

New Drugs In Hematology

Hodgkin Lymphoma
New Combo-Steps

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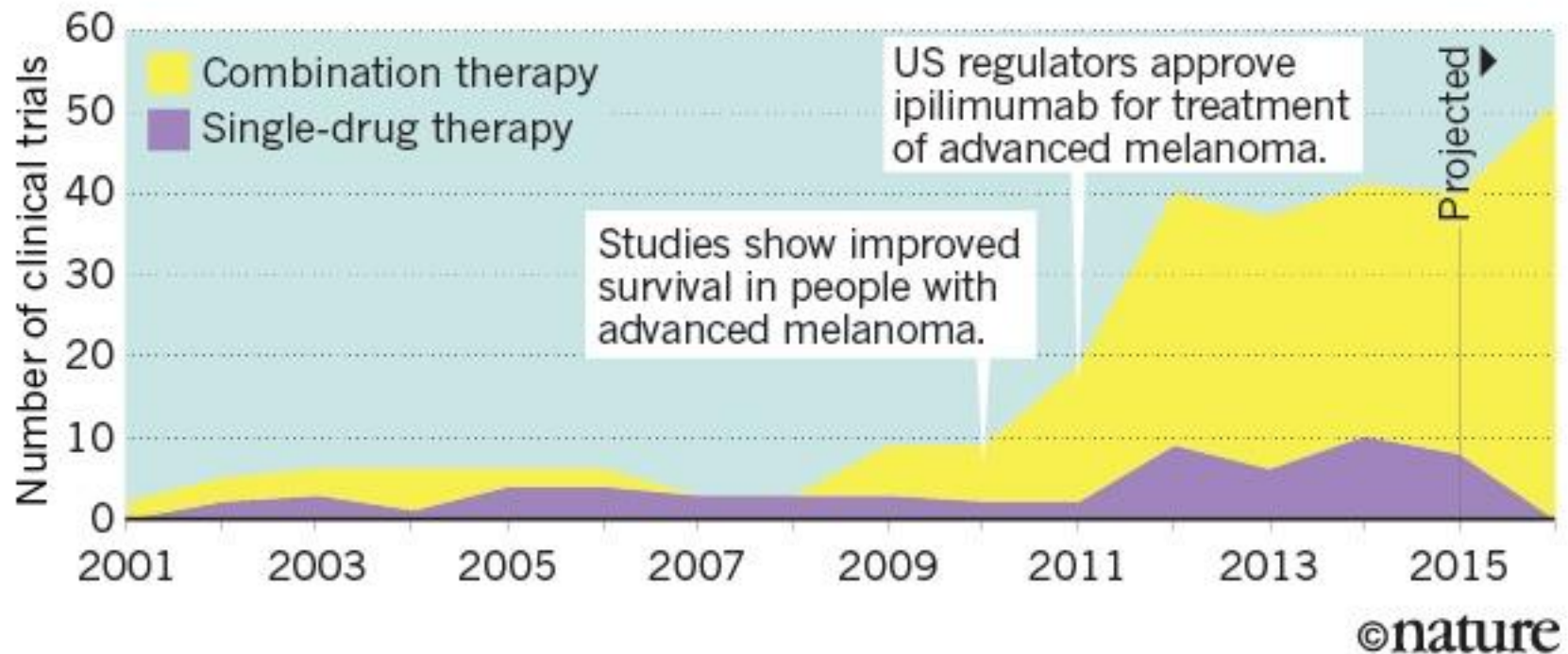
Monday, May 9, 2016

2:55-3:10 p.m

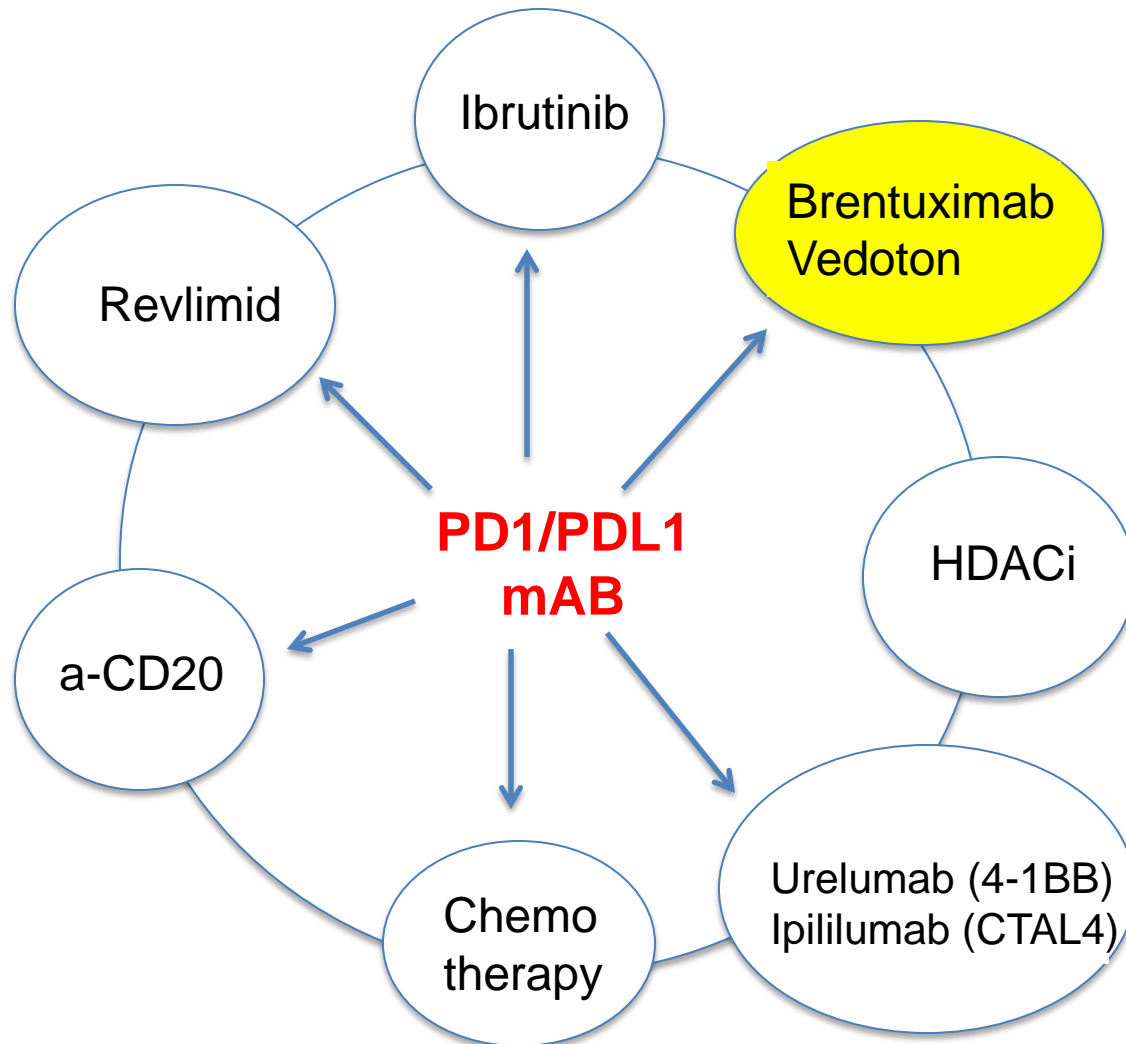
Combinations with Immune Checkpoint Inhibitors

COMBINATORIAL EXPLOSION

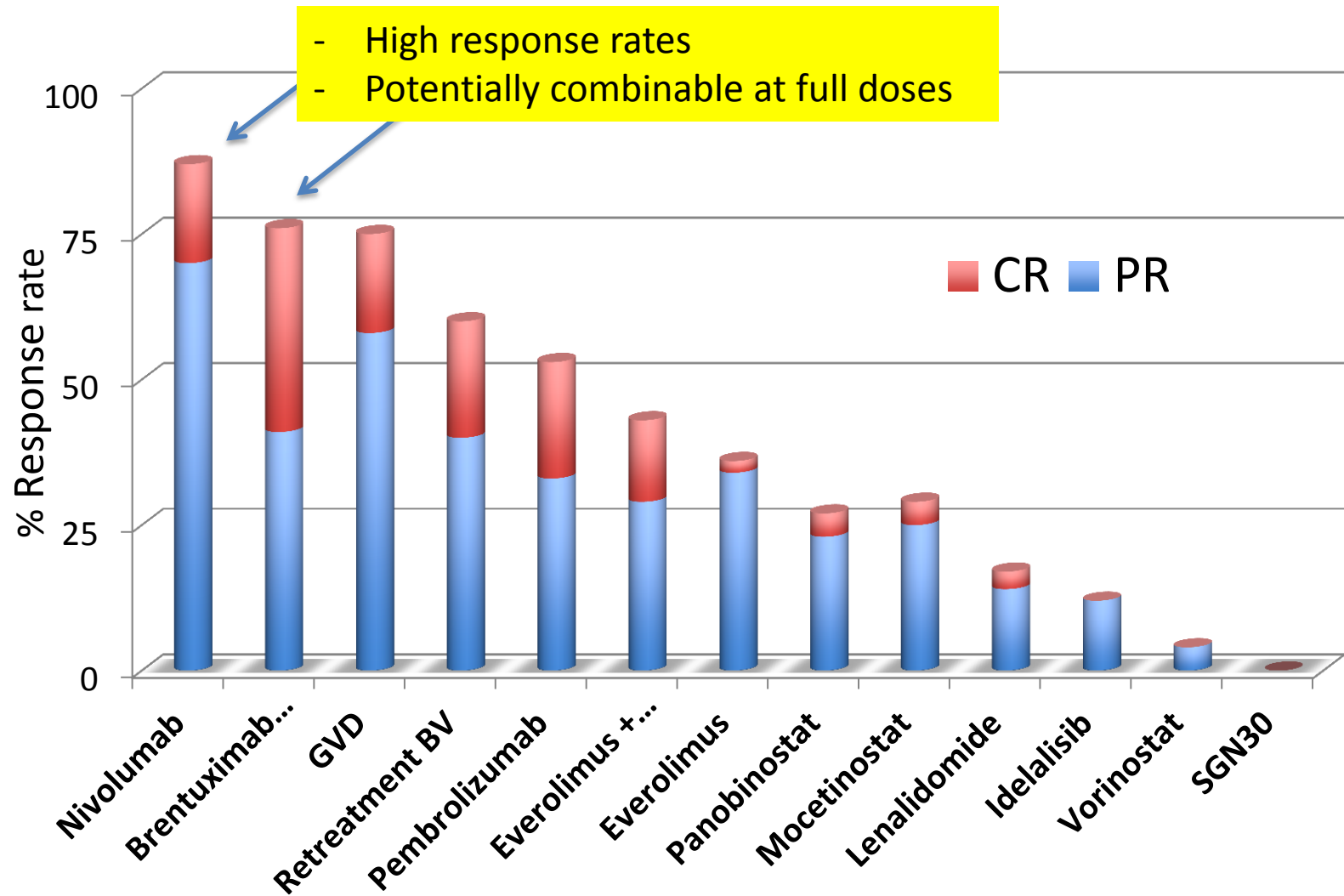
Ipilimumab, the first approved checkpoint inhibitor, has been tested in dozens of clinical trials since 2001. And like many other drugs in its class, it is increasingly being tested in combination with other therapies.



Development of Anti-PD1/PDL1-Based Therapy

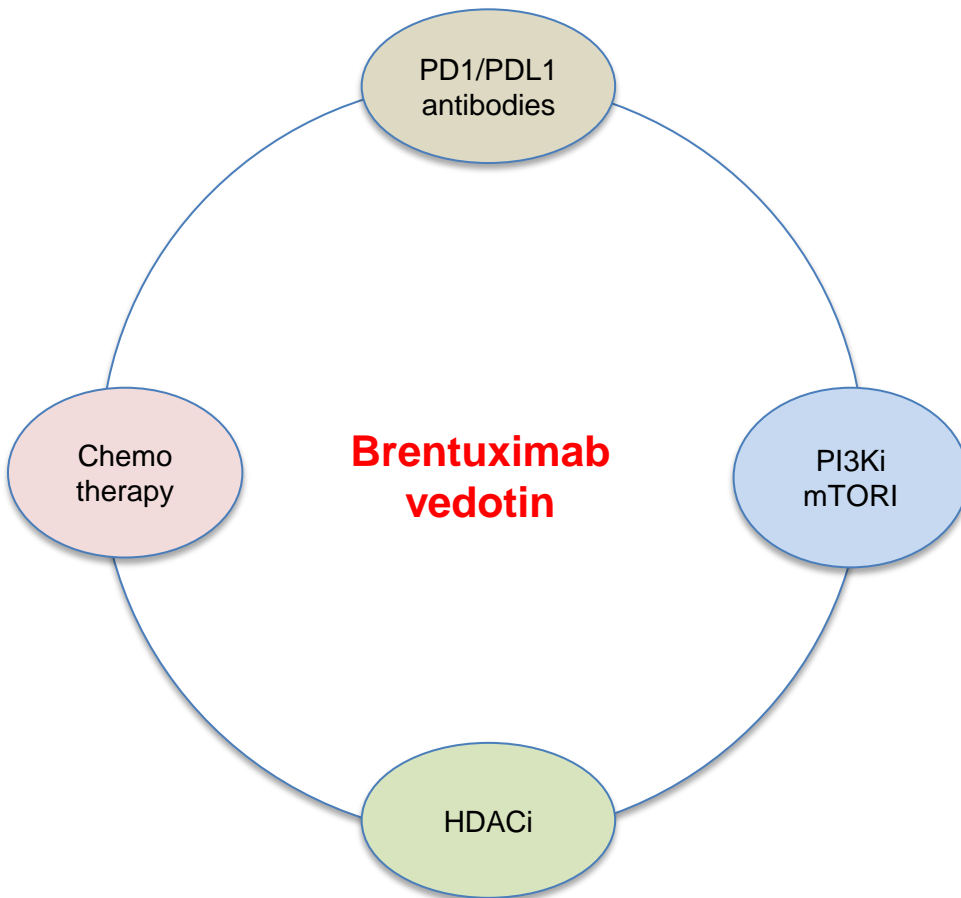


Single agent activity of novel agents in relapsed cHL

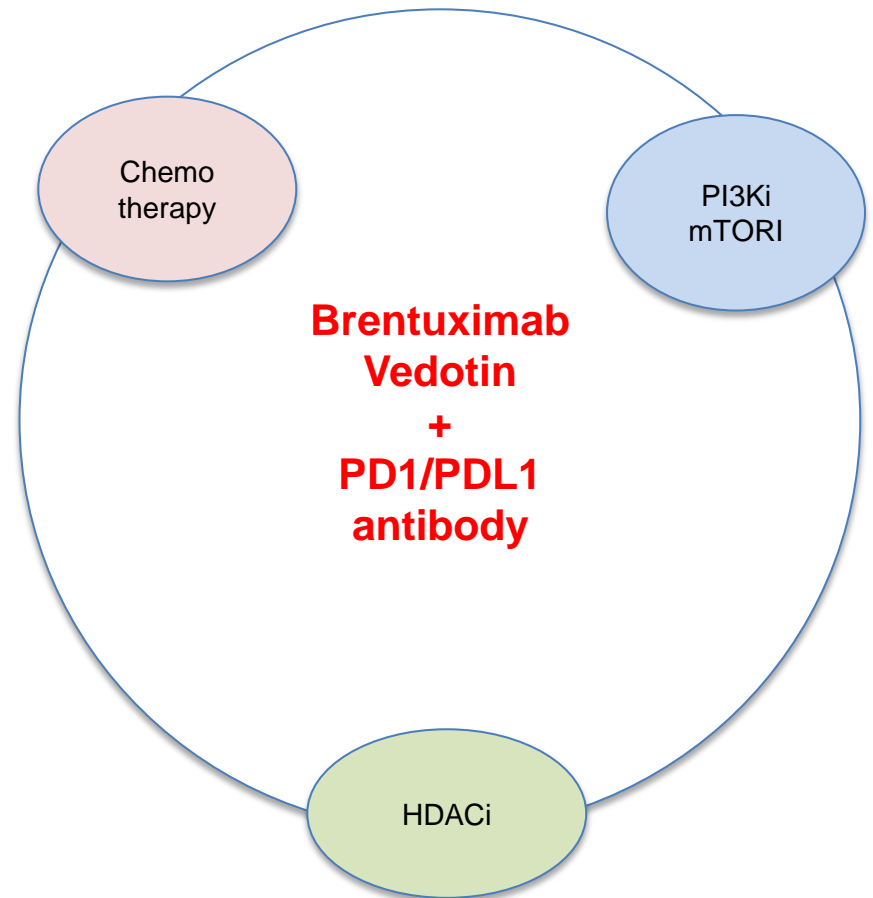


Hodgkin Lymphoma : Future Directions

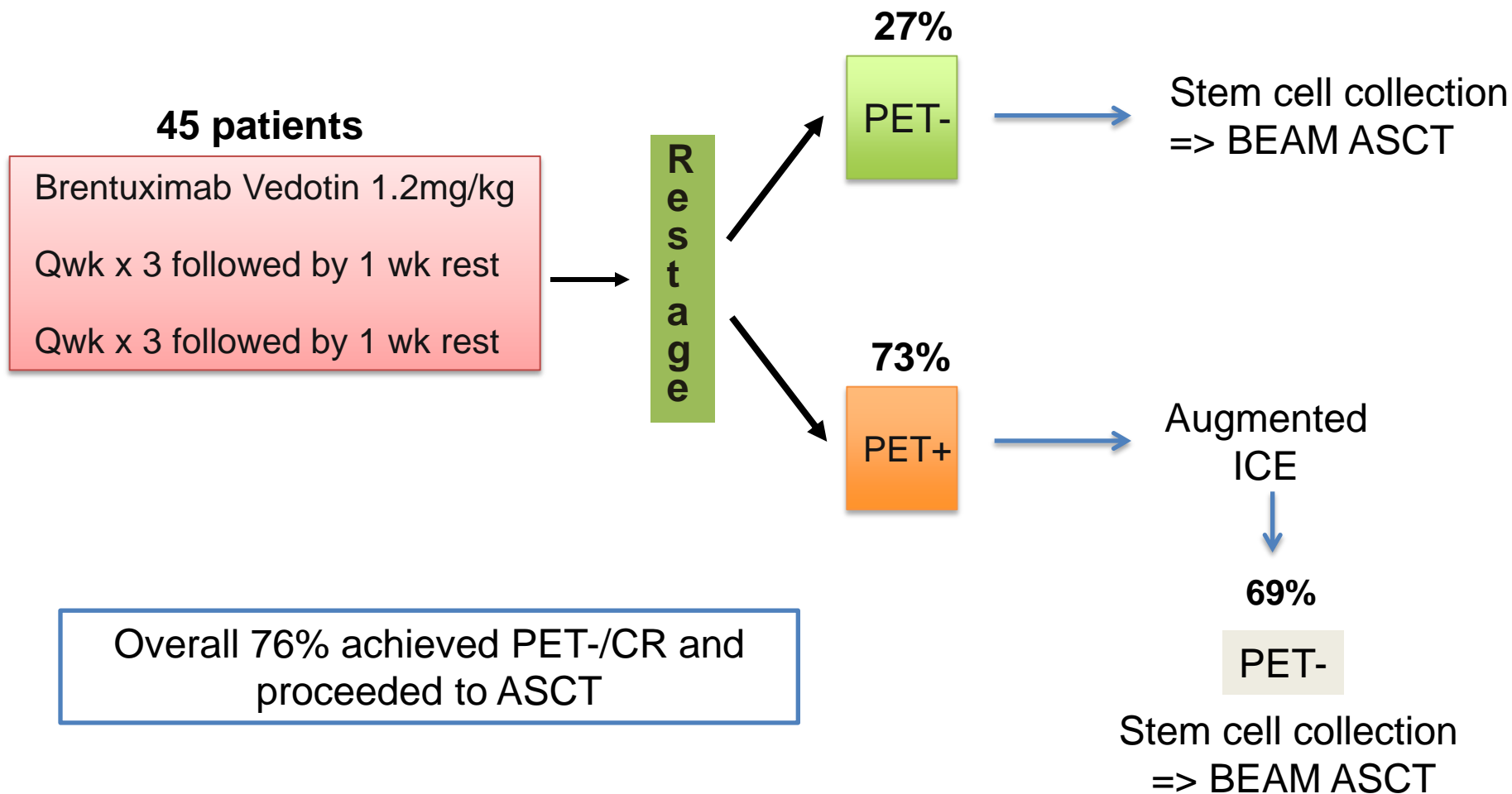
Strategy A



Strategy B

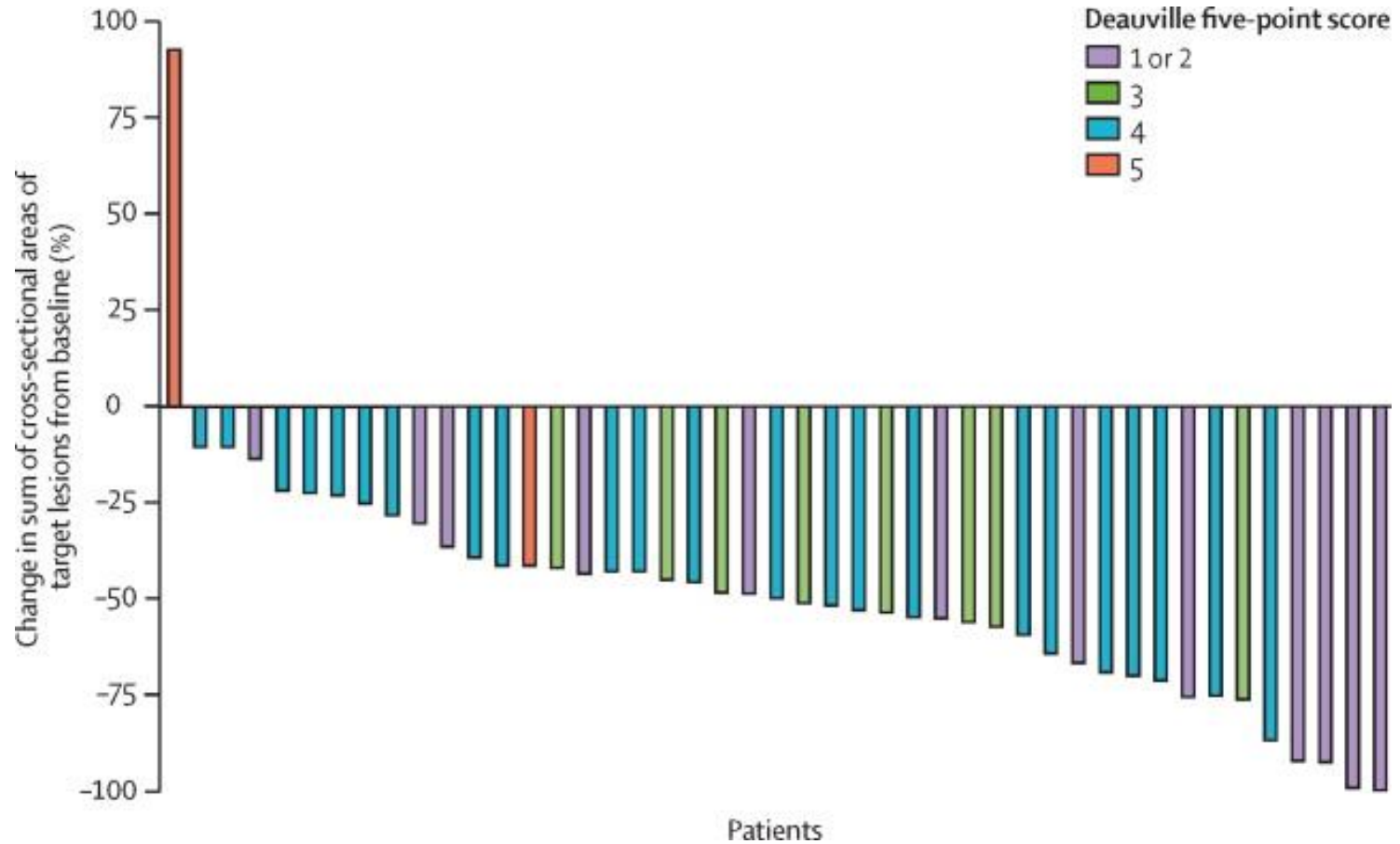


Response adapted salvage therapy for transplant eligible HL

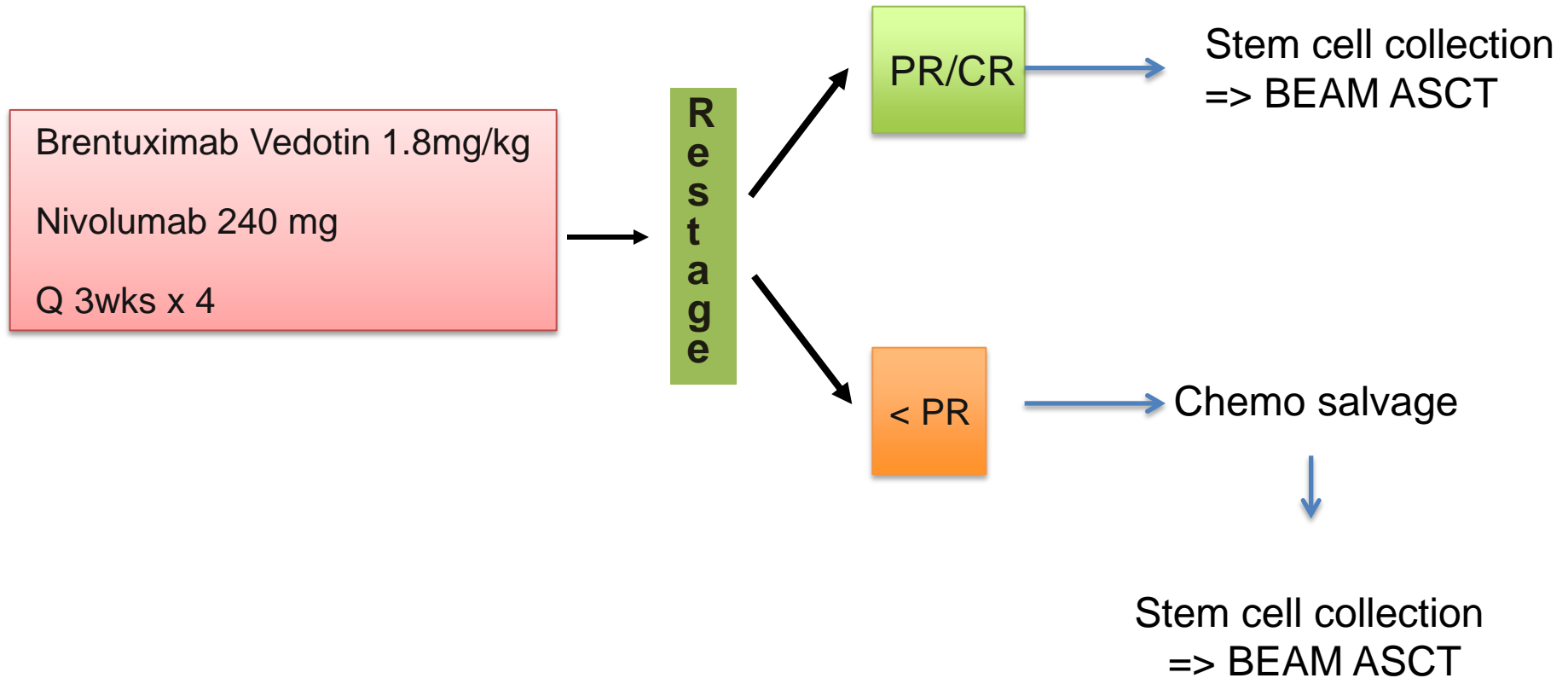


Tumour reduction after brentuximab vedotin

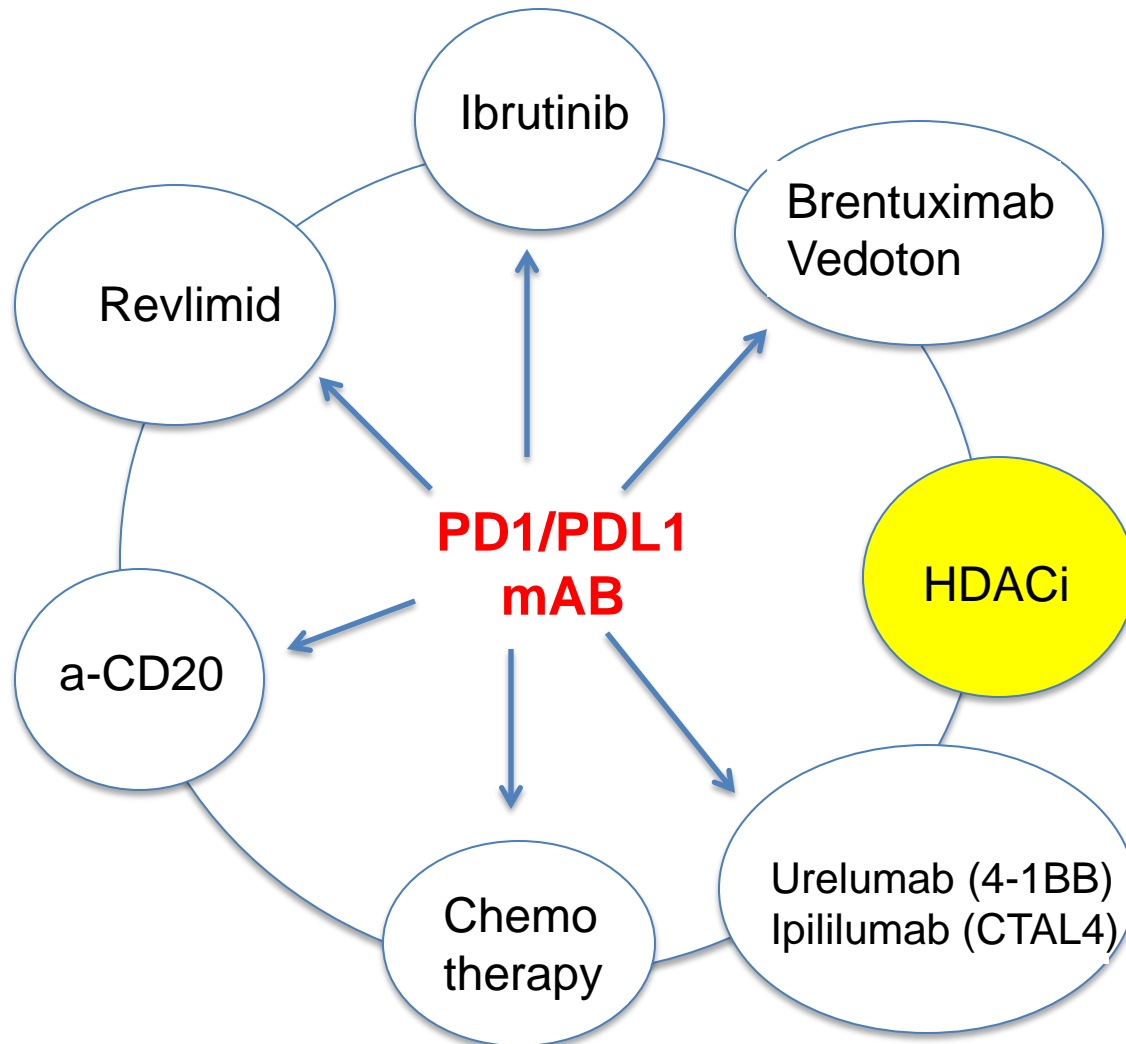
Data shows PET status according to the Deauville scores of 1–5



Nivolumab + Brentuximab Salvage Therapy for HL



Development of Anti-PD1/PDL1-Based Therapy



Hodgkin and Reed Sternberg (HRS) Cells

EBV
Infection

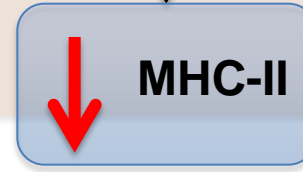
9p24.1
Gene amplification

CIITA-BX648577
Gene fusion

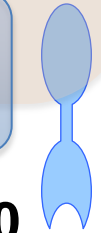
B2MG
mutations



JAK2



CD30



Brentuximab
Vedotin

Chemotherapy

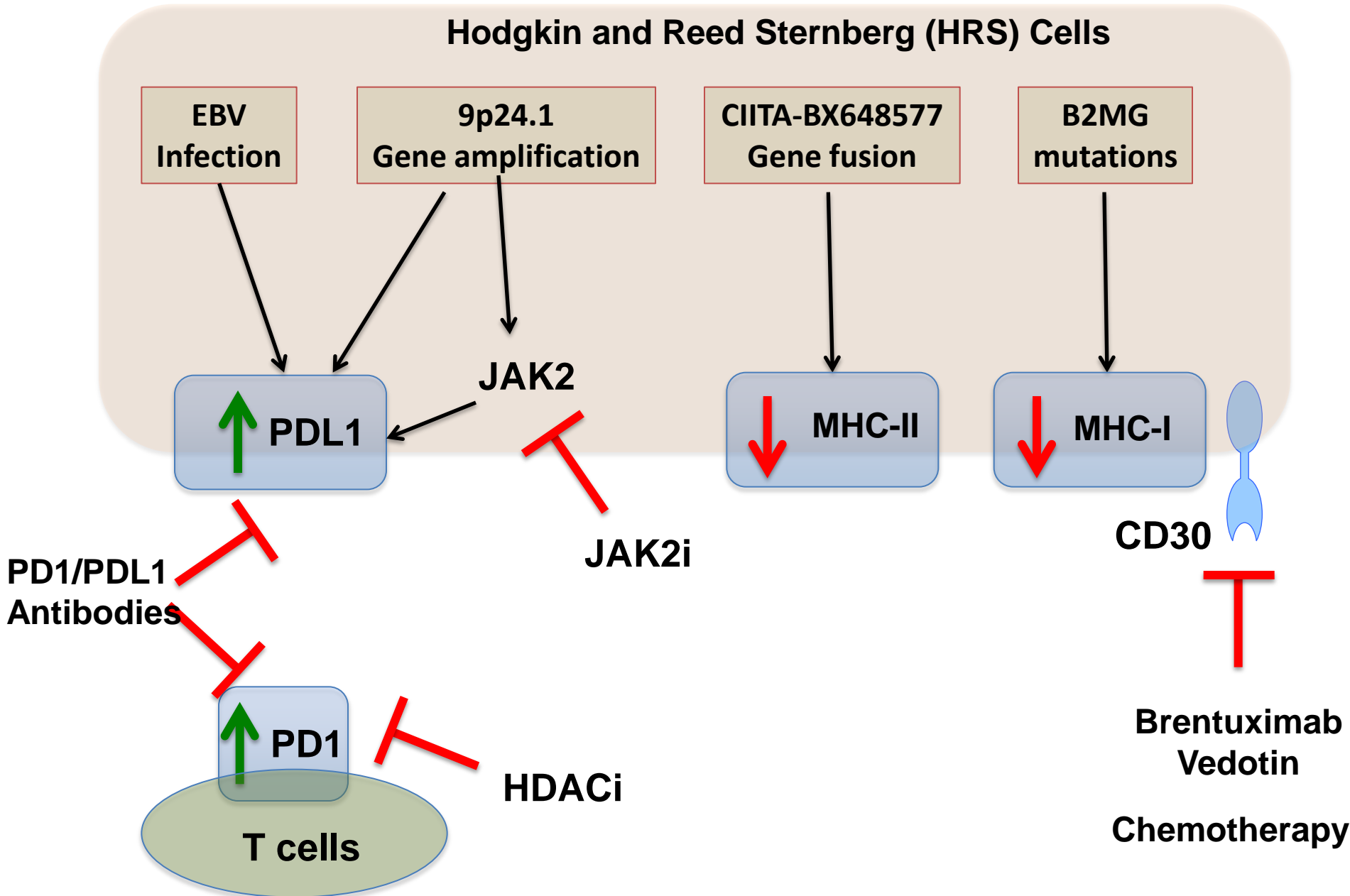
PD1/PDL1
Antibodies



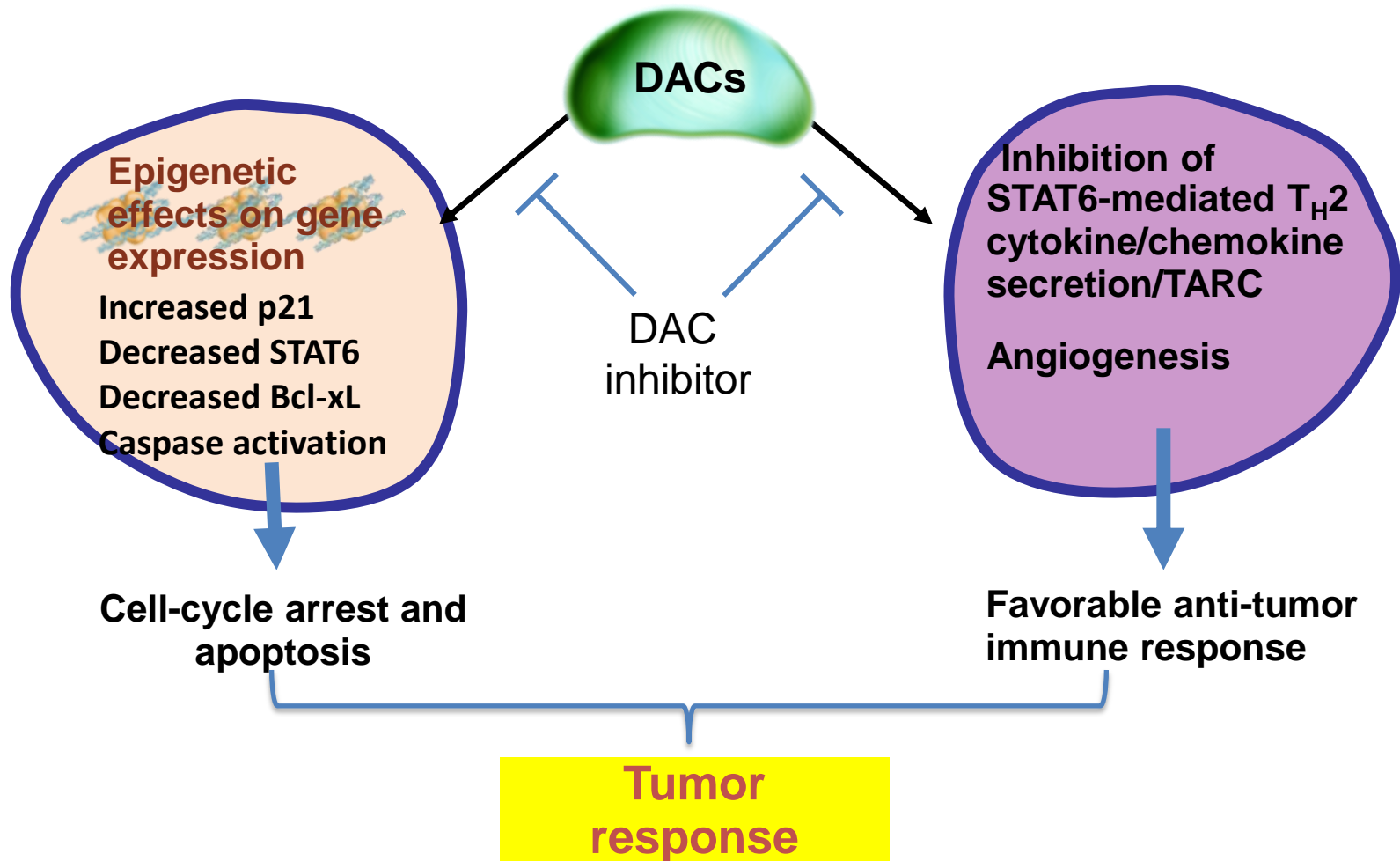
T cells

HDACi

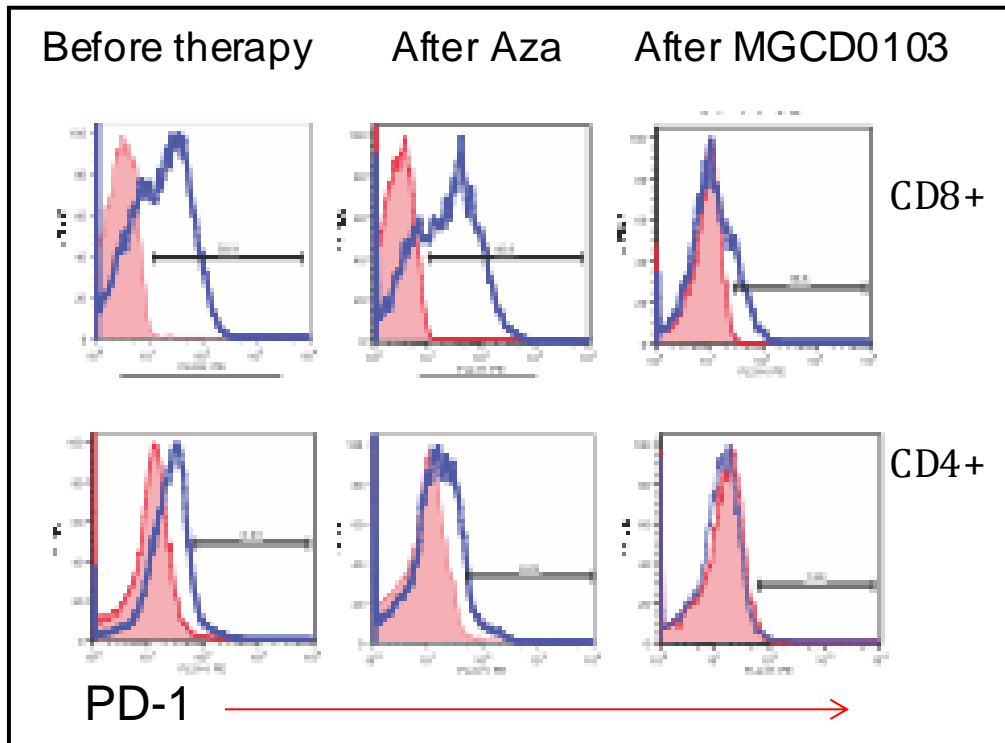
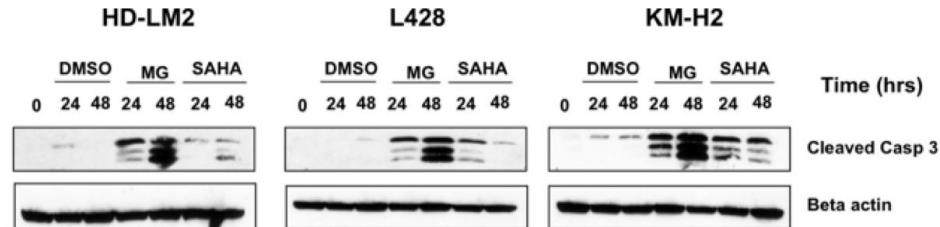
JAK2i



DAC Inhibitors: Regulation of Cell Survival and Immunity

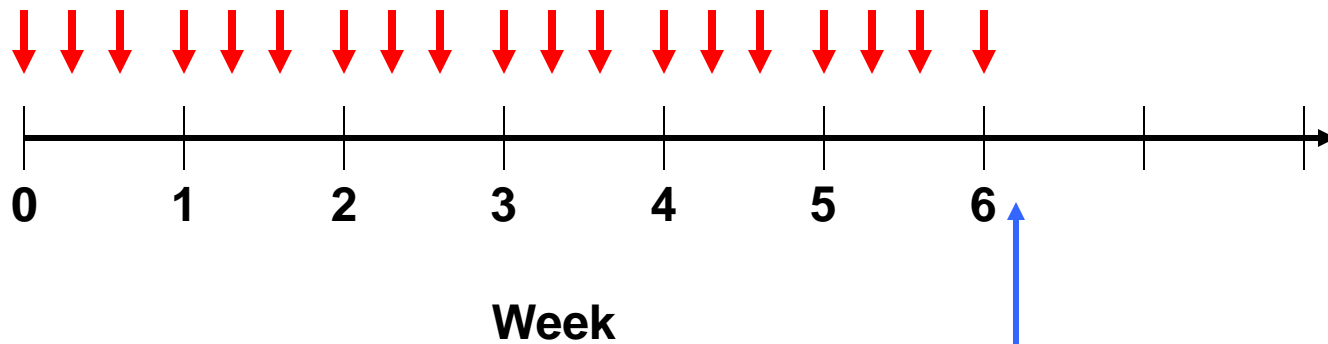


DAC Inhibitors in HL: Regulation of Cell Survival and Immunity



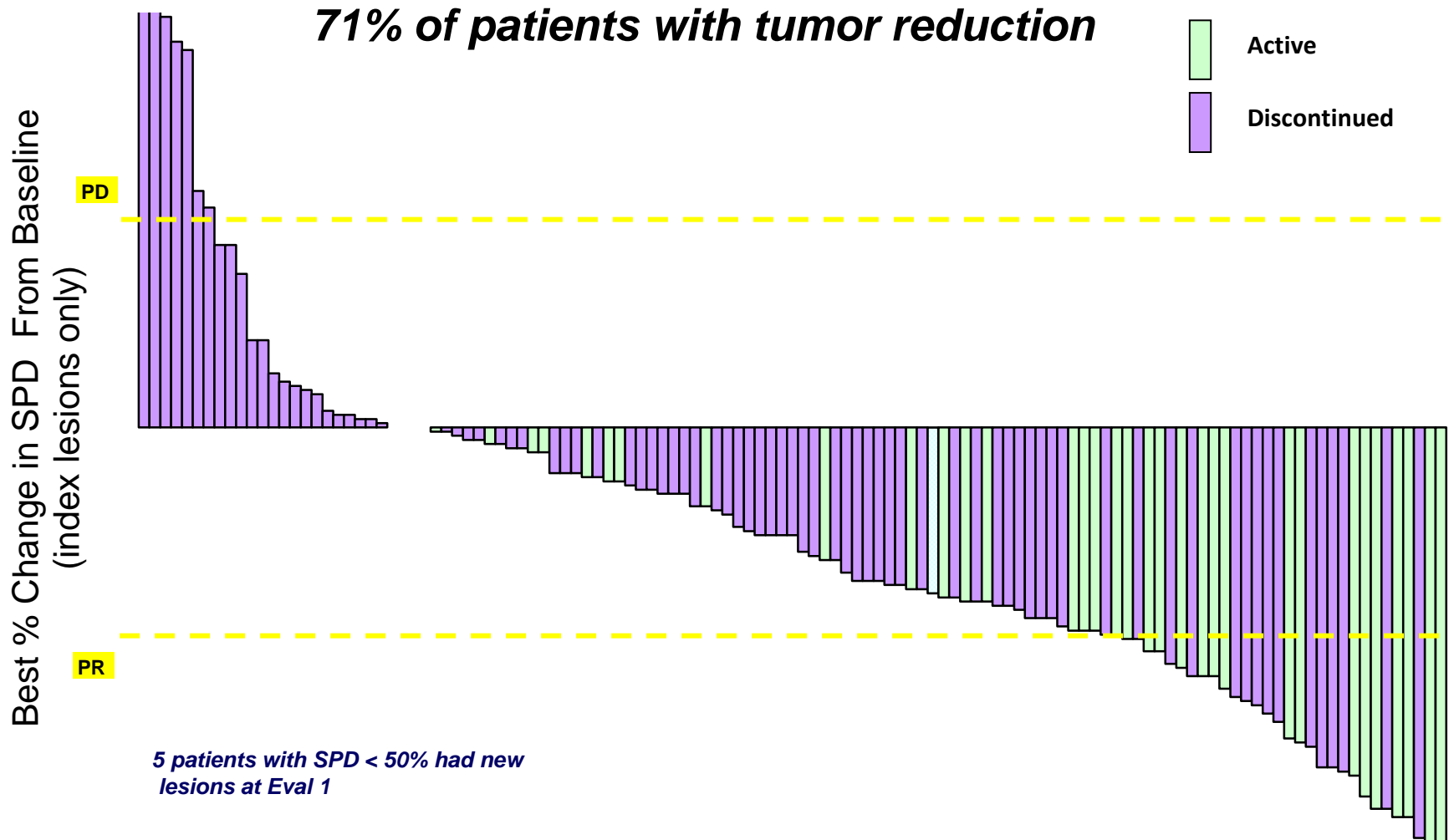
Panobinostat in Patients with Relapsed/Refractory HL

40 mg (fixed dose) orally, 3 times/week



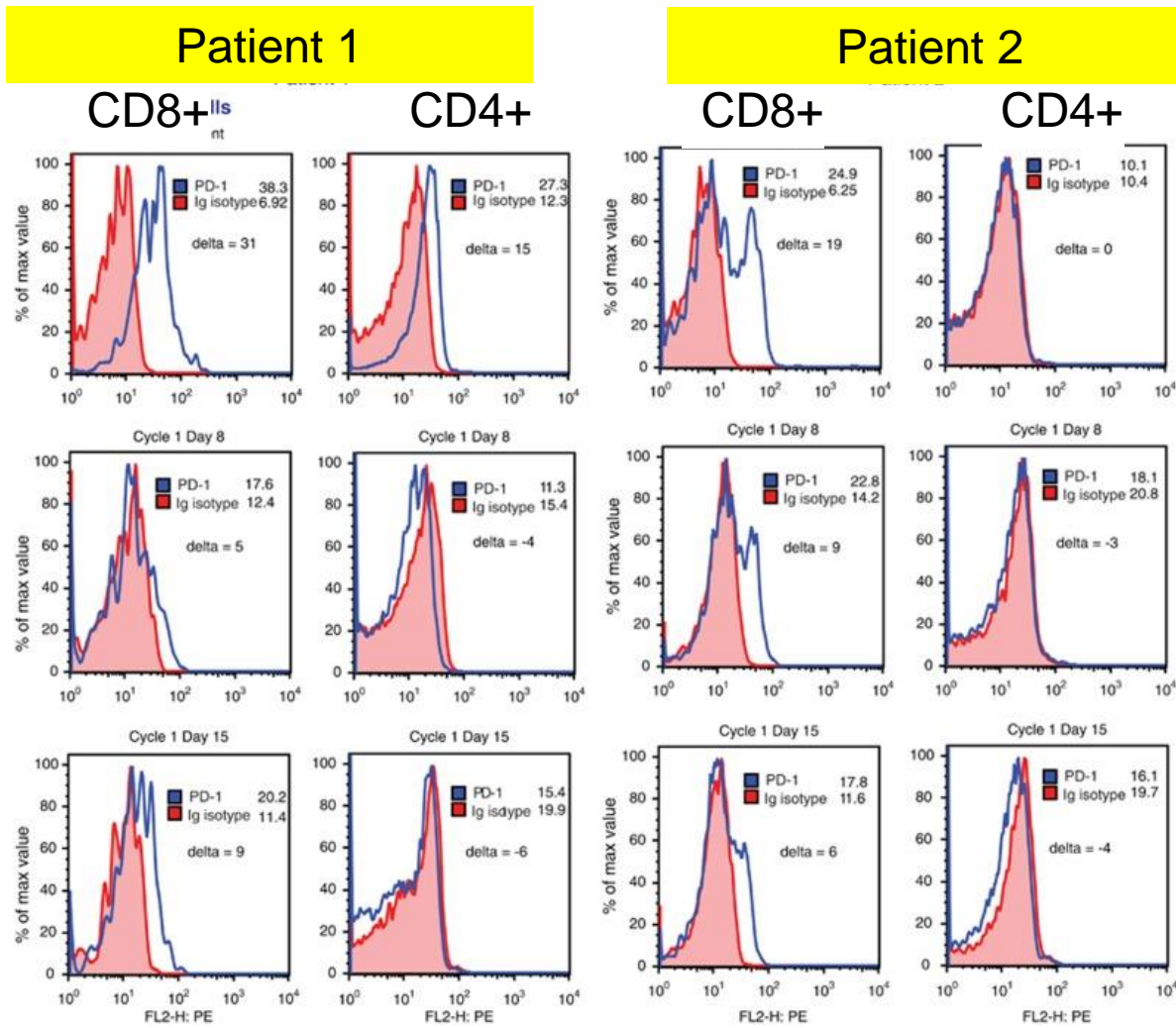
Restage:
If no PD Give
Panobinostat
until PD or tox

Panobinostat Phase II Study in Relapsed HL



Panobinostat Downregulates PD-1 on T cells of Patients with Relapsed HL in Vivo

Pretreatment



Day 8

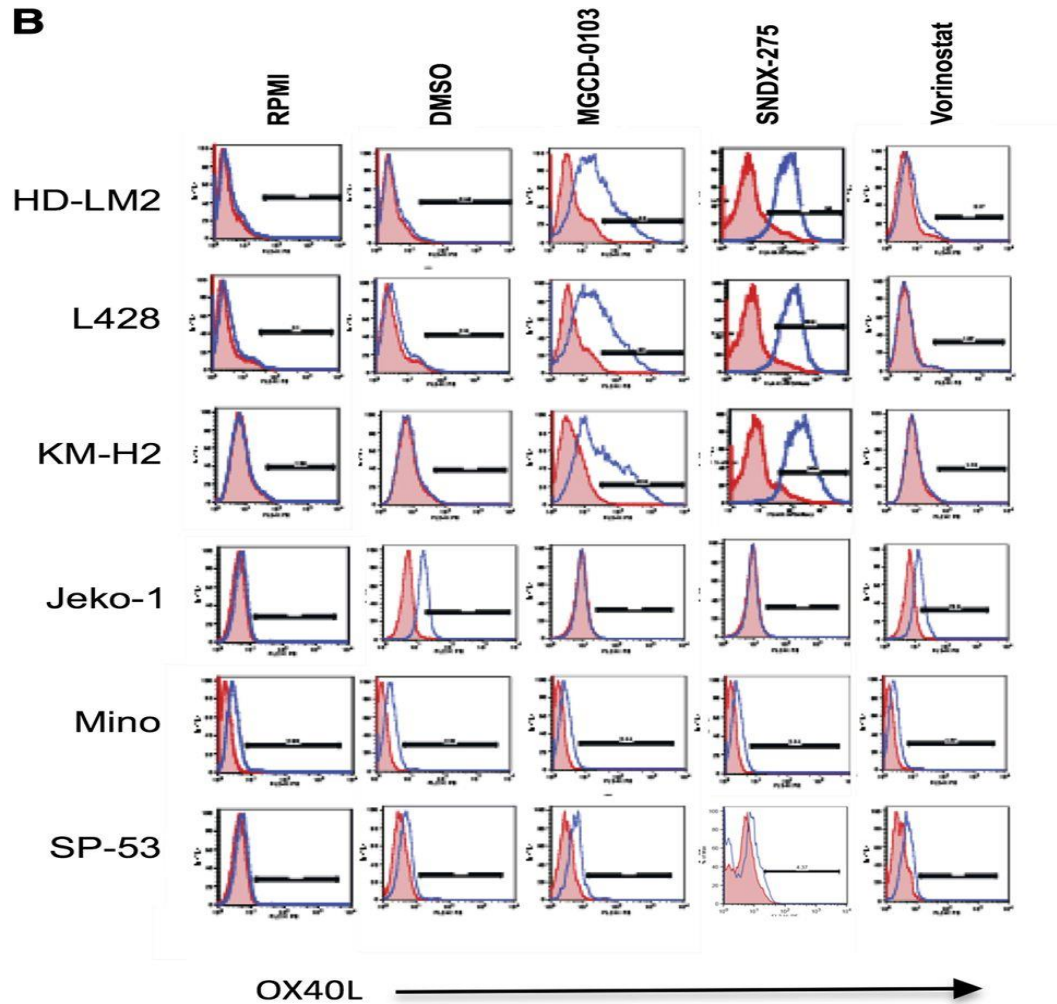
Day 15

PD1 →

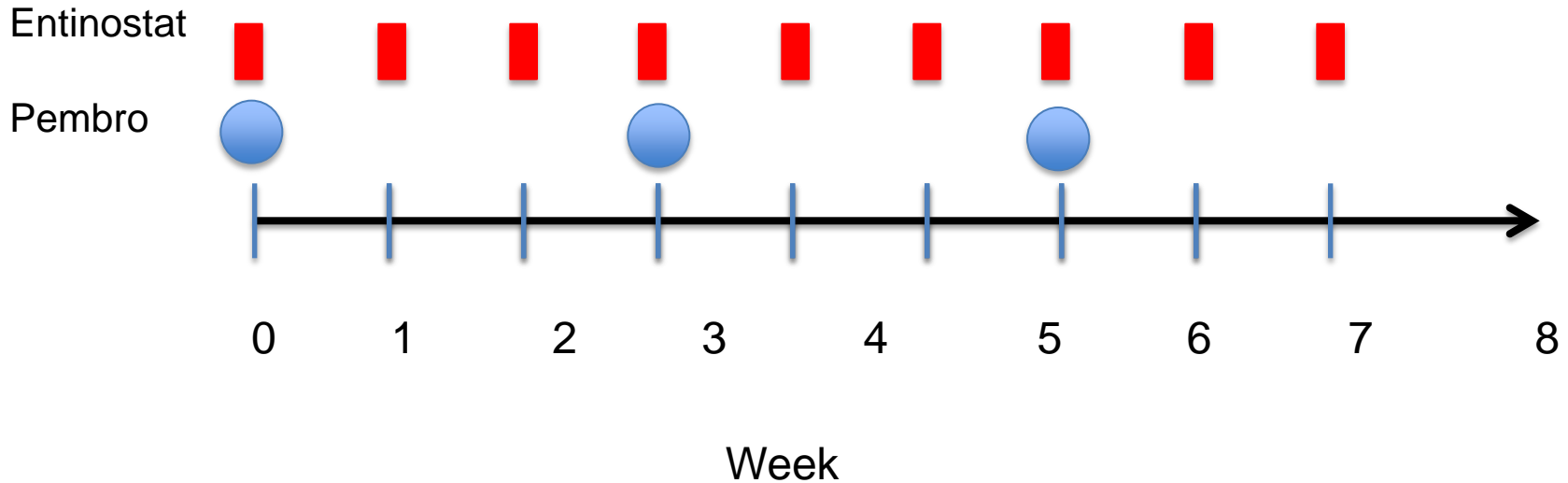
HDACi Upregulate OX40L on HRS Cells

Inhibition of T-reg function

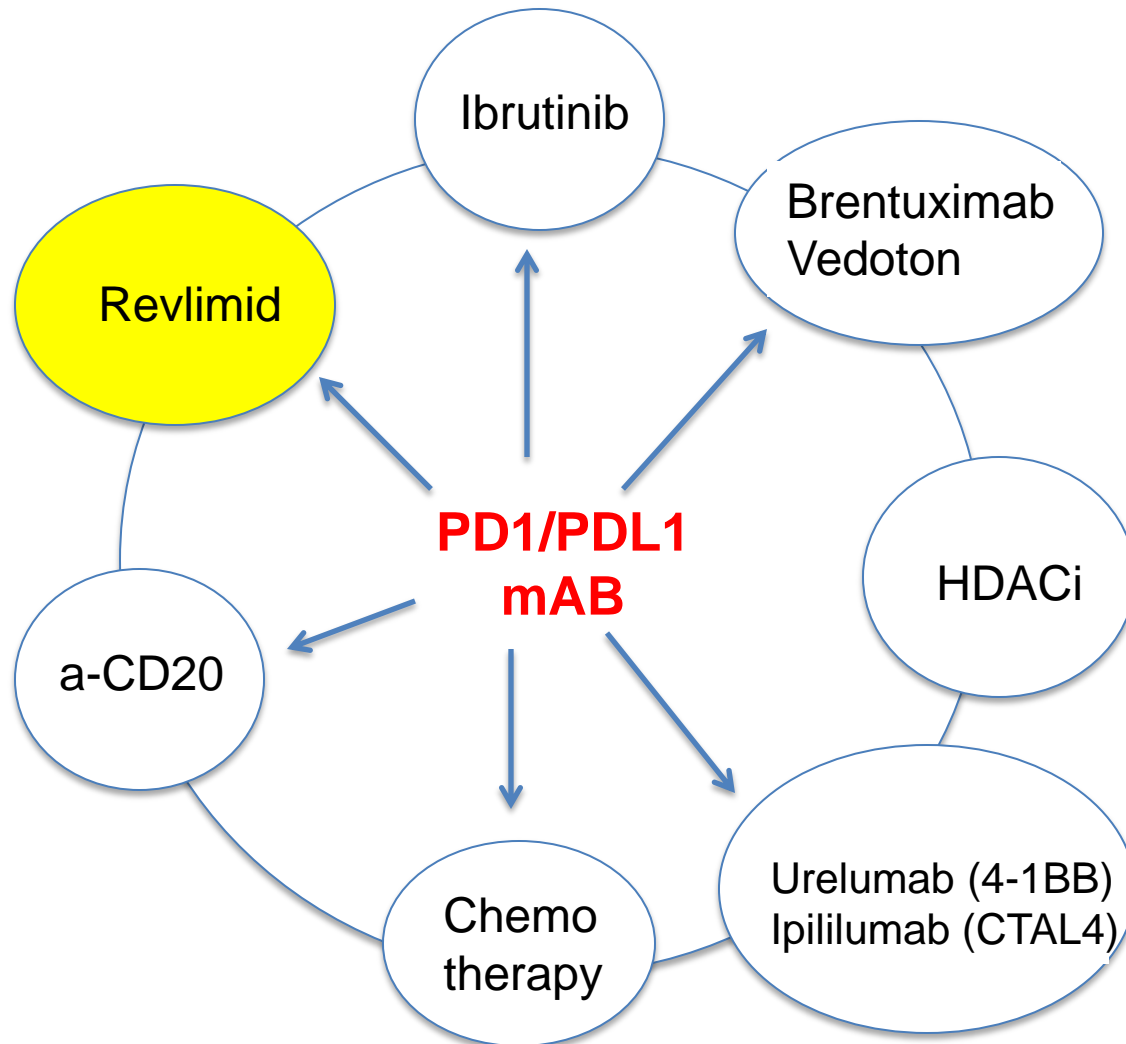
B



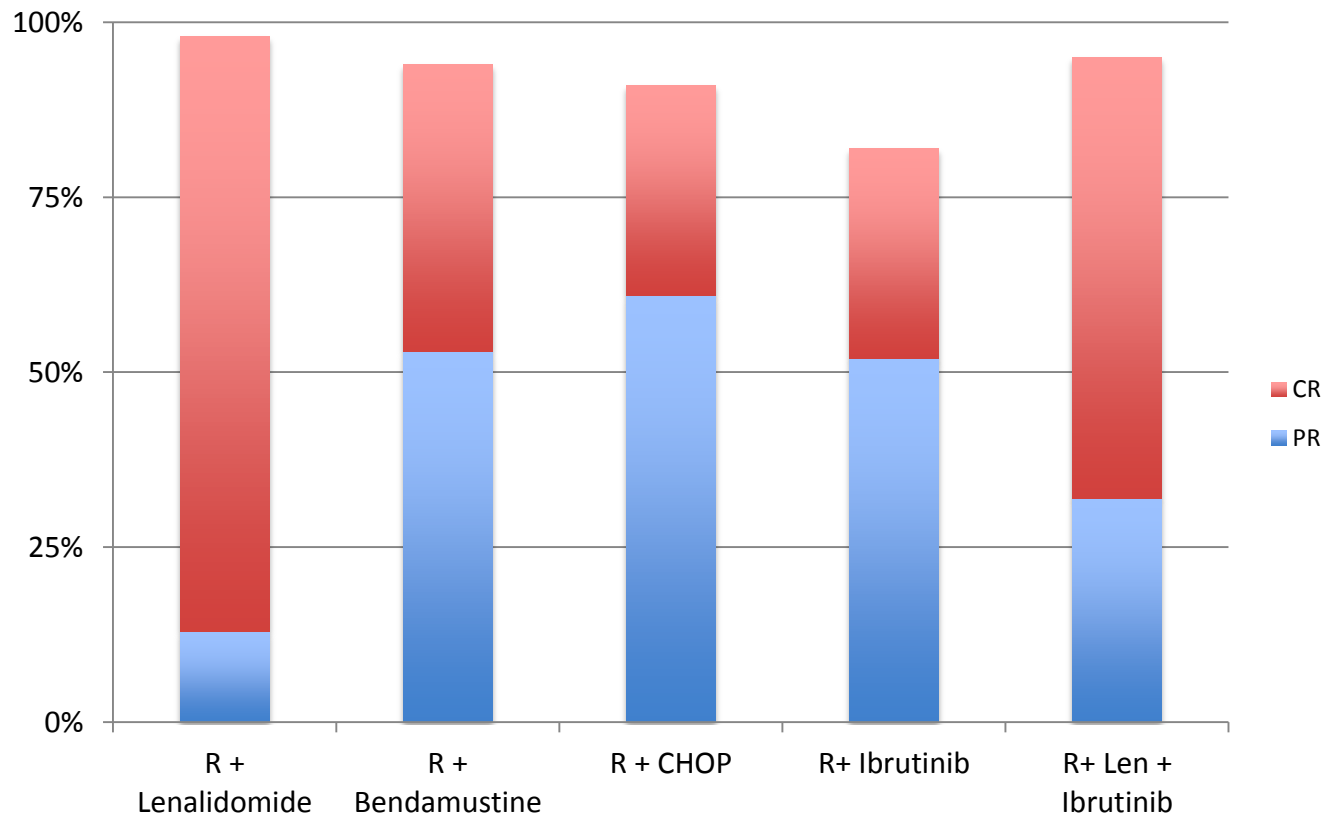
Phase I/II Study of Entinostat (HDACi) + Pembrolizumab (anti-PD1)



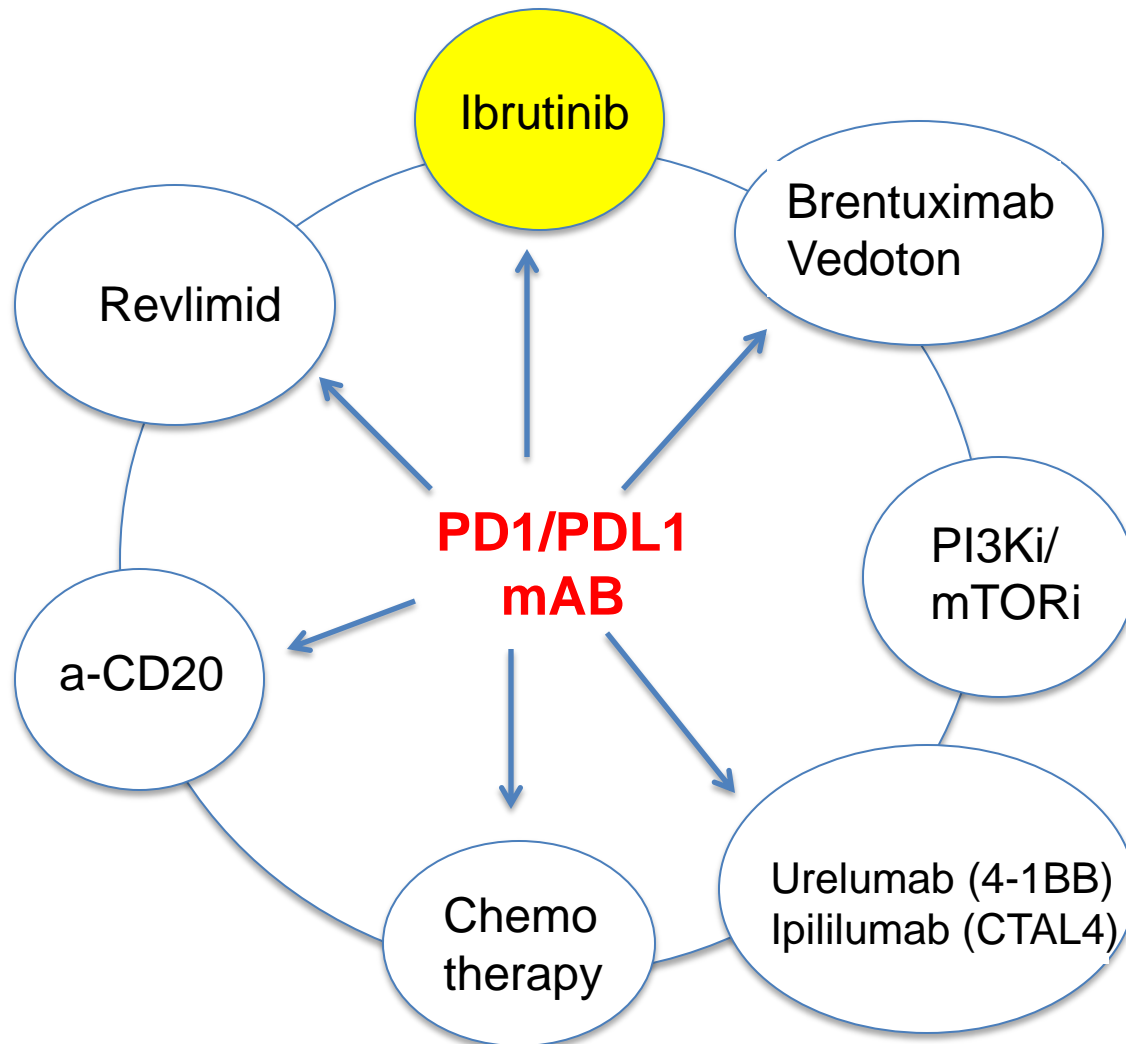
Development of Anti-PD1/PDL1-Based Therapy



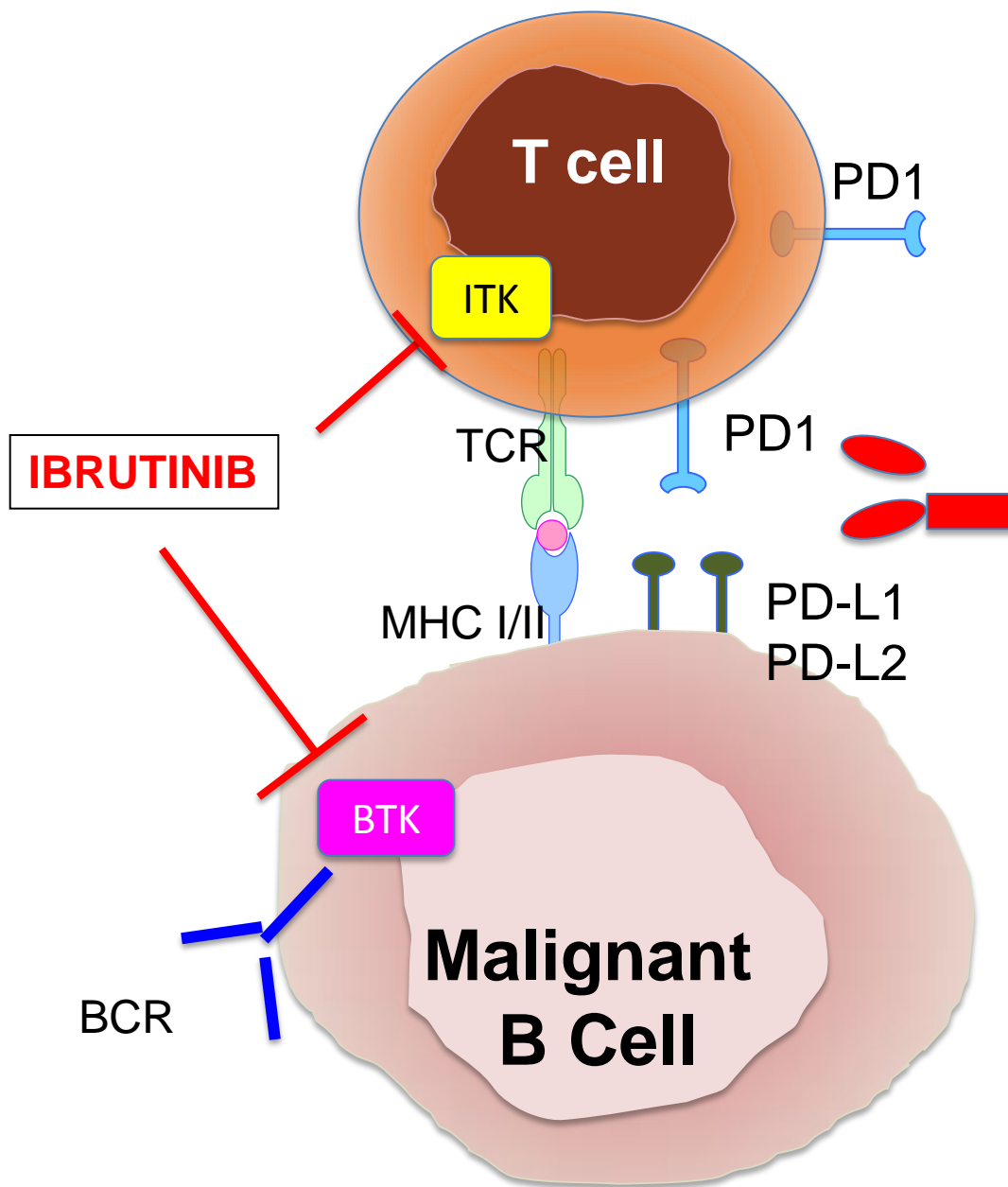
Emerging Role for Chemo-Free Therapy Newly diagnosed follicular lymphoma*



Development of Anti-PD1/PDL1-Based Therapy

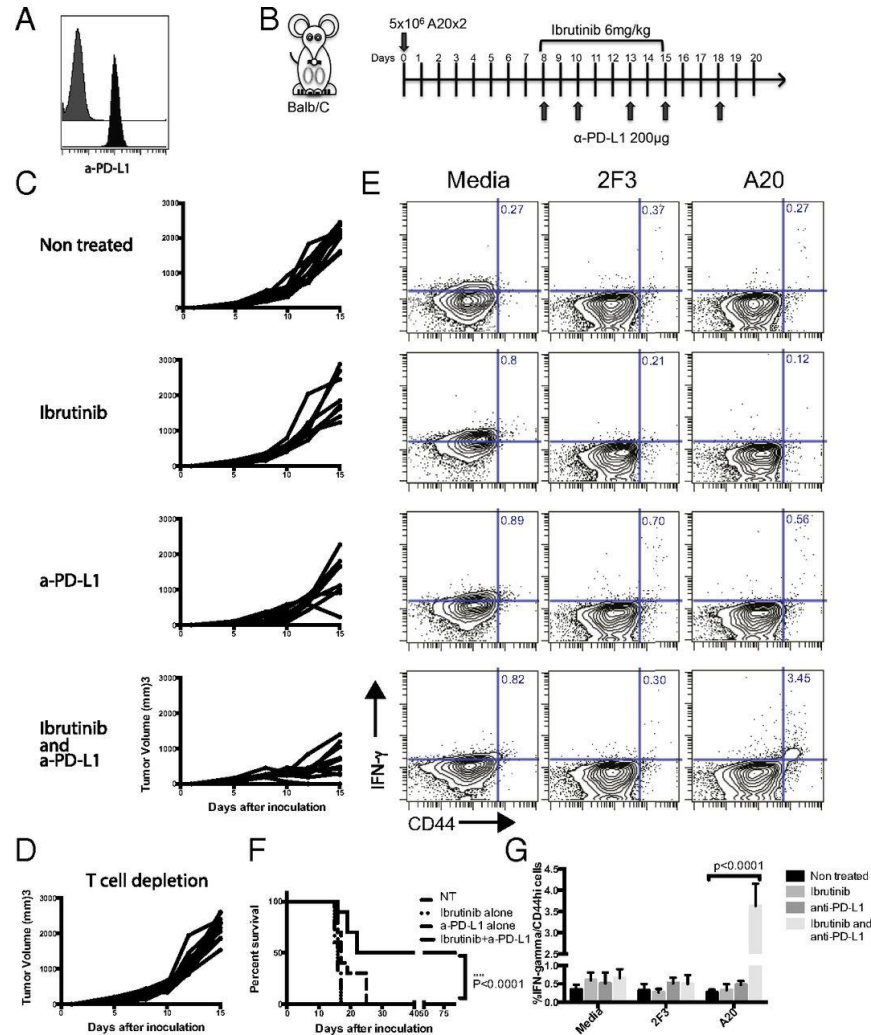


Rationale for combining Ibrutinib with PD1/PDL1 antibodies



Ibrutinib in combination with anti-PD-L1 induces an antitumor immune response

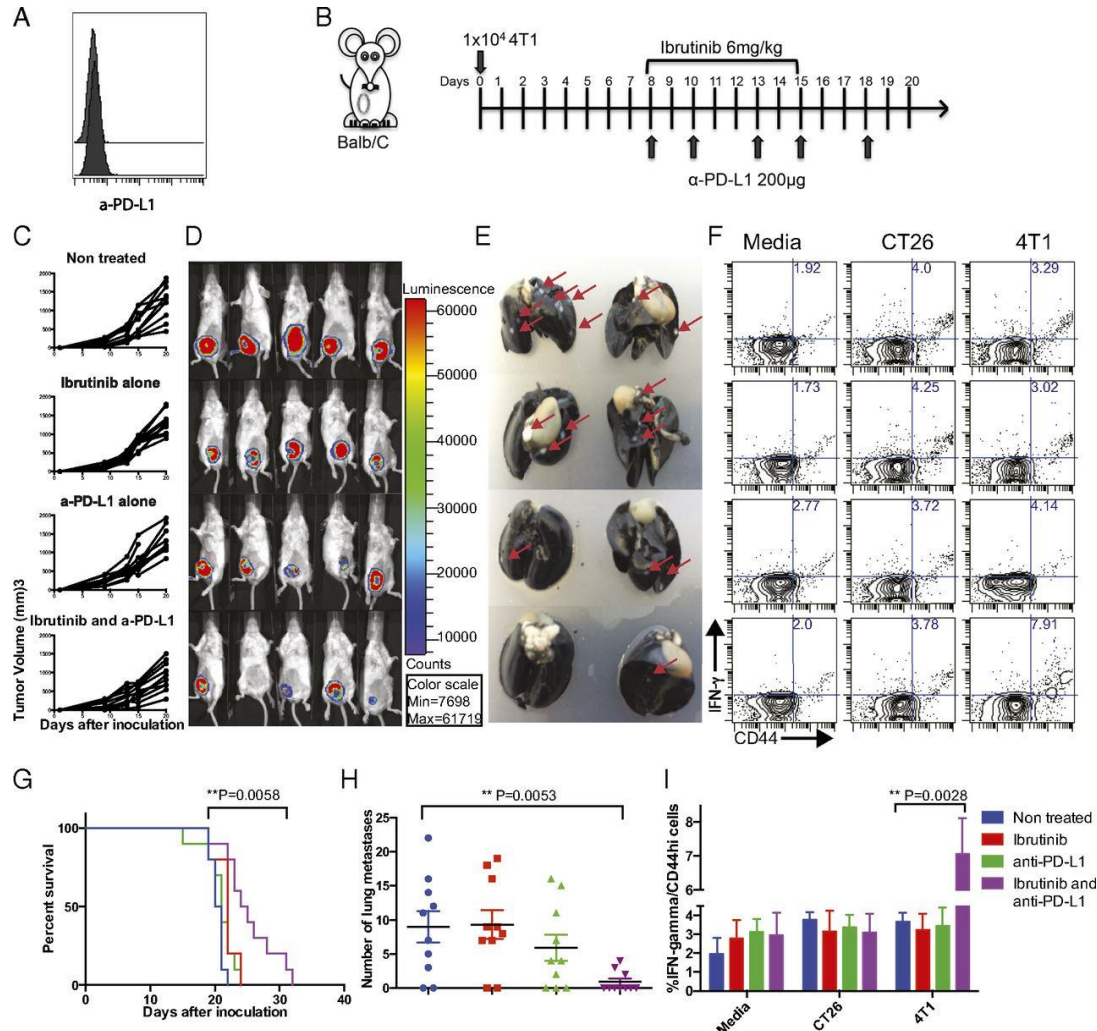
A20 mouse B cell lymphoma model



Idit Sagiv-Barfi et al. PNAS 2015;112:E966-E972

PNAS

The combination of ibrutinib with anti-PD-L1 reduces tumor burden in 4T1 (Mouse Triple Negative Breast Carcinoma) tumor-bearing mice.



Idit Sagiv-Barfi et al. PNAS 2015;112:E966-E972

PNAS

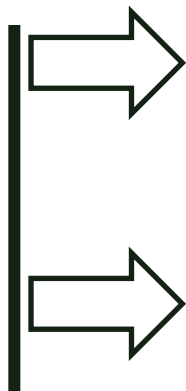
PCI32765-LYM-1002: Study Design

Nivolumab + Ibrutinib in relapsed B-cell malignancies

Part A n=18
(Dose Optimization)

A-1
I: 420 mg, po, qd
N: 3mg/kg, i.v., q14d

A-2
I: 560 mg, p.o., qd
N: 3 mg/kg, i.v., q14d



Part B (n=30 in each cohort)
(Expansion Cohort: Two-stage design)

B 1: I: 420 mg/qd PO + N: 3 mg/kg/q14d

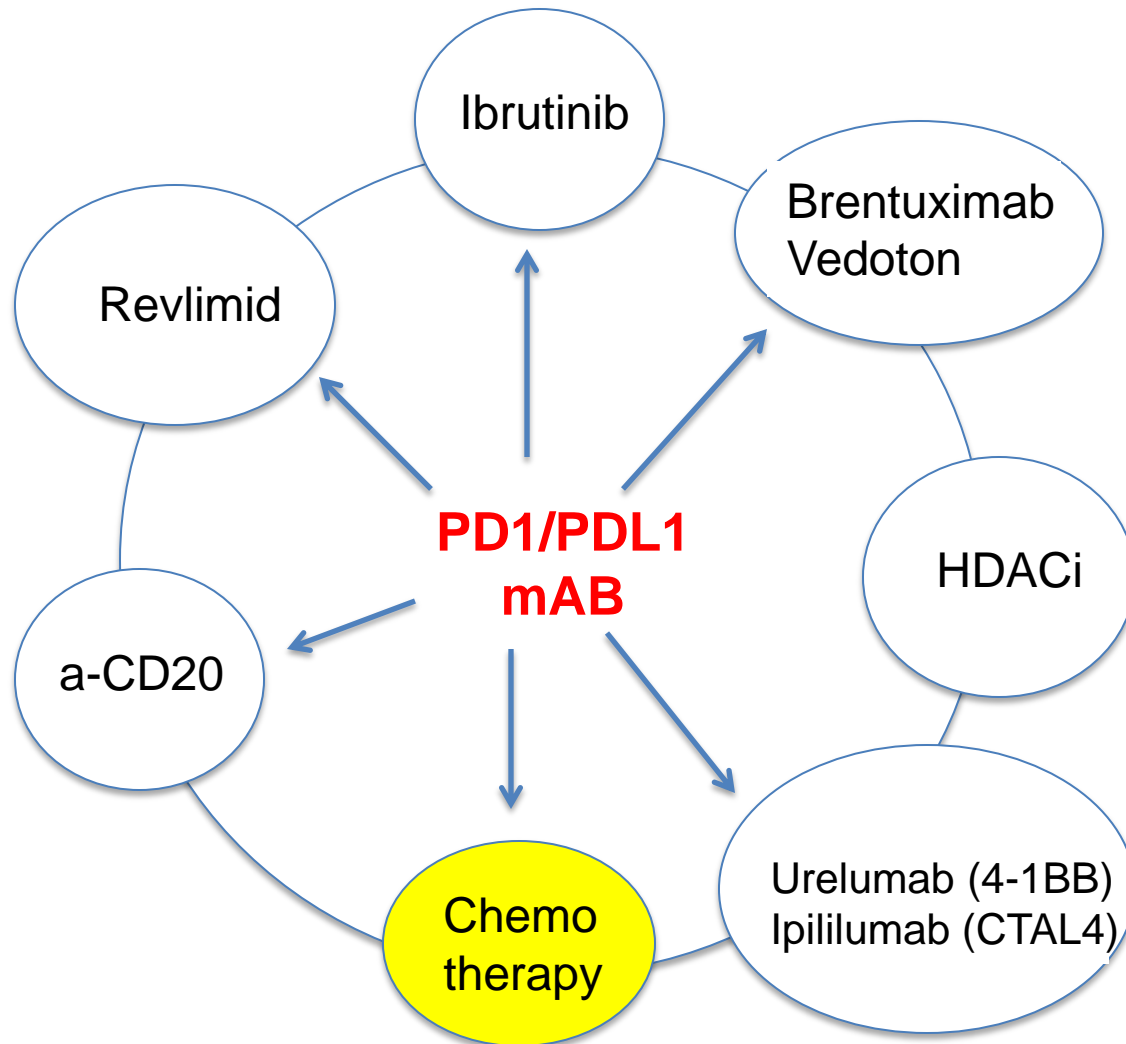
B1: CLL (del 17p or del 11q)

B 2 and B 3: I: 560 mg/qd PO + N: 3 mg/kg/q14d

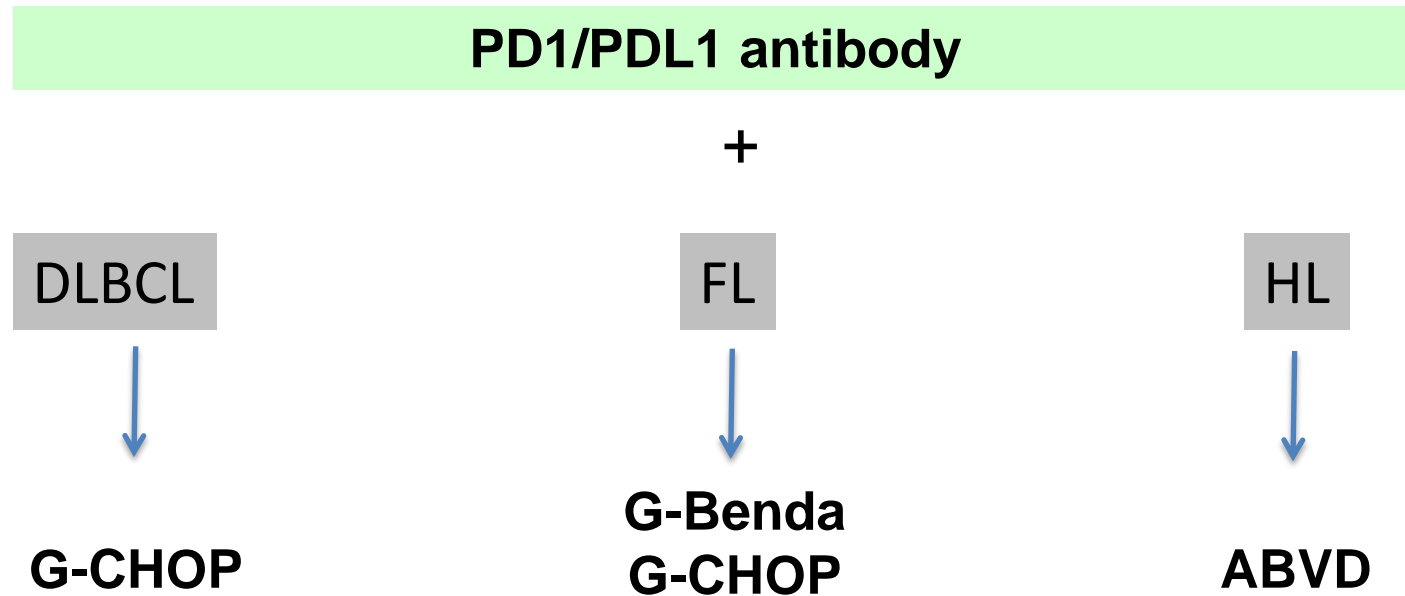
B2: Follicular Lymphoma

B3: DLBCL

Development of Anti-PD1/PDL1-Based Therapy

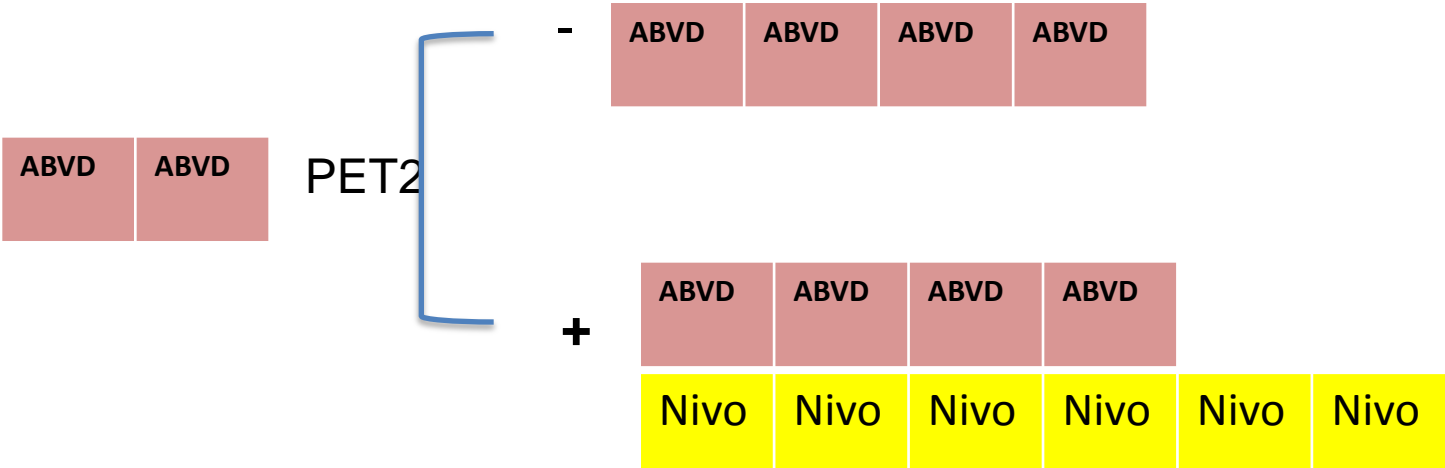
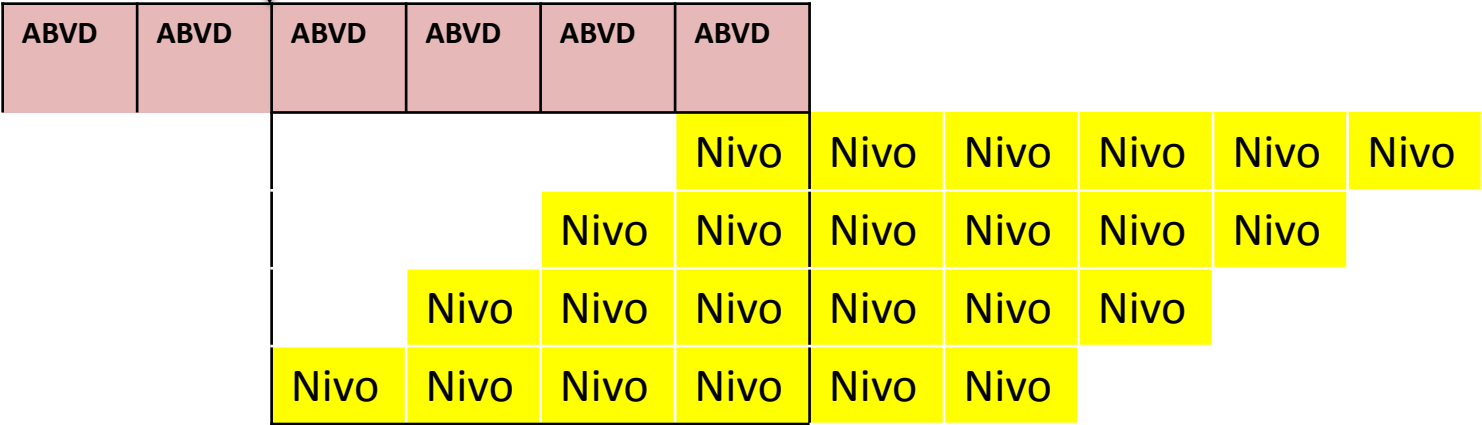


Development of Anti-PD1/PDL1-Based Therapy Frontline Regimens



Phase I/II ABVD + Nivolumab in Advances Stage HL

PET2



Evaluating ctDNA in Curable Lymphomas (HL and DLBCL)

