# Novel Therapeutic Targets for Hodgkin Lymphoma

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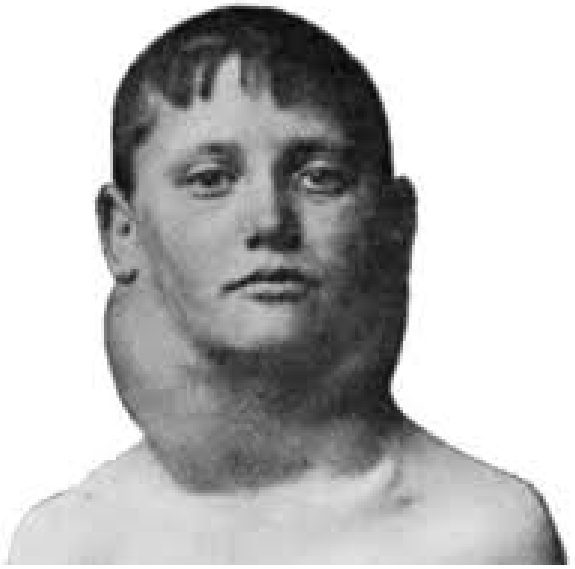
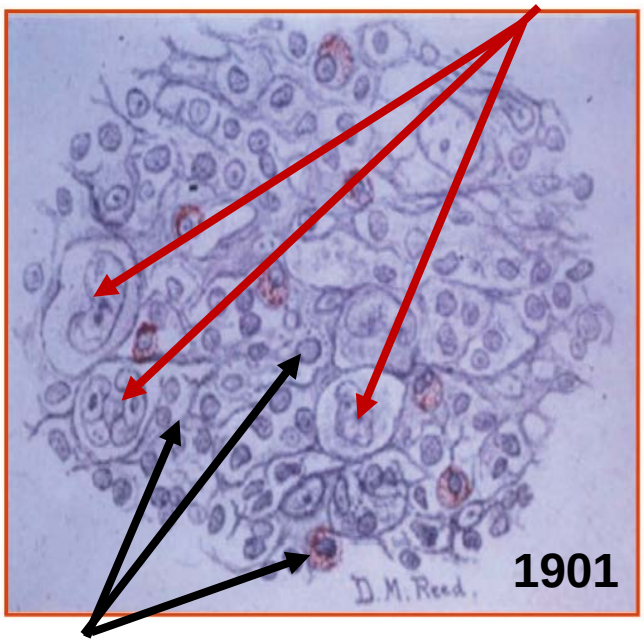
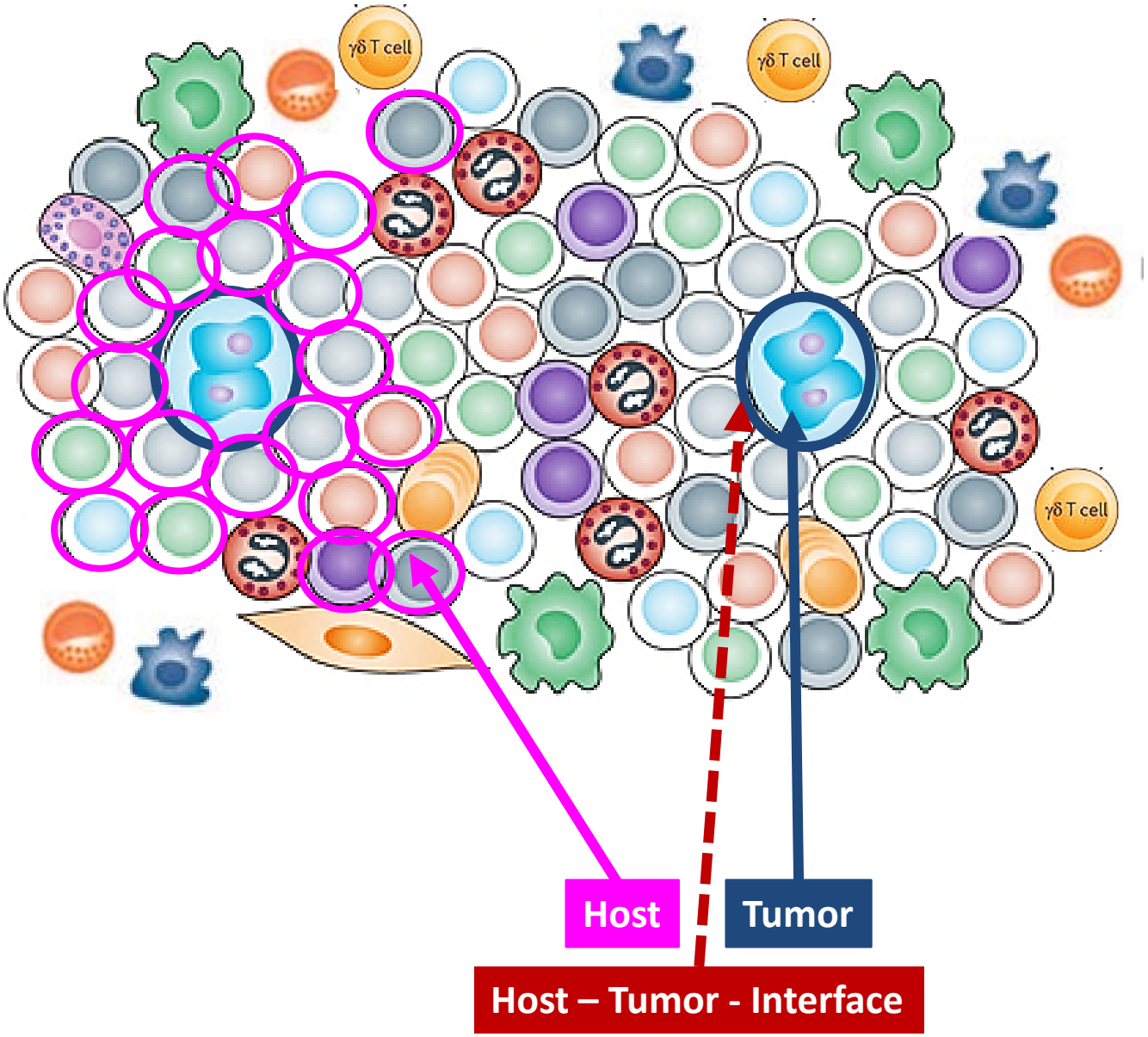
ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale





# *Hodgkin Lymphoma: Leading actors, bit actors, walkers-on & set decor*



# RR-Hodgkin Lymphoma: ...Developmental Therapeutics…

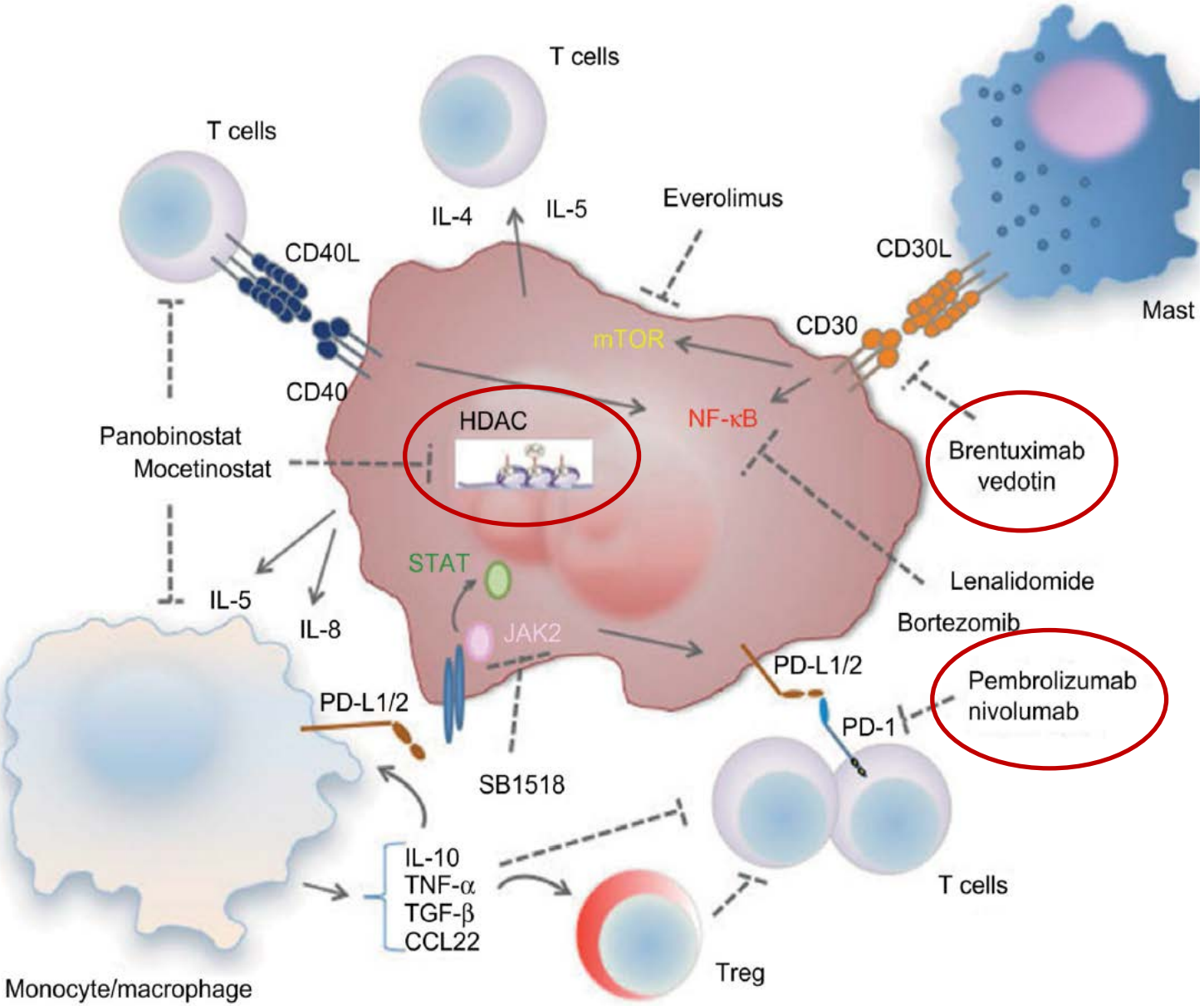


**Table 3. Selected clinical studies on treatment options with novel agents in patients with relapsed/refractory cHL after ASCT**

| Agent | No. of patients | Prior ASCT | Response, % | PFS | Reference |
|---|---|---|---|---|---|
| Brentuximab | 102 | 102 | ORR, 75<br>CR, 34<br>PR, 41 | 5.6 mo | 28 |
| Nivolumab | 23 | 18 | ORR, 87<br>CR, 17<br>PR, 70 | 24-wk 86% | 29 |
| Pembrolizumab | 15 | 10 | ORR, 53<br>CR, 20<br>PR, 33 | NR | 30 |
| Lenalidomide | 36 | 31 | ORR, 19<br>CR, 3<br>PR, 16 | 6 mo | 31<br>58<br>59 |
| Rituximab | 22 | 18 | ORR, 22<br>CR, 4.5<br>PR, 18 | 7.8 mo | 60 |
| Everolimus | 19 | 16 | ORR, 47<br>CR, 5<br>PR, 42 | 7.2 mo | 32 |
| Vorinostat | 25 | 11 | ORR, 4<br>CR, 0<br>PR, 4 | 4.8 mo | 61 |
| Panobinostat | 129 | 129 | ORR, 27<br>CR, 4<br>PR, 23 | 6.1 mo | 33 |

H-RS

µEnv

H-RS + µEnv

*Blood.* 2016;127(3):287-295

# PD1 blockade in Hodgkin Lymphoma

Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma

Michael R. Green,[1] Stefano Monti,[2] Scott J. Rodig,[3] Przemyslaw Juszczynski,[1] Treeve Currie,[3] Evan O'Donnell,[1] Bjoern Chapuy,[1] Kunihiko Takeyama,[1] Donna Neuberg,[4] Todd R. Golub,[2] Jeffery L. Kutok,[3] and Margaret A. Shipp[1]

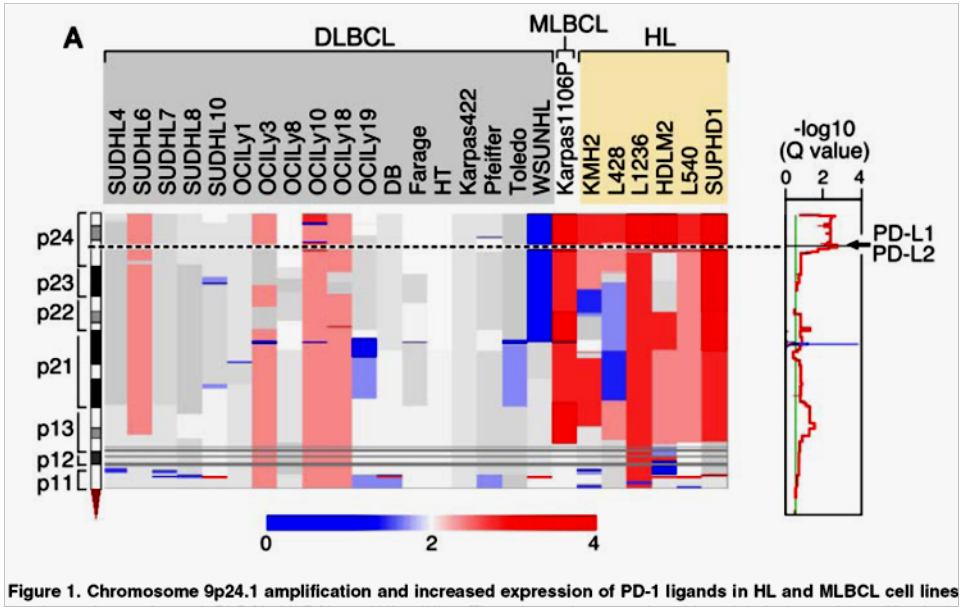
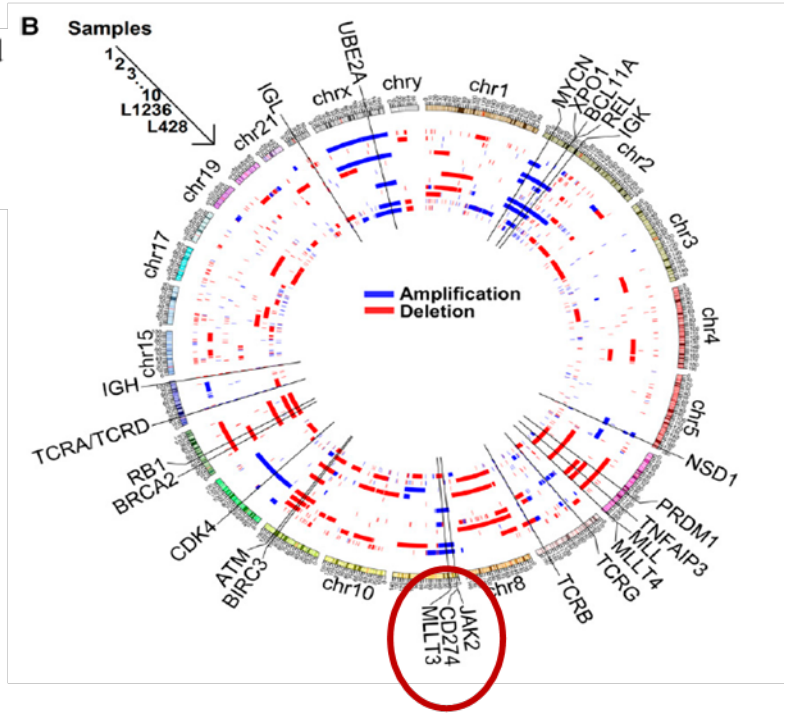



Figure 1. Chromosome 9p24.1 amplification and increased expression of PD-1 ligands in HL and MLBCL cell lines

*Blood. 2010;116(17):3268-3277*

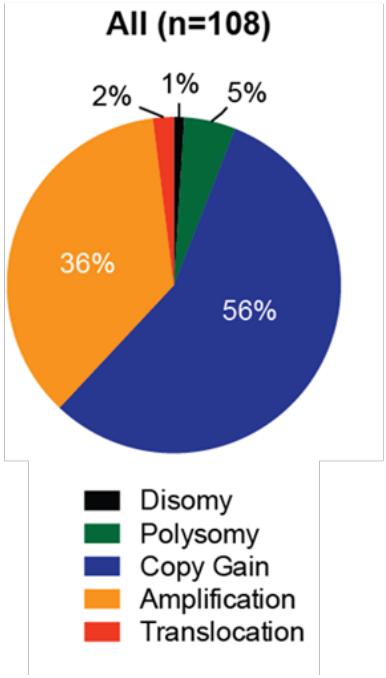


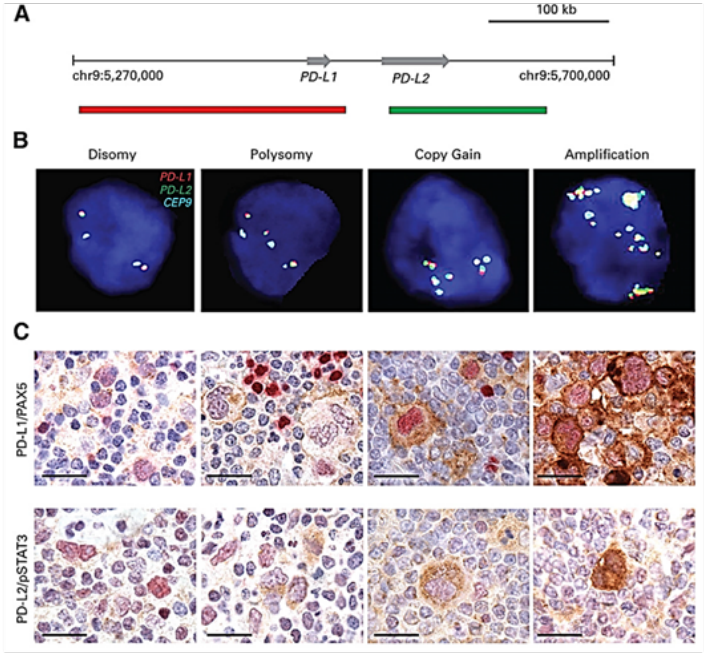

**9p24.1 Amplicon Block**

# Hodgkin Lymphoma: ...Therapeutic Biology...

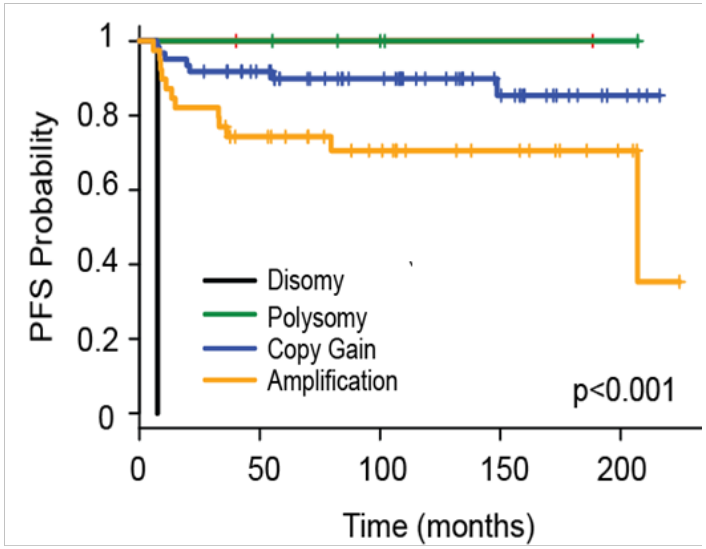
## The 9p24.1 Amplicon Block in cHL

- *9p24.1 alterations are a typical and constant (>95% of cases) genetic trait of cHL*
- *The type of 9.24.1 alteration predicts intensity of PD-L1/2 expression on H-RS cells*
- *Amplification of 9p24.1 predicts for advanced stage and shorter PFS (ABVD)*



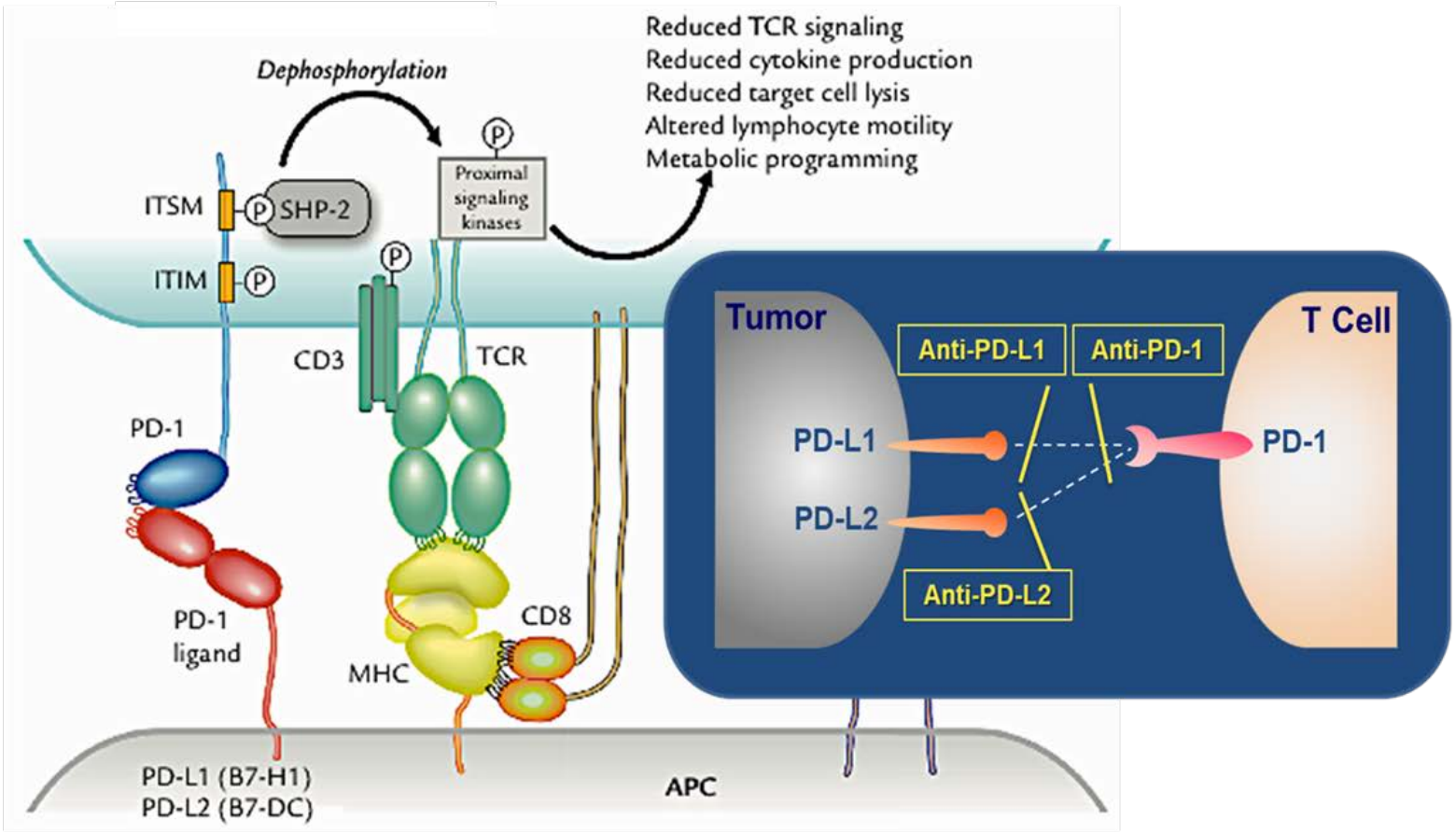

Roemer MGM, et al. J Clin Oncol 34, 2016.



# PD1/PD-L1 signal transduction in activated T and NK cells

PD1

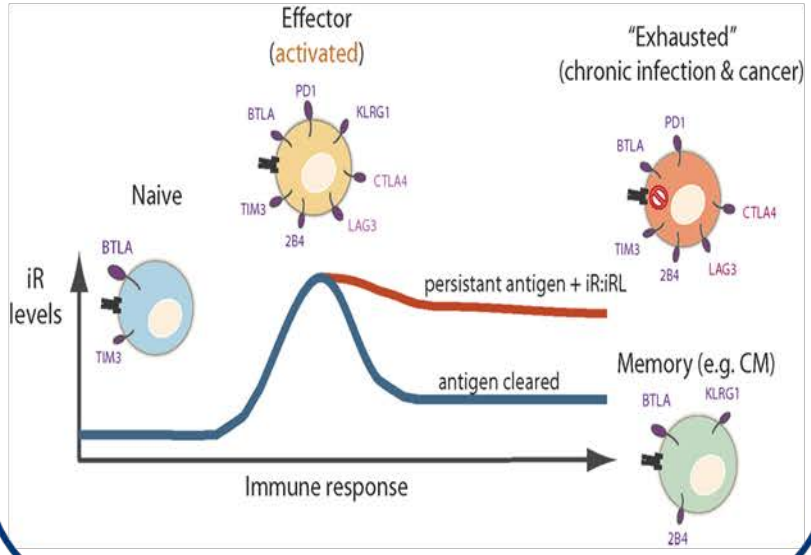
PD-L1

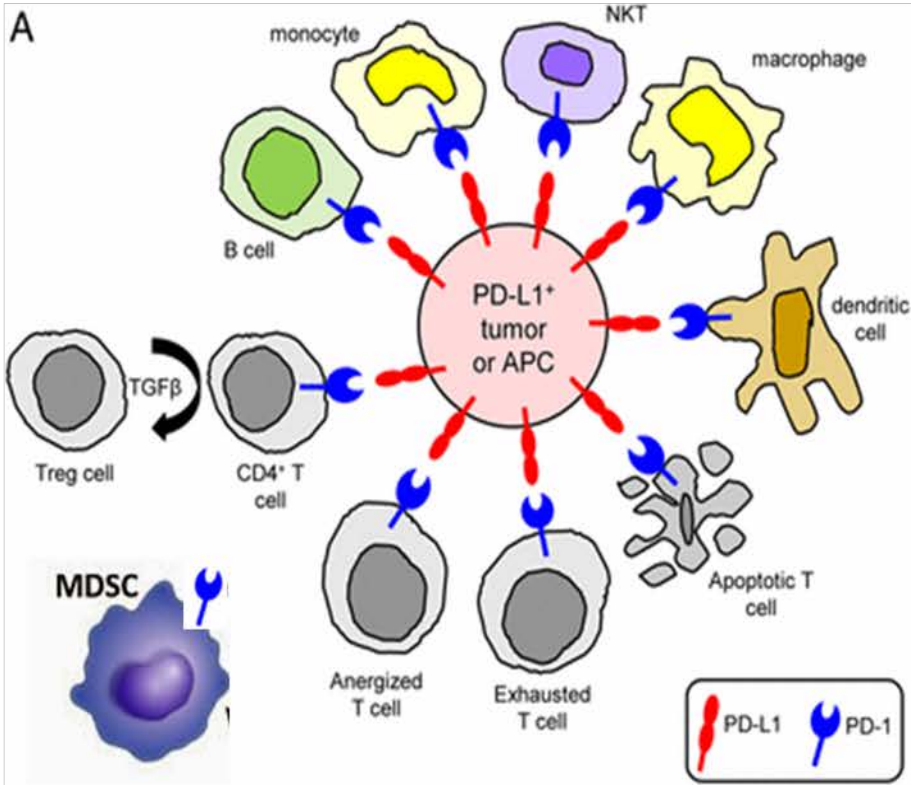



Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

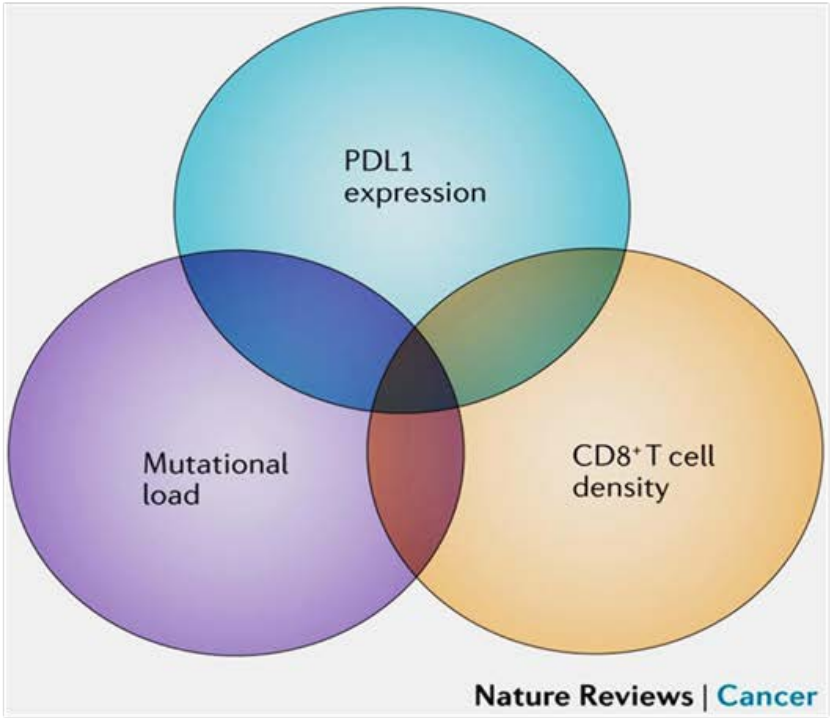
# PD1 expression in immune cells

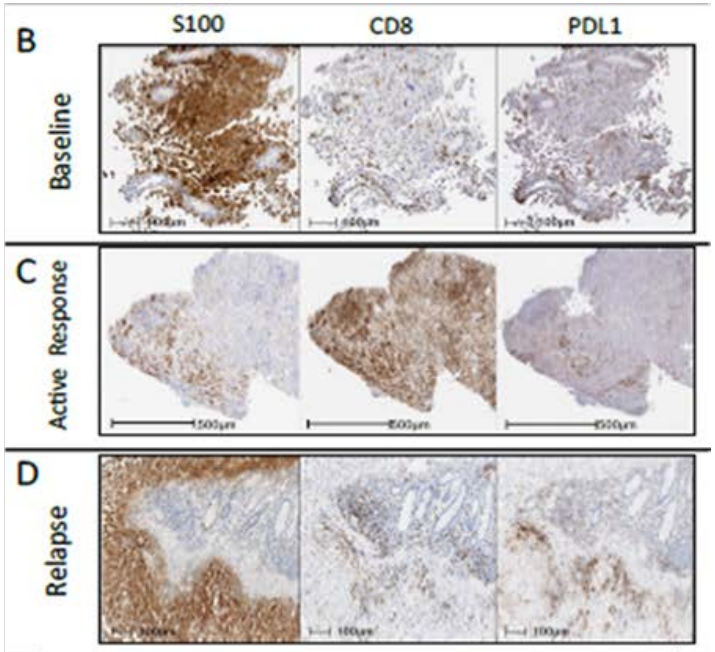
***PD1 is overexpressed in 'exhausted' T-cells***

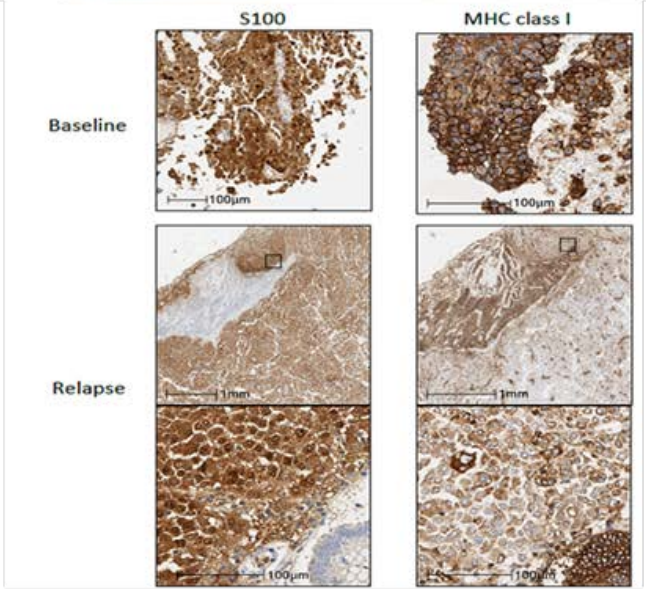


# *Hodgkin Lymphoma: ...Therapeutic Biology…*



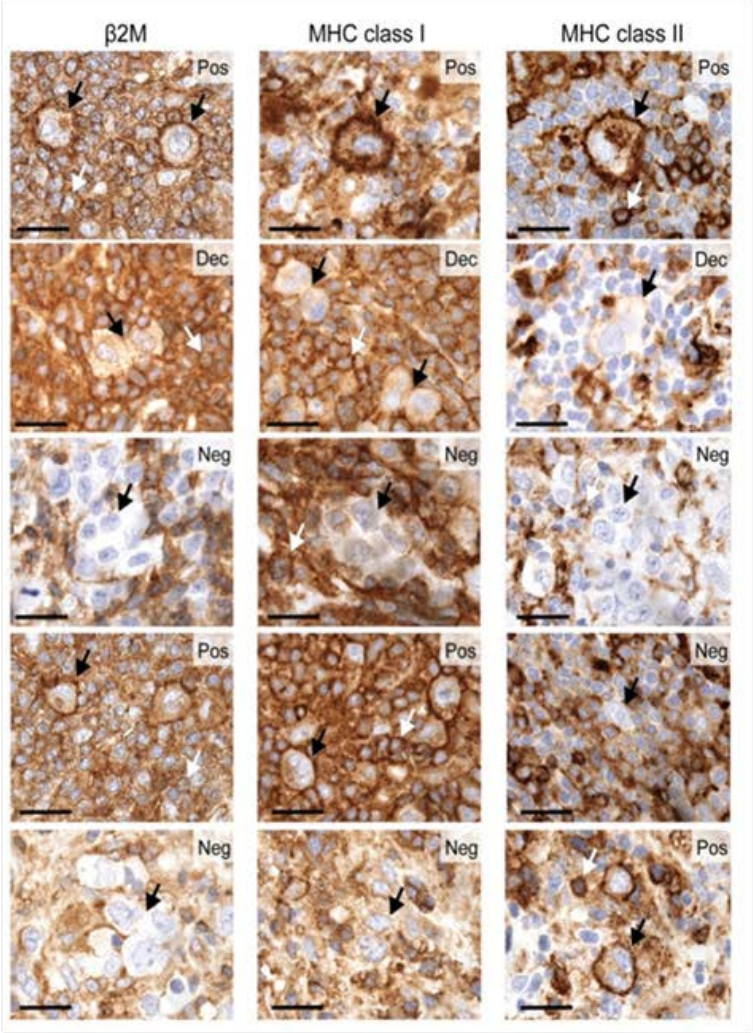




- CD8+ T Cell infiltration is associated to tumor response in melanoma
- Loss of surface HLA-Class I expression by β2M mutation is a mechanism of acquired resistance to Pembrolizumab in melanoma

Zaretsky JM et al. N Engl J Med 2016;375:819-829.

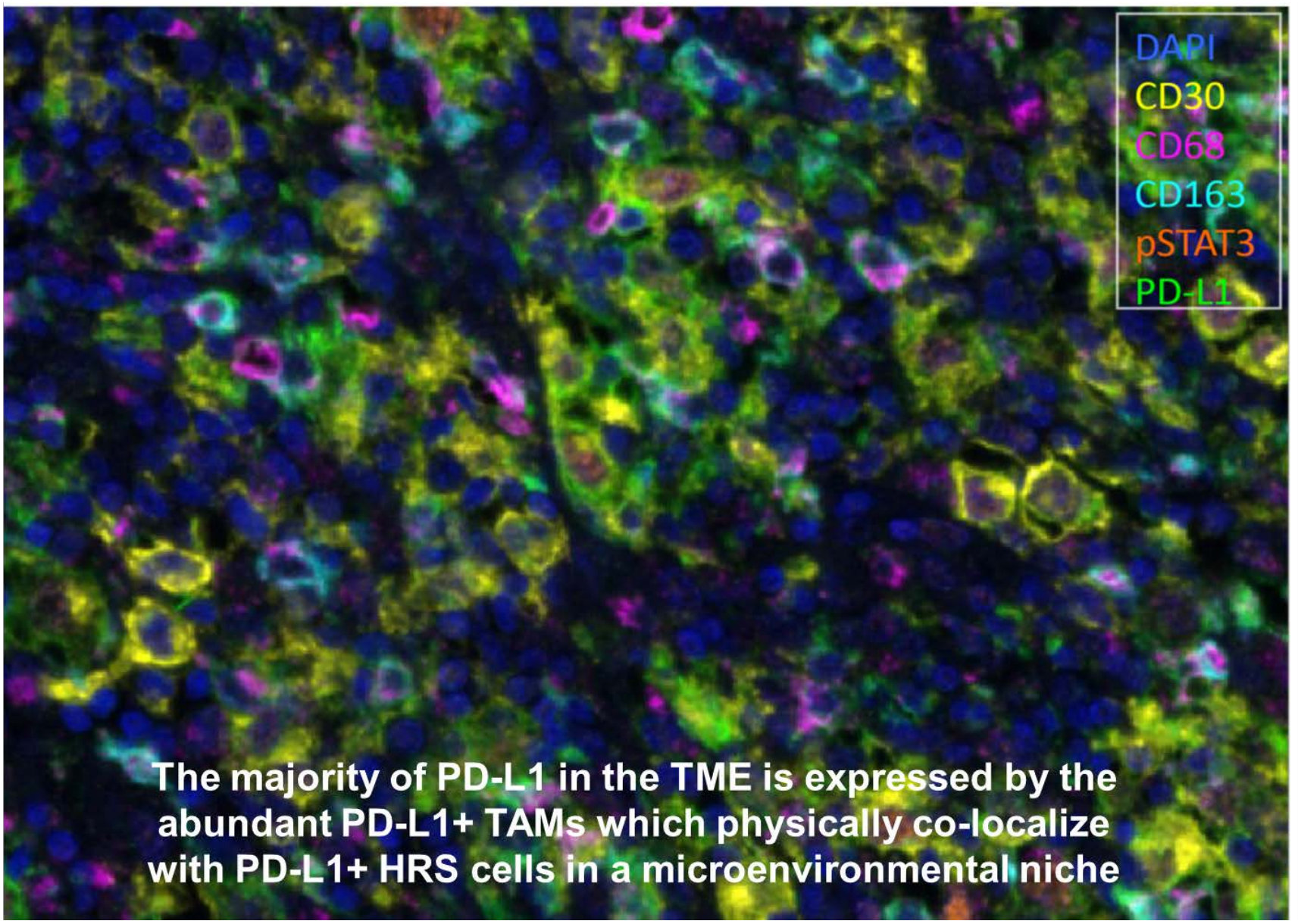
# *Hodgkin Lymphoma: ...Therapeutic Biology…*

- **H-RS cells display a 'structurally' deficient expression of HLA expression**
  - ***HLA Class I deficit***
    - 63% to 79% of cases
  - ***HLA Class II deficit***
    - 41% to 67% of cases
  - ***Both Class I and II deficit***
    - 46% of cases
  - ***Normal expression: 12% of cases***
- **Genetic alterations (mutations, breaks, translocations, etc.)**
  - β2 microglobulin,, CIITA, etc.
- **Low abudance of CD8+ (PD1+) cytotoxic T cells in HL microenvironment**
  - PD1 blockade: how it works ????
  - Mediated by cytotoxic T-cells
  - Requires intact Ag presentation by HLA

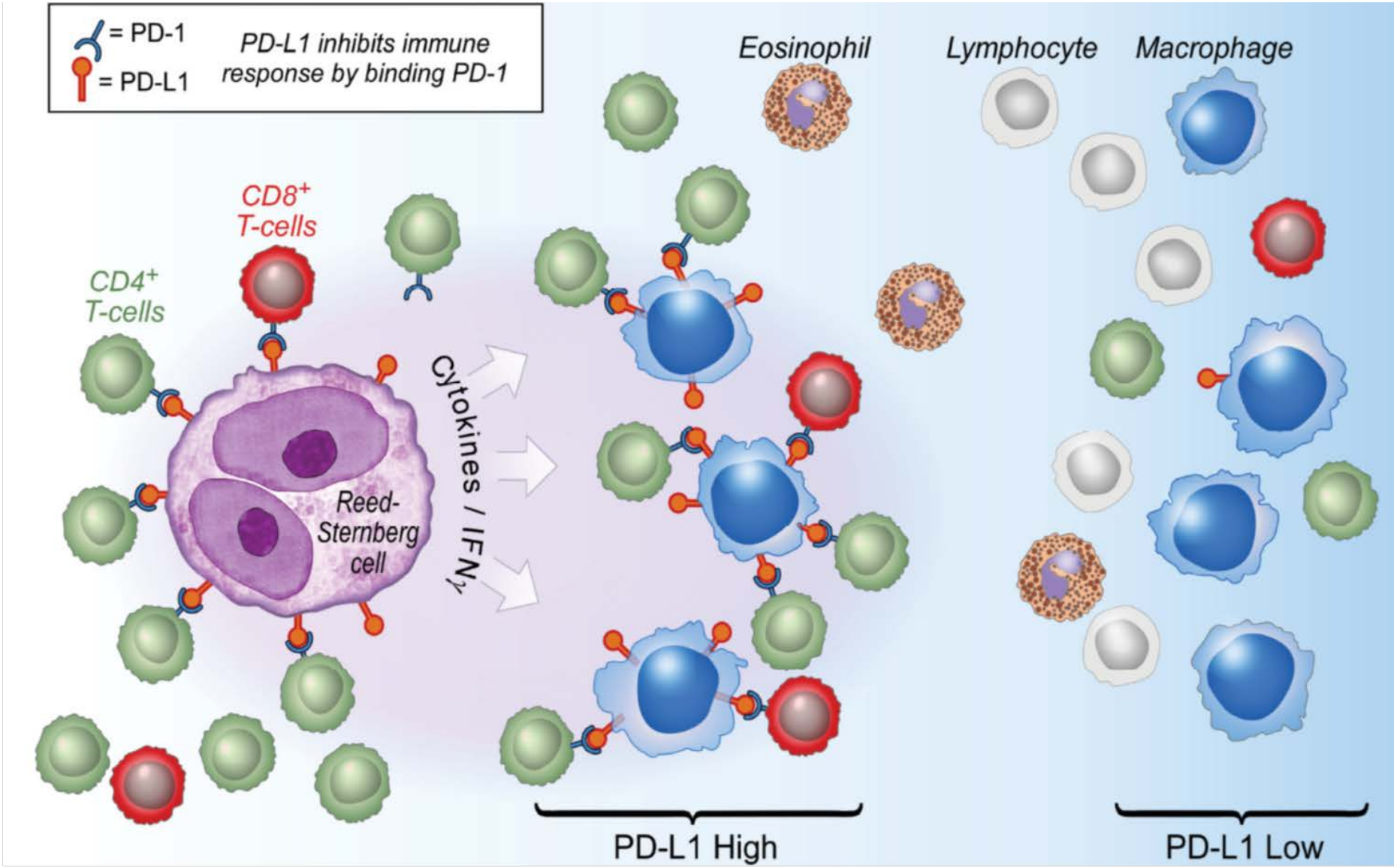



Reichel, *et al. Blood* 2015; 125: 1061
Diepstra et al. JCO 2007
Steidl, *et al., Nature* 2011; 471: 377
Roemer, *et al.* Cancer Immunol Res ; 2016

# *Hodgkin Lymphoma: ...Therapeutic Biology…*



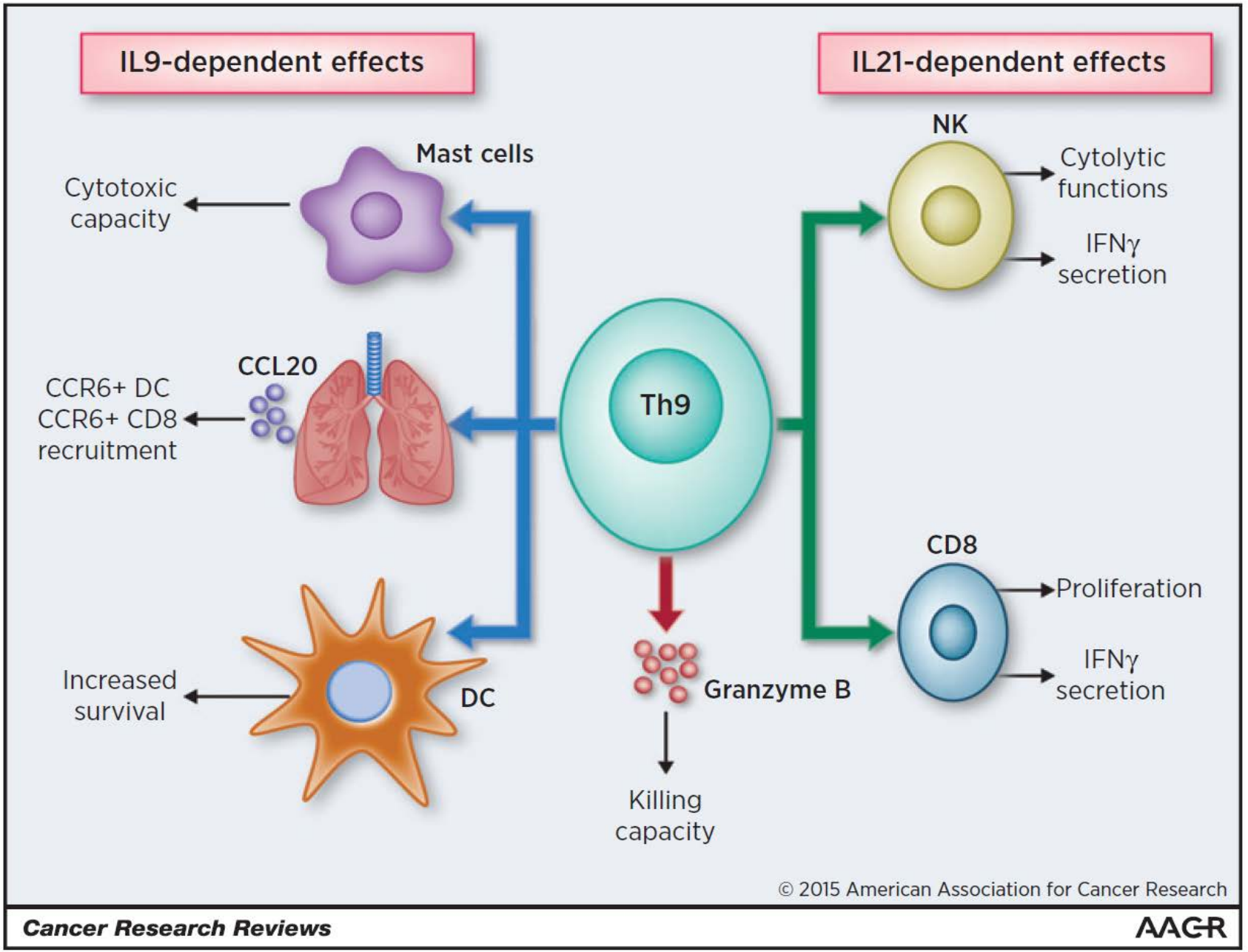
# Hodgkin Lymphoma: ...Therapeutic Biology…




*Carey CD, et al. Blood 2017*

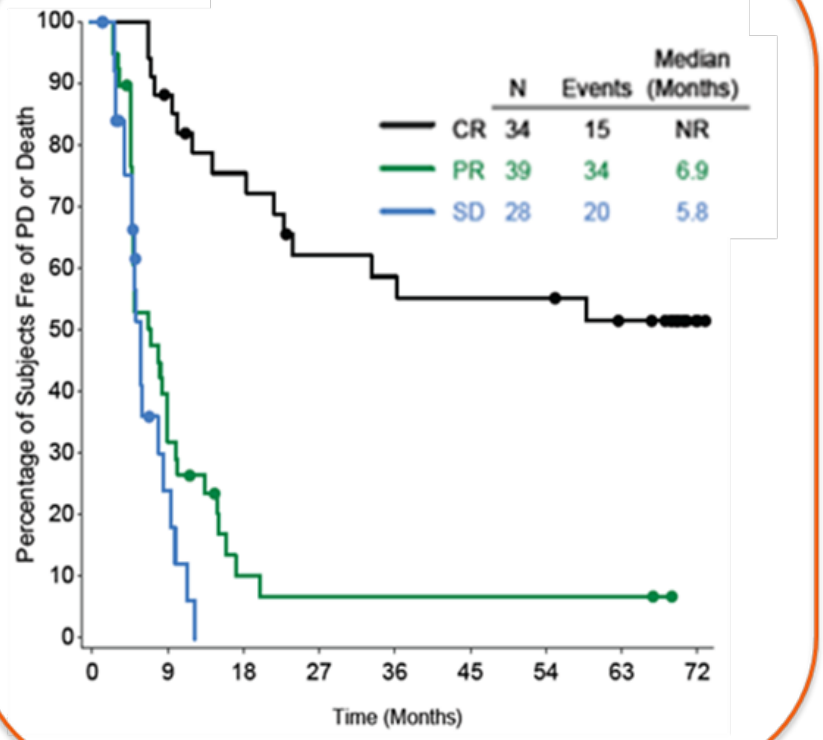
- **Nivolumab & Pembrolizumab Target PD1**
  - **HRS cells do not express PD1** (*indirect tumor targeting*)
  - **Potential PD1 expressing-cells in the HL microenvironment:**
    - CD8+ T cells (like in sold tumors ?)
    - CD4+ T cells (regulatory function ?)
    - γ/δ T cells
    - Macrophages
    - NK cells
    - Other cells ?
  - **PD1-blocking antibodies unleash all these cell types from PD-L1-mediated functional inhibition**
  - **One or more of these 'unleashed' PD1+ cell populations act as the effector(s) of antitumor efficacy**

# PD1-blockade: …Why it works…?



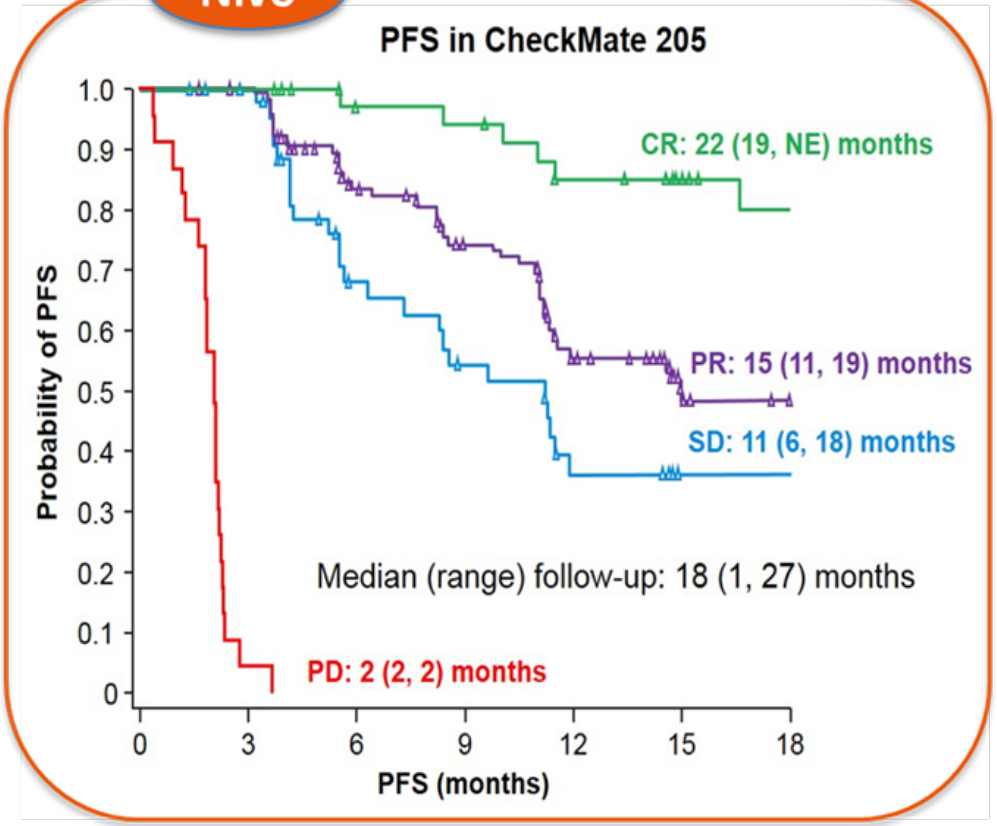
# *Brentuximab Vedotin in the Overall Treatment Strategy for HL*

**BV**




Chen et al., Blood 2016

**Nivo**




Fanale et al. ICML 2017 [Oral 125]

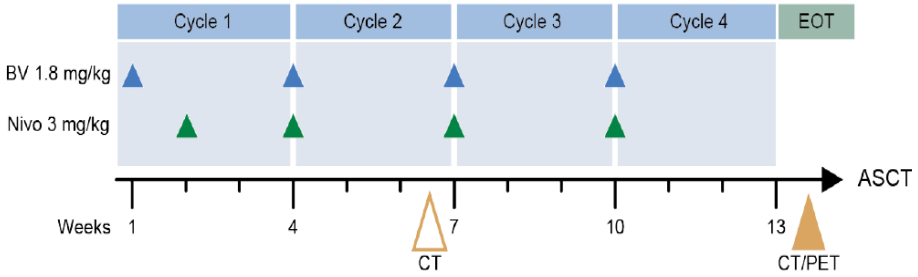
# Brentuximab Vedotin-based combinations for RR-HL

CLINICAL TRIALS AND OBSERVATIONS

## Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma

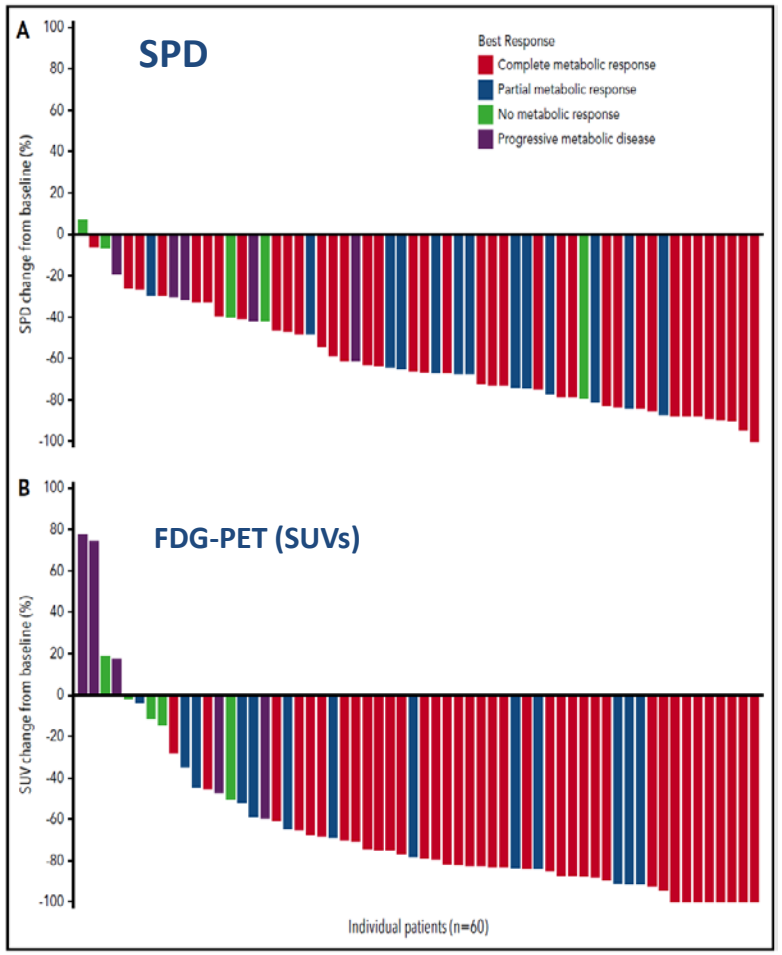
Alex F. Herrera,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Stephen M. Ansell,[8] Craig H. Moskowitz,[2] Keenan Fenton,[9] Carol Anne Ogden,[9] David Taft,[9] Qu Zhang,[9] Kazunobu Kato,[10] Mary Campbell,[9] and Ranjana H. Advani[11]

### Methods



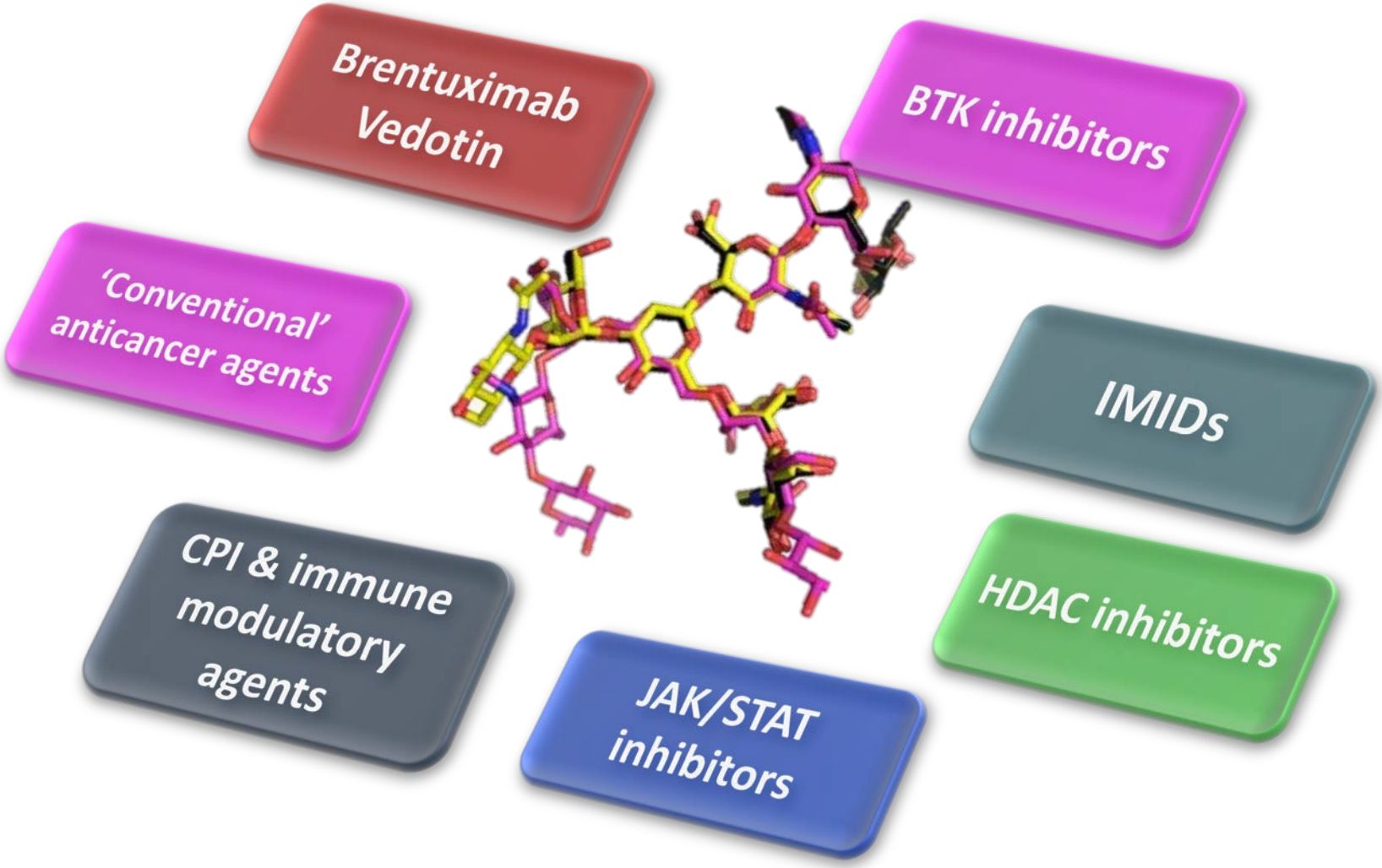

### Table 1. Baseline demographics and disease characteristics

| | n = 62 |
|---|---|
| Age (y), median (range) | 36 (18–69) |
| **Sex, n (%)** | |
| Male | 30 (48) |
| Female | 32 (52) |
| **Disease stage at initial diagnosis, n (%)** | |
| I/II | 37 (60) |
| III/IV | 24 (39) |
| Unknown | 1 (2) |




**CR rate: 61%,**
**ORR: 82%**
**6-mo.s PFS: 86%**

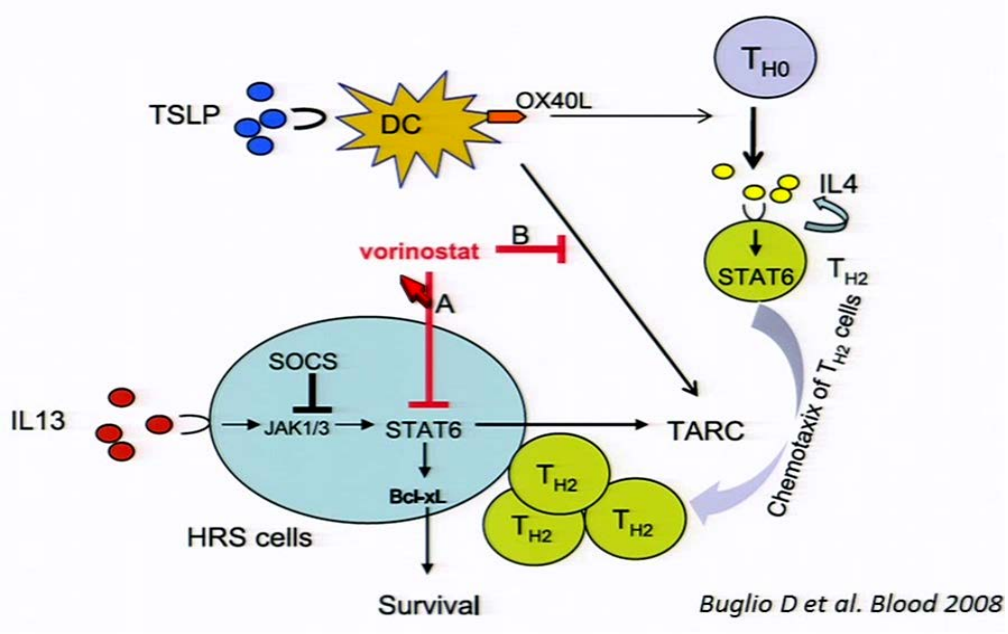
# … Anti-PD1 Antibodies as Platform Agents for Novel Strategies in HL …



# … Anti-PD1 Antibodies as Platform Agents for Novel Strategies in HL …

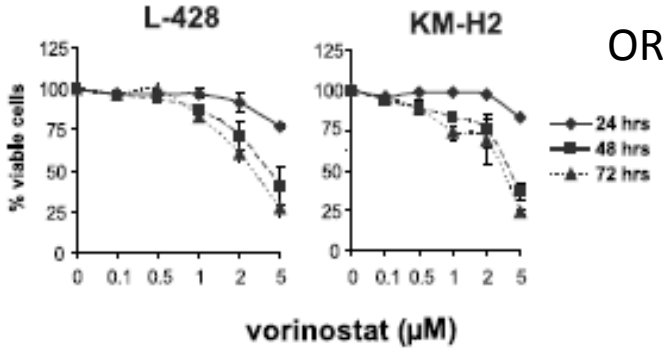
| | Relapsed/Refractory | Upfront |
|---|---|---|
| Chemotherapy | Nivolumab – ICE 2nd line<br>Pembrolizumab – ICE 2nd line<br>Pembrolizumab – GVD 2nd line | Nivo + Nivo/AVD Adv. HL<br>Nivo/AVD Early HL<br>A(B)VD + sequential nivo<br>Pembro/AVD Adv. HL<br>Pembro (ABVD ineligible) |
| Brentuximab Vedotin | Nivolumab + BV vs. BV<br>Nivolumab/BV ± Ipilimumab<br>Pembrolizumab after ASCT<br>Nivolumab/BV after ASCT | Nivolumab + BV older pts. |
| BTK inhibitors | Nivolumab + Ibrutinib<br>Pembrolizumab + aclabrutinib | |
| Immune modulators | Nivolumab + Lenalidomide<br>Pembrolizumab + Lenalidomide<br>Pembrolizumab + NG-monomethyl-L-arginine (L-NMMA) | |
| Radiotherapy | Pembrolizumab + IFRT<br>Early Stage RR-HL | |
| HDAC inhibitors | Pembrolizumab + Vorinostat in RR-NHL/HL | |

# Vorinostat: biologic & clinical activity in RR-HL



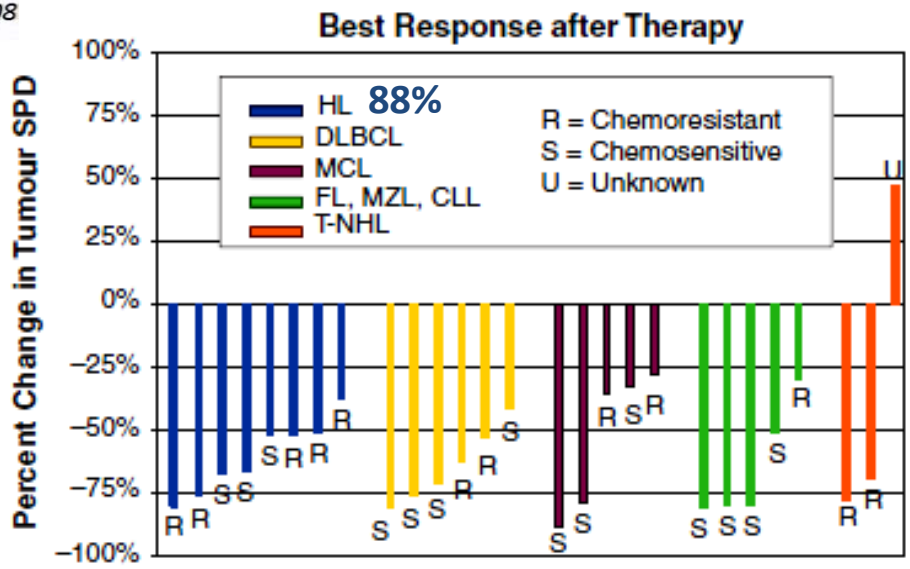


ORR




**Pulse high-dose vorinostat + ICE**

| Drug | Author | ORR% (CR%) |
|---|---|---|
| **HDAC Inhibitors** | | |
| Panobinostat n=13 | Dickinson | 58(0) |
| Panobinostat n=129 | Sureda | 26(3) |
| Vorinostat n=25 | Kirshbaum | 4(0) |
| Mocetinostat n=51 | Younes | 30(9.5) |
| Resminostat n= 37 | Walewsky | 35 (NR) |




Budde et al.,BJ H2013, 161, 183–191

# RR-HL: Effect of Pre-Transplant (ASCT) PET assessment

## 1. Works

| Parameter | No. | CR (%) | PR (%) | ORR (%) |
|---|---|---|---|---|
| Response (all pts) | 36 | 12(33) | 7 (19) | 19 (53) |
| Response to last Rx | | | | |
| Sensitive | 16 | 9 (56) | 2 (13) | 11 (69) |
| Resistant | 18 | 3 (17) | 5 (28) | 8 (45) |

| Reference | n | Dose | ORR | CR | Prior Rx |
|---|---|---|---|---|---|
| Corazzelli | 41 | 90-120 mg/m2, days 1 &2, every 3-4 wks | 58% | 31% | |
| Ghesquieres | 28 | 90-120 mg/m2, days 1 &2, every 4 wks | 50% | 29% | |
| Anastasia | 67 | 90-120 mg/m2, days 1 &2, every 4 wks | 57% | 25% | 67% failed auto SCT 33% failed allo SCT |
| Zinzani | 27 | 90 mg/m2, days 1 &2, every 4 wks | 56% | 37% | All received prior BV 56% refractory to BV |


Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-60

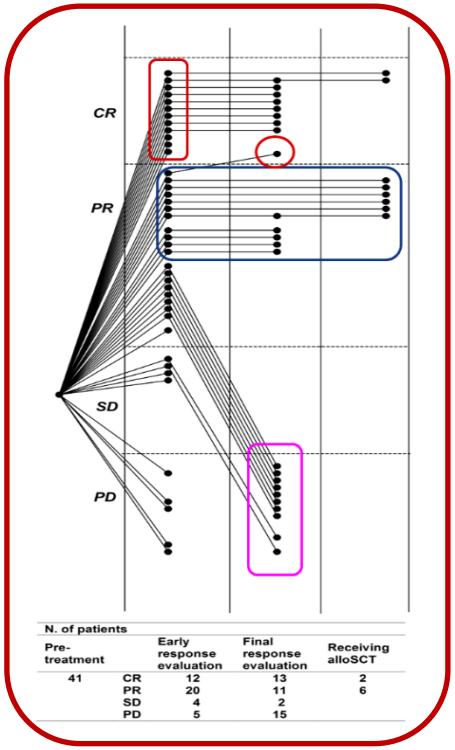
Corazzelli, et al. British Journal of Haematology, 2013;160:207-215

Ghesquieres, et al. Leukemia & Lymphoma, 2013;54(11):2399-2404

Anastasia, et al. British Journal of Haematology, 2014;166:140-153

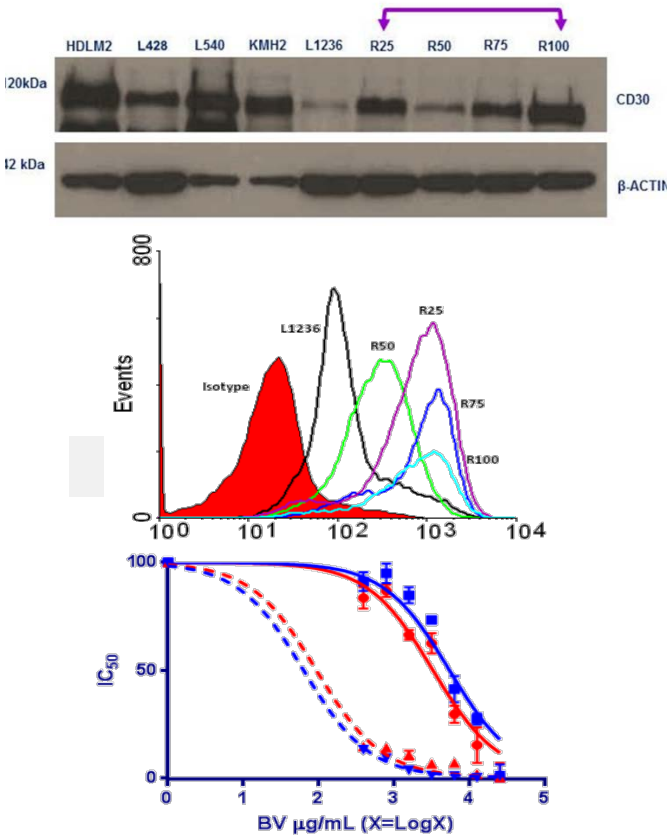
Zinzani, et al. Clinical Lymphoma, Myeloma & Leukemia, 2015;15(7):404-408


## 2. Works rapidly



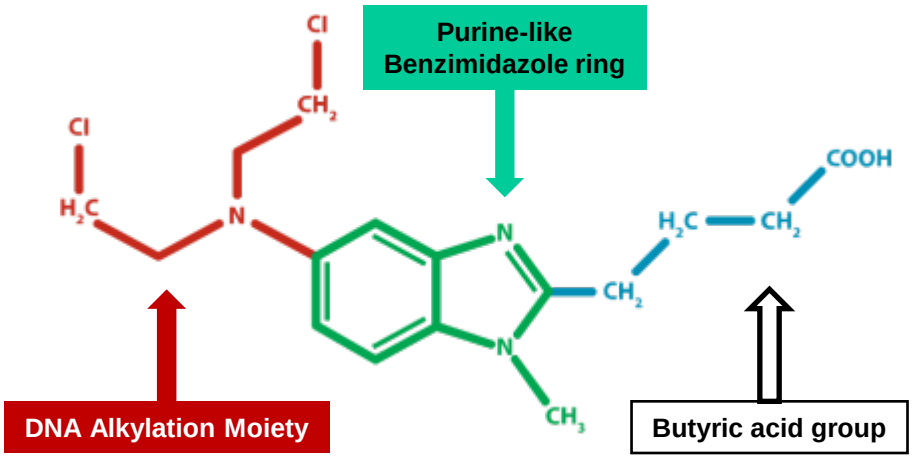

2-4 courses to best resp.

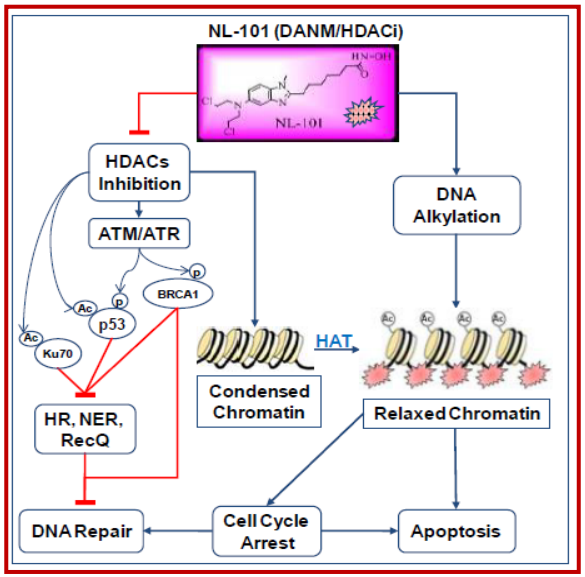
## 3. Synergizes with BV

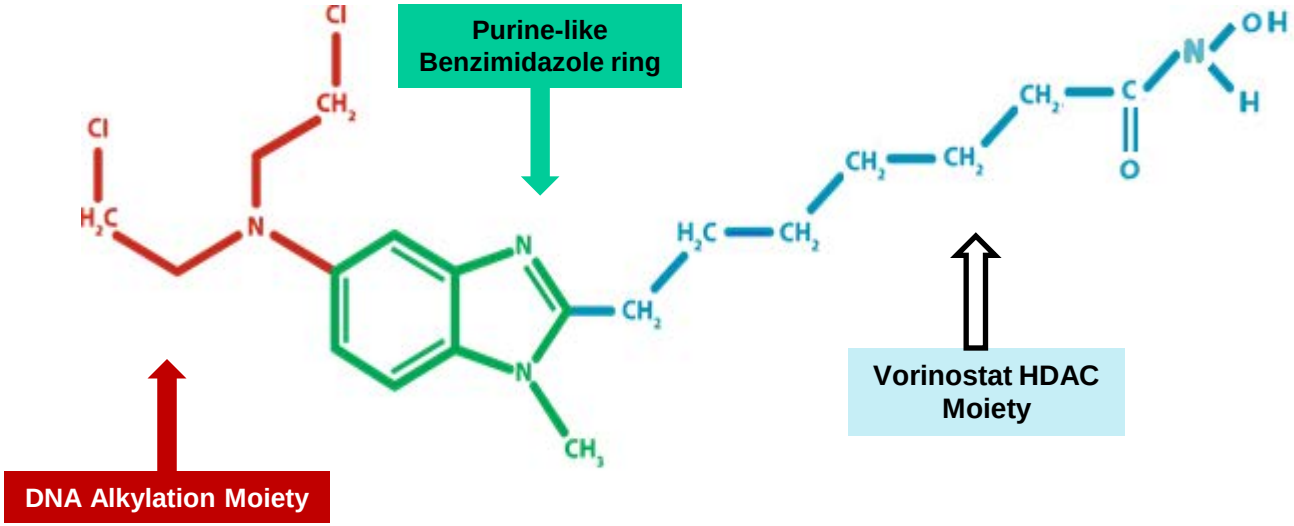



De Filippi *et al.* ASH 2015 Leoni *et al.* ASH 2003

# Tinostamustine (EDO-S101)

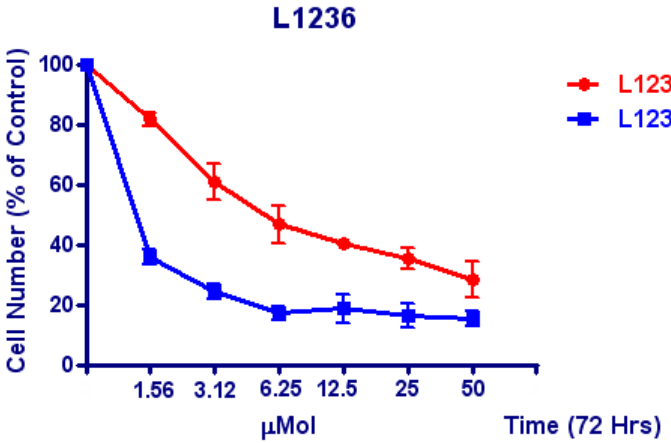


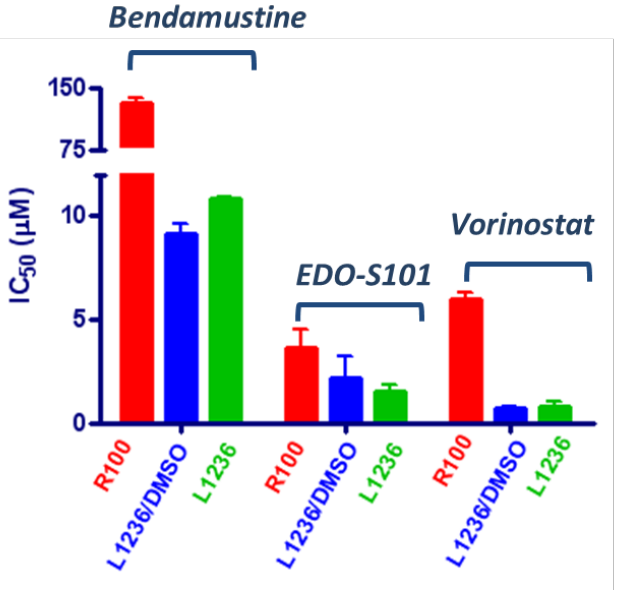



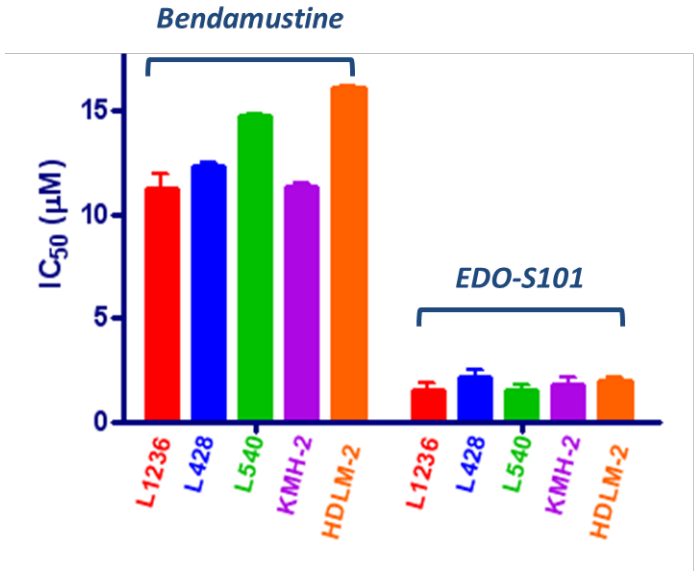



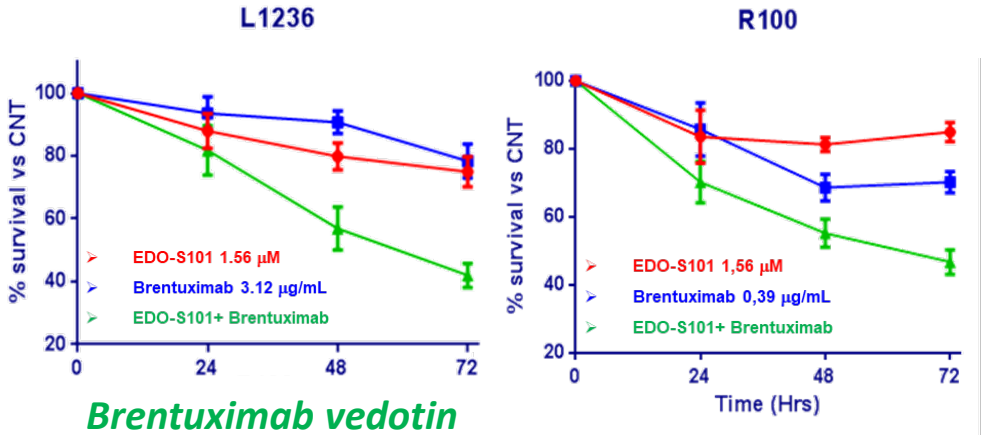
# Tinostamustine (EDO-S101): Preclinical evidences in HL

- EDO-S101 Inhibits HL Cell Growth @ IC50s ~10-fold lower than Bendamustine
- EDO-S101 exerts a potent antiproliferative effects on Bendamustine-resistant HL cells
- EDO-S101 is synergic with Brentuximab vedotin



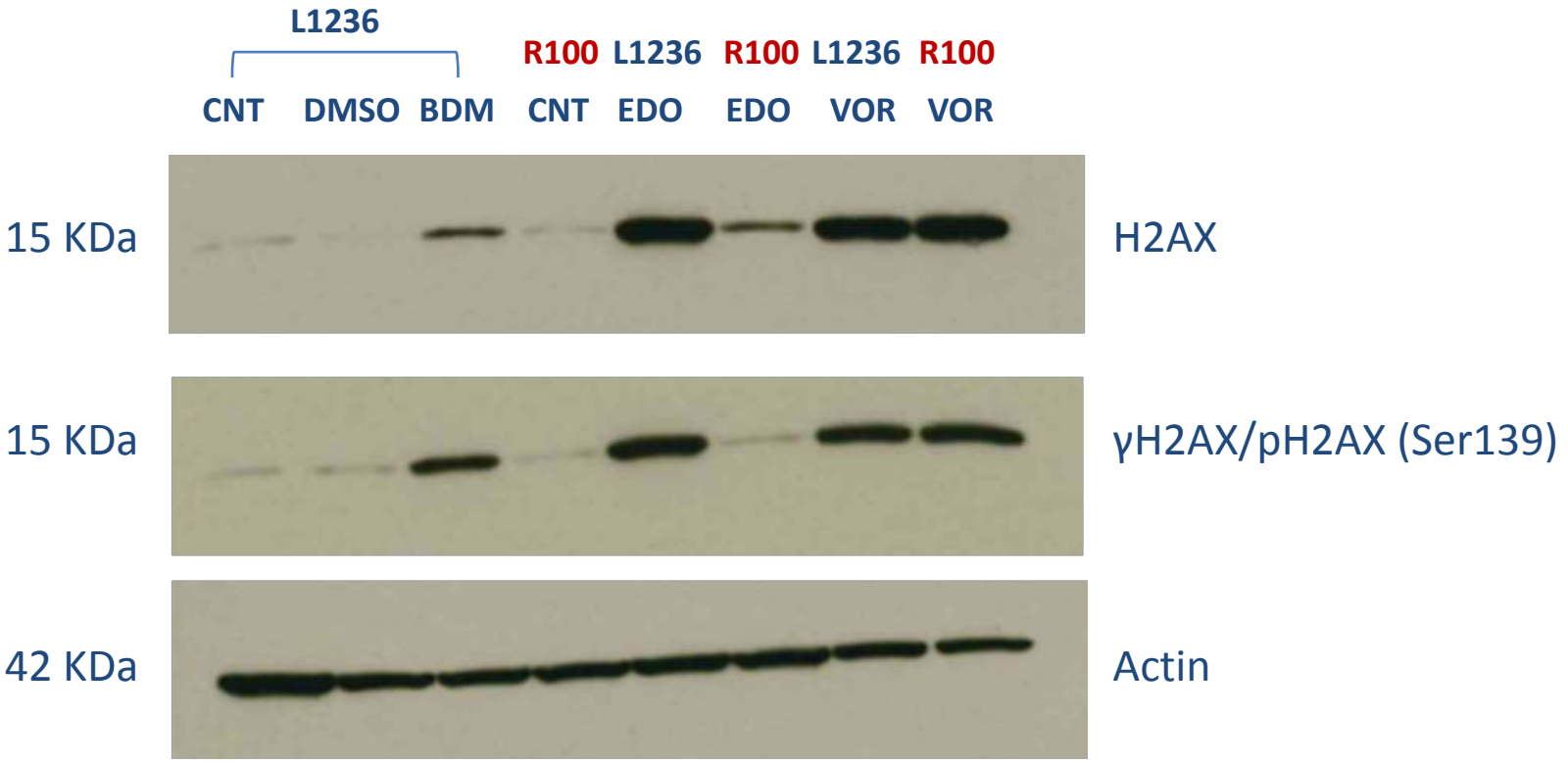




**Brentuximab vedotin**

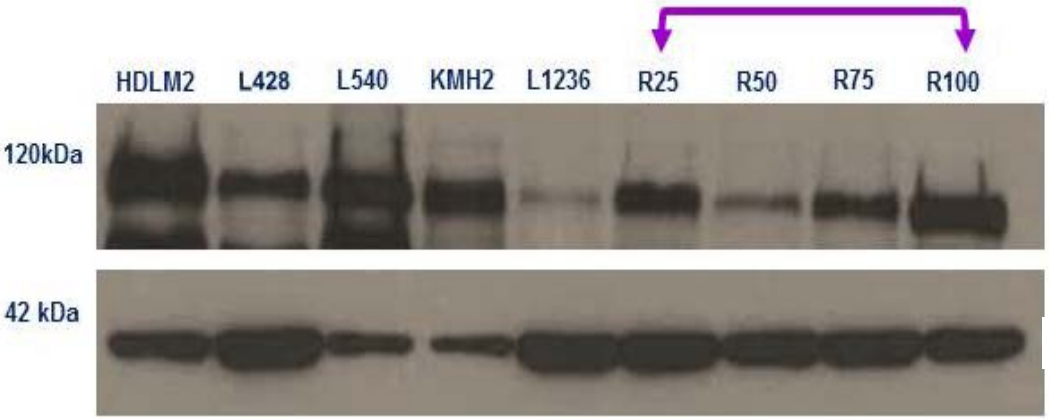
De Filippi R, et al. ASH 2015

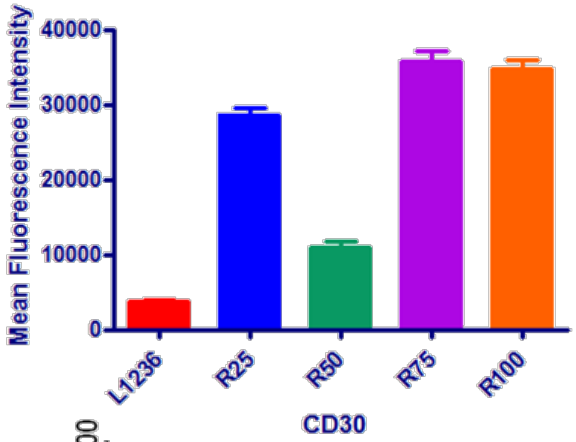
# Tinostamustine (EDO-S101): DNA damage response in HL cells

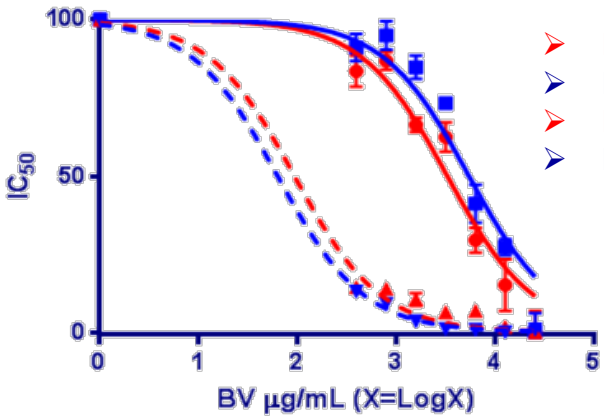
## EDO-S101 triggers DNA damage response in HL cells sensitive or resistant to BDM



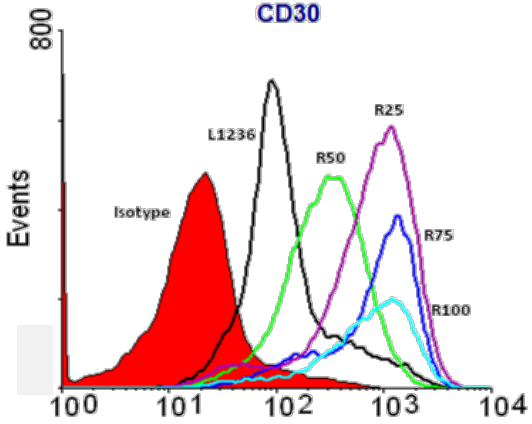
# Extended exposure to BDM of HL cells: CD30 upregulation



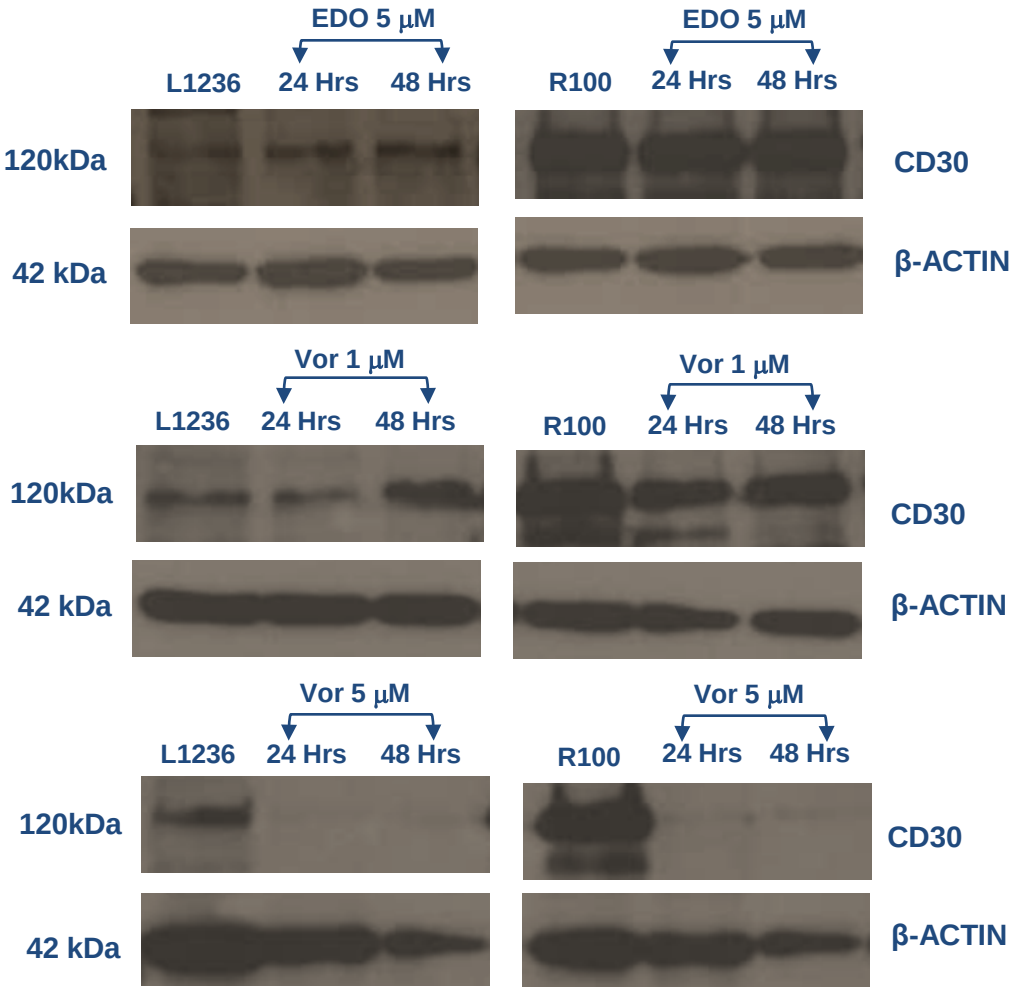




- L1236 48 Hrs IC50 = 3.16
- L1236 72 Hrs IC50 = 3.87
- R100 48 Hrs IC50 = 0.21
- R100 72 Hrs IC50 = 0.19

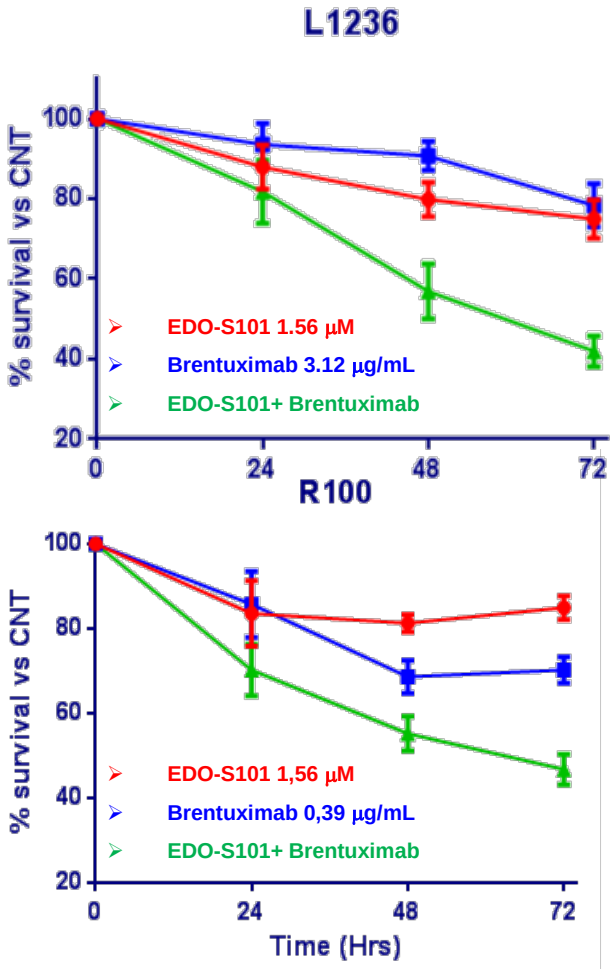



Extended exposure and resistance to Bendamustine in HL cells is associated to a stable upregulation of CD30 and increased sensitivity to Brentuximab Vedotin

# Tinostamustine (EDO-S101): Effects of HL cells proliferation

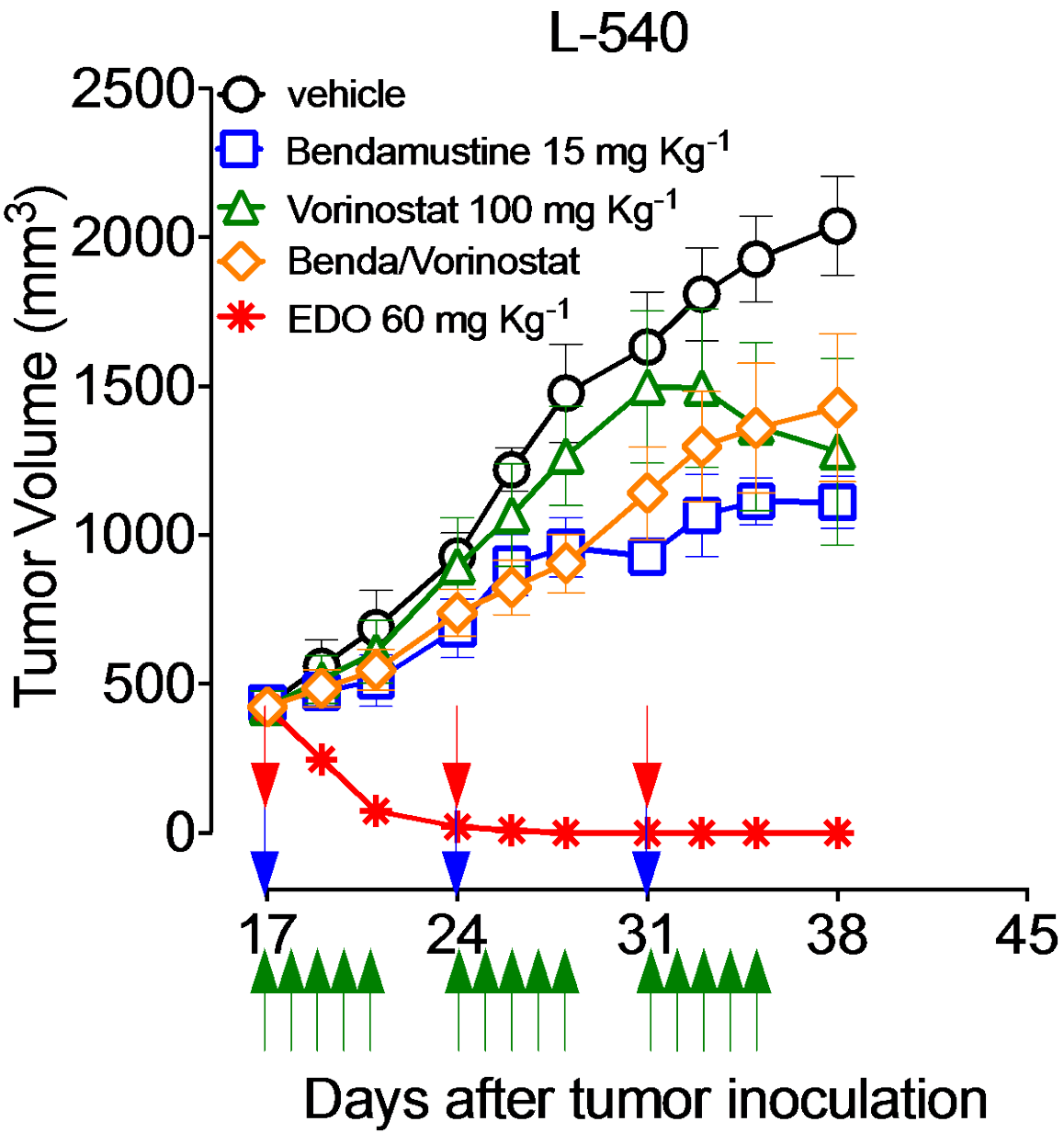



**Differently from Vorinostat, EDO-S101 does not downregulate CD30**




EDO-S101 is synergic with Brentuximab Vedotin at sub-IC concentrations allows low doses of Brentuximab Vedotin (10-fold lower than IC50) to exert a striking cytotoxic effect on BDM-resistant L1236 R100 cells which overexpress CD30

# Tinostamustine (EDO-S101): Effects on NOD-SCID-gammac-/- mice XG



# Tinostamustine (EDO-S101): First-in-Humans study

## Study of EDO-S101, A First-in-Class Alkylating HDACi Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies

**ClinicalTrials.gov Identifier:**
NCT02576496
First received: October 12, 2015
Last updated: April 21, 2016
Last verified: March 2016

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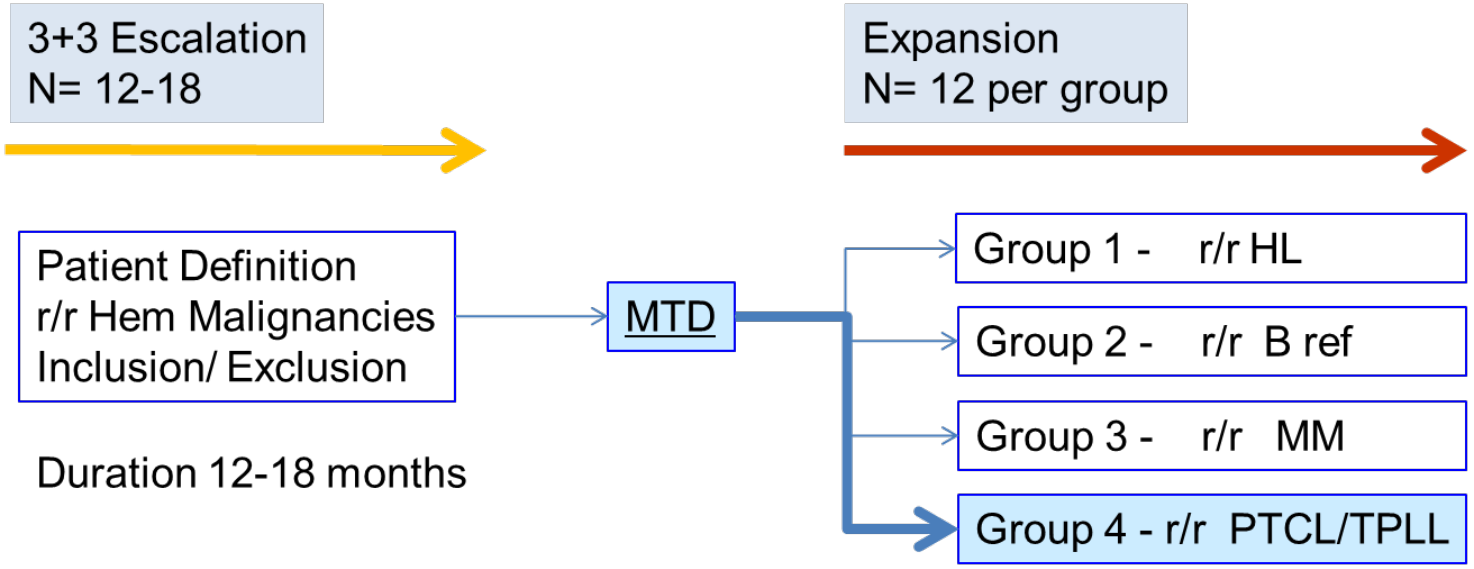
# Tinostamustine (EDO-S101): First-in-Humans study

A Phase 1 Study to Investigate the Safety, Pharmacokinetic Profiles and the Efficacy of EDO-S101, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies




5 centers actively recruiting: US (3), CH (1), IT (2)

Clinical trial applications underway: ES (1), F (3)

26 patients recruited up to date

Number of cycles: 1-8

Efficacy observations: SD, PR, CR

Key Objectives:

- Safety
- MTD & RP2D
- PK - /PK-PD
- Optimal infusion time
- Signals of efficacy
- Tumor samples for genetic testing

# Tinostamustine (EDO-S101): First-in-Humans study

A Phase 1 Study to Investigate the Safety, Pharmacokinetic Profiles and the Efficacy of EDO-S101, a First-in-Class Alkylating Histone Deacetylase Inhibition (HDACi) Fusion Molecule, in Relapsed/Refractory Hematologic Malignancies

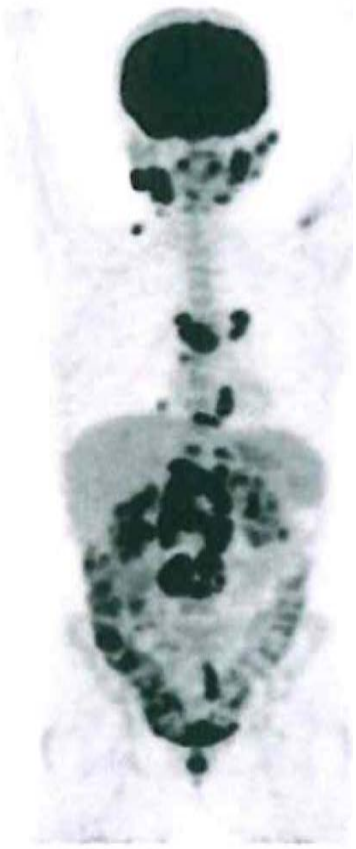
| | Dosing cohort in $mg/m^2$ / infusion time | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Disease Type** | **Pts No** | **20/1h** | **40/1h** | **60/1h** | **80/1h** | **100/1h** | **120/1h** | **80/45m'** | **60/30m'** | **80/30'** |
| **MM** | 19 | 0 | 2 | 1 | 1 | 7 | 0 | 5 | 3 | |
| **NHL** | 17 | 3 | 0 | 2 | 2 | 1 | 2 | 3 | 4 | |
| **HL** | 10 | 0 | 1 | 0 | 0 | 0 | 4 | 2 | 2 | 1 |
| **Total** | 46 | 3 | 3 | 3 | 3 | 8 | 6 | 10 | 9 | 1 |

# EDO-S101 for primary refractory HL (case # 1)

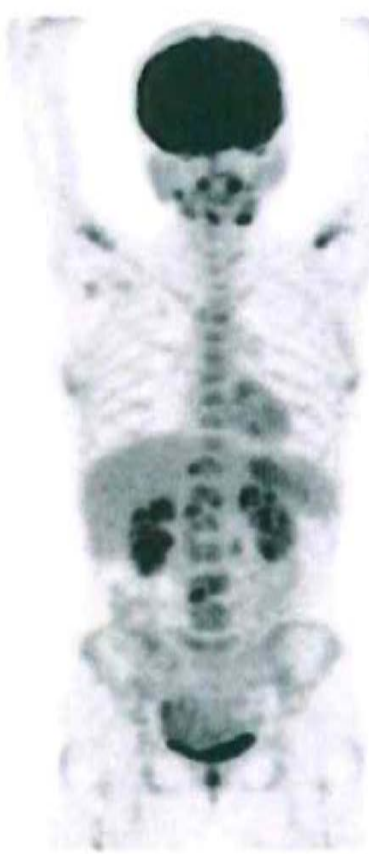
- 42-year-old female
- cHL diagnosed 2014

| | |
|---|---|
| • ABVD x 4 | PD |
| • EscBEACOPP x 2 | PD |
| • IGEV x 1 | PD |
| • Brentuximab vedotin x 4 | PD |
| • Pembrolizumab x 15 | SD |
| *stop due to lung toxicity* | |
| 3 mo.s afterwards | PD |

- **EDO-S101** 120 mg/m2 q21 days
  - 4 courses delivered
  - DLT G4 thrombocytopenia
  - Best clinical response:
    - ‘*conservative*’ PR
    - DOR: 5 mo.s



**17.07.17**

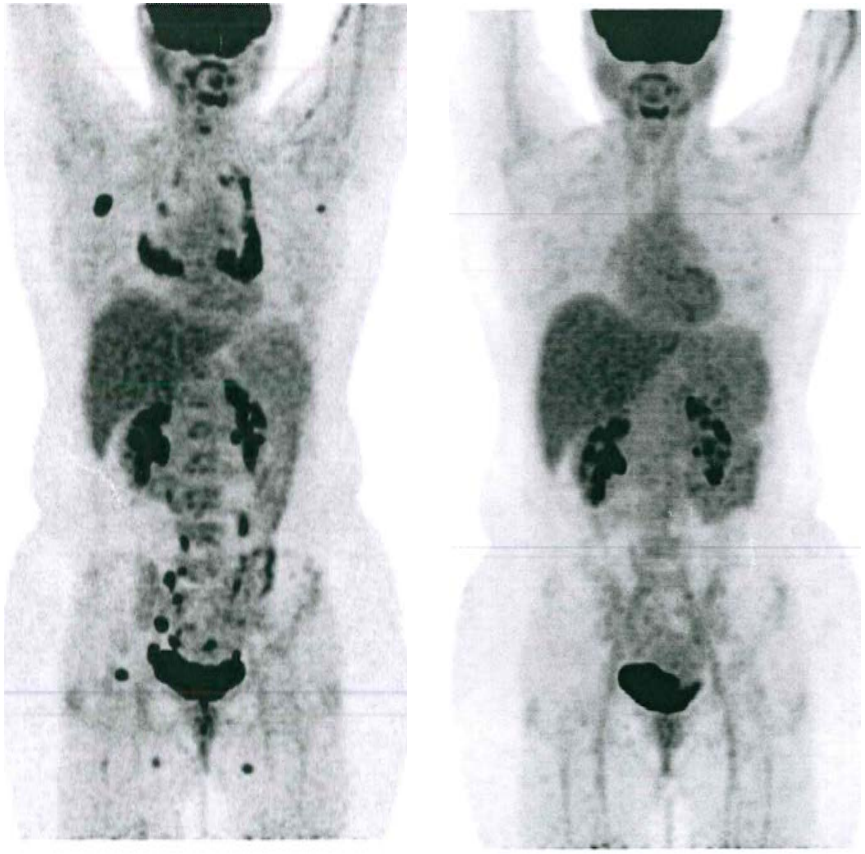


**07.09.17**

# EDO-S101 for primary refractory HL (case # 2)

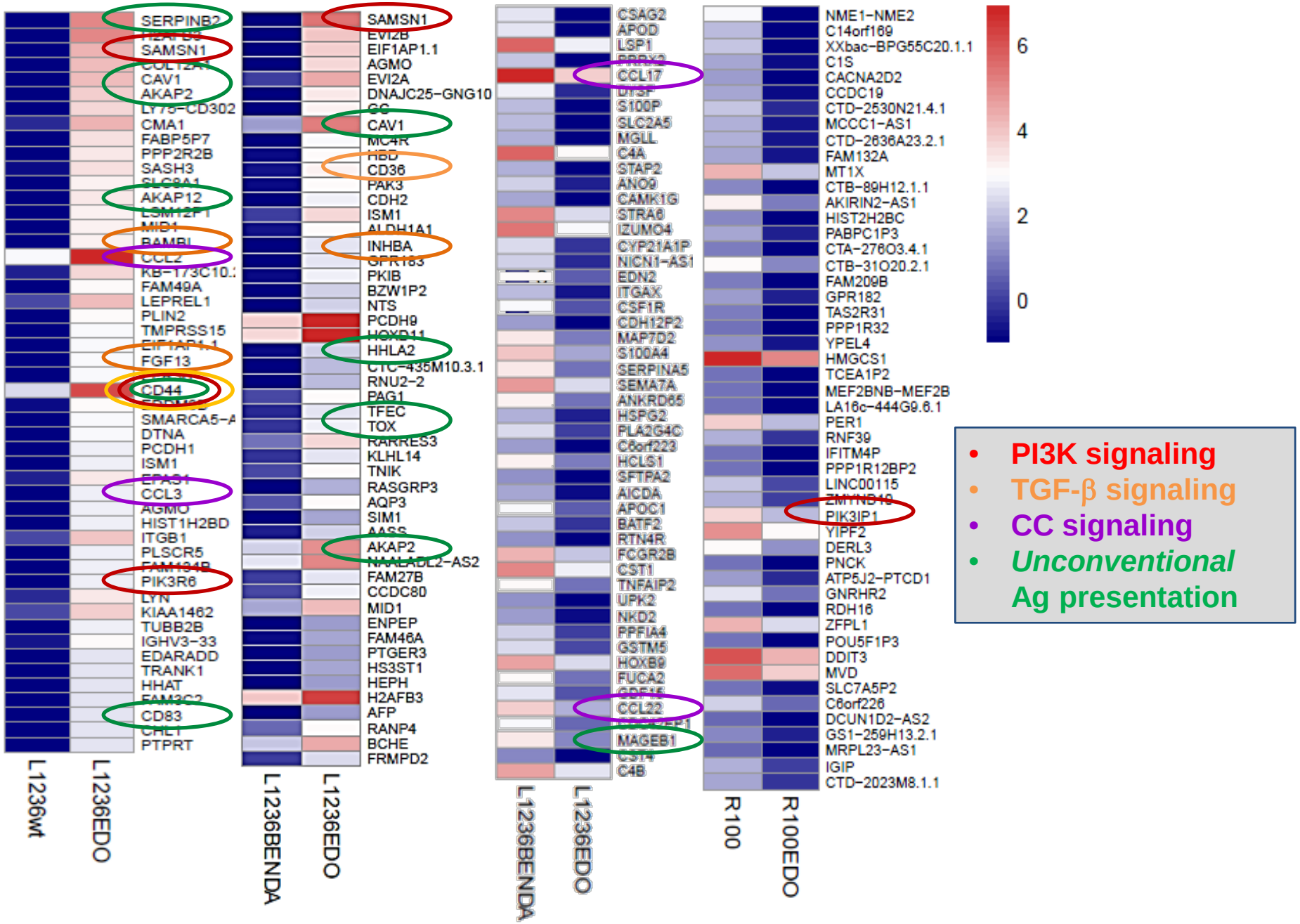
- 42-year-old female
- cHL diagnosed 2014
  - ABVD x 6 + med. RT — PD
  - IGEV x 2 — PD
  - Brentuximab vedotin x 6 — PD
  - Nivolumab x 6 — **PR**
    - declines ASCT
  - Nivolumab x 15 — SD
  - Nivolumab x 24 — PD

- **EDO-S101** 120 mg/m2 q21 days
  - 6 courses delivered
  - G3 thrombocytopenia
  - Best clinical response:
    - **CR**
    - DOR: continuos CR > 8 mo.s (w/o any further treatments)
    - Mobilization failure/BM hypoplasia
    - Referred for Haplo-SCT (sept. 2018)



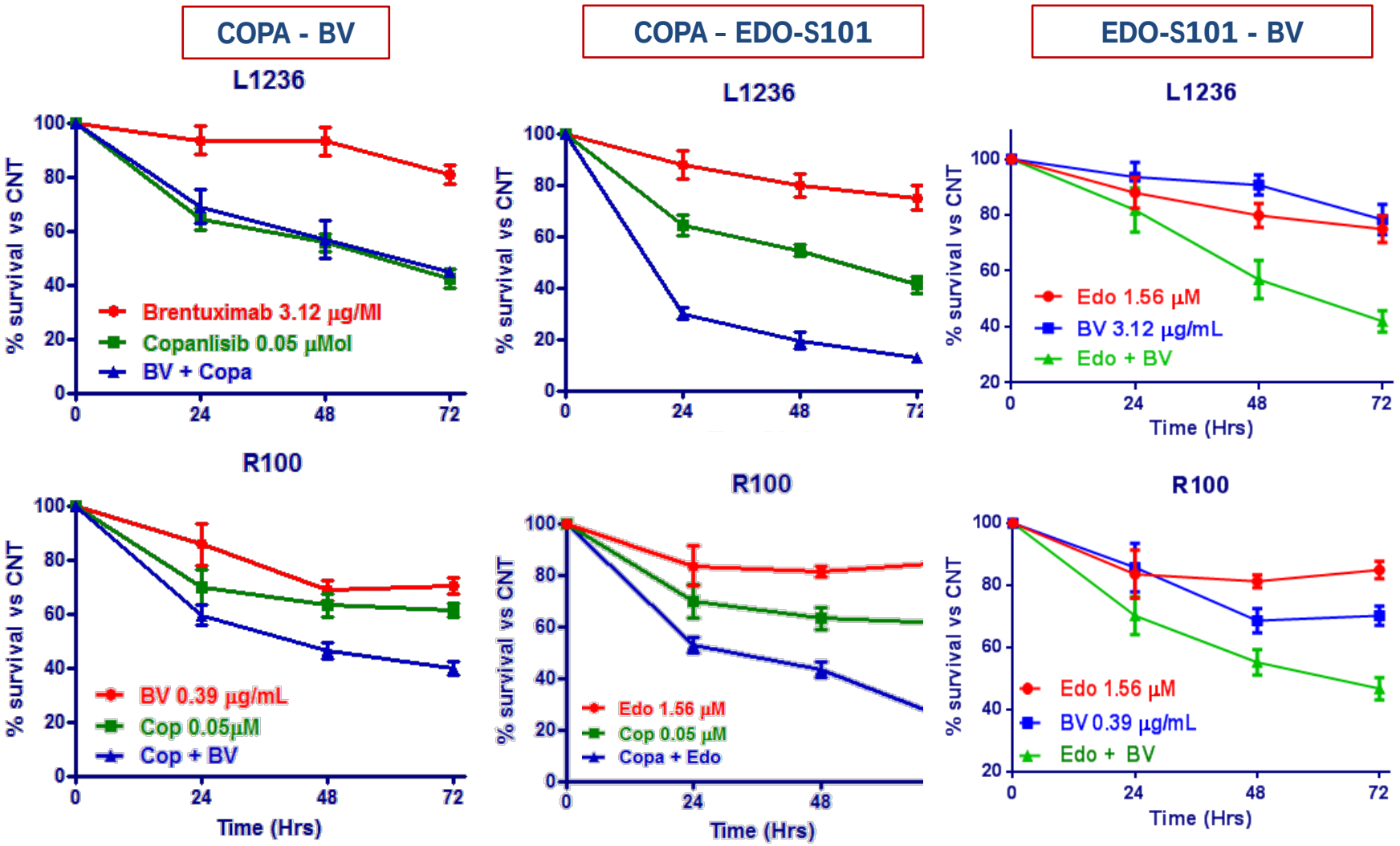
**27.07.17** **13.02.18**

# Tinostamustine (EDO-S101): Gene expression profiling studies

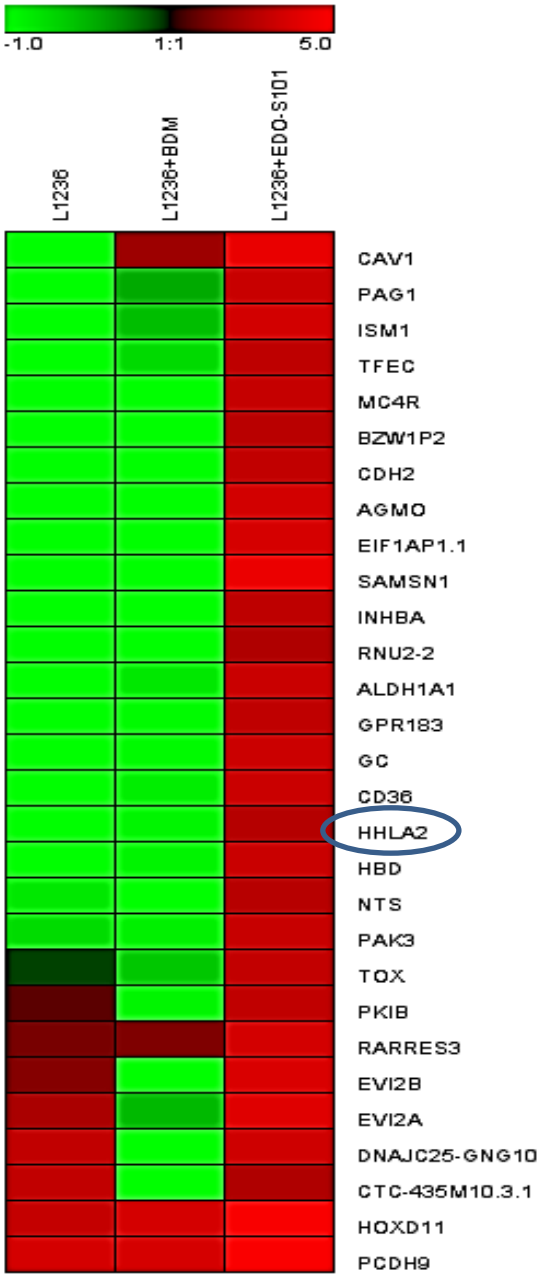


# Tinostamustine (EDO-S101): Gene expression profiling studies

- Copanlisib is synergic with BV in CD30 overexpressing cells
- EDO-S101 is synergic whit Copanlisib and BV regardless of CD30 expression levels



# Tinostamustine (EDO-S101): Gene expression profiling studies



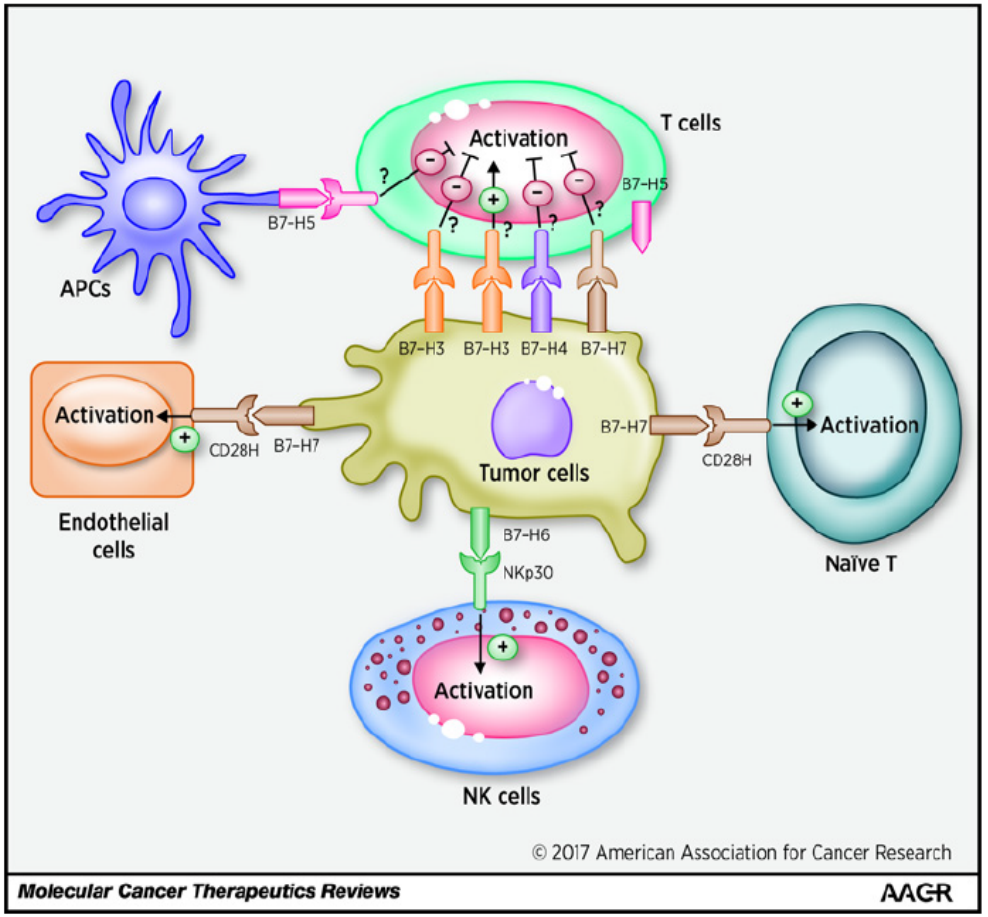



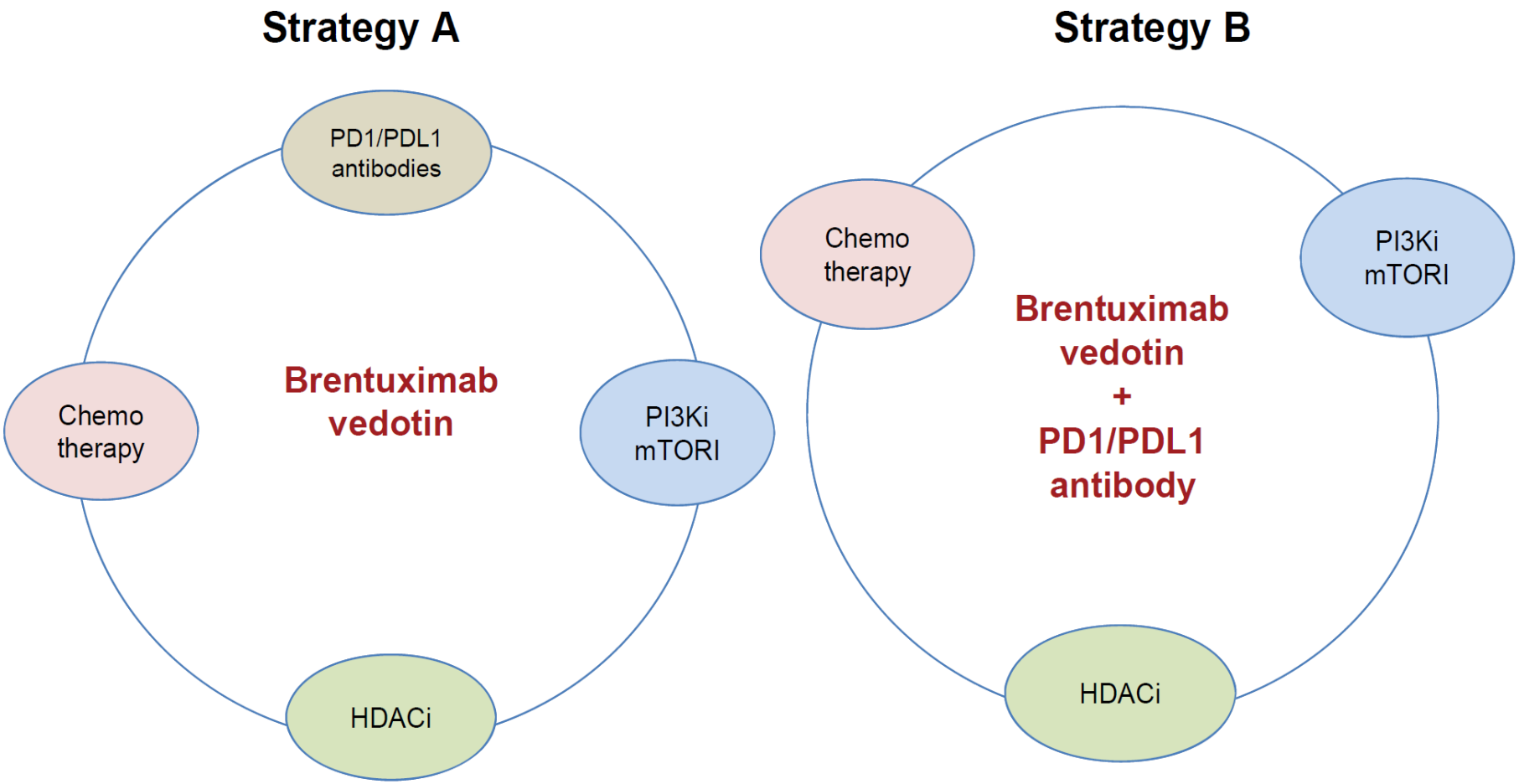

**Table 2.** HHLA2 protein expression in human cancers assessed by immunohistochemistry on tissue microarrays

| Cancer samples (number positive/total cores) | | |
|---|---|---|
| Breast (7/10) | Lung (6/9) | Thyroid (6/9) |
| Malignant melanoma (5/9) | Pancreas (5/10) | Ovary (4/8) |
| Liver (4/10) | Bladder (4/10) | Colon/rectum (3/8) |
| Prostate (3/9) | Kidney (2/6) | Esophagus (2/10) |
| Endometrial (0/9) | Gallbladder (0/10) | Larynx (0/10) |
| B-cell lymphoma (0/10) | Stomach (0/10) | Uterine cervix (0/10) |

# Tinostamustine (EDO-S101)

- **Conclusions**
  - EDO-S101 is a potent inhibitor of HL tumor cells growth and is currently being tested in a Phase 1 study
  - Activity signals have been obtained in pts. With RR-HL
  - DLT has been determined and expansion cohorts are recruiting
  - EDO-S101 activates a unique gene expression program encompassing regulatory pathways involved in:
    - PI3K signaling
    - TGF-β signaling,
    - CC signaling
    - Unconventional Ag presentation
  - This can guide identification of potential partners for EDO-S101-based combination therapy for HL
    - PI3k inhibitors
    - Brentuximab vedotin

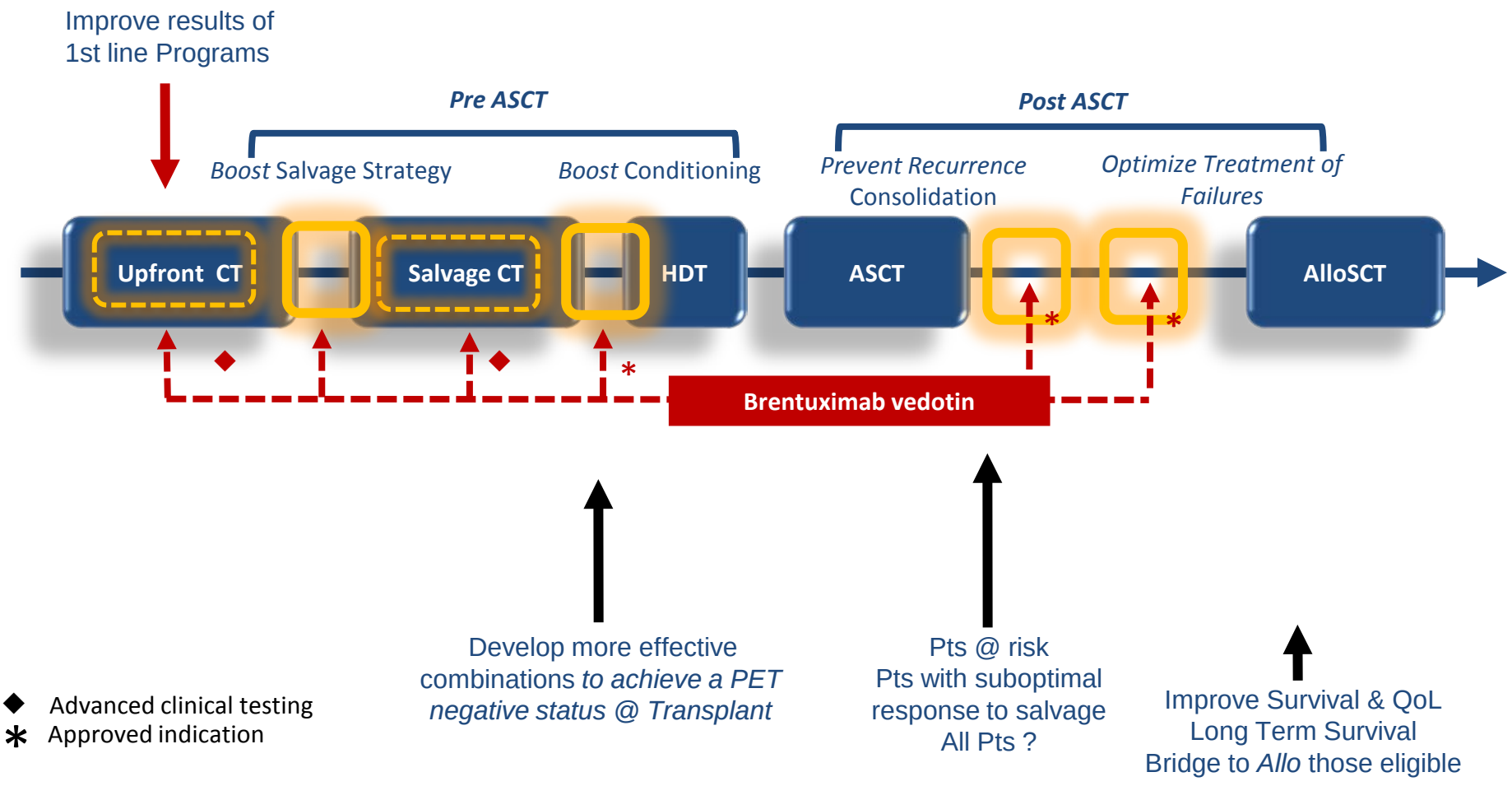
# Hodgkin Lymphoma: Future Directions



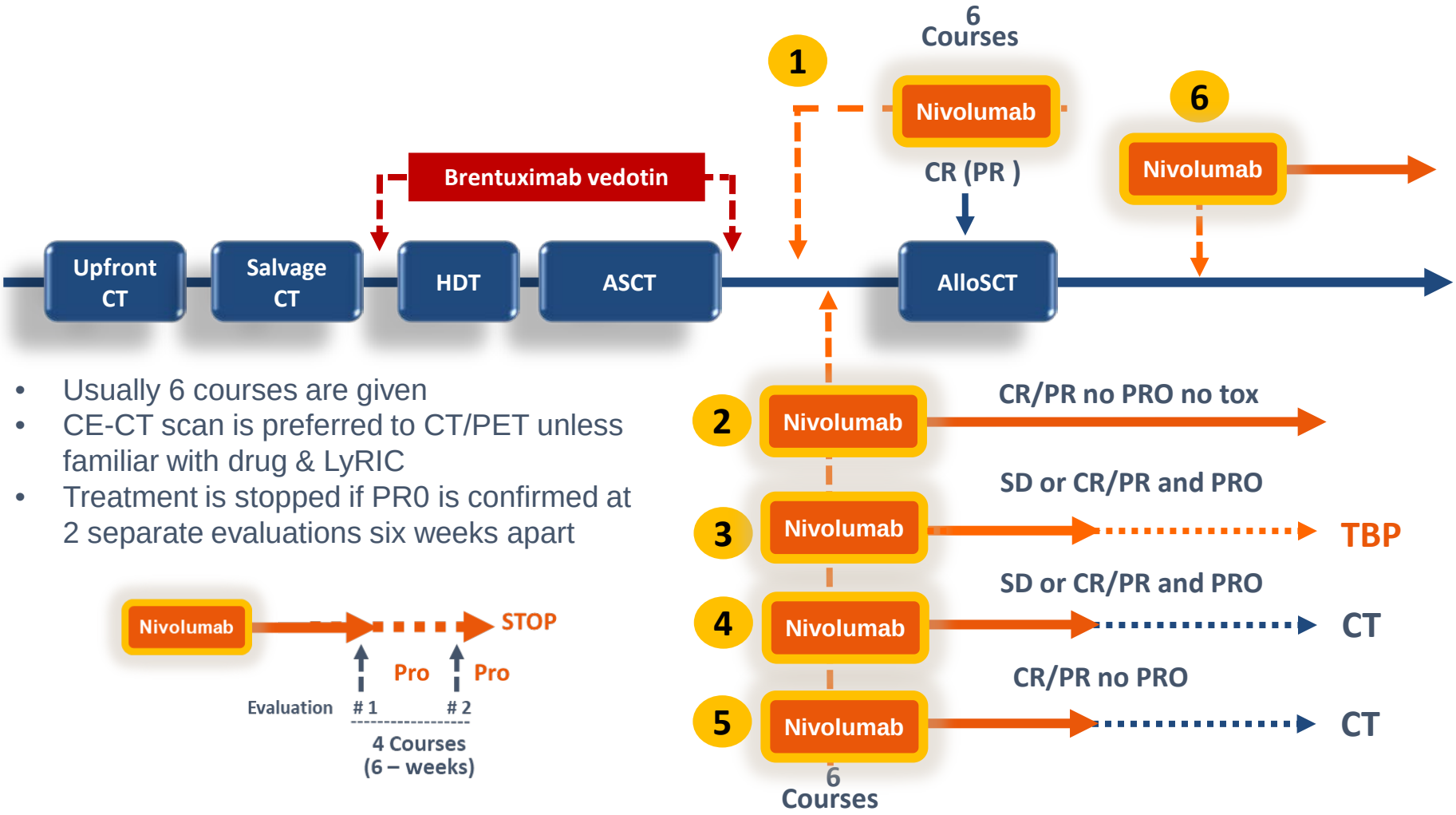
# *…No man is an island…*

**1572-1631**

# *Brentuximab Vedotin in the Overall Treatment Strategy for HL*

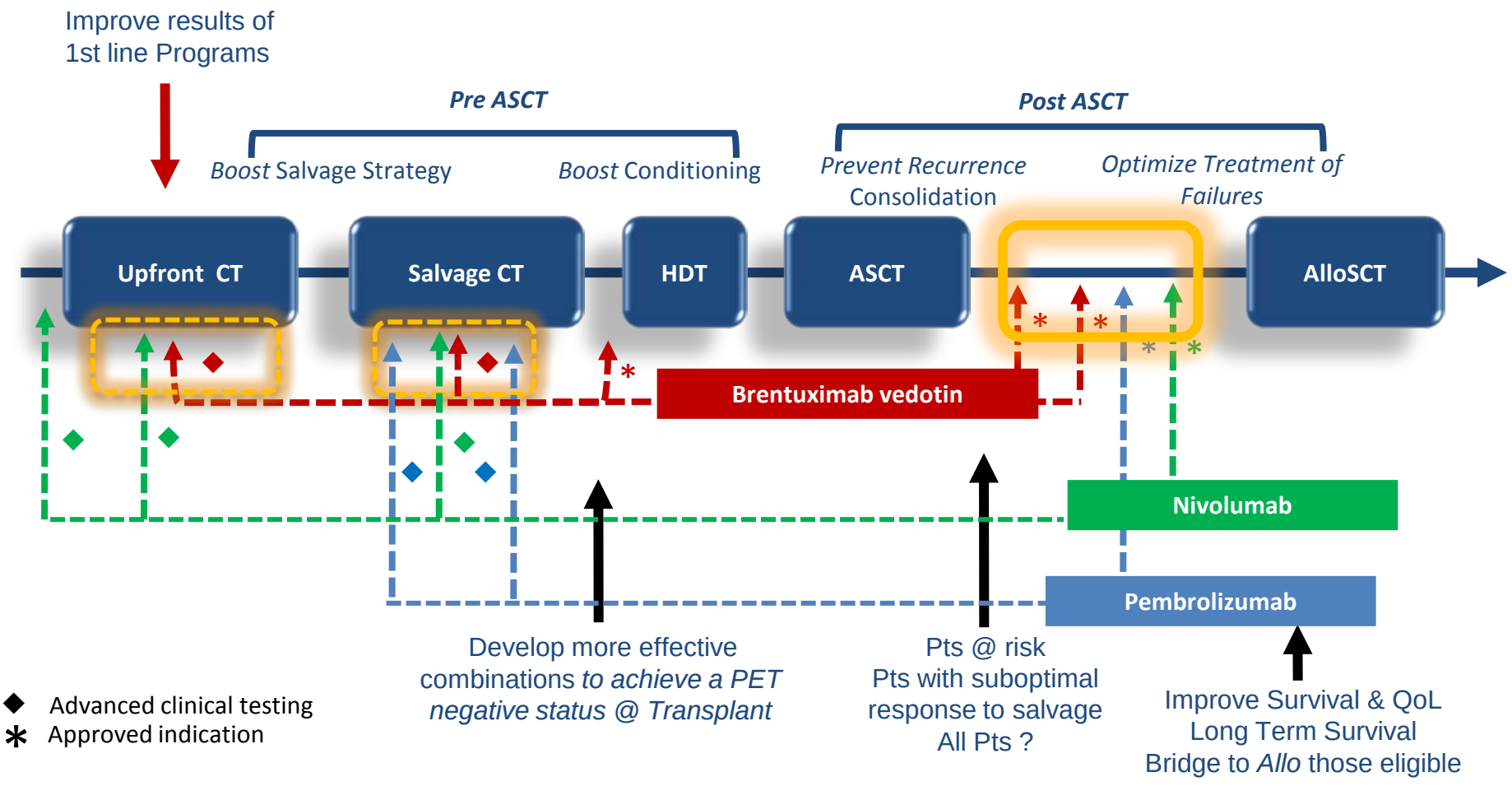


# PD1 blockade in the Overall Treatment Strategy for HL




- Usually 6 courses are given
- CE-CT scan is preferred to CT/PET unless familiar with drug & LyRIC
- Treatment is stopped if PR0 is confirmed at 2 separate evaluations six weeks apart

# *Brentuximab Vedotin in the Overall Treatment Strategy for HL*



# *Hodgkin Lymphoma: …Therapeutic Biology…*