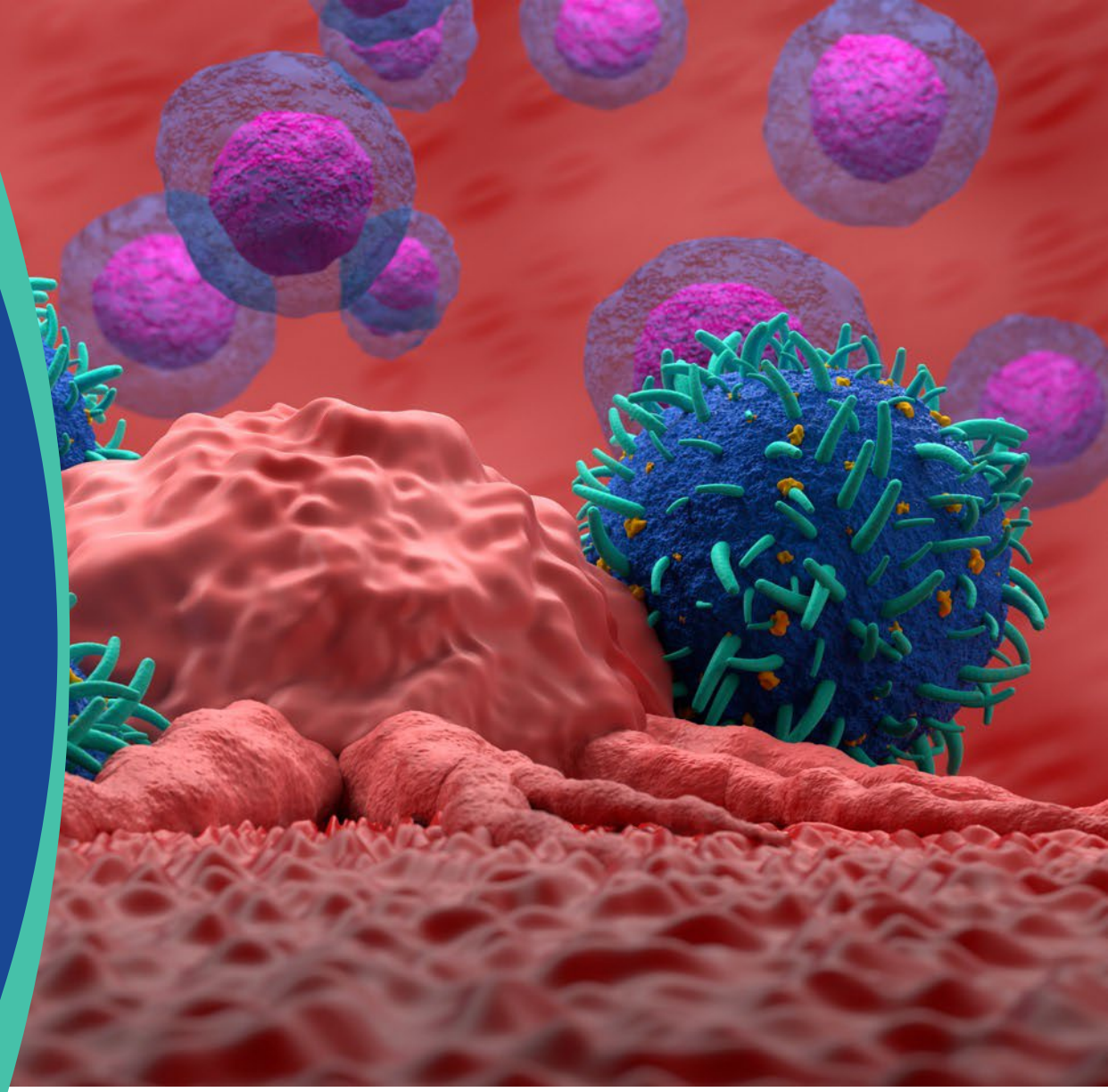
A Medscape LIVE! CONFERENCE

13th ANNUAL

T-CELL LYMPHOMA FORUM



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Oral CCR4 Antagonist FLX475 Antitumor Activity Against Extranodal NK/T-cell Lymphoma

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AGENDA

- Targeting Regulatory T Cells in the Tumor Microenvironment
- FLX475 Mechanism of Action
- Defining “Charged” Tumors
- EBV and CCR4
- FLX475-02 Study Design
- Activity in ENTCL

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

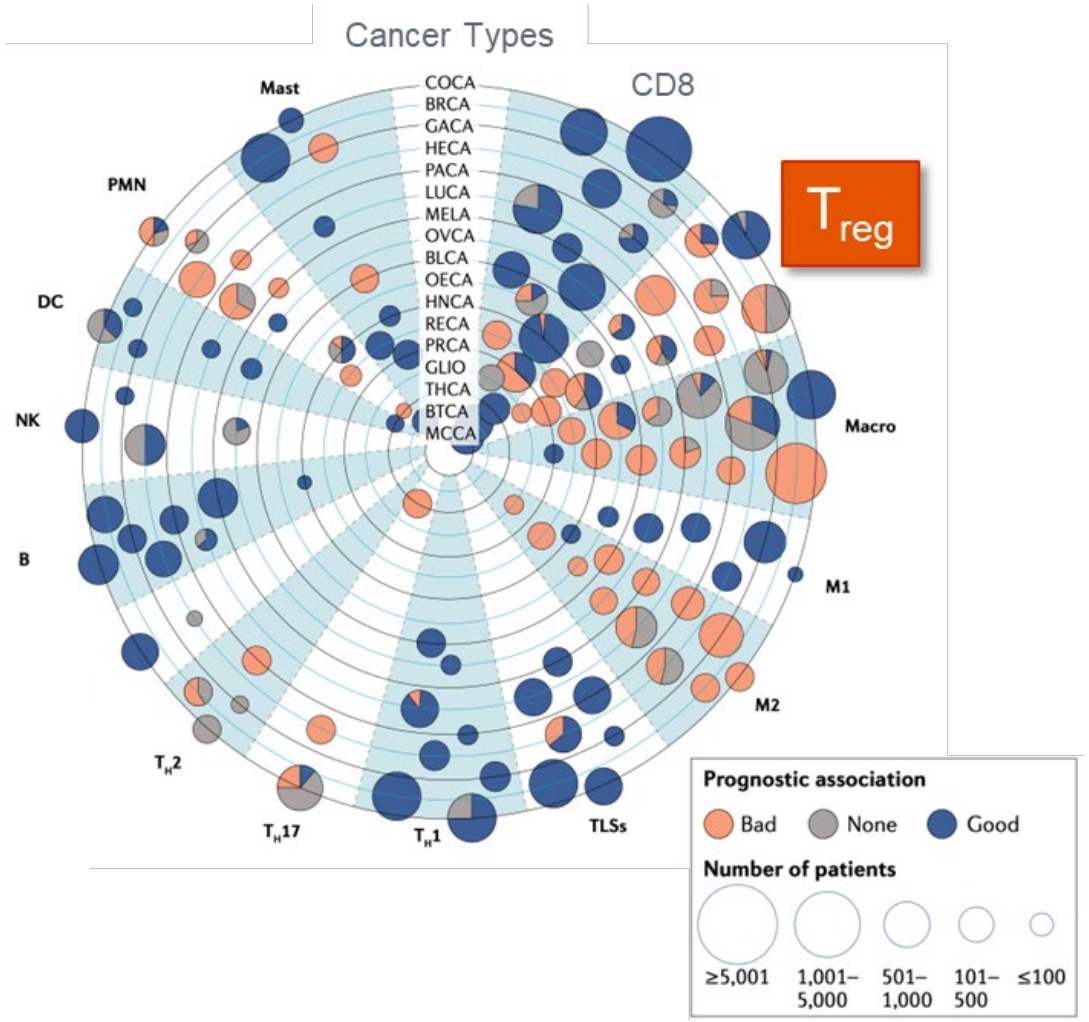
Correlate with poor prognosis across most cancers

Mechanism for immune evasion by viruses and tumors

Barrier to checkpoint inhibitor efficacy

Challenge: selective inhibition of T_{reg} in the TME

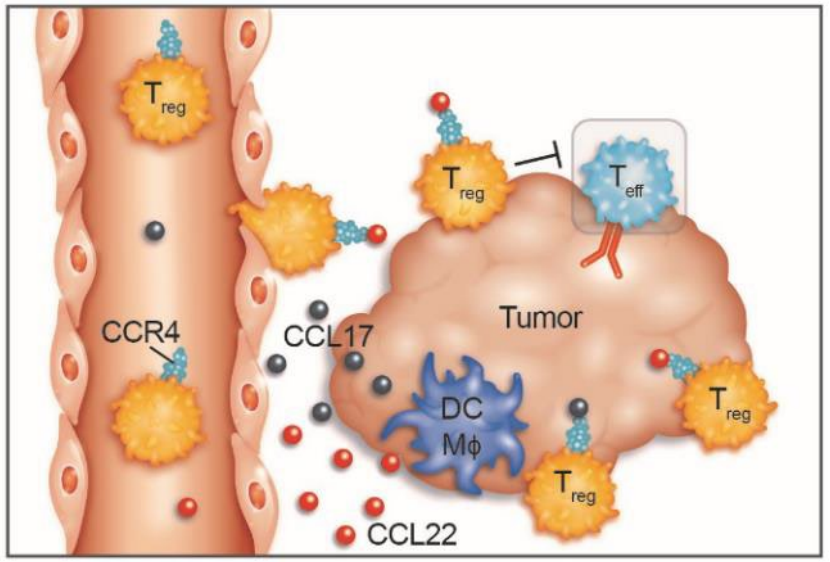
- Depleting antibodies targeting CD25, CCR4, etc. do not appear to have adequate selectivity

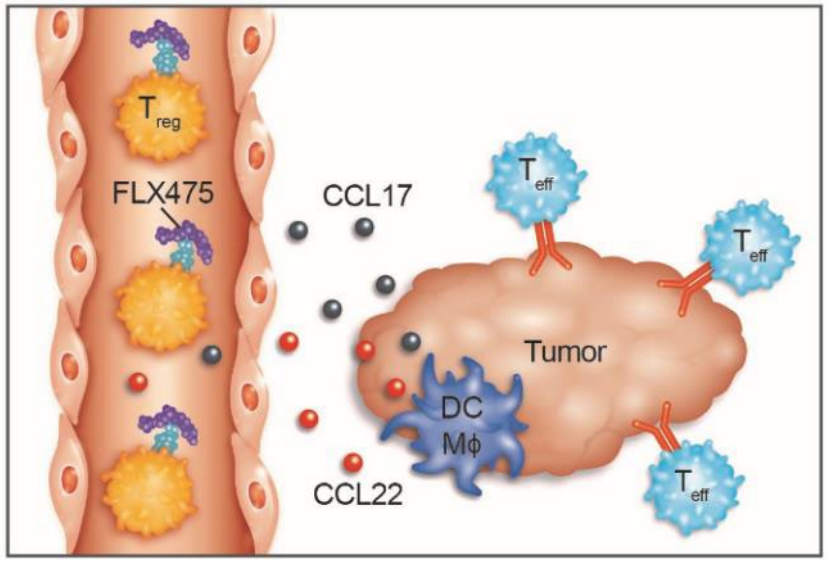


Bruni D et al. *Nat Rev Cancer* 2020

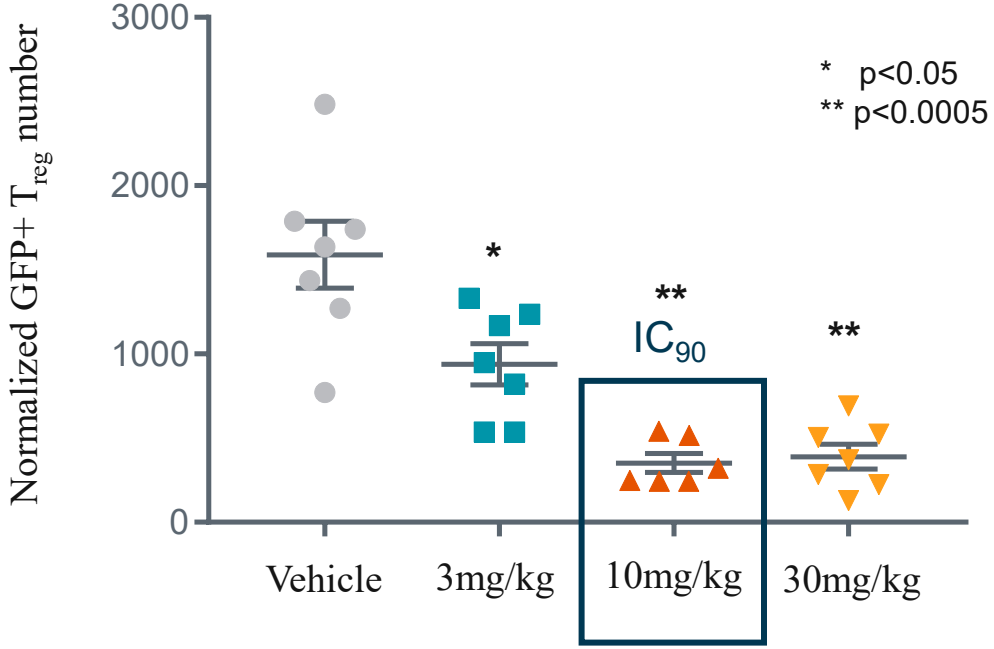
FLX475: CCR4 Antagonist Selectively Targets Tumor T_{reg}

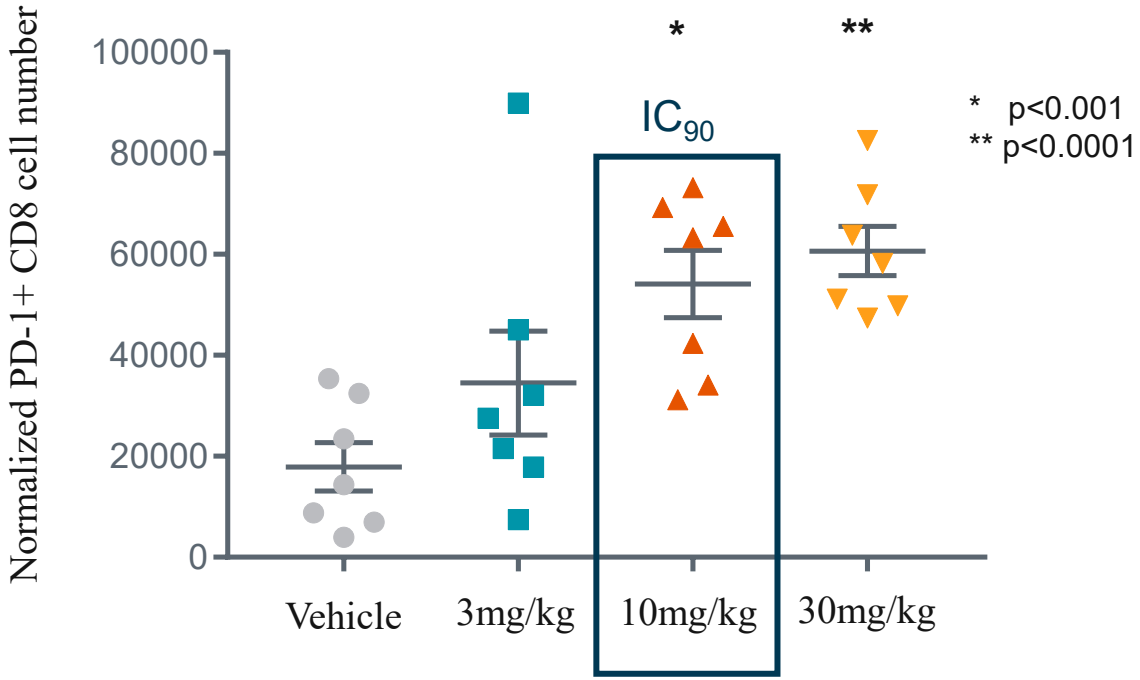
- Immune cells follow chemokines to migrate into target tissues
- CCR4 is the primary chemokine receptor expressed on human T_{reg}
- In response to inflammation, tumor cells and other cells in the TME highly express the chemokines CCL17 and CCL22 (ligands for CCR4), inducing the migration of T_{reg} into tumors
- T_{reg} can suppress the anti-tumor activity of effector T cells
- FLX475 is a potent, orally-available, small molecule antagonist of CCR4 designed to specifically block the recruitment of T_{reg} into tumors
  - With a goal of shifting the T_{eff}/T_{reg} balance in favor of tumor elimination





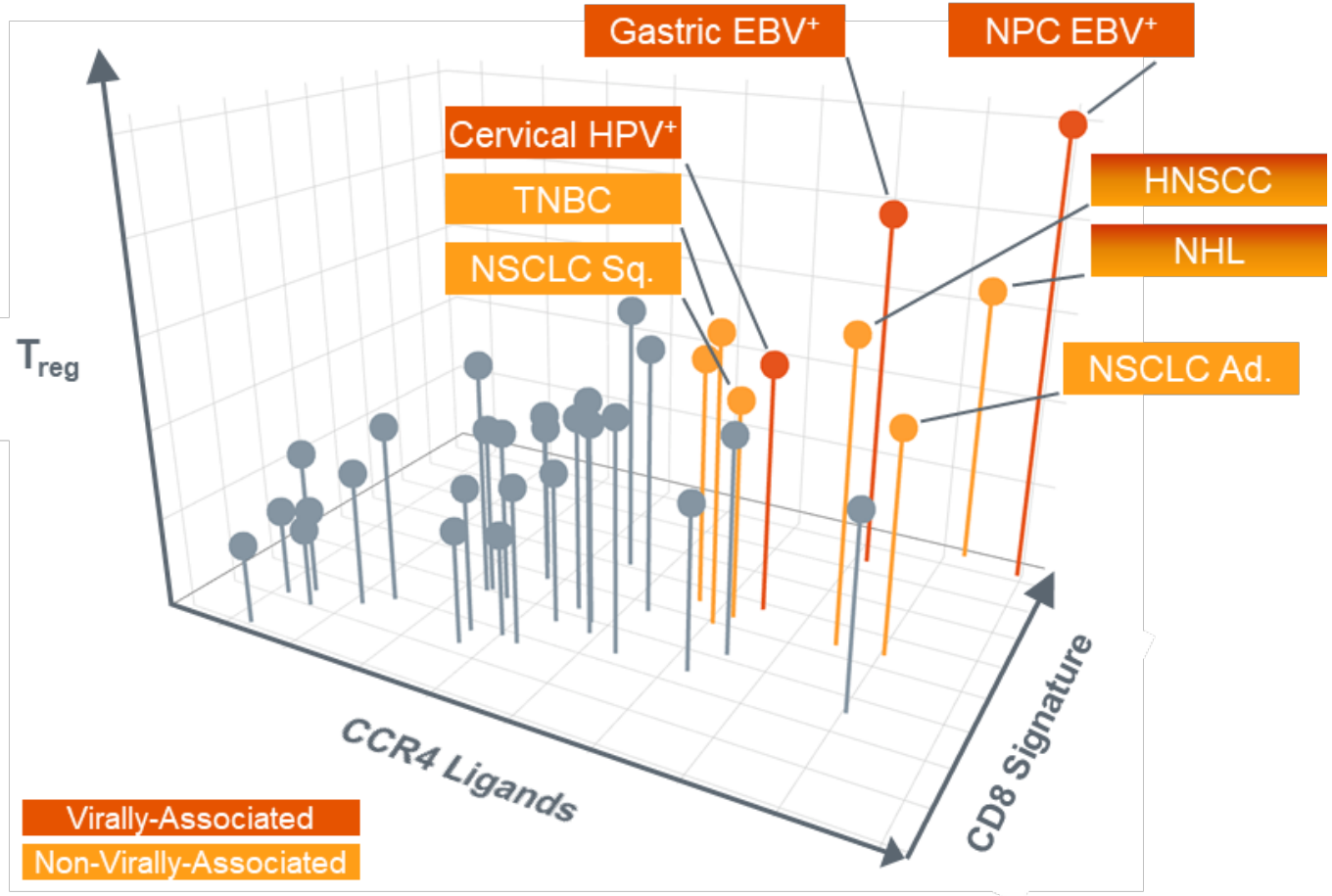
Blocking CCR4 is Sufficient to Inhibit T_{reg} Migration into the Tumor and Activate CD8 T cells





IC_{90} = concentration at which 90% of T_{reg} chemotaxis is inhibited

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 express high levels of CCR4 ligands, T_{reg} and CD8 T cells

- Expected to be "hot" with high levels of effector CD8 cells but also with high levels of T_{reg} that limit the antitumor immune response

Blocking CCR4-mediated T_{reg} recruitment would thus be more likely to shift the T_{eff}/T_{reg} ratio toward an enhanced antitumor microenvironment in these tumors

Potential for both monotherapy and combination activity

EBV Drives T_{reg} Recruitment to the Tumor through CCR4

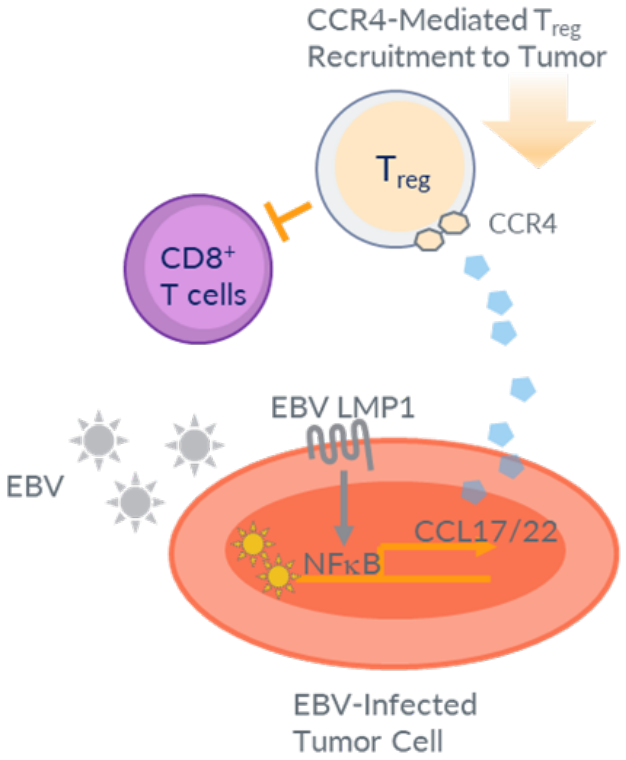
EBV upregulates CCR4 ligand expression to recruit T_{reg} and protect itself from the immune system

- EBV LMP1 drives CCL17 and CCL22 expression
- EBV+ tumors have increased T_{reg} infiltration

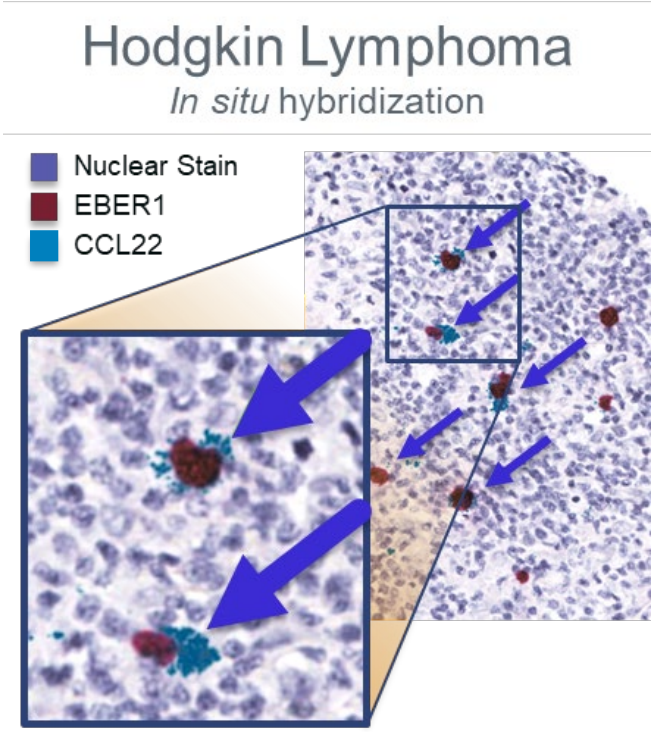
Epstein Barr Virus+ (EBV+) associated with multiple tumors:

- Nasopharyngeal carcinoma (~100%),
- Gastric (~5-10%),
- Hodgkin Lymphoma (~40%), other EBV+ NHL like ENTCL

EBV typing is already routine, enables access to pre-identified patients



Nakayama et al. *J Virol* 2004



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FLX475-02: Phase 1/2 Study of FLX475 as Monotherapy and in Combination with Pembrolizumab in Advanced Cancer

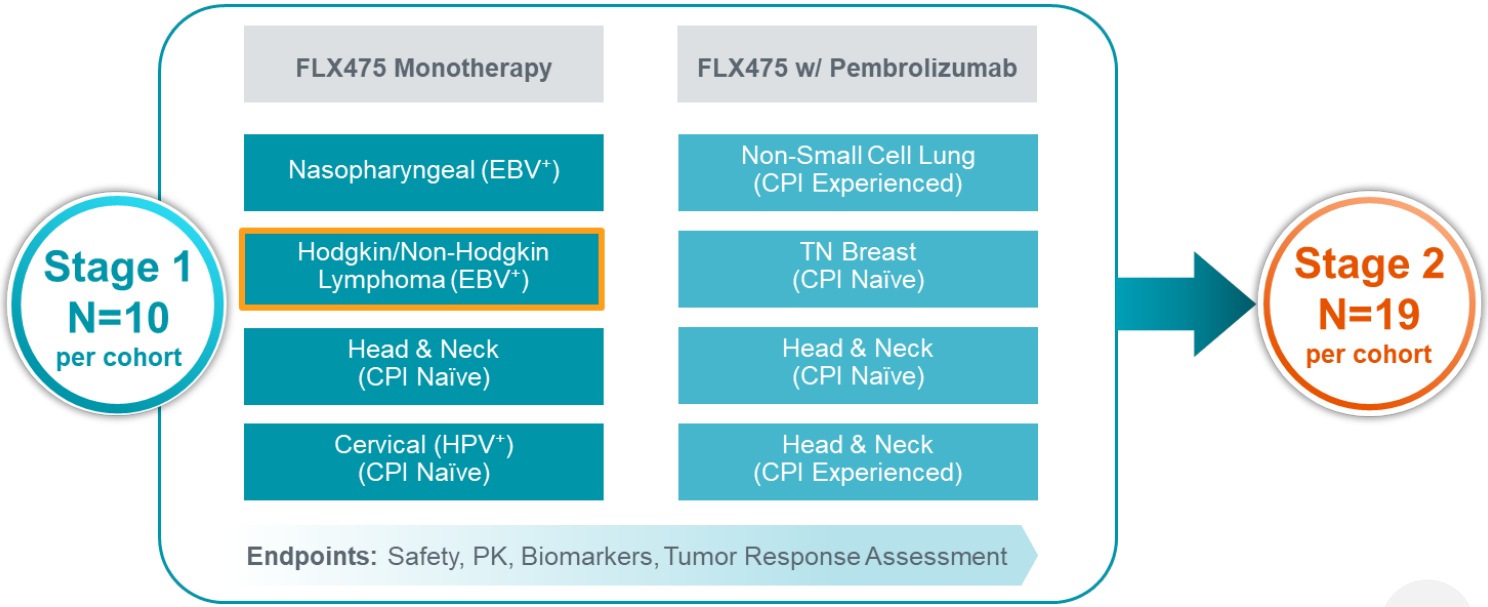
Phase 1 Dose Escalation

- Primary: safety and tolerability
  - Only FLX475-related (expected) AE was asymptomatic, reversible QT prolongation
- 100 mg PO QD selected as recommended Phase 2 dose

FLX475 Monotherapy N=19		FLX475 w/ Pembrolizumab N=18	
100 mg	N=6	100 mg	N=11
75 mg	N=7	75 mg	N=4
50 mg	N=3	50 mg	N=3
25 mg	N=3		

Phase 2 Expansion Cohorts

- Evaluate antitumor activity of FLX475 as monotherapy and in combination with pembrolizumab in potentially "charged" tumor types
- Simon 2-Stage Design
- One monotherapy cohort dedicated to EBV+ lymphoma



First EBV+ ENTCL Case: Complete Metabolic Response to FLX475 Monotherapy

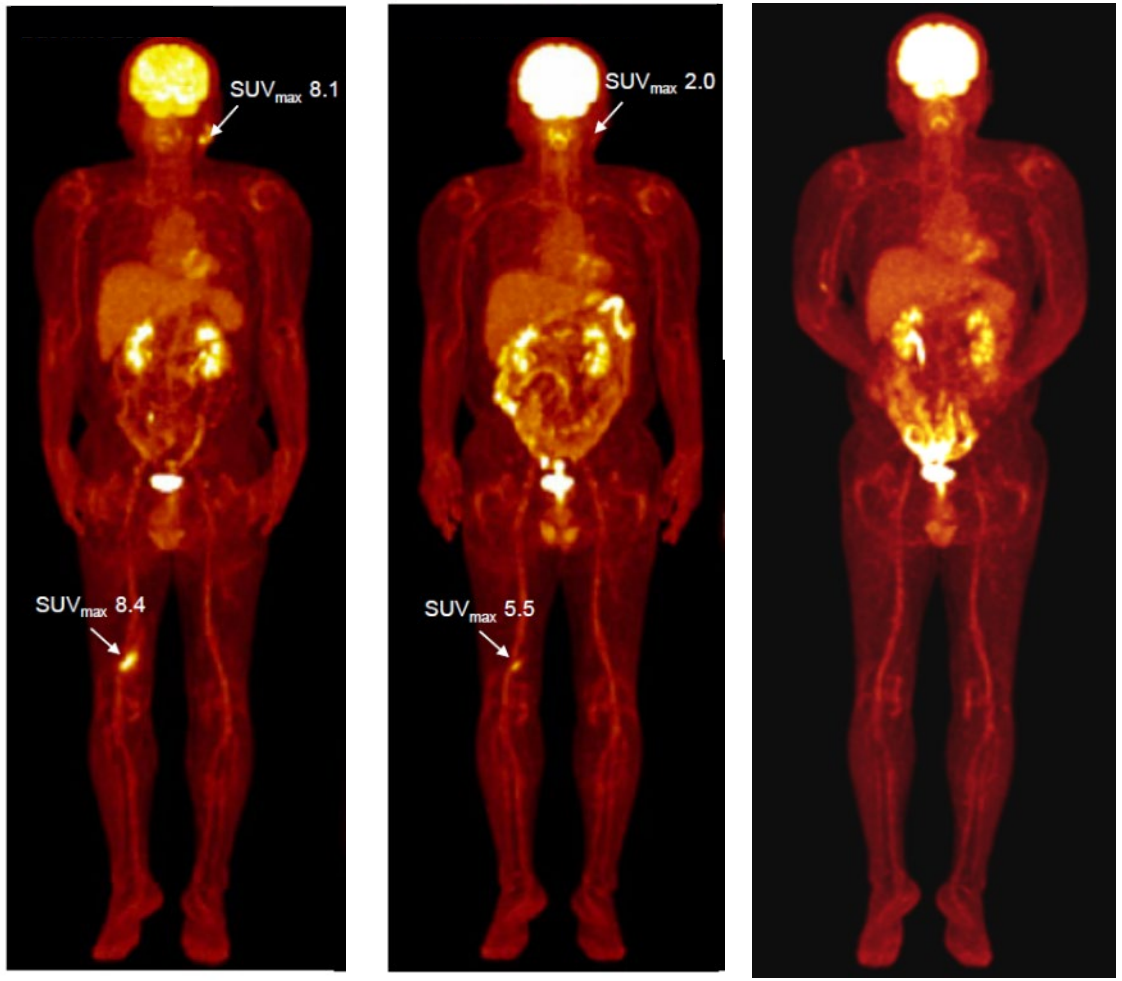
EBV+ ENTCL

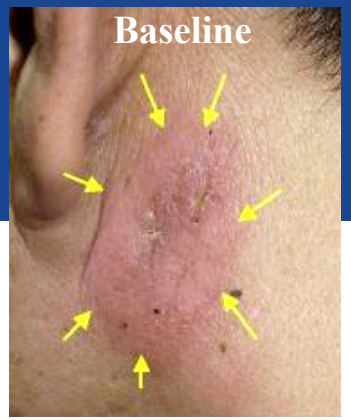
- 53 y/o, 1 line of prior chemotherapy 1H 2019
- 2 primary lesions
  - L posterior auricular (target), R distal anterior thigh (non target)

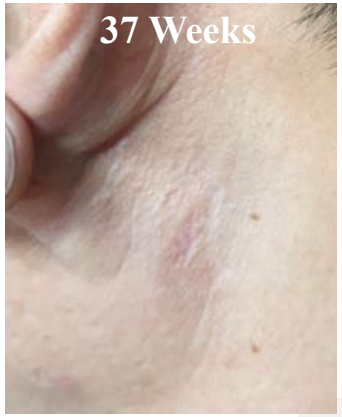
Deep Durable Response

- 8-week scan with complete metabolic response (Deauville score of 5 reduced to 2) and target lesion visibly improving by 12 weeks
- Disease continued to improve; patient remained in complete metabolic response for 16 months

Baseline PET | **8 Weeks** | **33 Weeks**







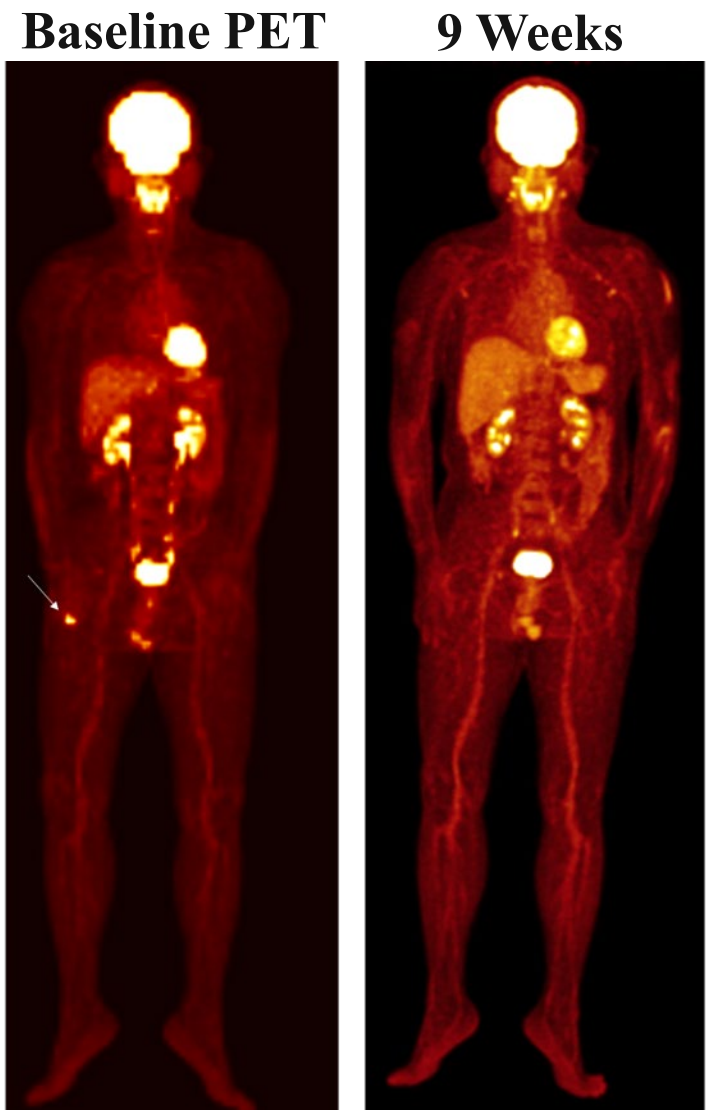
Second EBV+ ENTCL Case: Complete Metabolic Response to FLX475 Monotherapy

EBV+ ENTCL

- 53 y/o, 2 lines of prior chemotherapy
- 3 primary lesions
  - R buttock, thigh, and inguinal LN

Deep Durable Response

- Complete metabolic response noted after 3 cycles
- No measurable disease by CT scan after 9 cycles, continues beyond 12 cycles (9 months)



Summary

- Regulatory T cells can interfere with the antitumor immune response and result in poor clinical outcomes
- Hypothesis: FLX475, an oral CCR4 antagonist that can block the recruitment of suppressive T_{reg} into the TME, should selectively target tumor T_{reg} and enhance existing or developing antitumor immunity
- "Charged" tumors should be enriched for antitumor effector T cells, but also CCR4 ligands and suppressive T_{reg}, and thus may be responsive to CCR4 antagonism
- EBV+ tumors can recruit T_{reg} via CCR4 and are highly "charged"
- The ongoing FLX475-02 trial is exploring the clinical activity of FLX475 as monotherapy and in combination with pembrolizumab in patients with "charged" tumors, including EBV+ lymphoma
- The first two subjects with ENTCL enrolled on study have each had complete metabolic responses to FLX475 monotherapy, supporting the clinical hypothesis