossover
  - 6 enrolled and evaluable
  - 1 PR, 1uPR, 2 SD (1 with target reduction > 20%), 2 PD
- Combination Cohort
  - 17 enrolled; 10 evaluable
  - 1 CR, 5 SD (3 with target reduction > 20%), 4 PD
- ORR of pembrolizumab alone in CPI-naïve HNSCC is 16% (CR rate <1%)<sup>1</sup>
- Level of activity and totality of data support full Stage 2 CPI-naïve combination cohort

## Phase 2 Safety

- No new significant safety findings vs Phase 1
  - No evidence of increased severity or frequency of AEs in combination therapy vs either FLX475 or pembrolizumab given alone
  - Asymptomatic and reversible QTc prolongation continues to be the primary FLX475-related finding
- Serious adverse events potentially related to study treatment in the Phase 2 patients initially reported on (44 patients, 4 cohorts)
  - 1 QTc prolongation (asymptomatic) in a patient on monotherapy
  - 1 episode of colitis and concurrent renal insufficiency in one patient on combination therapy

# Phase 2: Stage 2 Decisions



# FLX475 Program Summary

- FLX475, a highly selective tumor  $T_{reg}$  inhibitor, appears to be an active agent in charged cancers
  - Demonstrated clinical activity of FLX475 as monotherapy
  - Demonstrated clinical activity of FLX475 in combination with pembrolizumab in checkpoint-naïve cancers beyond expected from checkpoint alone
  - Expanded multiple cohorts in EBV+ lymphoma, nasopharyngeal and head and neck cancers
- Favorable safety supportive of broad combinability
- Next data update planned in 2H 2021

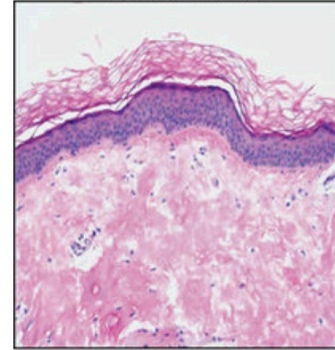


# RPT193: CCR4 Antagonist for Allergic Diseases

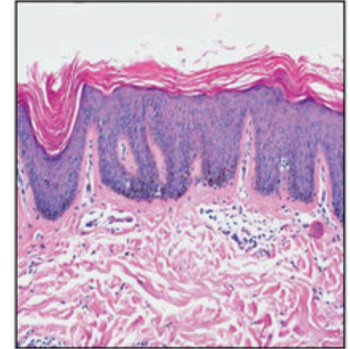
# RPT193: Oral CCR4 Antagonist for Allergic Diseases

- Targeting atopic dermatitis, asthma, others
- Oral convenience could provide substantial competitive advantage to injectables and topical agents
  - e.g.; Apremilast (Otezla) in psoriasis
- Preclinical studies and healthy volunteer data suggest an excellent safety profile
  - No monitoring or black box warning expected
- Phase 1b trial ongoing in atopic dermatitis patients with PoC readout in 1H 2021

Normal Human Skin

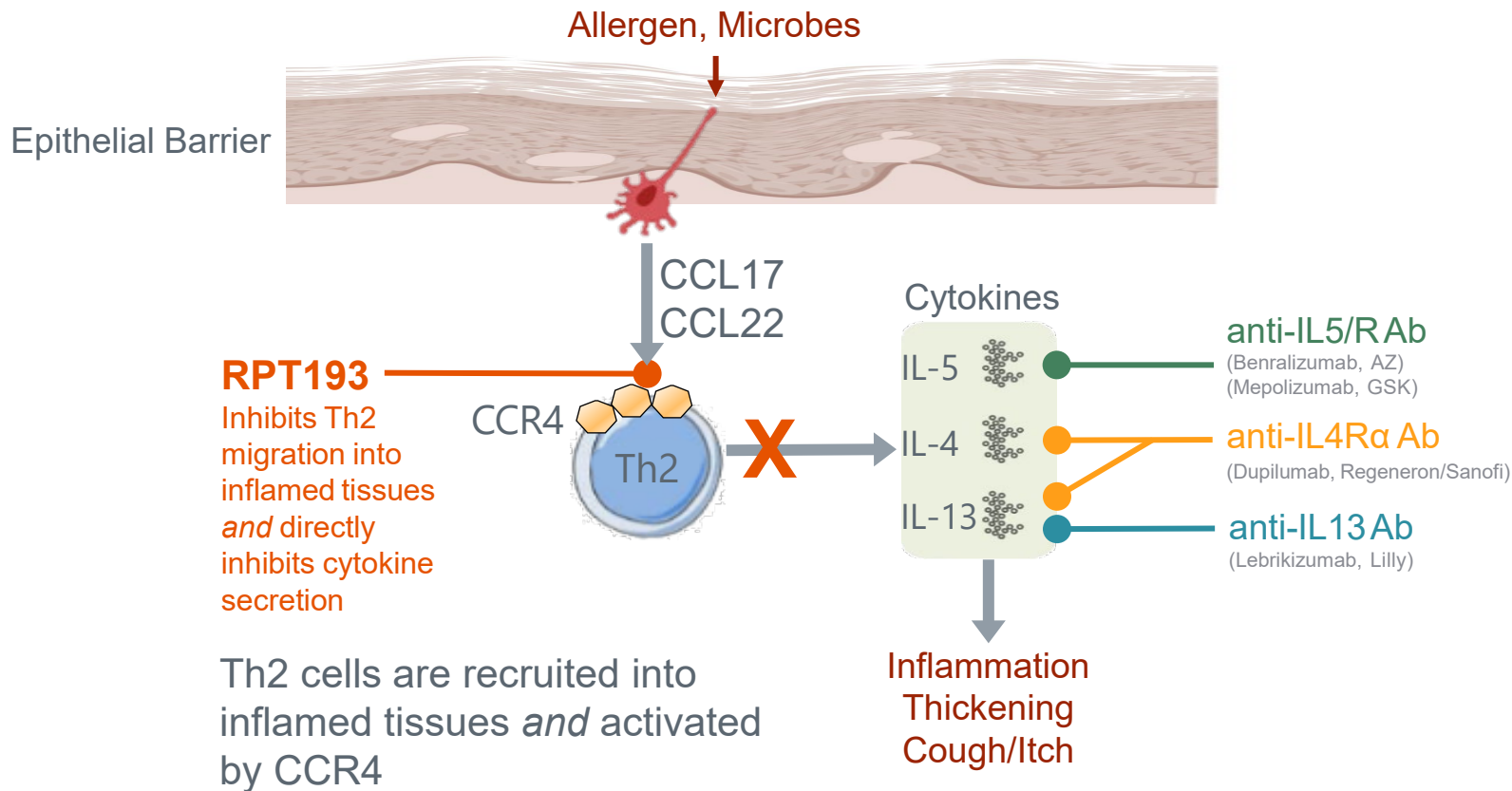


AD Lesional Skin

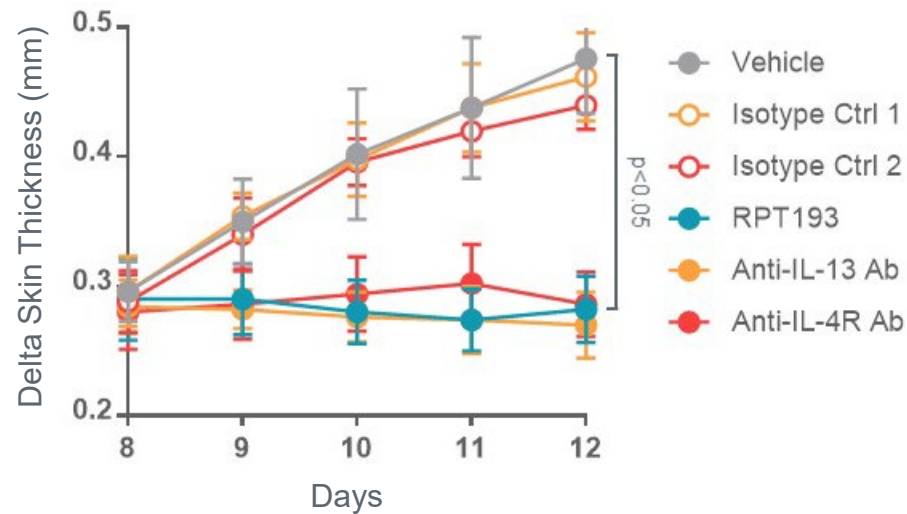
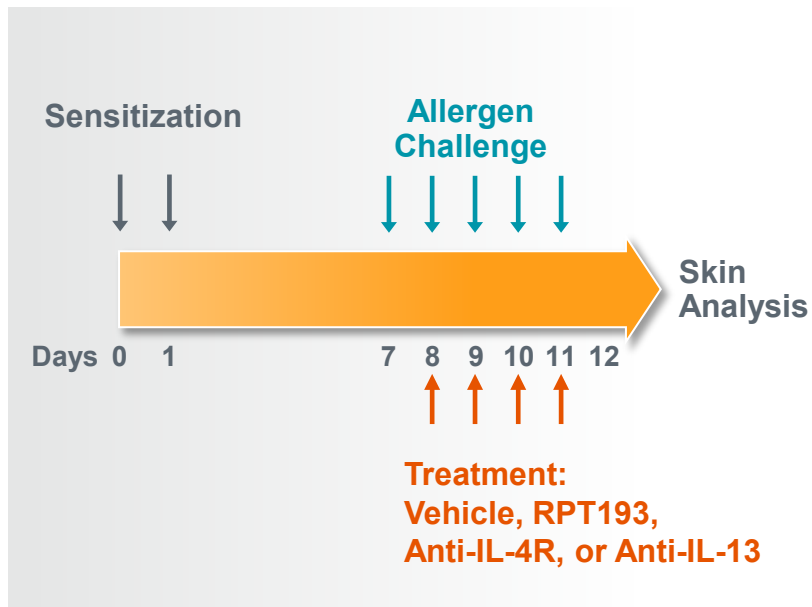




# RPT193 Acts on the Well Validated Th2 Pathway in Allergic Inflammation

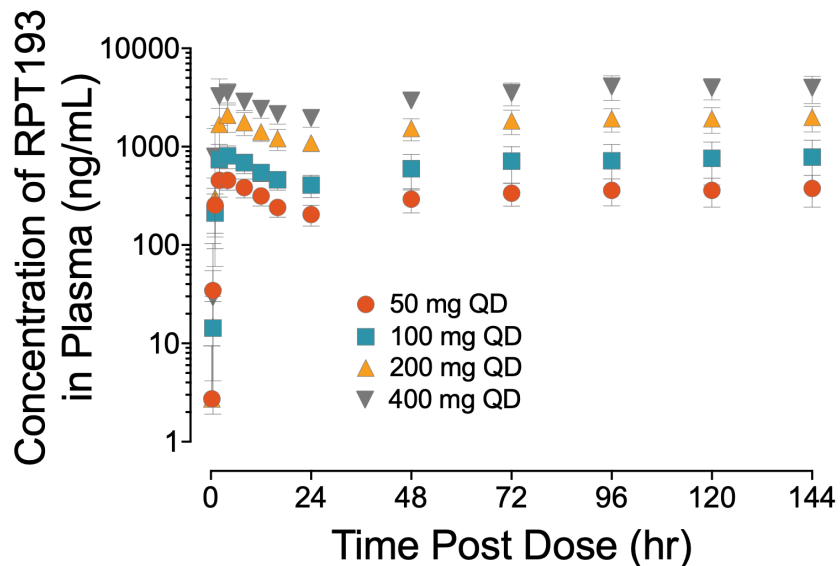


# RPT193 Reduces Skin Inflammation in a Therapeutic Th2-Driven Atopic Dermatitis Model

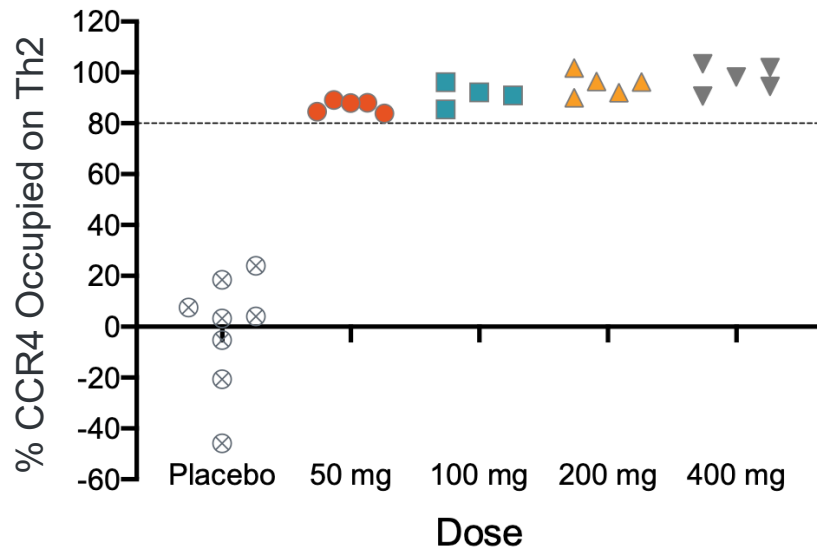


# Phase 1a Healthy Volunteer Data Support Once-Daily Dose

## Dose-Proportional Oral PK with ~24 Hr. Half-Life

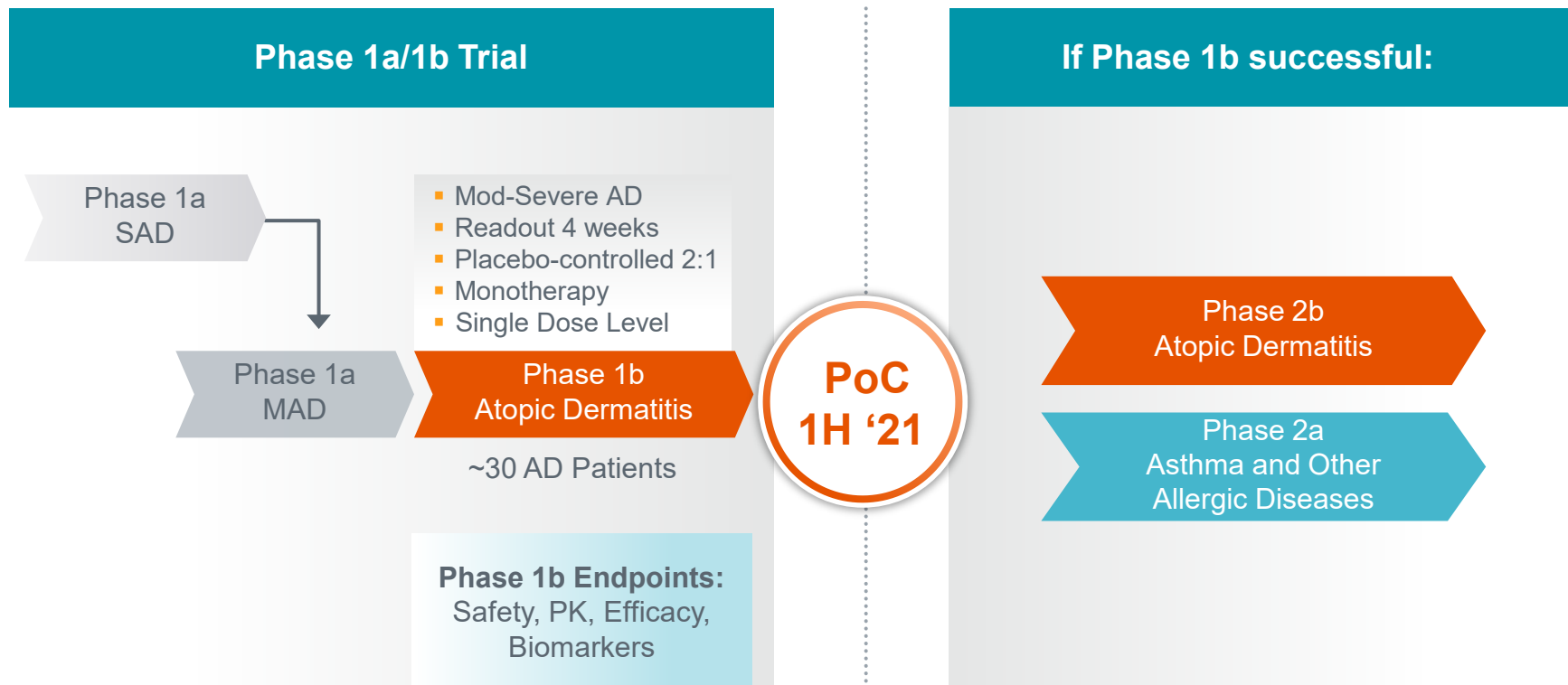


## Targeted Level of CCR4 Inhibition Exceeded Day 8 trough after last dose



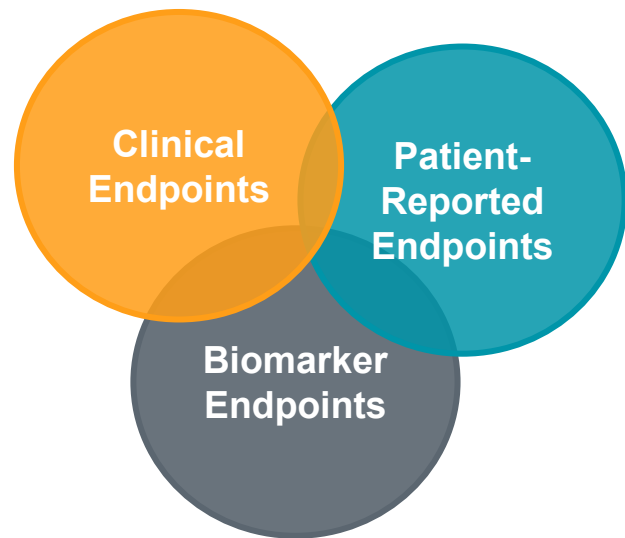
- Excellent safety and tolerability profile (blinded)

# Development Plan in Atopic Dermatitis, Asthma and Other Allergic Diseases



# Goals for the Phase 1b Trial

- Phase 1b is exploring a range of clinical, patient-reported, and biomarker endpoints
  - e.g.; EASI, vIGA, Itch NRS, serum CCL17
  - Trial not statistically powered on any specific measure
- An encouraging outcome would be data consistent with an effective oral agent that requires no safety monitoring, analogous to Otezla in psoriasis
  - A clear benefit (change from placebo) from RPT193 in at least one key clinical or patient-reported endpoint
  - Magnitude would not need to be similar to injectables
  - Potential positioning ahead of injectables



# Potential “Pipeline in a Product”

## Dermatology

- Atopic Dermatitis
- Alopecia Areata
- Prurigo Nodularis
- Bullous Pemphigoid

## Respiratory

- Asthma
- COPD (Th2 high)
- IPF

## Allergy

- Chronic Rhinosinusitis
- Allergic Rhinitis
- Eosinophilic Esophagitis

Th2-Driven Allergic Inflammatory Diseases

# Key Takeaways and Upcoming Milestones

- **FLX475**: a highly selective  $T_{reg}$  inhibitor with demonstrated clinical activity as monotherapy and in combination – PoC established
- **RPT193**: safe oral agent in well validated pathway for atopic dermatitis, asthma, and other allergic disorders
- **Next Key Milestones**
  - **1H 2021**: RPT193 Phase 1b PoC data in atopic dermatitis
  - **2H 2021**: FLX475 Phase 2 update





**Thank You**