Immunotherapy in Hodgkin Lymphoma & Non-Hodgkin Lymphomas

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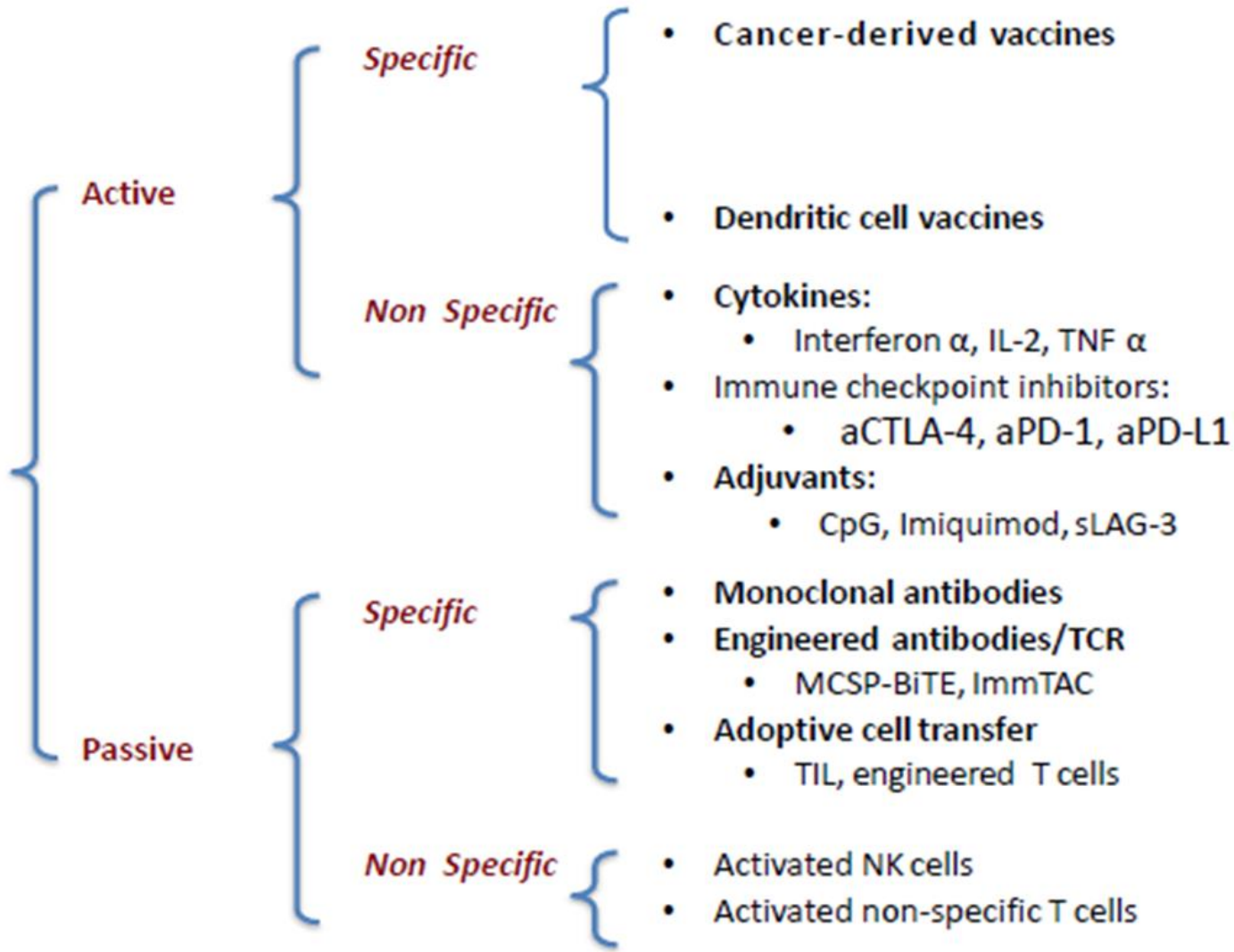
Immunotherapy Approach

- We examine two broad immunotherapy approaches that may be utilized for the treatment of pediatric malignancy :

1. Direct utilization of the immune system properties
2. Immune system modulation

Classification of immunotherapy



Immune System Function and Immune Response

Identify and destroy foreign or abnormal cells in the body

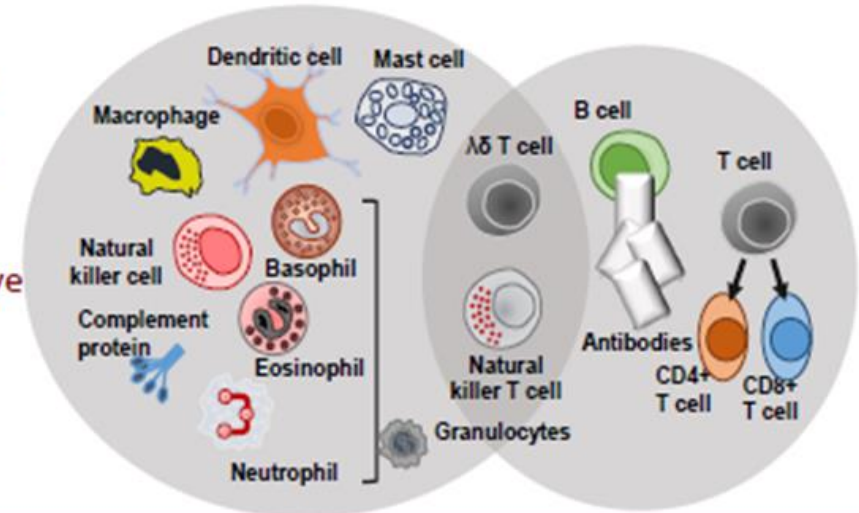
Innate Immunity | **Adaptive Immunity**

Nonspecific

First line of defense

WBCs (natural killer cells, neutrophils)

Activation of adaptive response



Specific

Adapts specifically to diverse stimuli

B-cell antibody production

T-cell stimulation

Memory functions

Immune surveillance

- Involves both innate and adaptive immune mechanisms
- **Non self-associated antigens can be identified by the immune system and destroyed**

Janeway CA Jr, et al. Immunobiology: the immune system in health and disease. 2001.

1. Direct Utilization of the Immune System

1.1. Oncolytic Virus-Based Therapy

1.2. Antigen-Targeting Therapy

1.3. Immune Checkpoint Inhibitors

2. Modulation of the Immune System

2.1. Tumor Microenvironment: Cancer-Associated Fibroblasts, Tumor-Associated Macrophages, and Myeloid-Derived Suppressor Cells

2.2. Cytokines and Growth Factors

2.3. Chimeric Antigen Receptor T Cell Therapy

2.4. Natural Killer Cell-Based Immunotherapy

2.5. Cancer Vaccines

Table 1. Immunotherapy clinical trials for pediatric solid tumors discussed in this review.

Immunotherapy Approach	Disease	Target	Agent/Compound	NCT #	Phase of Study
Viral therapy	Cerebellar Brain Tumor	N/A	G207 (HSV)	03911388	Phase I (recruiting)
Viral therapy	Supratentorial Brain Tumor	N/A	G207 (HSV) +/− radiation	02457845	Phase I (recruiting)
Viral therapy	DIPG	N/A	DNX-2401 (adenovirus)	03178032	Phase I (recruiting)
Viral therapy	Glioma	N/A	Recombinant Polio/Rhinovirus	03043391	Phase I (recruiting)
Antigen-targeting and growth factor therapy	Neuroblastoma	GD2	hu3F8 (mAB against GD2) and GM-CSF	01757626	Phase I/II (recruiting)
Immune checkpoint inhibitor	Solid tumors	CTLA-4	Ipilimumab	01445379	Phase I (completed)
Immune checkpoint inhibitor	Solid tumors or lymphoma	PD-1	Nivolumab with chemotherapy	03585465	Phase I/II (recruiting)
Immune checkpoint inhibitor	Hypermutated malignancies	PD-1	Nivolumab	02992964	Phase I/II (recruiting)
Immune checkpoint inhibitor	Solid tumors	PD-1	Nivolumab	02901145	Phase I/II (not yet recruiting)
Immune checkpoint inhibitor	Solid tumors or sarcoma	PD-1/CTLA-4	Nivolumab +/− ipilimumab	02304458	Phase I/II (recruiting)

Cytokine therapy	DIPG	N/A	Pegylated IFN-α2b	00041145	Phase II (completed)
Cytokine therapy	Plexiform neurofibroma	N/A	Pegylated IFN-α2b	00678951	Phase II (completed)
Cytokine therapy	Osteosarcoma	N/A	Pegylated IFN-α2b	00134030	Phase III (active, not recruiting)
Cytokine targeted therapy	Osteosarcoma	RANKL	Denosumab (mAB against RANKL)	02470091	Phase II (active, not recruiting)
Cytokine targeted therapy	Solid tumors	TRAIL-R2	Lexatumumab (mAB against TRAIL-R2)	00428272	Phase I (terminated)
Growth factor therapy	Osteosarcoma, Ewing sarcoma	N/A	Inhaled GM-CSF (Sargramostim)	00673179	Phase I (terminated)
CAR T cells	Neuroblastoma	GD2	Anti-GD2 CAR T cells	01822652	Phase I (active, not recruiting)
CAR T cells	Sarcoma	HER2	Anti-HER2 CAR T cells	00902044	Phase I (recruiting)
NK cells with cytokine therapy	Brain tumors, sarcoma, Wilms tumor, RMS	N/A	NK cells +/− rhIL-15 after lympho-depletion	01875601	Phase I (completed)
NK cells with antigen targeted therapy	Neuroblastoma	GD2	hu14.18K322A (anti-GD2), NK cells	01576692	Phase I (completed)
NK cells with antigen targeted therapy	Neuroblastoma	GD2	hu14.18K322A (anti-GD2), NK cells	01857934	Phase II (active, not recruiting)

CAR T cells	Neuroblastoma	GD2	Anti-GD2 CAR T cells	01822652	Phase I (active, not recruiting)
CAR T cells	Sarcoma	HER2	Anti-HER2 CAR T cells	00902044	Phase I (recruiting)
NK cells with cytokine therapy	Brain tumors, sarcoma, Wilms tumor, RMS	N/A	NK cells +/− rhIL-15 after lympho-depletion	01875601	Phase I (completed)
NK cells with antigen targeted therapy	Neuroblastoma	GD2	hu14.18K322A (anti-GD2), NK cells	01576692	Phase I (completed)
NK cells with antigen targeted therapy	Neuroblastoma	GD2	hu14.18K322A (anti-GD2), NK cells	01857934	Phase II (active, not recruiting)
NK cells	Solid tumors	N/A	NK cells	01287104	Phase I (completed)
NK cells	Ewing sarcoma, RMS	N/A	NK cells	00640796	Phase I (completed)
Cancer Vaccine	Neuroblastoma, sarcoma, RMS	Cancer testes antigen	Decitabine and DC vaccine + adjuvant	01241162	Phase I (Completed)

#, number; HSV, Herpes simplex Virus; DIPG, diffuse intrinsic pontine glioma; NK, natural killer; hu3F8, humanized 3F8; mAB, monoclonal antibody; GM-CSF, granulocyte-macrophage colony stimulating factor; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; PD-1, programmed cell death receptor 1; IFN, interferon; RANKL, receptor activator of nuclear factor-κB ligand; TRAIL-R, tumor necrosis factor-related apoptosis-inducing ligand receptor; CAR, chimeric antigen receptor; RMS, rhabdomyosarcoma; rhIL-15, recombinant human interleukin 15; DC, dendritic cell.

Hodgkin lymphoma

- Although classical Hodgkin lymphoma is usually curable, 20–30% of the patients experience treatment failure and most of them are typically treated with salvage chemotherapy and autologous stem cell transplantation.
- However, 45–55% of that subset further relapse or progress despite intensive treatment.

CLINICAL STAGING OF CLASSIC HODGKIN LYMPHOMA

Risk stratification is evolving. This table represents clinical trials with published data. Consider consultation with a center of expertise for patient management; enrollment in a clinical trial is preferred. Clinical trial staging may differ from this table, and close attention to trial eligibility and staging should be followed.

Clinical Stage (See ST-1)	Bulk (See PHL-D)	E-lesions[j] (See PHL-D)	Risk Group[k]
IA IIA	No	No	Low risk (per EuroNet-PHL-C1[l])
	Yes	No	Low risk (per EuroNet-PHL-C1[l]) or Intermediate risk (per AHOD0031)
	Yes	Yes	Intermediate risk (per EuroNet-PHL-C1[l] or AHOD0031)
IB	Any	No	Low risk (per EuroNet-PHL-C1[l])
	Any	Any	Intermediate risk (per AHOD0031)
IIB[i]	No	No	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1[l])
	No	Yes	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1[l])
	Yes	Any	High risk (per AHOD1331[l])
	Yes	Yes	High risk (per EuroNet-PHL-C1[l])
IIIA	Any	No	Intermediate risk (per AHOD0031 or EuroNet-PHL-C1[l])
	Any	Yes	Intermediate risk (per AHOD0031) or High risk (per EuroNet-PHL-C1[l])
IIIB, IV	Any	Any	High risk (AHOD1331[l] or EuroNet-PHL-C1[l])

See Low-Risk Disease (PHL-3)
See Intermediate-Risk Disease (PHL-4)
See High-Risk Disease (PHL-5)

[i] Only IIB with bulk was upstaged to high risk in the most recent series of COG clinical trials. The panel acknowledges that current trials have modified these groupings.

[j] E-lesions are defined by the HD10 study as localized involvement of extralymphatic tissue (by contiguous growth from an involved lymph node or in close anatomic relation) that is treatable by irradiation. (Engert A, et al. N Engl J Med 2010;363:640-652; Lister TA, et al. J Clin Oncol 1989;7:1630-1636.)

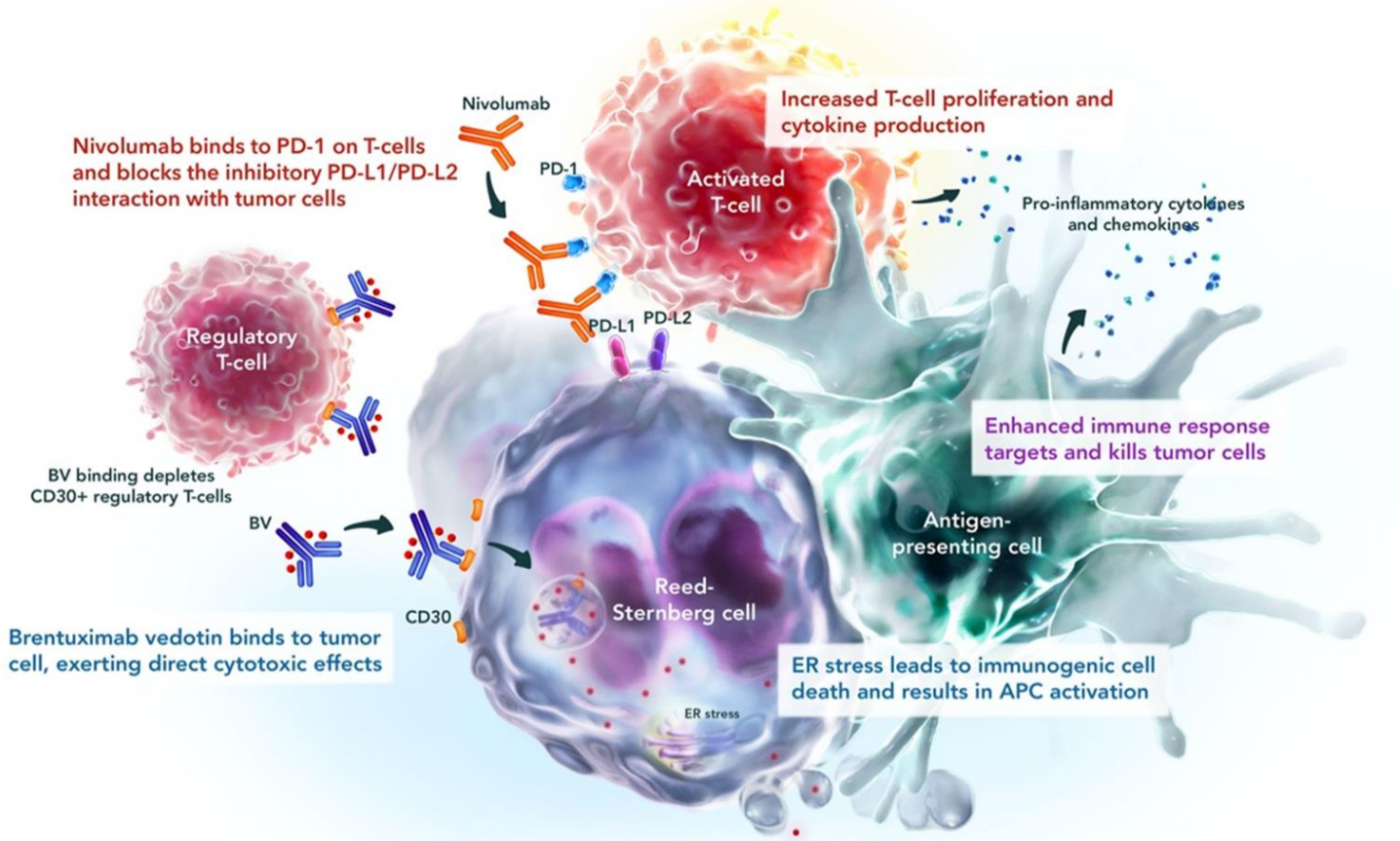
[k] GPOH-HD-2002: Mauz-Körholz C, et al. J Clin Oncol 2010;28:3680-3686; EuroNet-PHL-C1: Landman-Parker J, et al. Hematologica/ISHL10, 2016 [Abstract #P064];101:35; AHOD0031: Friedman DL, et al. J Clin Oncol 2014;32: 3651-3658; AHOD1331: Kelly KM, et al. Br J Haematol 2019;187:39-48; Castellino SM, et al. Klin Padiatr 2020; 232(02):82-83.

[l] Study is complete and data are emerging.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Immunotherapy

- At the advanced stage of the disease course, recently developed immunotherapeutic approaches have provided very promising results with prolonged remissions or disease stabilization in many patients.

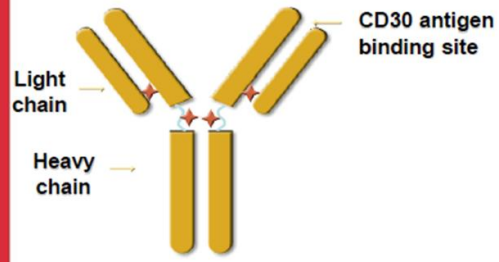


Brentuximab vedotin

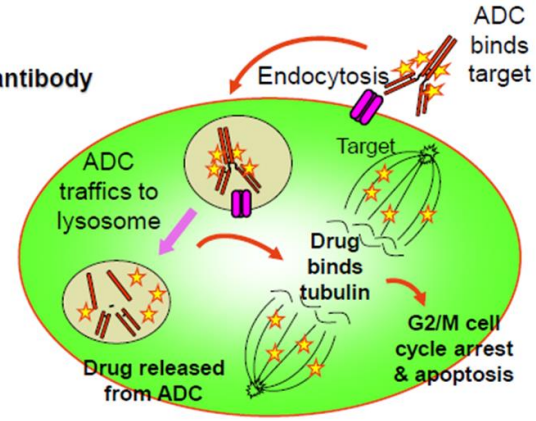
- Brentuximab vedotin (BV) has been approved for patients with relapsed/refractory cHL (rr-cHL) who have failed autoSCT, as a consolidation after autoSCT in high-risk patients, as well as for patients who are ineligible for autoSCT or multi-agent chemotherapy who have failed ≥ two treatment lines.

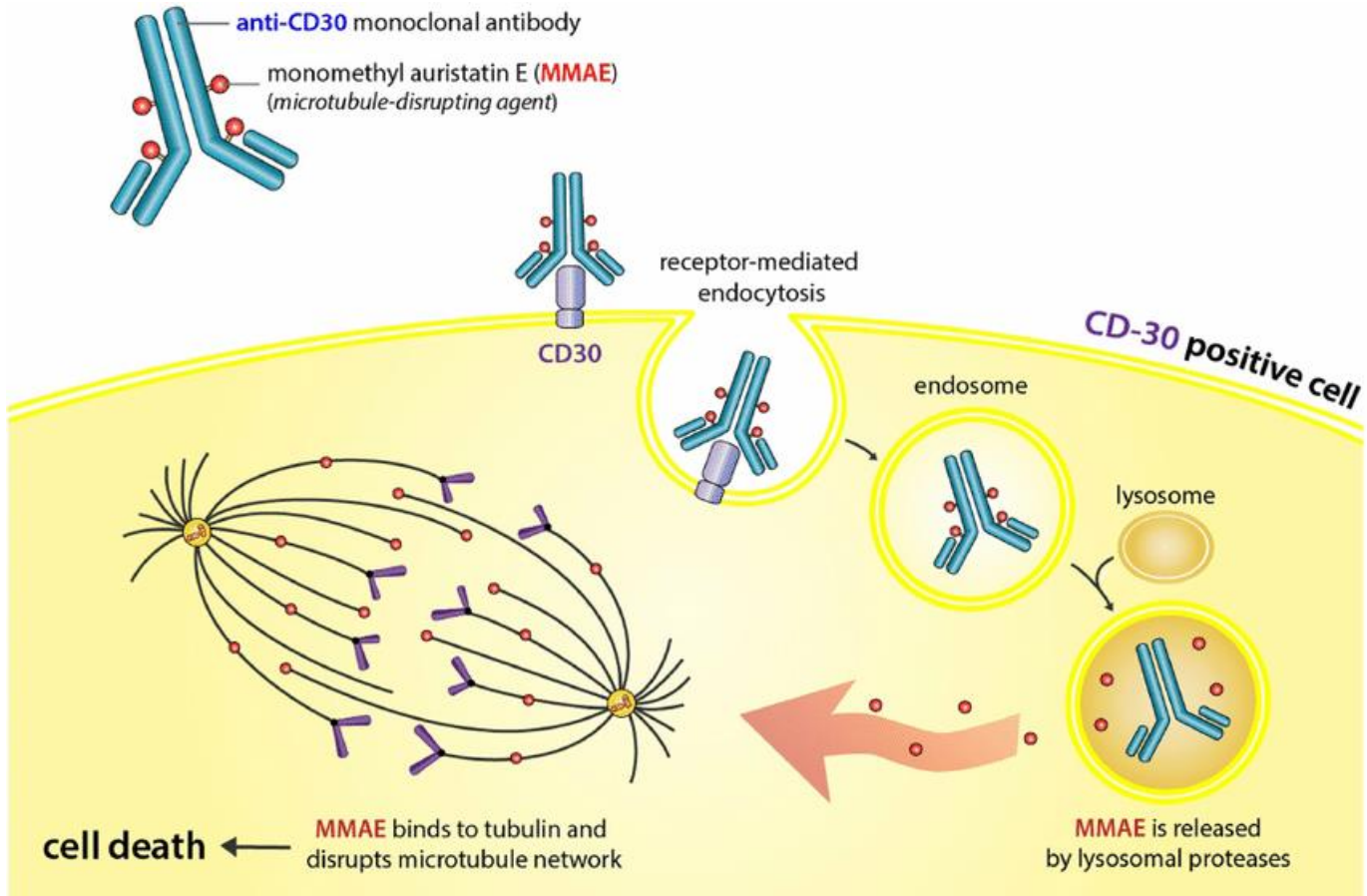
National Cancer Institute

Brentuximab Vedotin (SGN-35): CD30 Targeted Antibody-Drug Conjugate

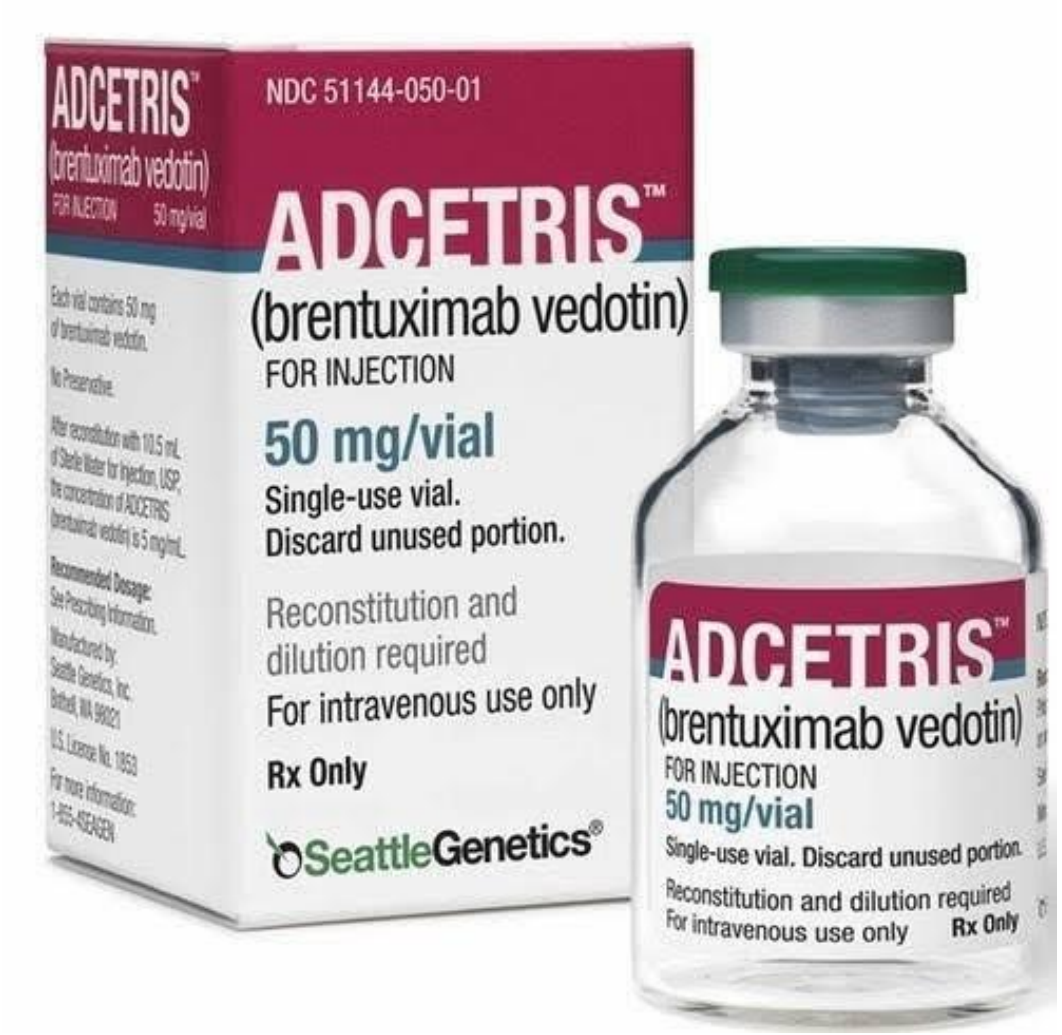


Auristatin derivative:
average of 4 molecules per antibody





Brentuximab vedotin (trade name Adcetris) is an antibody-drug conjugate medication used to treat relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL).



PRINCIPLES OF SYSTEMIC THERAPY
Treatment for Relapsed or Refractory Disease

- Consider the following when selecting re-induction or subsequent therapy:
  - Referral to a center with expertise given lack of data
  - Clinical trial enrollment
  - Primary therapy and prior RT exposure
  - Cumulative short- and long-term toxicity
  - Opportunity to harvest stem cells
  - Fertility preservation (option for some patients); refer to fertility clinic for further discussion when able prior to initiation of chemotherapy.
- Consider use of RT as part of therapy for relapsed/refractory disease.
- Additional options may be considered for patients over the age of 18, see NCCN Guidelines for Hodgkin Lymphoma.

Relapsed/Refractory Disease

	Re-Induction Therapy Options[b] (in alphabetical order)	Subsequent Therapy Options[d] (in alphabetical order)	Maintenance (post-transplant)
CHL	• Brentuximab vedotin + bendamustine[c,6] • Brentuximab vedotin + gemcitabine[c,7] • Brentuximab vedotin + nivolumab[c,8] • DHAP (dexamethasone, cytarabine, cisplatin) • GV (gemcitabine, vinorelbine)[c] • IEP-ABVD (ifosfamide, etoposide, prednisone; doxorubicin, bleomycin, vinblastine, dacarbazine)[9] • IGEV (ifosfamide, gemcitabine, vinorelbine)[10] • IV (Ifosfamide, vinorelbine)[11]	• Bortezomib, ifosfamide, + vinorelbine[12] • Nivolumab[c,e,13,14] • Pembrolizumab[c,e,f,15,16] • GDP (gemcitabine, dexamethasone, cisplatin)[17] • ICE (ifosfamide, carboplatin, etoposide)[18] • EPIC (etoposide, prednisolone, ifosfamide, cisplatin)[19]	Useful in certain circumstances, for select high-risk[g] patients: • Brentuximab vedotin[h,20]

References

[b] Reasonable to try multiple different re-induction regimens as needed prior to ASCR to minimize disease burden with a goal of achieving a metabolic CR prior to transplant.
[c] Should be considered in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function is observed.
[d] Subsequent therapy options include re-induction options that were not previously used.
[e] Emerging data are showing utility as a re-induction option; consider for subsequent therapy if not previously used.
[f] Pembrolizumab is indicated for the treatment of pediatric patients with refractory CHL, or who have relapsed after 2 or more prior lines of therapy.
[g] High-risk: any patient with progressive disease, refractory disease, or relapse within 1 year of original diagnosis.
[h] For relapsed CHL, brentuximab vedotin is indicated for the treatment of adult patients after failure of autologous hematopoietic stem cell transplant (HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates. It is not currently approved for pediatric patients.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2021
Hodgkin Lymphoma (Age ≥18 years)

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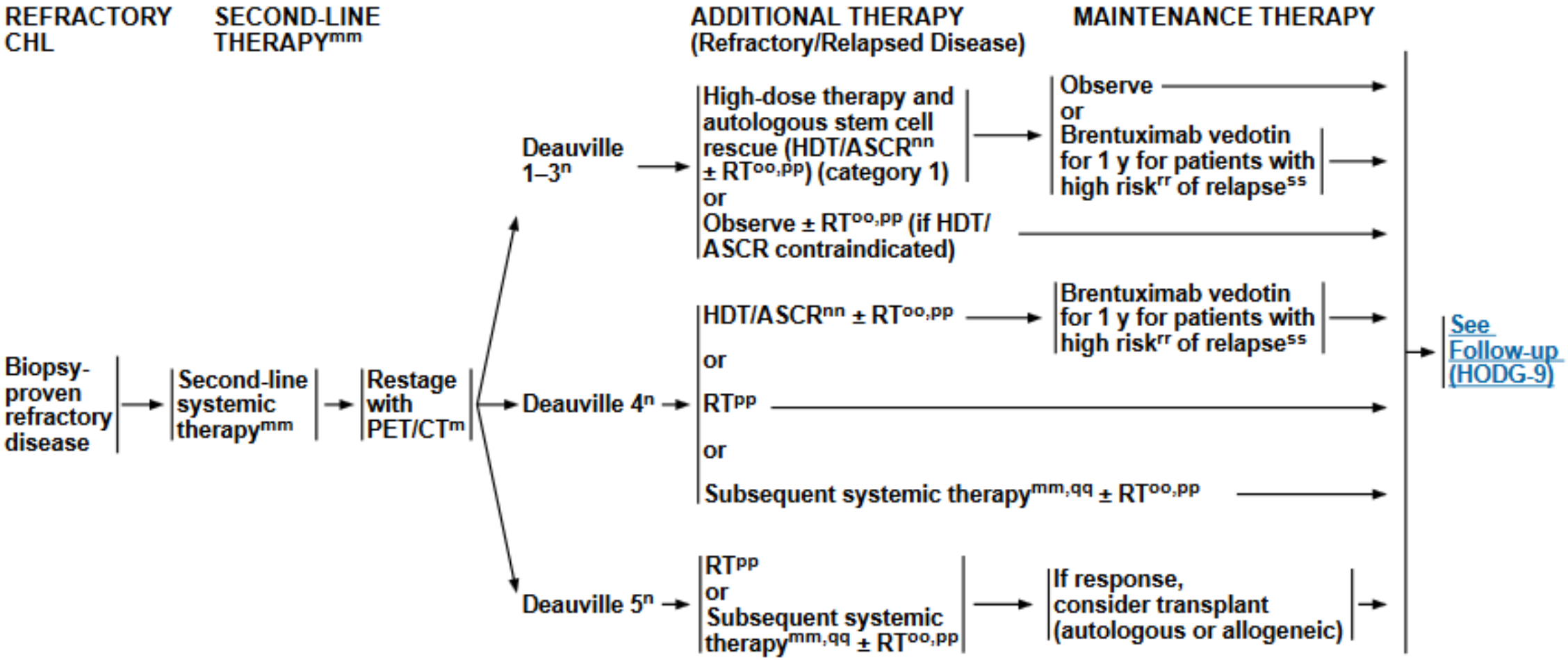


Immune Checkpoint Inhibitors

- However, except of the consolidation setting, 90–95% of the patients will progress and require further treatment.
- In this clinical setting, immune checkpoint inhibitors (CPIs) have produced impressive results.
- Both nivolumab and pembrolizumab have been approved for rr-cHL after autoSCT and BV failure
- while pembrolizumab has also been licensed for transplant ineligible patients after BV failure.

Immunotherapy in HD

- As a result of their success in heavily pretreated disease, BV and CPIs are moving to earlier lines of treatment.
- BV was recently licensed by the FDA for the first-line treatment of stage III/IV Hodgkin lymphoma (HL) in combination with AVD (only stage IV according to the European Medicines Agency (EMA)).
- CPIs are currently being evaluated in combination with AVD in phase II trials of first-line treatment.

Table 1. Approved indications of brentuximab vedotin, nivolumab, and pembrolizumab according to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

EMA: European Medicines Agency	FDA: US Food and Drug Administration
Brentuximab vedotin	
1. rr-cHL, CD30+ following	1. rr-cHL after failure of
1.1 autoSCT or	1.1 autoSCT or
1.2 ≥2 prior therapies, when autoSCT or multi-agent chemotherapy is not a treatment option	1.2 ≥2 prior multi-agent chemotherapy regimens in patients who are not autoSCT candidates
2. CD30+ HL at increased risk of relapse or progression following autoSCT	2. cHL at high risk of relapse or progression, as post autoSCT consolidation
3. Adult patients with previously untreated stage IV, CD30+ cHL, in combination with AVD *	3. Previously untreated stage III/IV cHL, in combination with AVD *
Nivolumab	
1. As monotherapy in adult patients with rr-cHL after autoSCT and treatment with BV	1. Adult patients with cHL that have relapsed or progressed after
	1.1 autoSCT and BV or
	1.2 ≥3 lines of systemic therapy that included autoSCT
Pembrolizumab	
1. As monotherapy in adult patients with rr-cHL	1. Adult and pediatric patients with refractory cHL, or who have relapsed after ≥3 prior lines of therapy
1.1 who have failed autoSCT and BV, or	
1.2 who are transplant-ineligible and have failed BV	

HL = Hodgkin lymphoma; cHL = classical Hodgkin lymphoma; rr-cHL = relapsed/refractory classical Hodgkin lymphoma; autoSCT = autologous stem cell transplantation; BV = brentuximab vedotin. * AVD = combination of doxorubicin, vinblastine, and dacarbazine.

Table 2. Summary of studies of brentuximab vedotin in chemorefractory, transplant-ineligible patients with relapsed/refractory classical Hodgkin lymphoma.

Patients' Characteristics and BV Efficacy Measures	UK-Wide [68]	Italian [69]	USA [70]	German [71]	Greek [58]	Italian [57]
Patients (#)	99	30	15	9	20	71
Age (median (range))	32 (13–70)	27 (NR)	31 (16–64)	36 (24–71)	27	24% > 60 y
ECOG PS ≥ 2	5%	NR	NR	44%	NR	0%
Previous lines of Tx (median(range))	2 (2–4)	2 (2–4)	2 (2–4)	3 (2–6)	3 (2–11)	NR
Salvage regimen	P/G	P/G/B	P	NR	NR	NR
Response to salvage regimen						
Refractory (SD + PD)	52% (15 + 37)	PET + in all pts	73% (60 + 13)	89%	75%	NR
PR	38%	PET + in all pts	27%	11%	20%	NR
CR	10%		0%		5%	NR
Time from last treatment to BV (months; median (range))	2.5 (0.7–34.8)	NR	NR	2 (1–22)	NR	NR
Response to BV						
ORR	56%	40%	NR	55%	NR	51%
CR	29%	30%	53%	33%	NR	25%
Subsequent autoSCT (or allo)						
Proceeded directly	34% *	47% †	80% §	44%	40% ¶	NR
Proceeded after further Tx	27%	13%	20%	0%	0%	NR
No SCT	39% **	40%	0%	55%	60% ¶	NR

PS = performance status; Tx = treatment; SD = stable disease; PD = progressive disease; PR = partial remission; CR = complete response; ORR = overall response rate; SCT = alloSCT = allogeneic stem cell transplantation; NR = not reported; P =platinum-based; G = Gemcitabine-based; B = BEACOPP. * Almost all had responded to BV; 2/3 had CR after BV; ** typically refractory to BV and subsequent therapy, if given; 26% achieved short-lived PRs of 3.6 months median duration; † including 14 patients; nine in CR and five refractory to BV, § including 12 patients; eight in CR and four refractory to BV; ¶ Among 8/20 patients who proceeded to autoSCT only three responded (all PR); among 12/20 who did not undergo SCT, two responded (CR and PR) but refused further therapy.

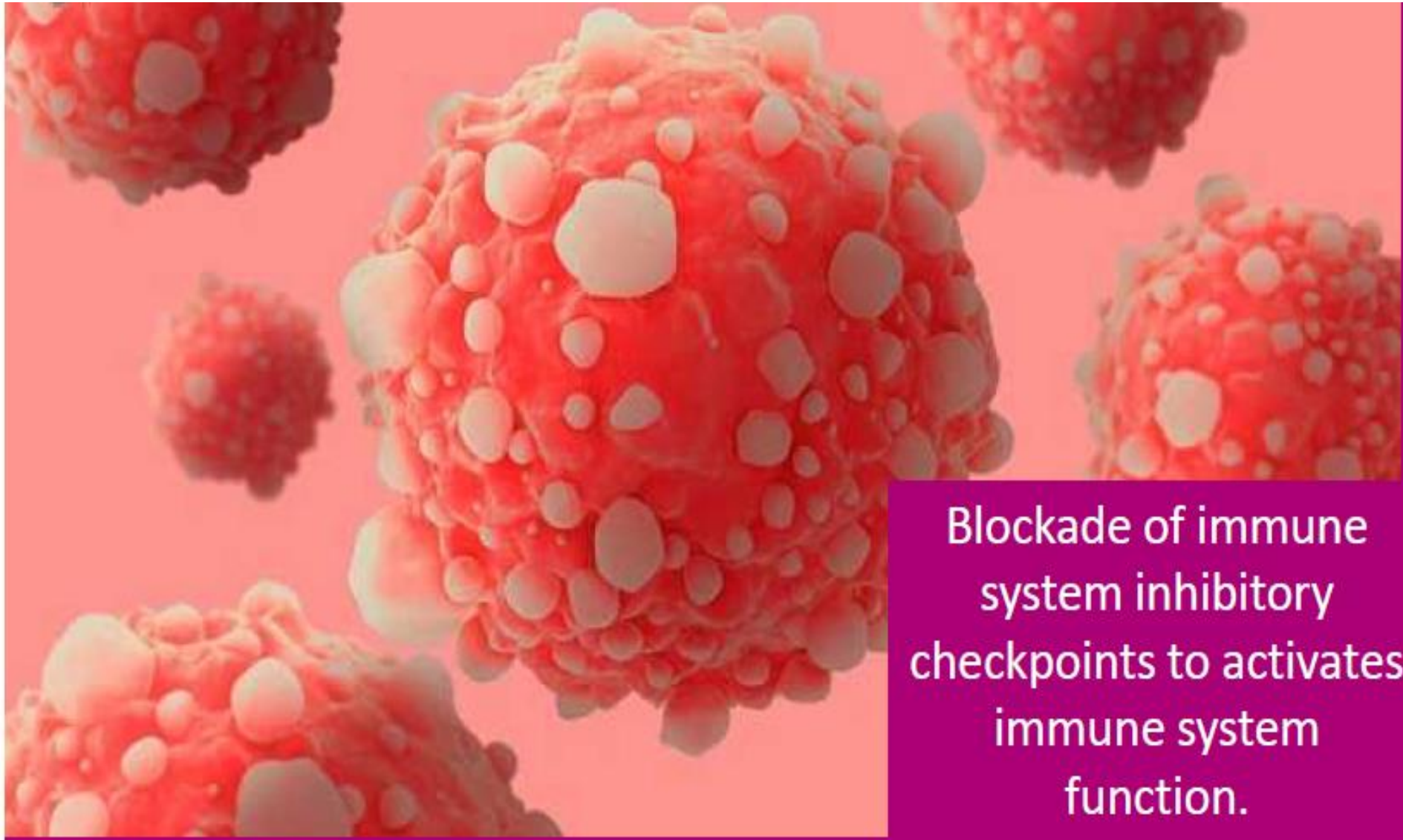
Immunotherapy in HD

- The impact of BV and CPIs was also investigated in the setting of second-line salvage therapy.
- Finally, combinations of targeted therapies are under evaluation.
- Based on these exciting results, it appears reasonable to predict that an improvement in survival and a potential increase in the cure rates of cHL will soon become evident.

Table 6. Summary of clinical trials combining brentuximab bedotin with salvage regimens (typically used to mobilize stem cells) prior to autoSCT either in sequential or concurrent design.

Author	Regimen	Pts (#)	Median Age (Range)	Primary Refractory (%)	BEACOPP (%)	CR Definition	ORR (%)	CMR (%)	ASCT Performed (%)	P(E)FS
Moskowitz AJ [92,93]	BV × 2 * plus AugICE if no CMR	45	31, (13–65)	56	7	D5PS 1–2	NR	27 to BV, 76 to both **	98 **	80% at 3 years
Moskowitz AJ [93]	BV × 3 * plus AugICE if no CMR	20	35, (19–59)	45	NR	D5PS 1-=2	NR	30 to BV, 80 to both	100	85% at 2 years
Chen R [94] & Herrera A [95]	BV × 2–4 § plus chemo if no CMR	37	34, (11–67)	65	5	Per Cheson 2007	68 to BV	35 to BV, 75 to both §§	92 §§§	72% at 2 years ¶¶
Herrera A [96]	BV × 4 ¶ plus additional Tx at phys's discretion	20	25, (15–57)	60	0	Per Cheson 2007	75 to BV	50 to BV, 70 to both	90, (18/20)	NR
Garcia-Sanz R [97]	BrESHAP × 3 + BV × 1 plus consBV × 3	66	36, (18–66)	61	3	Per Cheson 2007	91	70 ¶¶¶	91	71% at 2.5 years
Hagenbeek A [98]	BV–DHAP × 3	61	29, (19–71)	38, (no CR)	18	NR	87	79	87	76% at 2 years
Cassaday RD [99]	BV–ICE × 2 †	16	32, (23–60)	69, (no CR)	0	Per Cheson 2007	94	88	75	19% relapses at medfup 6.5 mo
LaCasce AS [100]	BV–Benda up to 6 plus cons BV up to 16	55	36, (19–79)	51, (no CR)	0	Per Cheson 2007	92	74	75 †	70% at 2 years †
Herrera A [102]	BV–Nivo	62	36, (18–69)	45	3	Per Lugano 2014	83	50 †††	89 †††	89% at 6 months

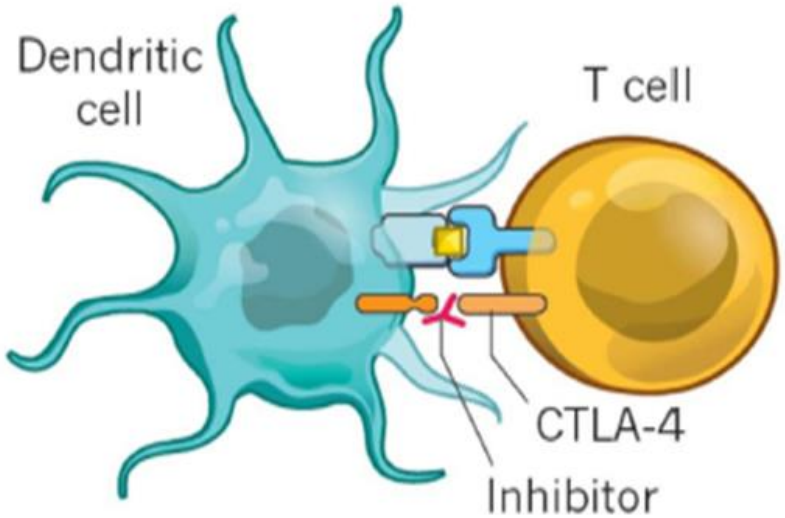
CR = Complete Remission; ORR = Overall Response Rate; CMR = Complete Metabolic Remission; ASCT = autologous stem cell tranaplantation; P(E)FS = Progression (Event) Free Survival. * BV 1.2 mg/kg on days 1, 8, 15 of each cycle; § Standard BV cycles 1.8 mg/kg every 21 days; ¶ Escalated to 2.4 mg/kg every 21 days if no CMR achieved with two standard 21 day cycles at 1.8 mg/kg; † BV 1.5 mg/kg on days 1 and 8 combined with ICE every 21 days. ** 80% (36/45) if D5PS score 3 considered as CR. A single patient LFU after a positive PET with BV × 2. ¶¶¶ 76% if D5PS score 3 considered as CR (similar outcomes for D5PS scores 3 and 2). ††† 60% if D5PS score 3 considered as CR. §§ Five additional patients were forwarded to autoSCT directly after BV with a positive PET (4 PR, 1 SD with IF-RT). §§§ Including two patients who received alloSCT for PR and SD after chemo. ¶¶ Only the 32/37 patients who received autoSCT were included (80% for those transplanted after BV only). ††† 42 patients proceeded to autoSCT after BV plus Nivo and 12 after additional salvage therapy. † PFS restricted to patients who received autoSCT (most after BV-Benda × 2). Several patients did not undergo autoSCT for willingness or logistic reasons despite being eligible.



Blockade of immune system inhibitory checkpoints to activates immune system function.

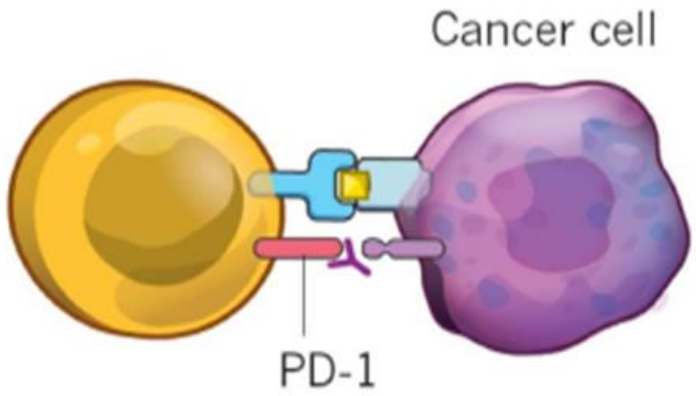
Immune checkpoint blockade

Immune checkpoints inhibitors



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

CTLA-4 blockade (e.g. Ipilimumab)



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

PD- (L)1 blockade (e.g. Nivolumab, pembrolizumab, Atezolizumab)

Immune Checkpoint Inhibitors

- Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), the first immune-checkpoint receptor to be targeted clinically, is expressed on the surface of activated T cells and transmits an inhibitory signal to T cells.

- CTLA-4 signaling is utilized by some tumor cells to evade T cell anti-tumor activity. Thus, CTLA-4 blockade potentiates effective immune responses against tumor cells

CTLA-4

- Preclinical data suggest that pediatric solid tumors have high expression of CTLA-4.
- In a panel of 34 adult and pediatric tumor cell lines, including osteosarcoma, hodgkin disease ,rhabdomyosarcoma, and neuroblastoma, CTLA-4 expression was found at different densities on 88% of the cell lines examined, with higher intensity of staining in osteosarcoma.
- In addition, 20 pediatric patients, 11 with osteosarcoma and 9 with Ewing sarcoma, had significantly increased expression of CTLA-4 on both CD4+ and CD8+ T cells obtained from peripheral blood samples compared to healthy controls .
- These findings indicate that targeting CTLA-4 may be useful in these pediatric tumor types.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(5 mg/mL)
NDC 0003-2327-11
Rx only
YERVOY™
(ipilimumab)
Injection
50 mg/10 mL
(5 mg/mL)
For Intravenous Infusion Only
Single-use vial; Discard unused portion
DISPENSE ENCLOSED MEDICATION GUIDE TO EACH PATIENT
Bristol-Myers Squibb

Ipilimumab FDA-Approved

- Ipilimumab is a mAb directed toward CTLA-4 signaling. Ipilimumab is FDA-approved for the treatment of adults and children with unresectable or metastatic melanoma.
- Recently, a phase I clinical trial (NCT01445379) included a total of 33 patients aged 2–21 years with recurrent or refractory solid tumors treated with CTLA-4 blockade.
- In this study, ipilimumab was well tolerated and resulted in increased activation of cytotoxic T lymphocyte without increased infiltration of Tregs; however, no objective tumor regression was observed

Phase I Clinical Trial of Ipilimumab in Pediatric Patients with Advanced Solid Tumors

Melinda S Merchant [1], Matthew Wright [2], Kristin Baird [2], Leonard H Wexler [3], Carlos Rodriguez-Galindo [4], Donna Bernstein [2], Cindy Delbrook [2], Maya Lodish [5], Rachel Bishop [6], Jedd D Wolchok [7], Howard Streicher [8], Crystal L Mackall [2]

Affiliations + expand

PMID: 26534966 PMCID: PMC5027962 DOI: 10.1158/1078-0432.CCR-15-0491

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Abstract

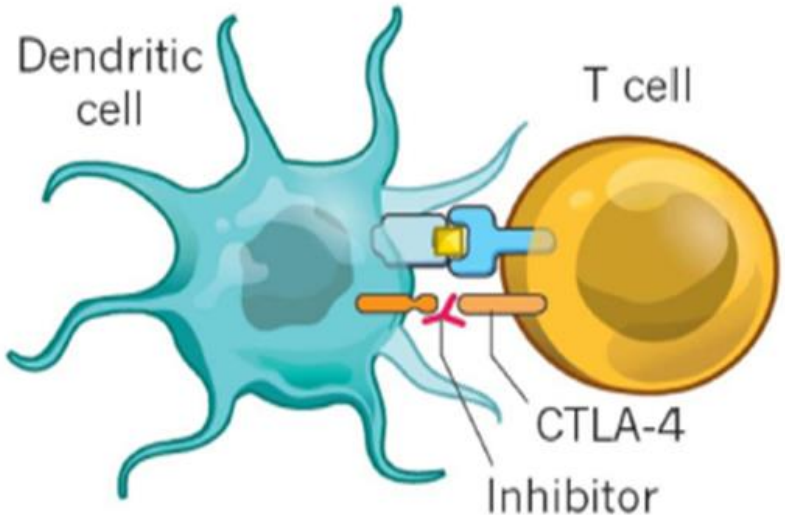
Purpose: Ipilimumab is a first-in-class immune checkpoint inhibitor approved for treatment of metastatic melanoma but not studied in children until this phase I protocol.

Experimental design: This study examined safety, pharmacokinetics, and immunogenicity, and immune correlates of ipilimumab administered to subjects ≤21 years old with recurrent or progressive solid tumors. Dose escalation cohorts received 1, 3, 5, or 10 mg/m(2) intravenously every 3 weeks in a 3 + 3 design. Response was assessed after 6 weeks and 12 weeks, and then every 3 months. Treatment was continued until disease progression or unacceptable toxicity.

Results: Thirty-three patients received 72 doses of ipilimumab. Patients enrolled had melanoma (n = 12), sarcoma (n = 17), or other refractory solid tumors (n = 4). Immune-related adverse events included pancreatitis, pneumonitis, colitis, endocrinopathies, and transaminitis with dose-limiting toxicities observed at 5 and 10 mg/kg dose levels. Pharmacokinetics revealed a half-life of 8 to 15 days. At day 21, subjects had increased levels of cycling T cells, but no change in regulatory T-cell populations. Six subjects had confirmed stable disease for 4 to 10 cycles (melanoma, osteosarcoma, clear cell sarcoma, and synovial sarcoma).

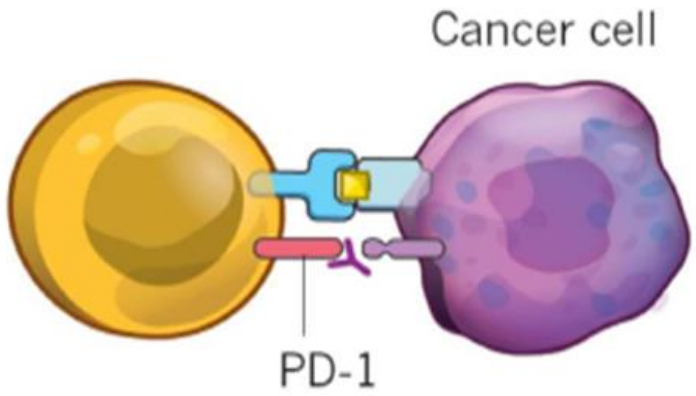
Conclusions: Ipilimumab was safely administered to pediatric patients using management algorithms for immune-related toxicities. The spectrum of immune-related adverse events is similar to those

Immune checkpoints inhibitors



The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

CTLA-4 blockade (e.g. Ipilimumab)



The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

PD- (L)1 blockade (e.g. Nivolumab, pembrolizumab, Atezolizumab)

Programmed Cell Death Receptor 1 (PD-1)

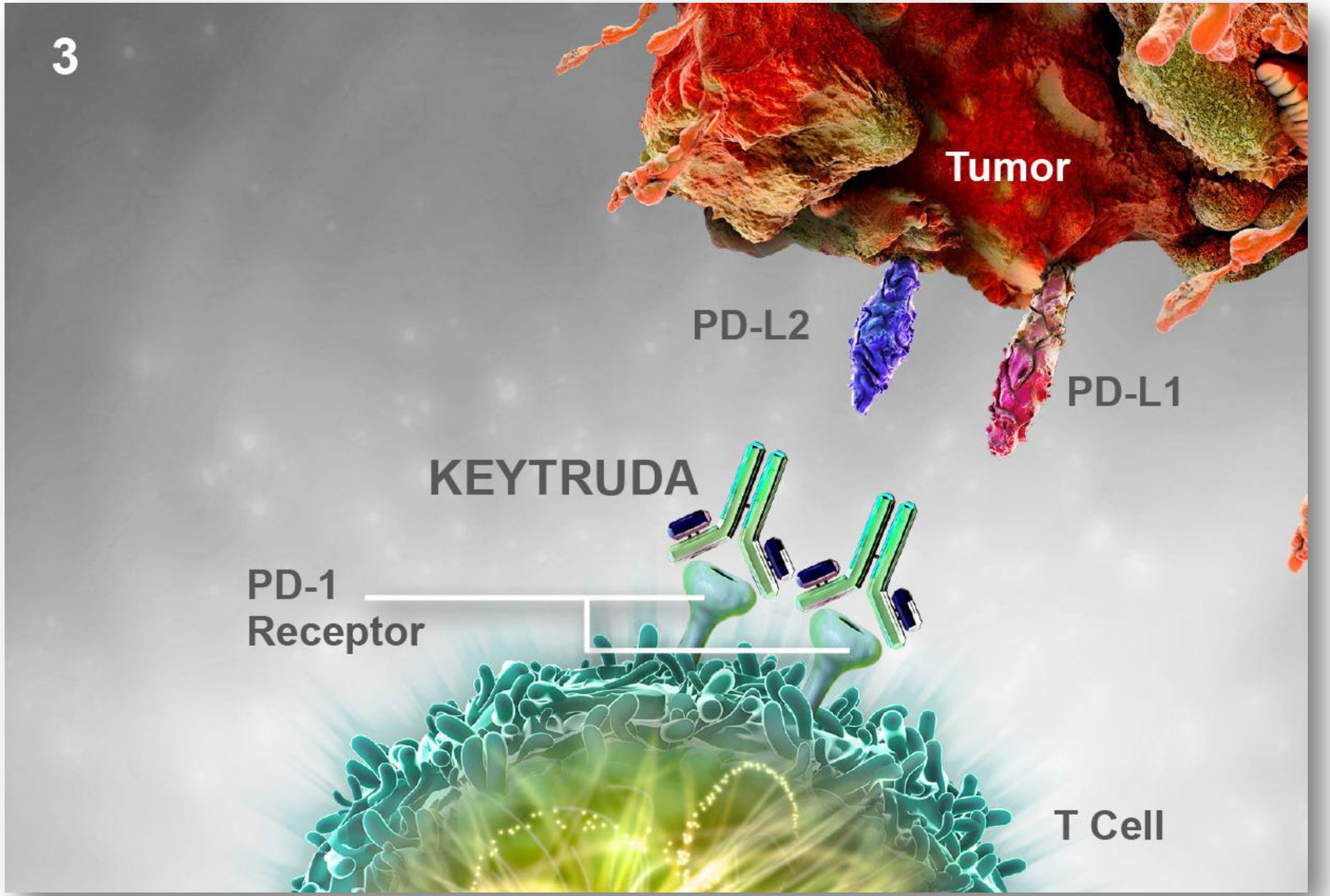
- PD-1 and its ligands (PD-L1 and PD-L2) are also part of the immune checkpoint pathway.
- PD-1 plays a role in downregulating T cell activation, which leads to tumor tolerance, while PD-Ls inhibit cytokine production and anti-tumor lymphocytes in the TME.
- PD-1 is also highly expressed on Tregs and, when engaged by its ligand, is thought to enhance the activity and proliferation of these cells
- Regulatory T cells (Tregs) are a specialized subpopulation of T cells that act to suppress immune response, thereby maintaining homeostasis and self-tolerance. It has been shown that Tregs are able to inhibit T cell proliferation and cytokine production and play a critical role in preventing autoimmunity.

Clinical studies of PD-1 and PD-L1

- Several preclinical studies examined the expression of PD-1 and PD-L1 in pediatric cancer subtypes, with conflicting results.
- Only 9% of 451 pediatric tumors expressed PD-L1 in at least 1% of tumor cells, with the highest expressors being Burkitt lymphoma (80%), glioblastoma multiforme (36%), and neuroblastoma (14%).
- Conversely, in another study of children with advanced melanoma, relapsed or refractory solid tumors, or lymphoma, 33% of 689 screened tumors were positive for PD-L1 expression .
- Of note, PD-L1 staining was associated with inferior survival among neuroblastoma patients ,and higher expression of PD-1 correlated with *disease progression in patients with osteosarcoma*

Anti-PD-1 antibody, FDA-approved

- Pembrolizumab, an anti-PD-1 antibody, is FDA-approved for the treatment of both adults and children with refractory Hodgkin's lymphoma.
- Nivolumab, another anti-PD-1 antibody, has shown responses in adult solid tumors. In pediatric solid tumors, these therapies remain under investigation.
- In five children aged 3–7 years with brain tumors treated with pembrolizumab, all progressed, and the median survival was 3.2 months .
- In a retrospective review of 10 children with recurrent or refractory brain tumors treated with nivolumab, 9 patients had radiographic disease progression. Three patients had partial response at the primary tumor site, of whom two had progression of metastatic disease


3
Tumor
PD-L2
PD-L1
KEYTRUDA
PD-1
Receptor
T Cell

Pembrolizumab

FDA approves pembrolizumab for adults and children with TMB-H solid tumors

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On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Today, the FDA also approved the FoundationOneCDx assay (Foundation Medicine, Inc.) as a companion diagnostic for pembrolizumab.

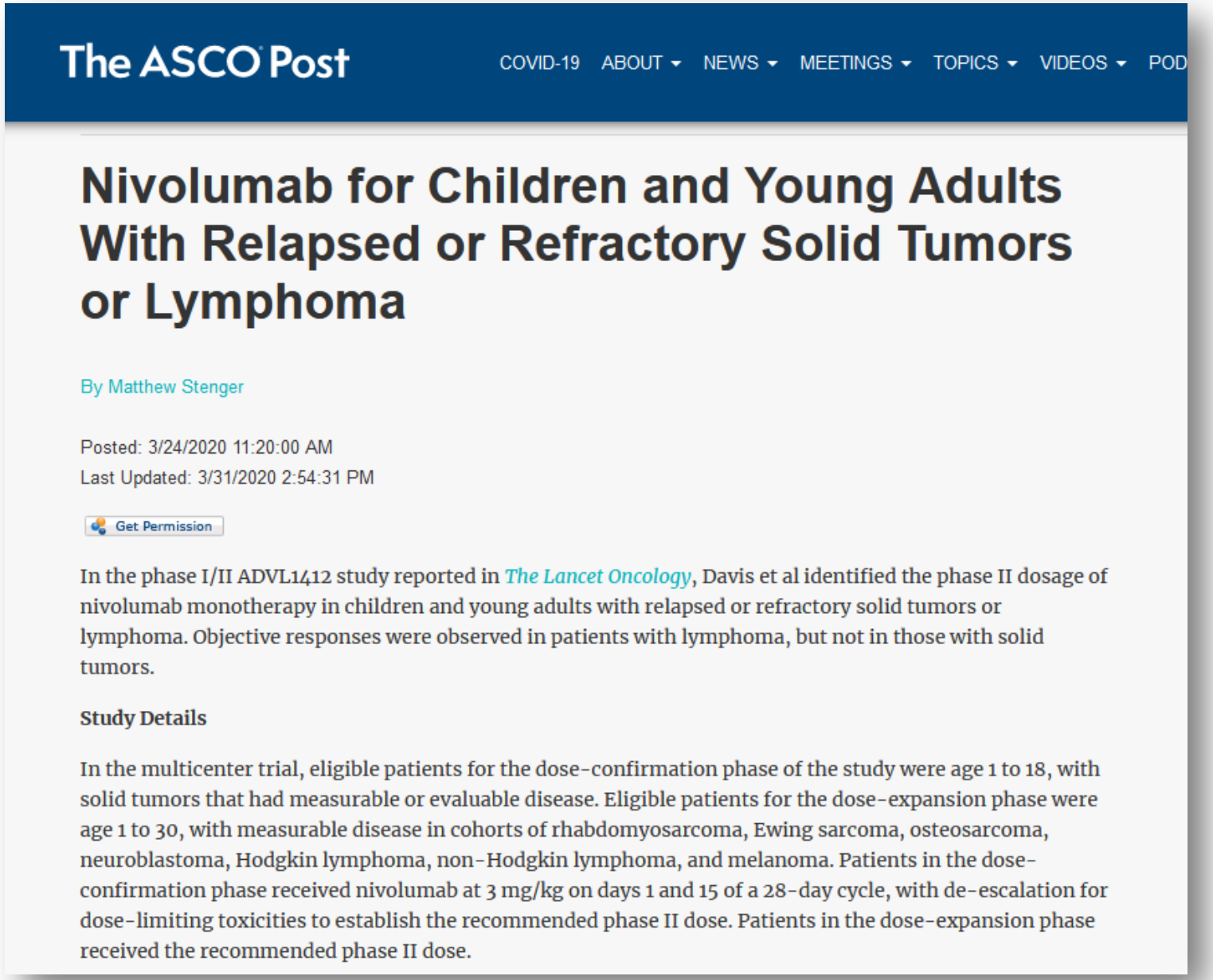
Efficacy was investigated in a prospectively-planned retrospective analysis of 10 cohorts of patients with various previously treated unresectable or metastatic TMB-H solid tumors enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression.

Nivolumab

- In other small studies of nivolumab treatment in pediatric brain tumor patients, results were mixed. Currently, a phase I/II trial (NCT03585465) is assessing nivolumab in combination with chemotherapy in pediatric patients with refractory/relapsing solid tumors or lymphoma.

Two other trials are evaluating nivolumab alone:

NCT02992964 is a pilot study of nivolumab in pediatric patients with refractory/recurrent hypermutated malignancies NCT02901145 is evaluating nivolumab in progressive/relapsed pediatric solid tumors, including osteosarcoma, Ewing sarcoma, neuroblastoma, NHL, and rhabdomyosarcoma.



The ASCO Post

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Nivolumab for Children and Young Adults With Relapsed or Refractory Solid Tumors or Lymphoma

By Matthew Stenger

Posted: 3/24/2020 11:20:00 AM
Last Updated: 3/31/2020 2:54:31 PM

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In the phase I/II ADVL1412 study reported in *The Lancet Oncology*, Davis et al identified the phase II dosage of nivolumab monotherapy in children and young adults with relapsed or refractory solid tumors or lymphoma. Objective responses were observed in patients with lymphoma, but not in those with solid tumors.

Study Details

In the multicenter trial, eligible patients for the dose-confirmation phase of the study were age 1 to 18, with solid tumors that had measurable or evaluable disease. Eligible patients for the dose-expansion phase were age 1 to 30, with measurable disease in cohorts of rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, neuroblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and melanoma. Patients in the dose-confirmation phase received nivolumab at 3 mg/kg on days 1 and 15 of a 28-day cycle, with de-escalation for dose-limiting toxicities to establish the recommended phase II dose. Patients in the dose-expansion phase received the recommended phase II dose.

KEY POINTS

Three mg/kg of nivolumab was confirmed as the pediatric recommended phase II dose.

Among all 75 evaluable patients, the most common overall toxicity was anemia (47%) and the most common nonhematologic toxicity was fatigue (37%).

Objective responses were observed in 3 of 10 patients with Hodgkin lymphoma and 1 of 10 patients with non-Hodgkin lymphoma, with all responders having programmed cell death ligand 1–positive disease.

No objective responses were observed in other tumor types.

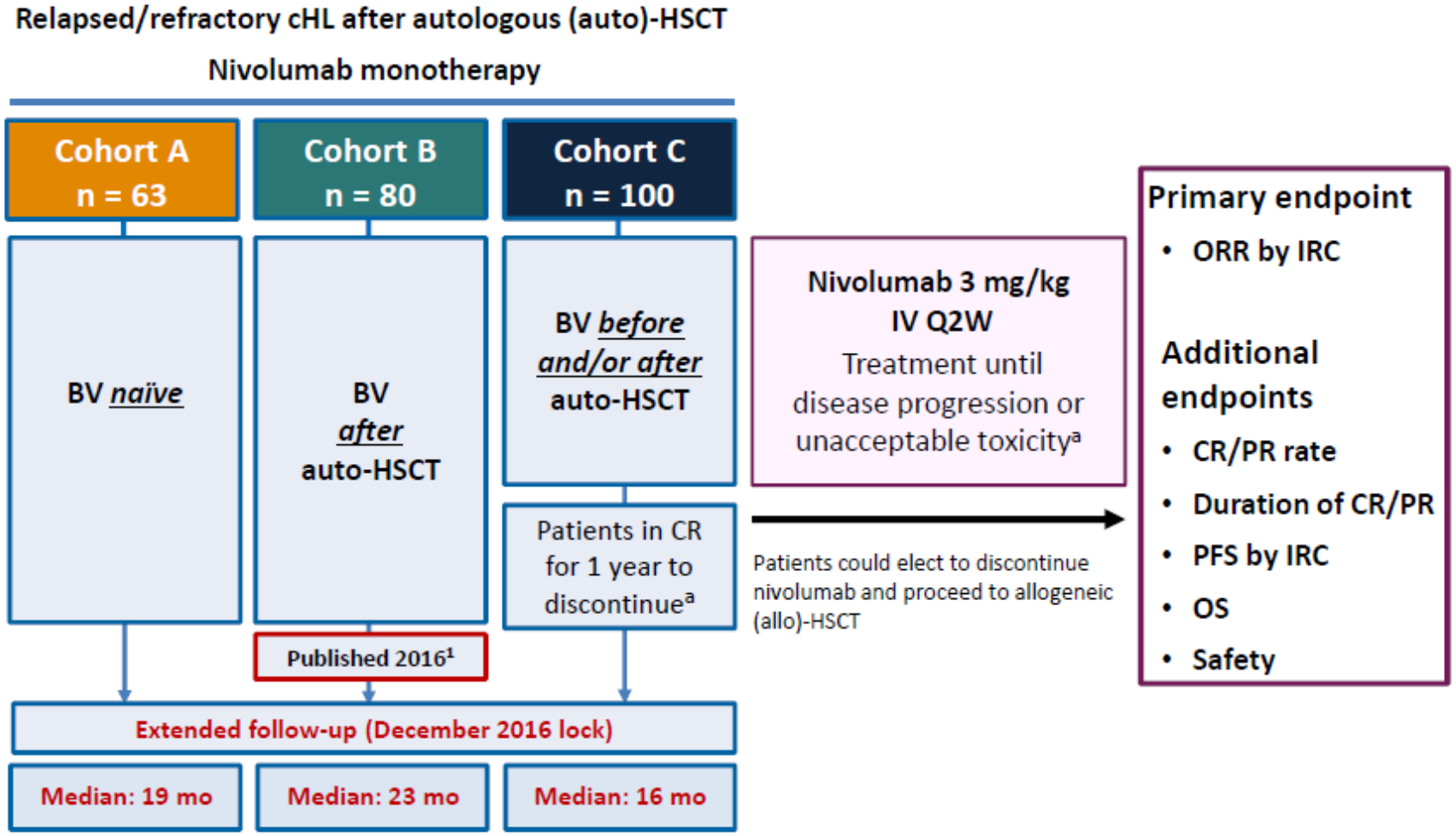
Dual checkpoint blockade

- Dual checkpoint blockade is hypothesized to prevent immune escape and may be promising in the treatment of pediatric solid tumors. Combinations of CTLA-4 and PD-1 antibodies are currently being investigated

Results of PD1 Blocking Antibodies in Relapsed HL: Phase-I Studies

Drug	Dose/ Schedule	N	% ORR	% CR	ORR in BV treated HL	1st Author
Pembrolizumab (humanized IgG4)	10 mg/kg IV Q 2 wks	29	66%	21%	66% (n =1 9)	Armand P. JCO 2016
Nivolumab (fully human IgG4)	3 mg/kg IV Q 2 wks	23	87%	17%	70% (n = 16)	Ansell S. NEJM 2015

Phase 2 CheckMate 205 Study Design

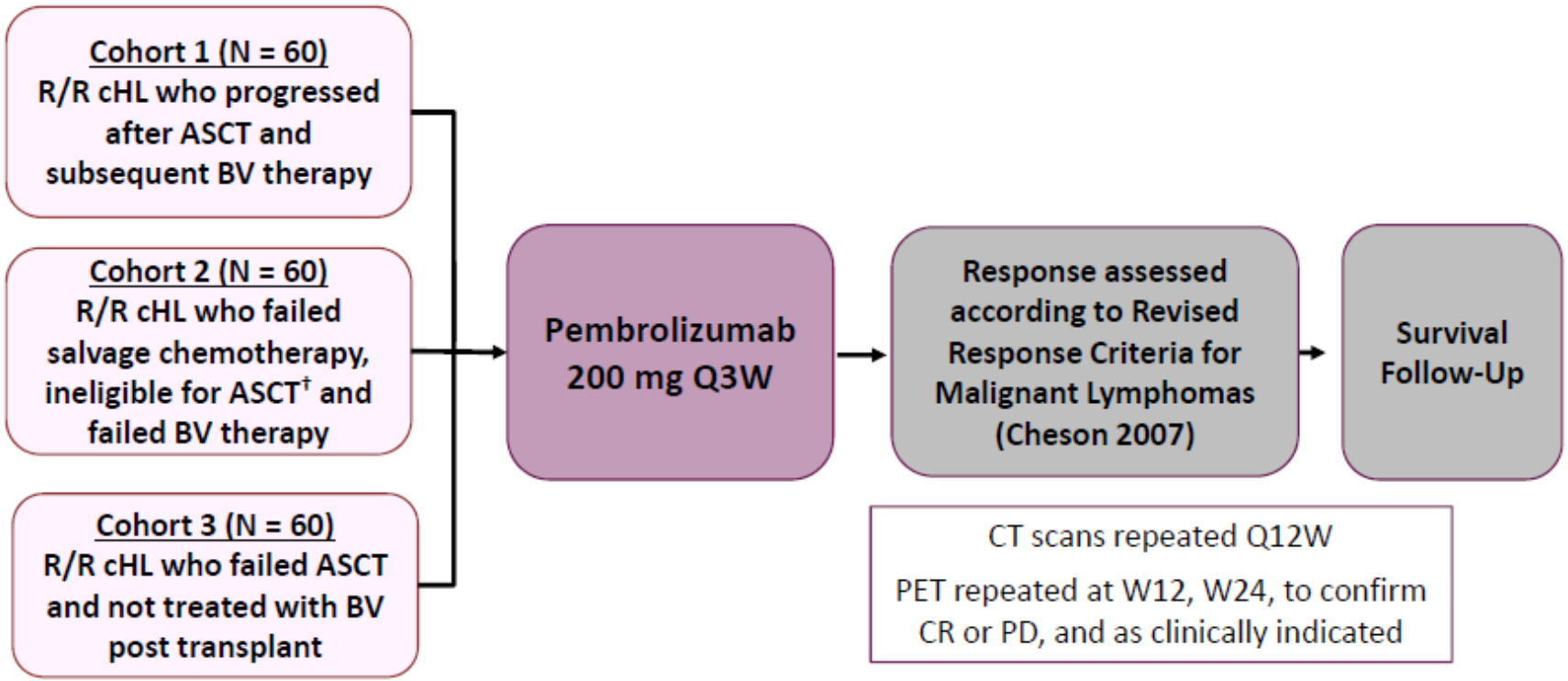


[a]Could restart treatment if relapse within 2 years.

BV=brentuximab vedotin; CR=complete remission; IRC=Independent Radiology Review Committee; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PR=partial remission; Q2W=every 2 weeks

[1]Younes A, et al. *Lancet Oncol.* 2016;17(9):1283-1294.

Pembrolizumab: KEYNOTE-087 Study Design



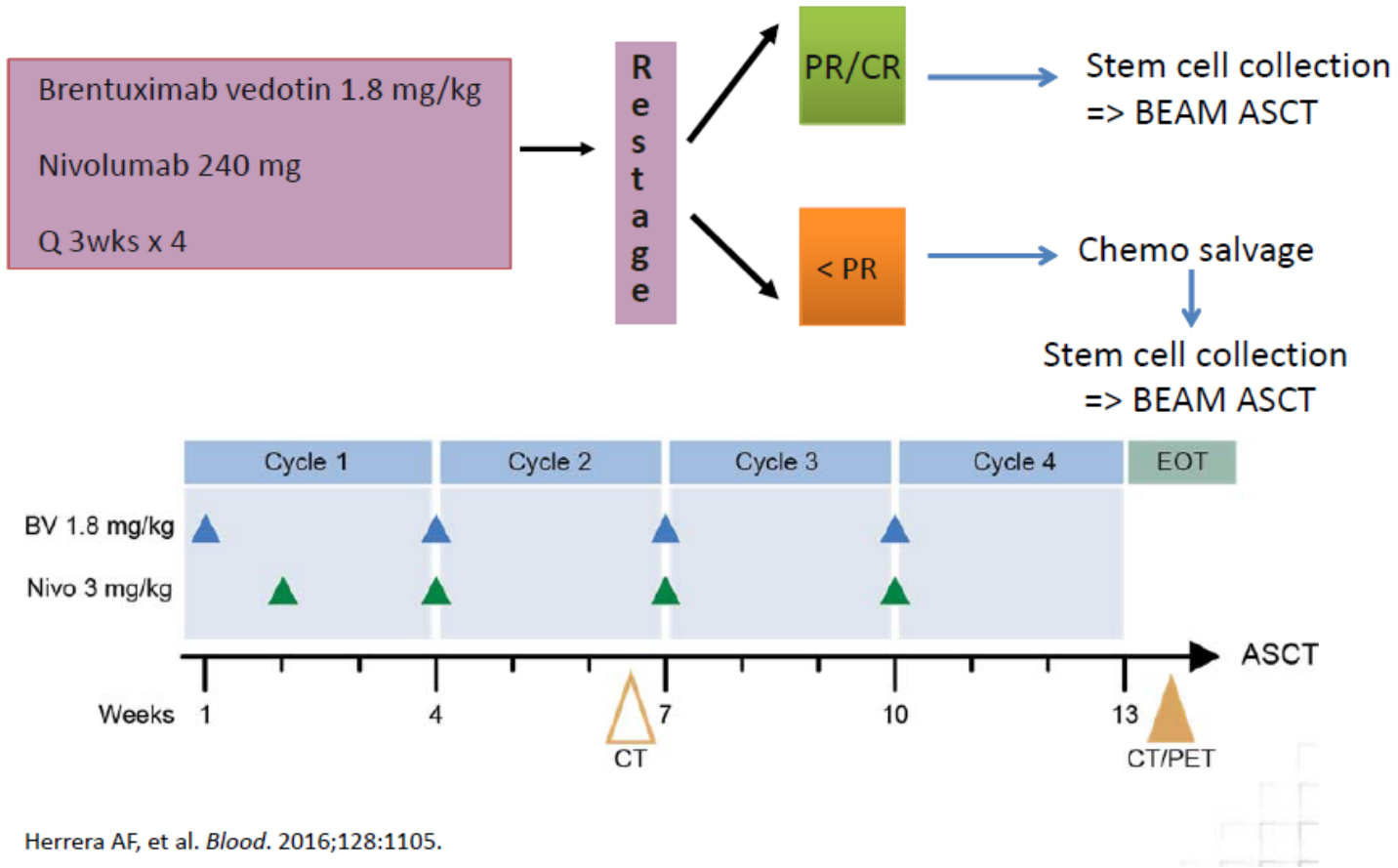
- **Primary endpoint:** ORR (central review)
- **Secondary endpoints:** ORR (investigator review), PFS, OS
- Prespecified interim analysis, based on investigator-assessed response, performed after 30 patients in all three cohorts reached first response assessment

†Unable to achieve a CR or PR to salvage chemotherapy

ClinicalTrials.gov Identifier: NCT02453594.

Moskowitz C, et al. *Blood*. 2016;128:1107.

Nivolumab + Brentuximab Salvage Therapy for HL

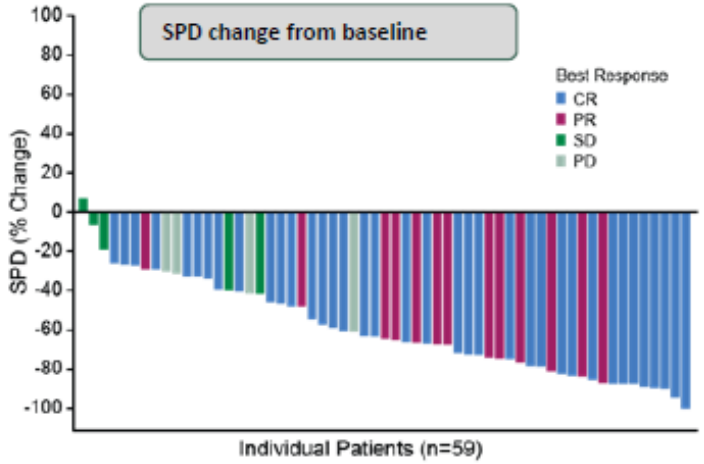


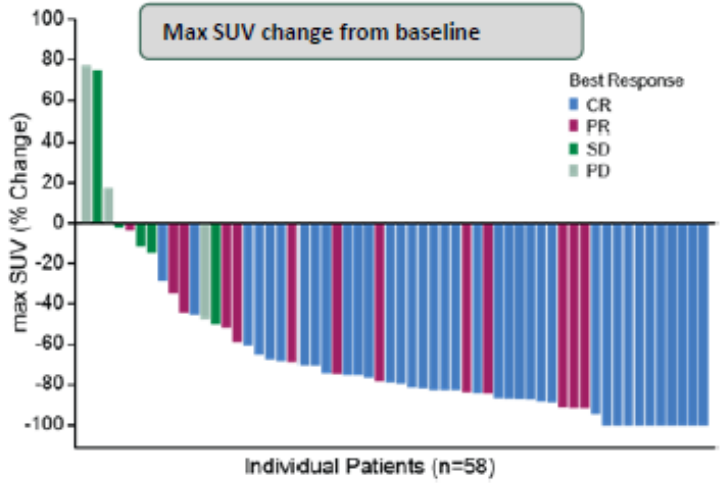
Herrera AF, et al. *Blood*. 2016;128:1105.

In this trial, patients were treated with four doses of these two drugs, and if you respond, you can go to autologous transplant. This trial can give you an idea about the response rate but unfortunately, does not give you an idea about the median time to progression because patients who responded were then offered autologous transplant ,but regardless, the data was very impressive.

Tumor Response (N=59)

85% objective response rate with 63% complete responses





	N = 59 n (%)
Complete response (CR)	**37 (63)**
Deauville ≤2	29 (49)
Deauville 3	7 (12)
Deauville 5[a]	1 (2)
Partial response (PR)	**13 (22)**
Deauville 4	7 (12)
Deauville 5	6 (10)
No metabolic response (SD)	**5 (8)**
Deauville 5	5 (8)
Progressive disease (PD)	**3 (5)**
Deauville 5	2 (3)
Missing	1 (2)
Clinical Progression (CP)	**1 (2)**

[a]One patient had uptake in lymph node, but no evidence of disease was found on biopsy

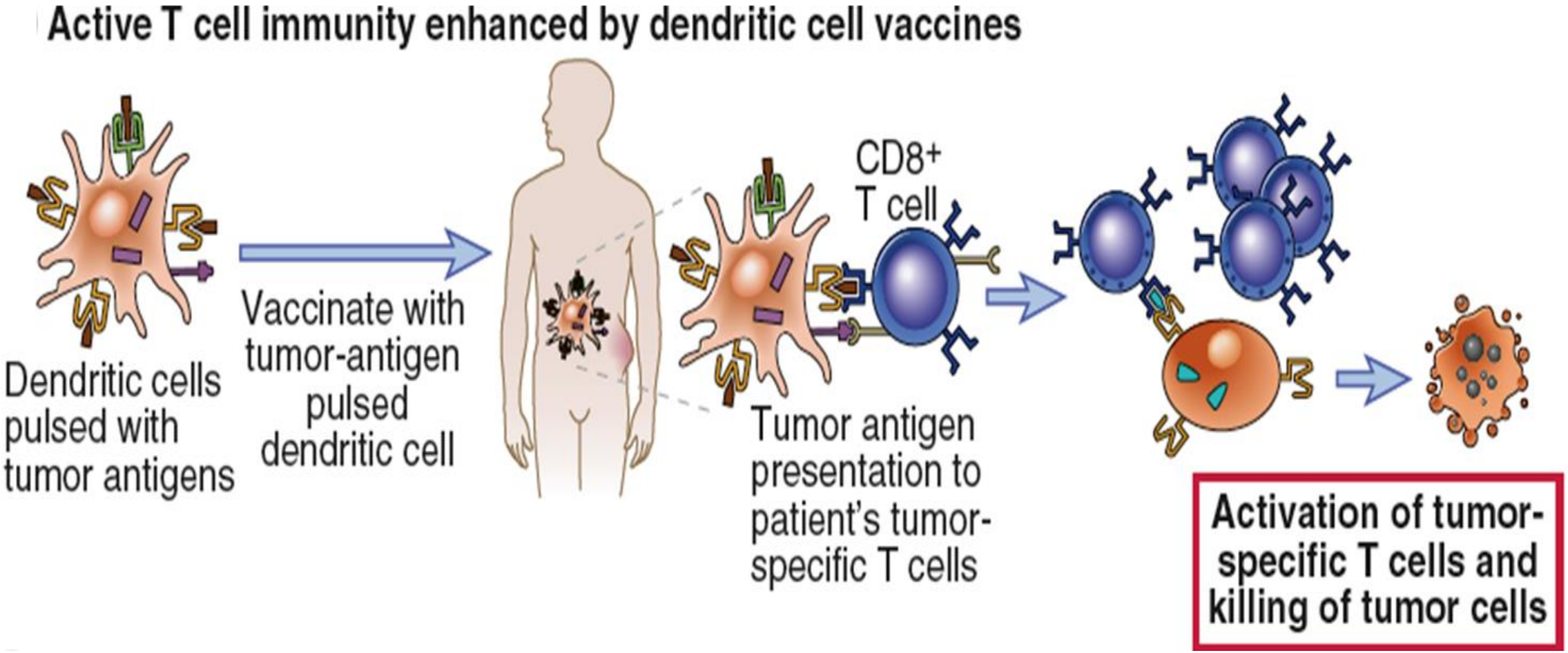
SPD=sum of the product of the diameters; SUV=standard uptake value

Herrera AF, et al. *Blood*. 2018;131(11):1183-1194.

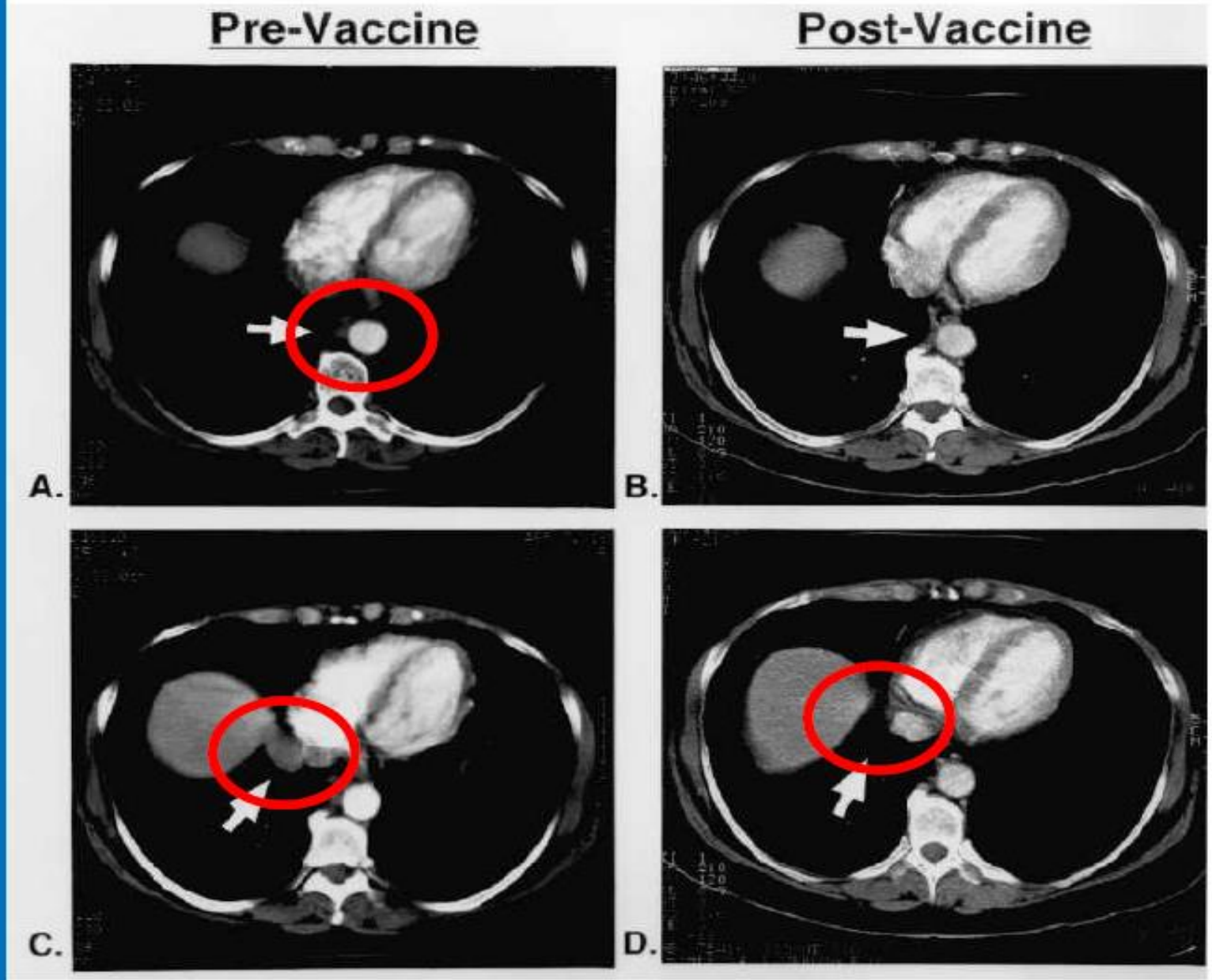
incorporated into the first-line therapy

- Finally, BV is gradually being incorporated into the first-line therapy of cHL with improvements in disease control and potentially OS at least in subgroups of patients with advanced disease, while similar applications of nivolumab and pembrolizumab appear promising.

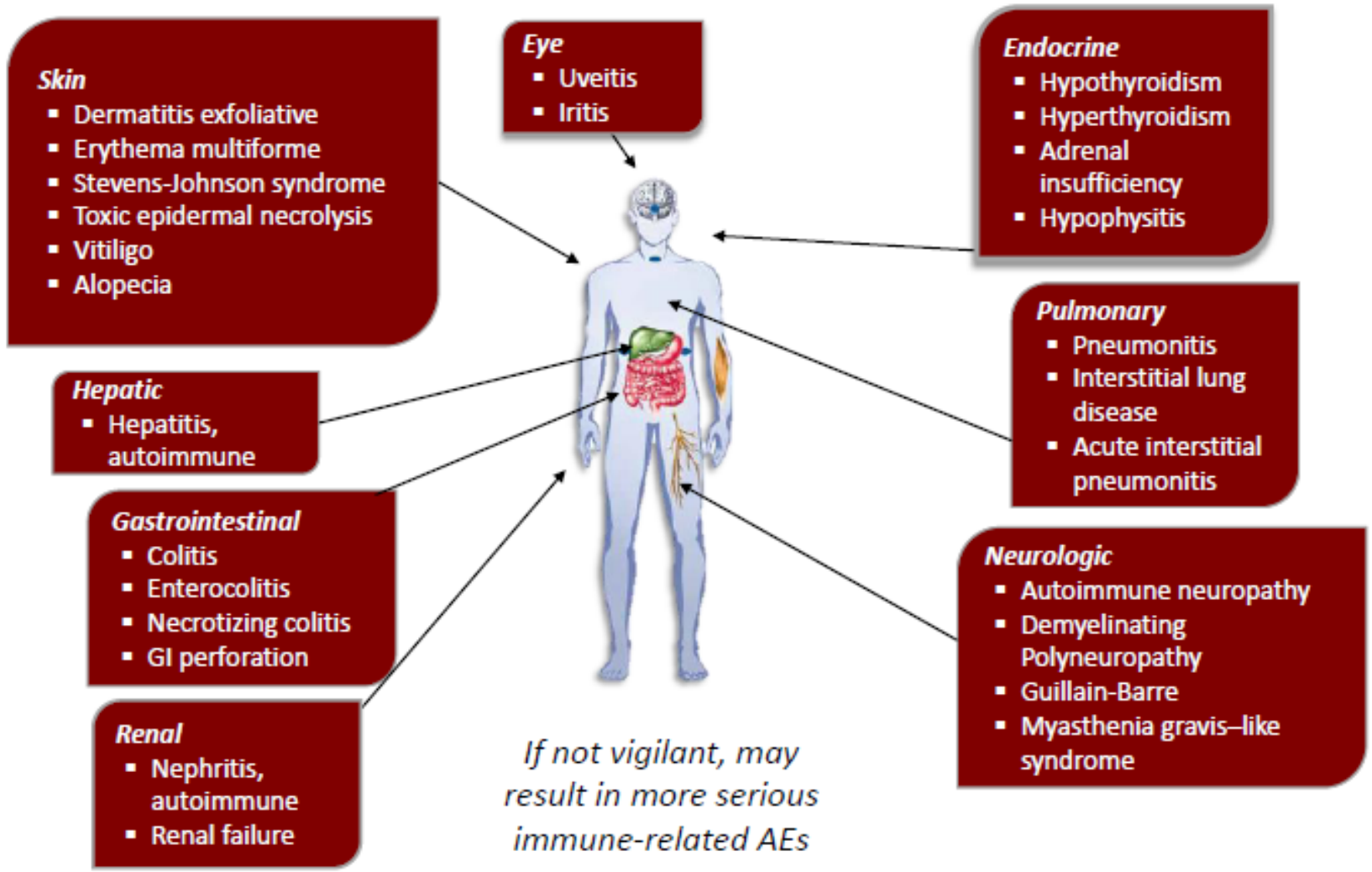
Dendritic cell vaccination



Clinical response to dendritic cell vaccination in a patient with non-Hodgkin.s lymphoma. Prevaccine CT scan images demonstrate **(a)** *periaortic lymph nodes and* **(c)** *a paracardial mass.* ***(b) and (d)*** *demonstrate complete resolution of tumors 10 months following* vaccination with dendritic cells.



Immune-Related AEs With Immunotherapy



Most Common Treatment-Related Adverse Events with PD-I Inhibitors in cHL

Common Therapy-Related Grade 1-2 occurring in 10% to 15%	Most Common Grade 3 or greater
Fatigue	Neutropenia
Infusion reaction	Dyspnea
Rash	Diarrhea
Thrombocytopenia	Pancreatitis
Hypothyroidism	
Fever	
Diarrhea	
Immune Related Adverse Events	
Pneumonitis	
Colitis	
Hepatitis	
Hypophysitis	

Younes A, et al. *Lancet Oncol.* 2016;17(9):1283-1294.
Chen R, et al. *J Clin Oncol.* 2017; 35:2125-2132.

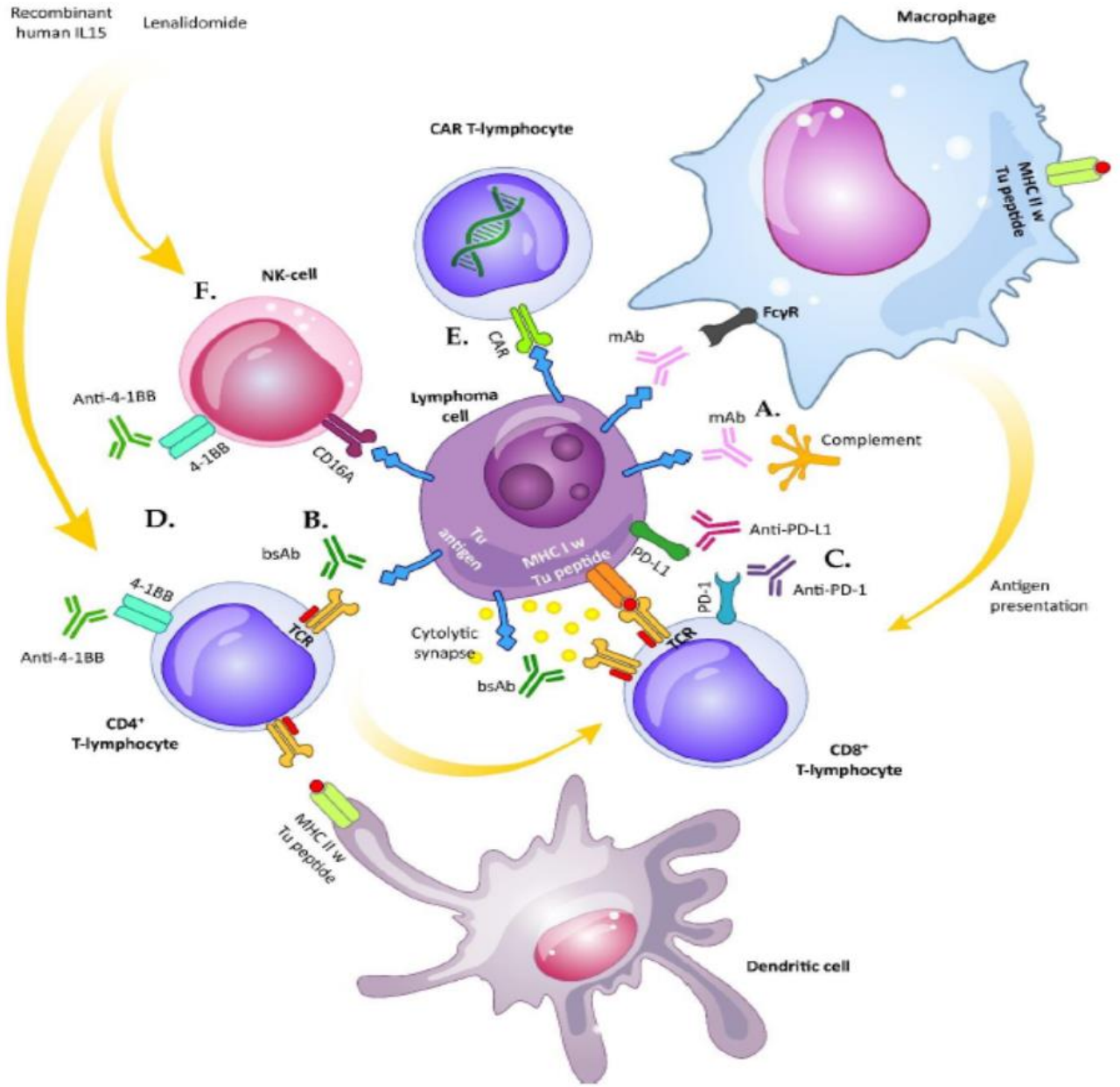
Keys to Optimal Pt Management

- Education of healthcare team, pts, and caregivers
- Rapid and timely intervention
  - Corticosteroids for some intolerable grade 2 irAEs and any grade 3/4 irAEs
  - SLOW taper of glucocorticoids
- Reinitiation of treatment may be possible

This goal is attainable through communication between all members of the healthcare team and pts

Overview of immunotherapy approaches in non-Hodgkin lymphomas

- Monoclonal antibodies (A)
- Bispecific antibodies (B)
- Checkpoint inhibitors (PD-1, PD-L1) (C)
- Activators of co-stimulatory molecules (D)
- CARs (E)
- immunomodulation (F)



Bispecific Antibodies

- Bispecific antibodies, unlike normal antibodies, elicit a cytotoxic T cell response against a specific tumor target. The Bispecific T Engager (BiTE) technology activates a T cell response by binding to CD3 on T cells .The molecule combines the CD3 binding site with a second site that is tumor-specific.
- BiTE directly targets the cancer and limits damage to non-malignant tissue .The direct activation of cytotoxic T cells limits the need for other anti-cancer interventions. Currently, clinical trials with BiTE antibodies are limited to just two TAA: CD19 and EpCAM.

Blincyto (blinatumomab) is a medicine for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia . Blinatumomab targets CD19 and CD3

Blinatumomab was the first approved canonical BiTE molecule and targets CD19 surface antigens on B cells, making blinatumomab largely independent of genetic alterations or intracellular escape mechanisms.

Additional BiTE molecules in development target other hematologic malignancies (eg, multiple myeloma, acute myeloid leukemia, and ***B-cell non-Hodgkin lymphoma***) and solid tumors (eg, prostate cancer, glioblastoma, gastric cancer, and small-cell lung cancer).

Blinatumomab

- Of the two, only anti-CD19 (blinatumomab) has been investigated in children and it has been limited to hematologic malignancies.
- Blinatumomab was administered to children with relapsed/refractory ALL. In this phase I/II study, 39% of the children that received the determined dosage and treatment plan achieved a minimal residual disease response.
- Elitzur and colleagues reported 11 pediatric patients with ALL who were treated with blinatumomab as a bridge to further therapy after suffering from severe chemotherapy toxicities.
- All 11 children went on to resume standard chemotherapy with an overall survival of 80% . Further preclinical studies and clinical trials with other TAA for BiTE antibodies will be required before this promising technology may be translated for clinical use in the treatment of pediatric solid tumors.

Table 1. Selected clinical trials that incorporate blinatumomab in experimental therapy of B-NHL.

Drug Combination	Target Antigens	Mode of Action of the Combination Agent(s) Other Than Bispecific Antibody	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
blinatumomab	CD19/CD3		2	R/R indolent B-NHL	December 2023	NCT02811679
blinatumomab	CD19/CD3		1	R/R indolent B-NHL	May 2022	NCT02961881
blinatumomab	CD19/CD3		1	DLBCL after ASCT	December 2023	NCT03072771
blinatumomab + lenalidomide	CD19/CD3	immunomodulatory agent lenalidomide	1	R/R B-NHL	December 2020	NCT02568553
blinatumomab + pembrolizumab	CD19/CD3	immune check-point PD-1 inhibitor pembrolizumab	1	R/R DLBCL	January 2026	NCT03340766 (KEYNOTE-348)

Abbreviations: ASCT= autologous stem cell transplantation; DLBCL= diffuse large B-cell lymphoma; PD-1= programmed death 1; R/R= relapsed/refractory; B-NHL= B cell non-Hodgkin lymphomas.

Table 2. Selected clinical trials that incorporate mosunetuzumab in experimental therapy of B-NHL.

Drug Combination	Target Antigens	Mode of Action of the Combination Agent(s) Other Than Bispecific Antibody	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
Mosunetuzumab ± atezolizumab	CD20/CD3	immune check-point PD-L1 inhibitor atezolizumab	1	R/R B-NHL and CLL	October 2021	NCT02500407
Mosunetuzumab + polatuzumab vedotin compared to bendamustine + rituxumab + polatuzumab vedotin	CD20/CD3	anti-CD79B antibody-drug conjugate polatuzumab-vedotin, anti-CD20 rituximab, new cytostatic agent bendamustine	1B/2	R/R DLBCL and R/R FL	June 2022	NCT03671018
Mosunetuzumab + lenalidomide, glofitamab + lenalidomide or glofitamab + lenalidomide + obinutuzumab	CD20/CD3	immunomodulatory agent lenalidomide, glycoengeneered anti-CD20 mAb obinutuzumab	1	newly dg DLBCL, R/R DLBCL and R/R FL	August 2022	NCT04246086
Mosunetuzumab + CHOP or mosunetuzumab + polatuzumab vedotin + CHP	CD20/CD3	chemotherapy CHOP, anti-CD79B antibody drug conjugate polatuzumab-vedotin	1B/2	newly dg DLBCL, R/R B-NHL	June 2022	NCT03677141
Mosunetuzumab	CD20/CD3		1B/2	newly dg DLBCL	April 2023	NCT03677154
Mosunetuzumab or Glofitamab + GemOx	CD20/CD3	chemotherapy gemcitabine and oxaliplatin (GemOx)	1	R/R DLBCL	March 2021	NCT04313608

Abbreviations: CHOP= cyclophosphamide + doxorubicin + vincristine + prednisone; CLL= chronic lymphocytic leukemia; DLBCL= diffuse large B-cell lymphoma; FL= follicular lymphoma; PD-L1= programmed death ligand 1; R/R= relapsed/refractory; B-NHL= B cell non-Hodgkin lymphomas.

Immune Checkpoint Inhibitors

- The role of immune checkpoint inhibitors in eradicating minimal residual disease or circulating tumor DNA in both Hodgkin lymphoma and non-Hodgkin lymphoma being investigated.
- There are trials combining that with R-CHOP for example and G-bendamustine for non-Hodgkin low-grade B-cell lymphoma, plus maintenance strategies looking at the effect of these agents on circulating tumor DNA in both Hodgkin and non-Hodgkin lymphomas and also in solid tumors.

Table 5. Selected checkpoint inhibitors currently being evaluated in patients with NHL.

Name	Trade Name	Developed by	Structure	Target	First Approval by US FDA for the Treatment of Cancer	Number of Studies in Patients with NHL Registered at ClinicalTrials.gov
Ipilimumab	Yervoy	Bristol-Myers-Squibb	human IgG1	CTLA-4	2011	13
Tremelimumab	N/A	AstraZeneca	human IgG2	CTLA-4	N/A	3
Pembrolizumab	Keytruda	Merck	humanized IgG4	PD-1	2014	60
Nivolumab	Opdivo	Bristol-Myers-Squibb	human IgG4	PD-1	2014	41
Pidilizumab	N/A	Medivation	human IgG1	PD-1	N/A	3
Durvalumab	Imfinzi	AstraZeneca	human IgG1	PD-L1	2020	19
Avelumab	Bavencio	Merck, Pfizer	human IgG1	PD-L1	2017	9
Atezolizumab	Tenetriq	Roche	humanized IgG1	PD-L1	2016	20

N/A—not applicable.

Table 6. Selected clinical trials that incorporate immune checkpoint inhibitors in experimental therapy of NHL.

Drug Combination	Mode of Action of the Combination Agent(s) Other Than Immune Checkpoint Inhibitors	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
Nivolumab + R(ituximab)-GemOx compared to R-GemOx	immunochemotherapy gemcitabine + oxaliplatin (GemOx)	2/3	R/R elderly B-NHL	November 2024	NCT03366272 (NIVEAU)
Avelumab +/− Utomilumab +/− Rituximab +/− Azacitidine +/− bendamustin +/− Gemcitabine +/− Oxaliplatine	CD137 (4-1BB) antigen agonist antibody utomilumab, anti-CD20 antibody rituximab, epigenetic modulator azacitidine, conventinal chemotherapy GemOx	1/3	R/R DLBCL	December 2019	NCT02951156 (JAVELIN DLBCL)
Nivolumab + DA-EPOCH-R + Nivolumab as a consolidation	immunochemotherapy regimen (dose-adjusted EPOCH-R)	2	B-NHL	December 2021	NCT03749018
Nivolumab + Copanlisib	pan-PI3K inhibitor copanlisib	2	R/R DLBCL, PMBCL	October 2021	NCT03484819
Pembrolizumab		2	untreated B-NHL	September 2024	NCT03498612
Pembrolizumab		2	R/R grey-zone lymphoma, R/R PCNSL, R/R DLBCL	July 2022	NCT03255018
Pembrolizumab + R-CHOP	R-CHOP immunochemotherapy regimen	2	DLBCL, high-grade B-NHL	August 2024	NCT03995147
Pembrolizumab + Rituximab +/− Lenalidomide	anti-CD20 antibody, immunomodulatory agent lenalidomide	2	R/R FL, R/R DLBCL	November 2021	NCT02446457

Future Directions

- Several pipelines of CAR-based strategies are currently being pursued. Selected ongoing clinical
- Trials evaluating CAR-based therapies in patients with diverse lymphoid malignancies are displayed.

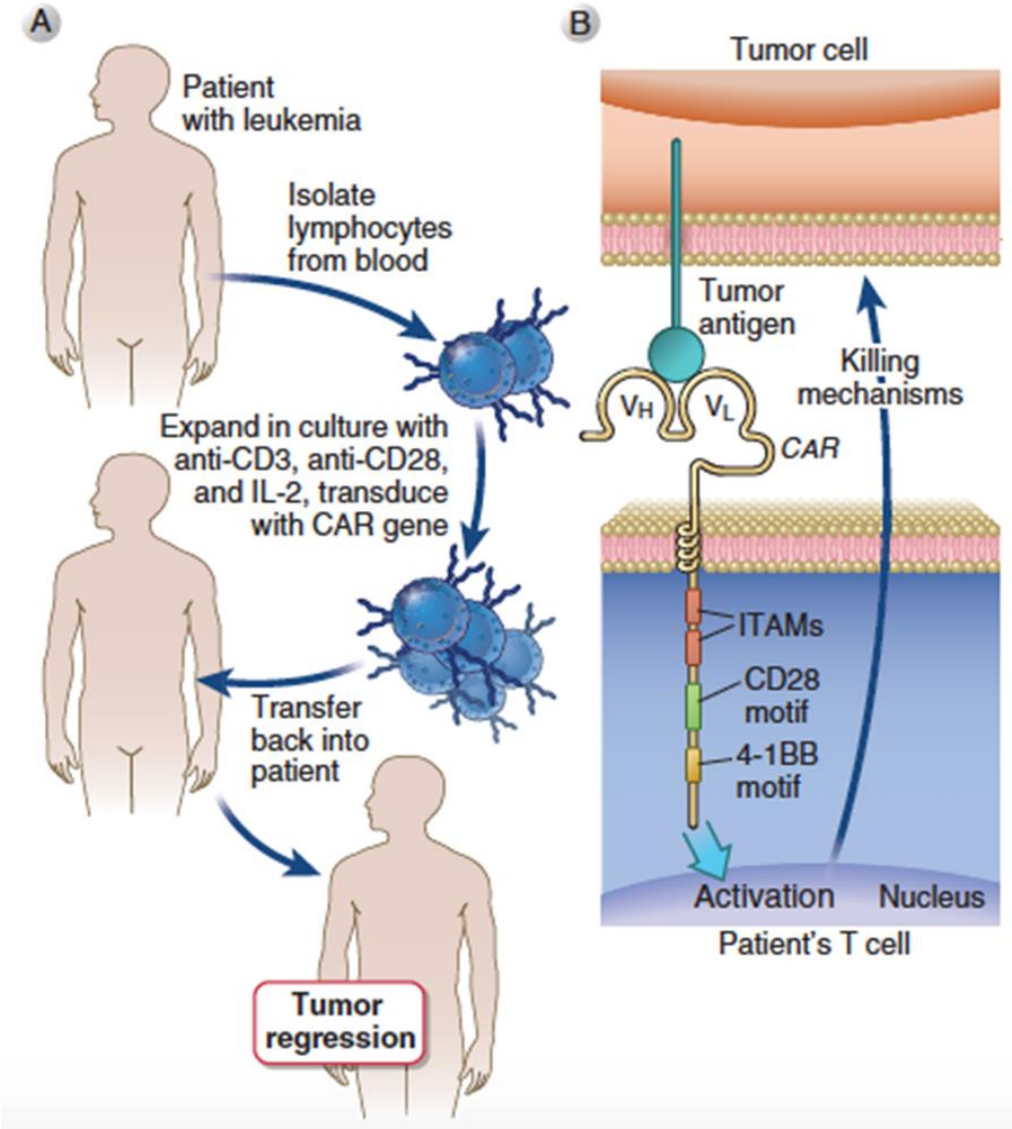
Table 8. Selected clinical trials that incorporate CAR T-cell products in experimental therapy of NHL.

Drug Combination	Mode of Action	Study Phase	Disease Status	Estimated Study Completion Date	ClinicalTrials.gov Identifier (Other Identifier)
Axi-cel	Anti-CD19 CAR T-cells versus ASCT (2nd line therapy)	3	R/R hgB-NHL	January 2022	NCT03391466 (ZUMA-7)
Liso-cel	Anti-CD19 CAR T-cells versus ASCT (2nd line therapy)	3	R/R hgB-NHL	January 2024	NCT03575351 (TRANSFORM)
Tisa-cel	Anti-CD19 CAR T-cells versus ASCT (2nd line therapy)	3	R/R hgB-NHL	December 2025	NCT03570892 (BELINDA)
Axi-cel	Anti-CD19 CAR T-cells	2	R/R FL, R/R MZL	February 2022	NCT03105336 (ZUMA-5)
Liso-cel	Anti-CD19 CAR T-cells	2	R/R B-NHL ineligible for ASCT	April 2021	NCT03483103 (TRANSCEND-PILOT-017006)
KTE-X19	Anti-CD19 CAR T-cells	1	R/R SLL/CLL	August 2021	NCT03624036
Liso-cel + ibrutinib	Anti-CD19 CAR T-cells + BTK inhibitor ibrutinib	1/2	R/R CLL/SLL	October 2021	NCT03331198
Axi-cel + acalabrutinib	BTK inhibitor acalabrutinib administered before leukapheresis	1/2	R/R hgB-NHL	March 2024	NCT04257578
CD30.CAR T cells	Anti-CD30 CAR T-cells	1	R/R HL, CD30+ NHL	April 2021	NCT02917083 (RELY-30)
AUTO4	Anti-TRBC1 CAR T-cells	1/2	R/R T-NHL	July 2021	NCT03590574
CD4CAR	Anti-CD4 CAR T-cells	1	R/R T-NHL	December 2022	NCT03829540
Axi-cel	Anti-CD19 CAR T-cells	1	DLBCL (PET+ after 2 cycles of therapy)	June 2021	NCT03761056 (ZUMA-12)
ALTCAR.CD30	ASCT followed by anti-CD30 CAR	1	R/R HL, CD30+ NHL	September 2021	NCT02663297

Chimeric Antigen Receptor T Cell Therapy

- CAR T cell therapy has been rapidly expanding in pediatric cancer therapeutics. In this approach, autologous T cells are collected from the patient, expanded, and subsequently engineered to express CARs, which are designed to redirect T cells to a selected tumor antigen.
- This non-physiologic T cell activation bypasses the need for tumor antigen presentation to major histocompatibility complex (MHC) Class I molecules, which are often down regulated in cancer, and allows antigen-expressing malignant cells to be recognized and destroyed by the CAR-redirected T cells.
- Different generations of CAR T cells exist.

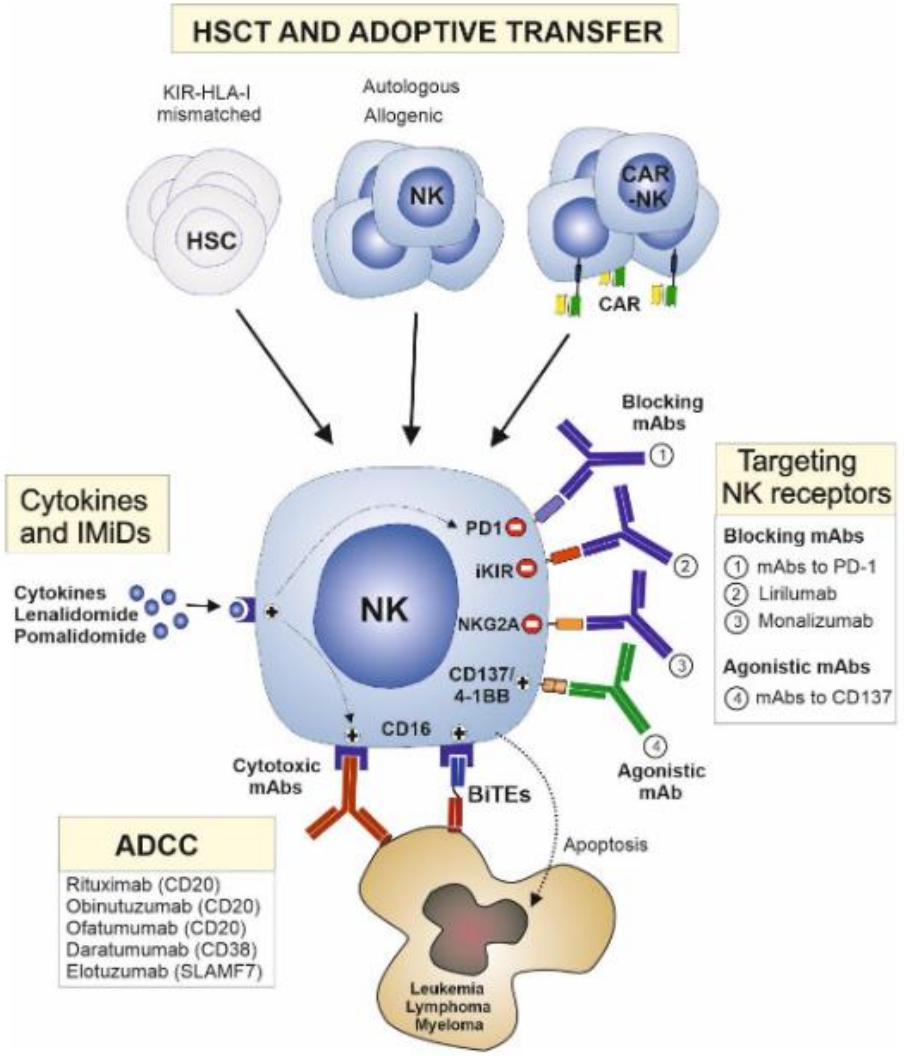
Chimeric antigen receptors



- Remarkable success in B cell acute leukemia (targeting CD19); up to 90% complete remission
- Risk of cytokine storm
- Outgrowth of antigen-loss variants of tumors?

Haploidentical Natural Killer Cells Induce Remissions in Non-Hodgkin Lymphoma Patients

- Phase 2 clinical trial in patients with poor prognosis refractory NHL testing the efficacy of haploidentical donor NK cell therapy (NK dose 0.5–3.27 × 107 NK cells/kg) with rituximab and IL-2.(clinicaltrials.gov NCT01181258)
- Therapy was tolerated without graft-versus-host-disease, cytokine release syndrome, or neurotoxicity.



NK Cell Therapy

- Observations support development of donor NK cellular therapies for advanced NHL as a strategy to overcome chemo resistance. Therapeutic efficacy may be further improved through disruption of the immunosupressive environment and infusion of exogenous IL-15.

Conclusions

- Antibodies targeting PD1 demonstrated significant clinical activity in HL, leading to regulatory approval of both nivolumab and pembrolizumab.

- Anti PD1/PDL1 antibodies have modest single-agent activity in NHL => combination strategies

- The role of immune checkpoint inhibitors in eradicating MRD/ctDNA in HL and NHL is being investigated.

- Therefore multiple combination strategies are now being investigated.
- So, none of these agents have been approved for non-Hodgkin lymphoma.
- The approval right now, only for classical Hodgkin lymphoma.


Thank You!