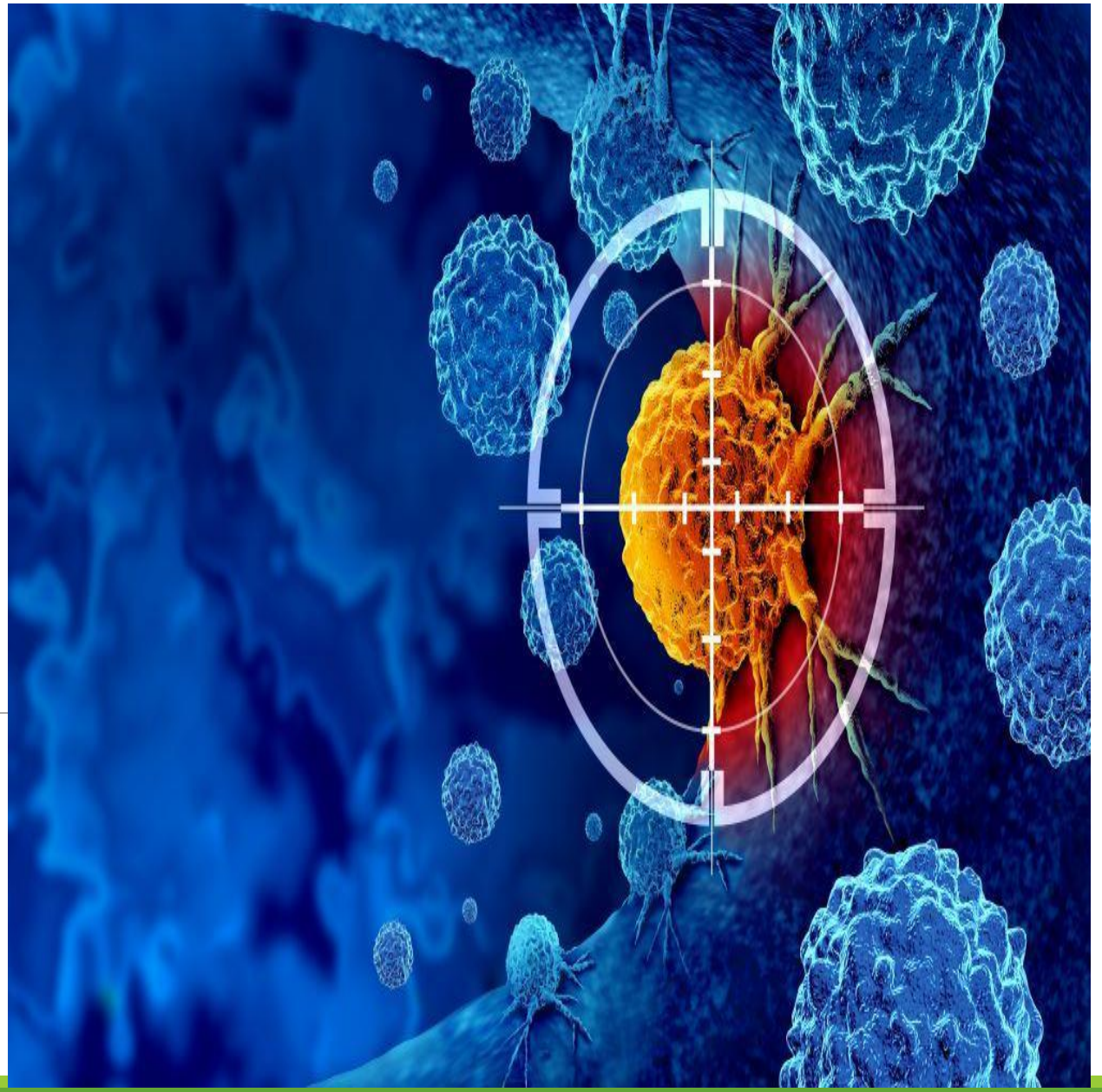

بسم الله الرحمن الرحيم

Checkpoint inhibitors before and after transplant in Hodgkin lymphoma



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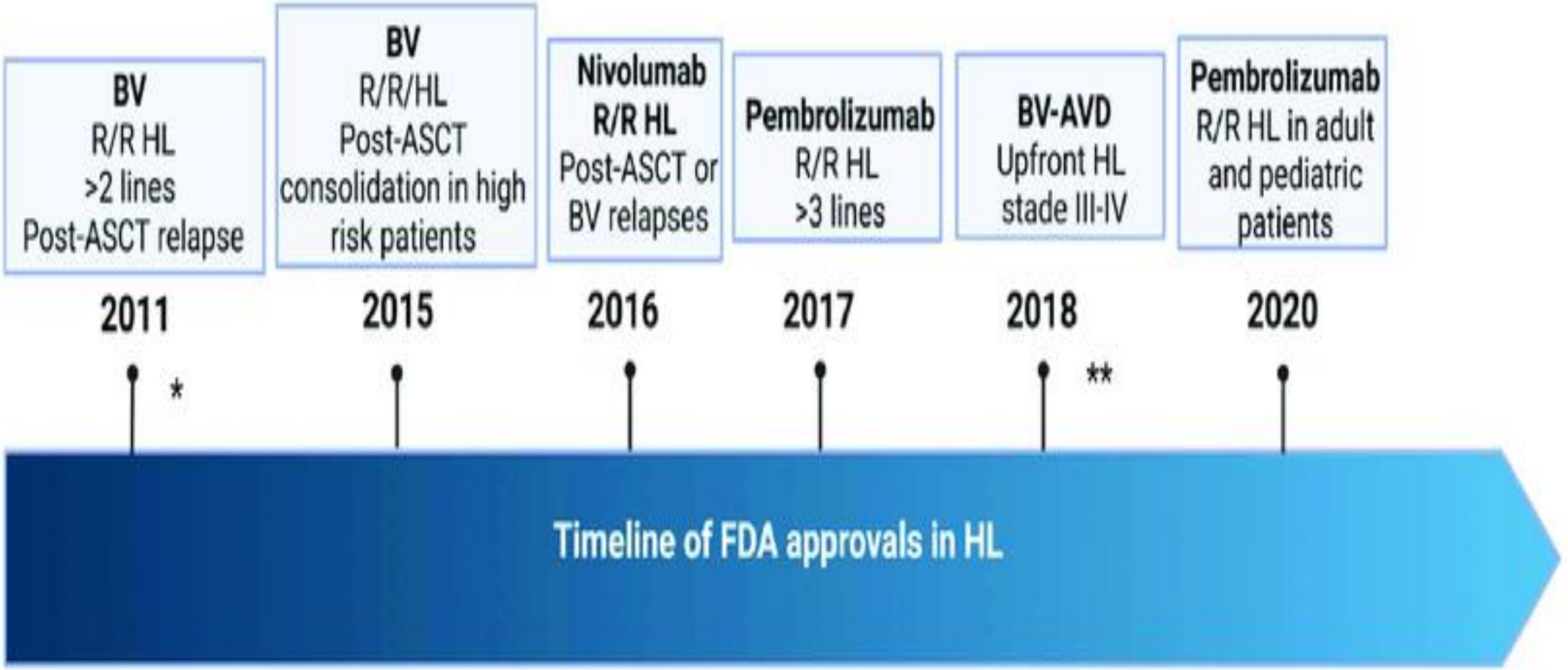


*first FDA-approved new treatment for HL since 1977

**first FDA-approved therapy in frontline HL in more than 40 years.

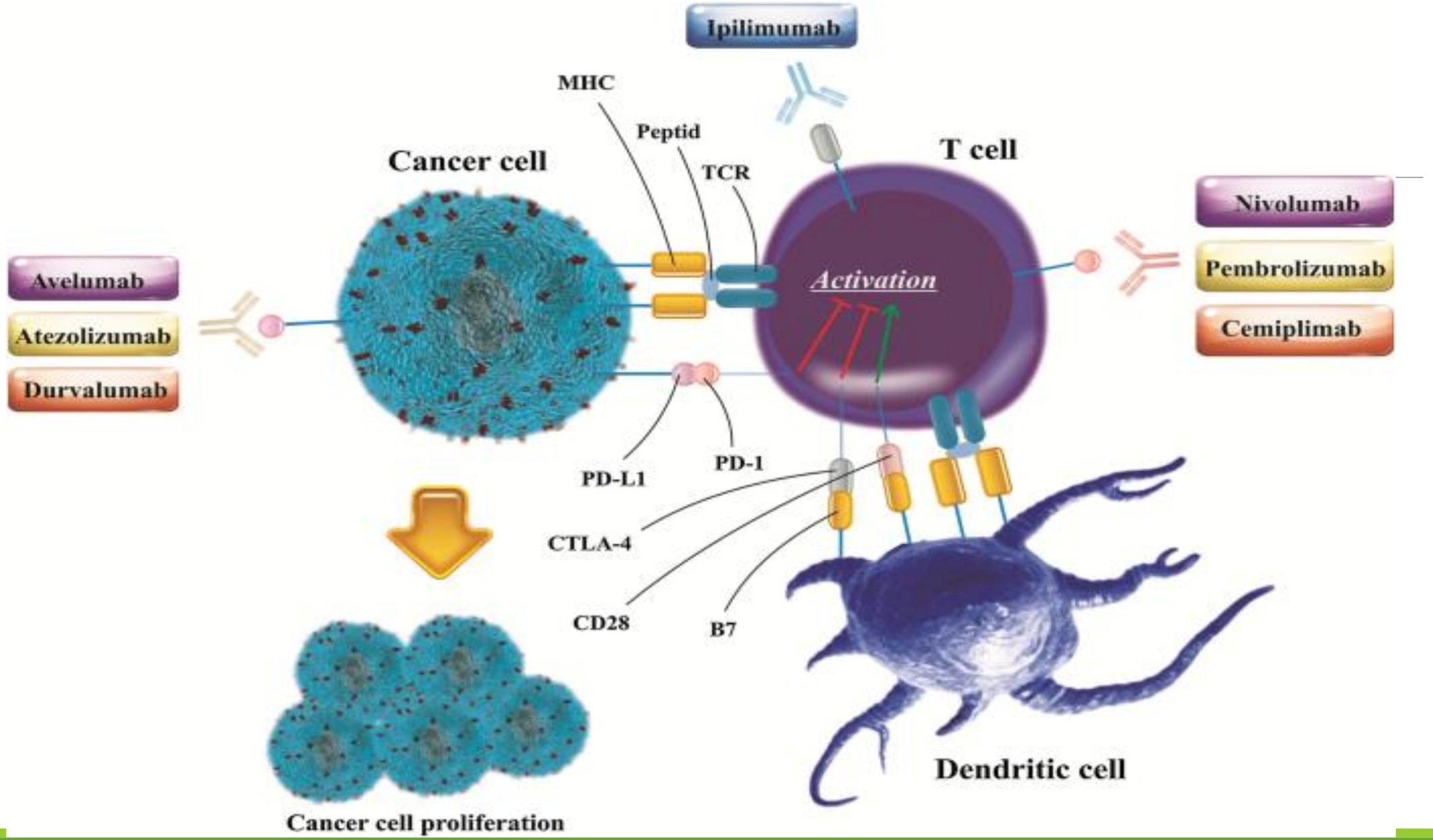
Mechanism of action:

Reed-Sternberg cells, exhibit genomic instability and overexpress the PD ligands

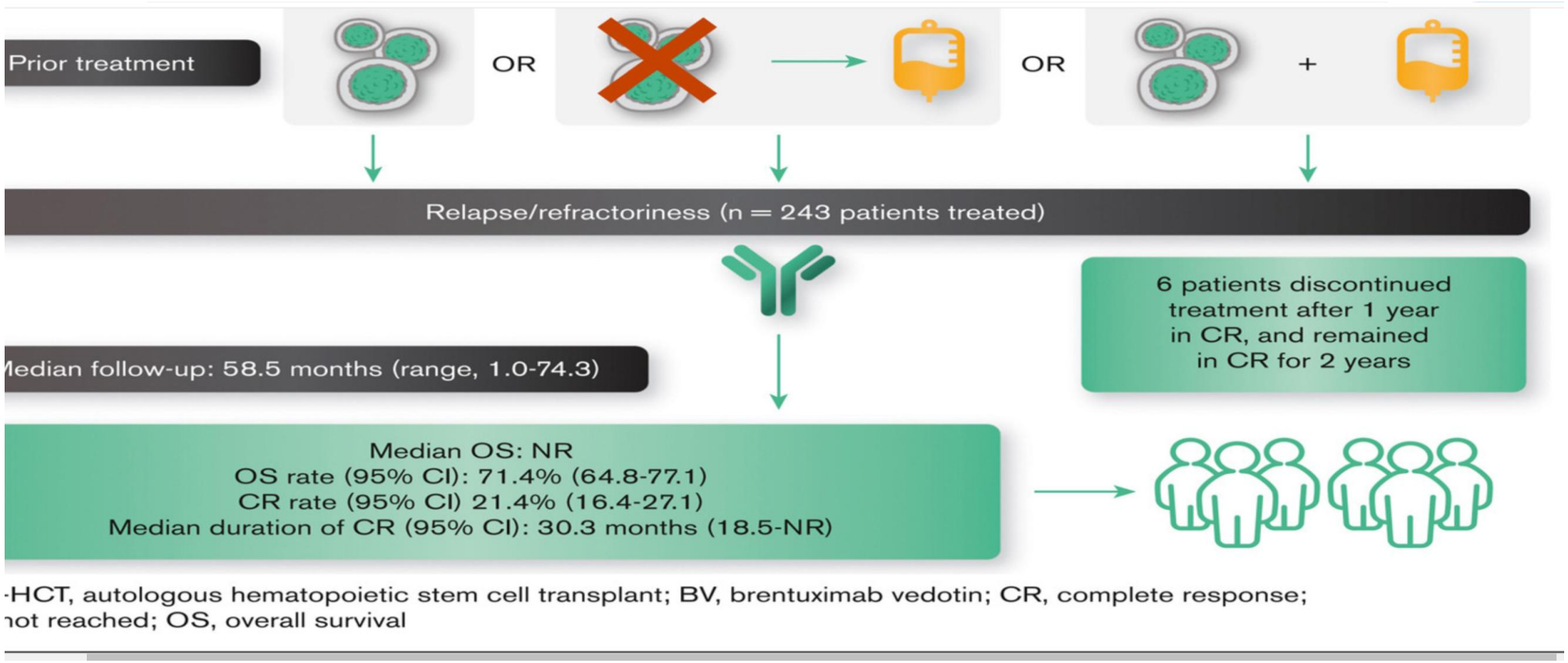
MHC class II dysfunction leading to downregulation of MHC class II and overexpression of PD-L1 and PD-L2

in the classic Hodgkin lymphoma microenvironment, the interaction of PD-L1 and PD-L2 with PD-1+ cytotoxic T lymphocytes may reduce T-cell activation and subsequently suppress T-cell proliferation and cytokine production.

Tumor-associated macrophages also express PD-L1 and PD-L2 and can further suppress cytotoxic T lymphocytes via a similar mechanism


Ipilimumab
MHC
Peptid
TCR
Cancer cell
T cell
Nivolumab
Pembrolizumab
Cemiplimab
Avelumab
Atezolizumab
Durvalumab
Activation
PD-L1
PD-1
CTLA-4
CD28
B7
Dendritic cell
Cancer cell proliferation

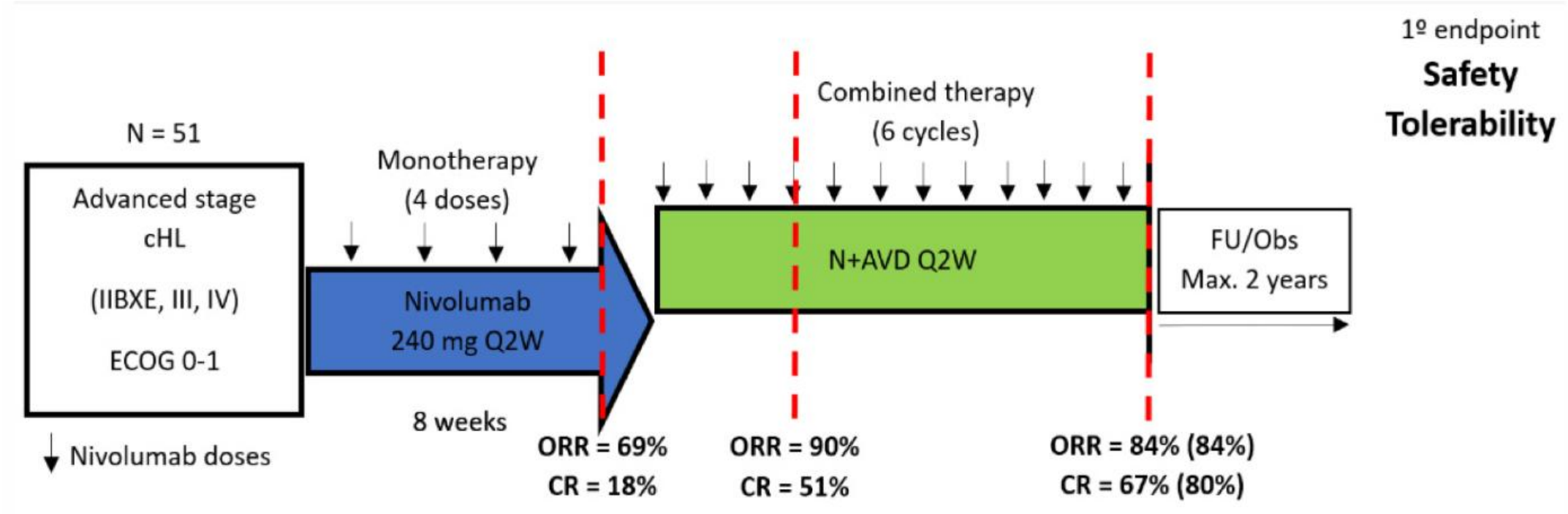
Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study



This 5-year follow-up of CheckMate 205 demonstrated favorable OS and confirmed efficacy and safety of nivolumab in R/R cHL after auto-HCT failure.

Results suggest patients may discontinue treatment after persistent CR and reinitiate upon progression

CHECKMATE 205: Evaluating Nivolumab in Newly Diagnosed Hodgkin Lymphoma



RESULTS:

Initial data from Cohort D of CheckMate 205 suggest that combining the checkpoint inhibitor nivolumab with multiagent AVD chemotherapy is a promising and well-tolerated alternative treatment option for newly diagnosed, advanced-stage cHL

Five-Year Follow-up of KEYNOTE-087: Pembrolizumab Monotherapy in Relapsed/Refractory Classical Hodgkin Lymphoma (cHL)

Context of Research: Study of pembrolizumab, an anti–PD-1 checkpoint inhibitor, in cHL

Key **Inclusion** Criteria
- R/R cHL
- ECOG PS ≤1
- No prior allo-SCT within 5 years of study initiation

Cohort 1
PD after ASCT and subsequent BV therapy — n = 69

Cohort 2
PD after salvage chemotherapy and BV therapy without ASCT — n = 81

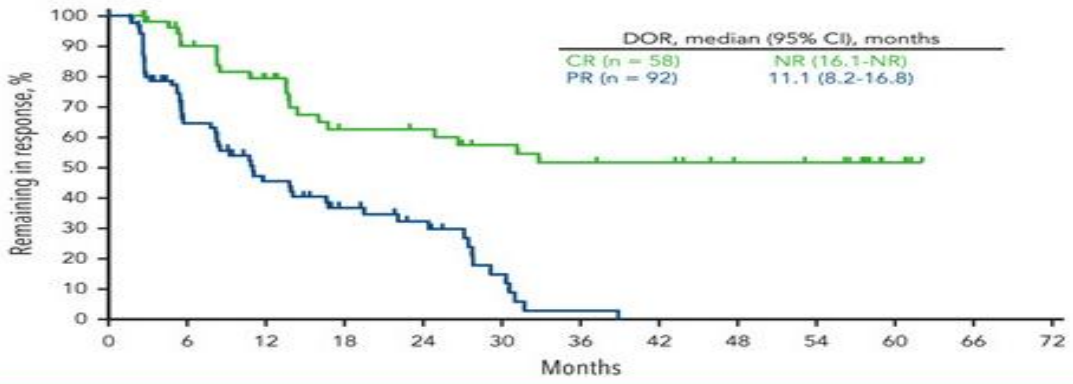
Cohort 3
PD after ASCT without subsequent BV therapy — n = 60

N = 210 → **Pembrolizumab**
200 mg IV Q3W for up to 2 years → **Survival follow-up**

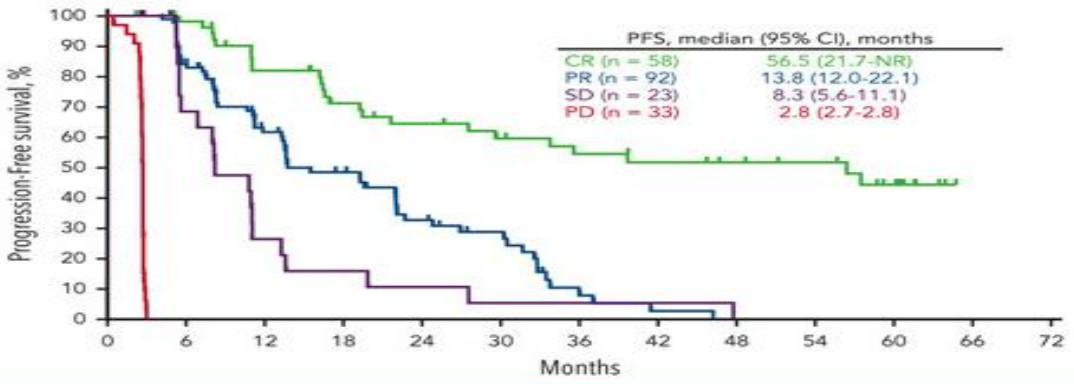
- At data cutoff, the median follow-up was 63.7 months (range, 59.8-68.7)

Main Outcomes

Duration of Response by Best Objective Response



Progression-Free Survival by Best Objective Response



Conclusion: Pembrolizumab monotherapy can produce very durable responses in a subset of patients with relapsed/refractory cHL (ClinicalTrials.gov identifier: NCT02453594)

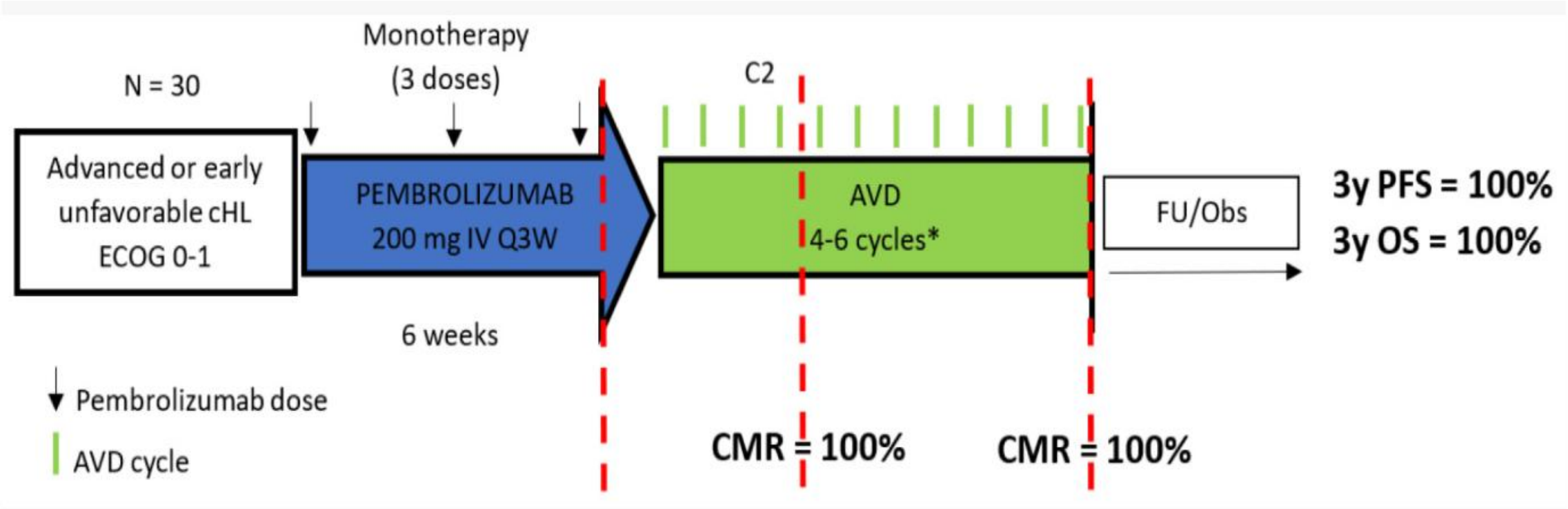
*Armand et al. DOI: 10.1182/**blood**.2022019386*

Blood Visual Abstract

Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087

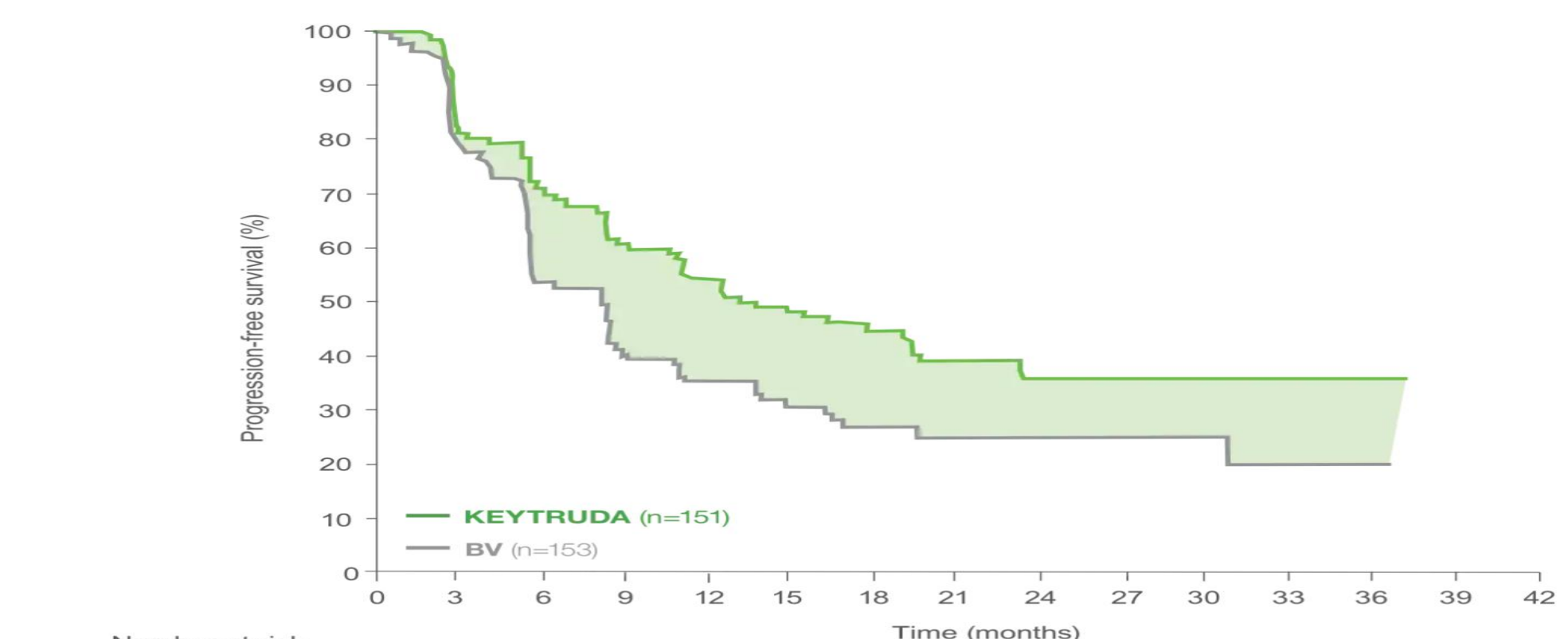
Results confirmed effective antitumor activity, durability of response, and manageable safety of pembrolizumab monotherapy in R/R cHL, regardless of prior treatment and including chemo resistant cHL

Sequential pembrolizumab and chemotherapy in newly diagnosed, early unfavorable, or advanced-stage classical Hodgkin lymphoma : The phase 2 KEYNOTE-C11 study.



Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study

Pembrolizumab showed statistically significant and clinically meaningful improvement in PFS compared with BV, with safety consistent with previous reports.



35% reduction in the risk of disease progression or death with KEYTRUDA vs BV

SWOG S1826, a randomized study of nivolumab-AVD versus brentuximab vedotin-AVD in advanced stage classic Hodgkin lymphoma.

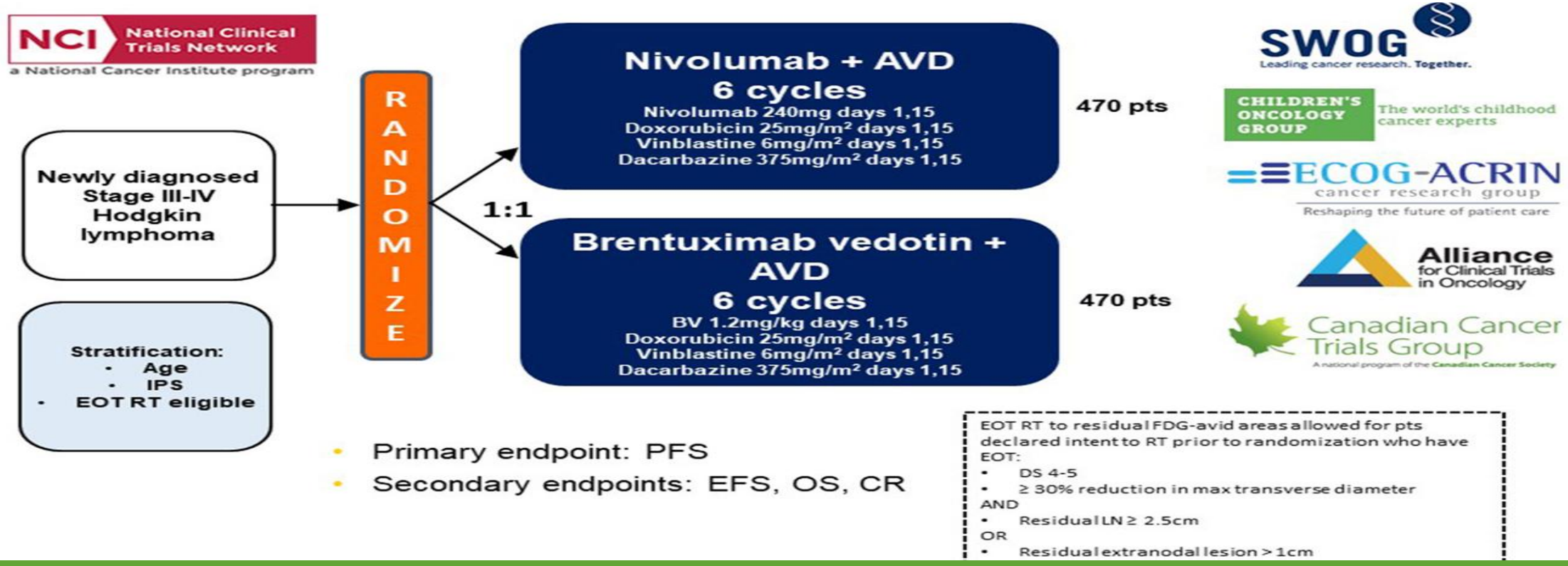
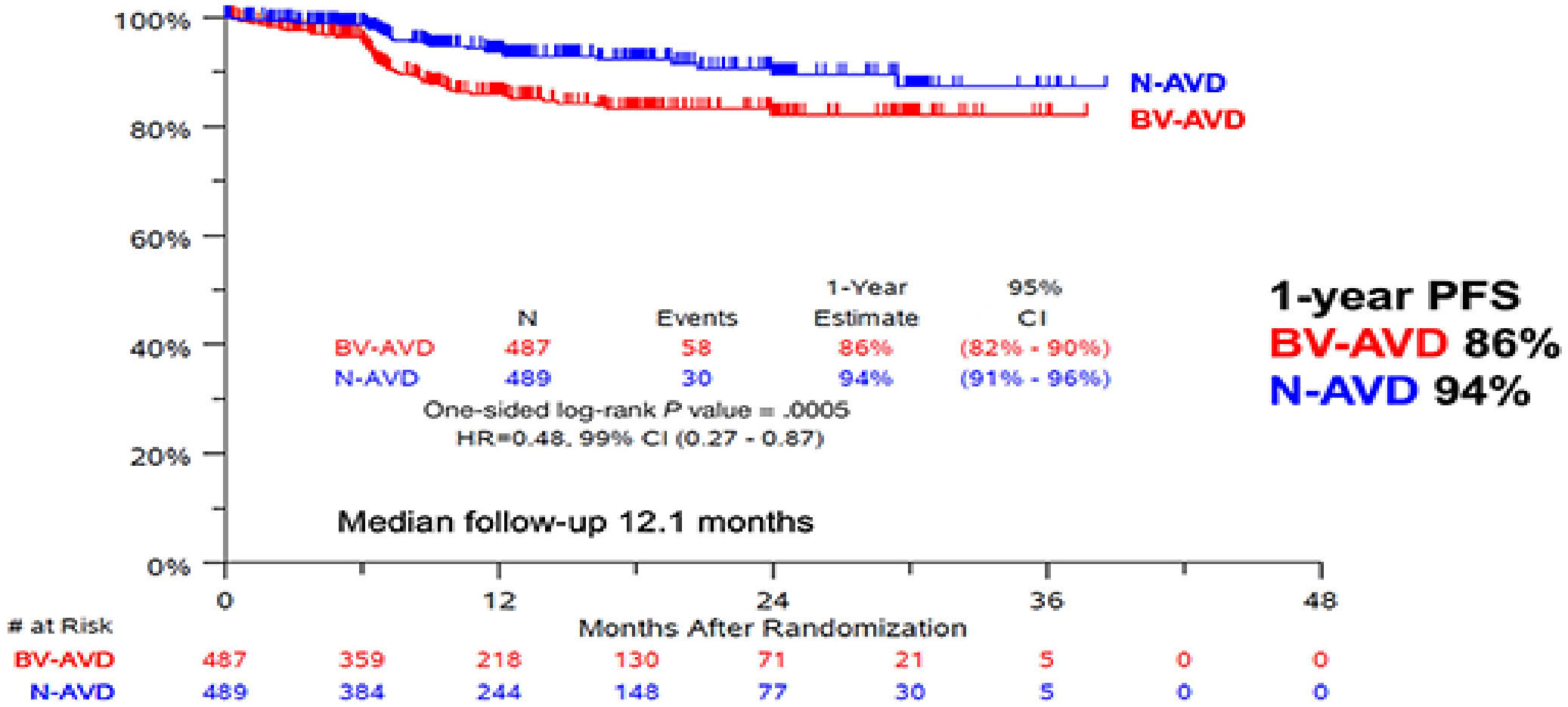


Figure 1. N/AVD Improves PFS Compared to BV/AVD



Abbreviations: AVD, doxorubicin, vinblastine, and dacarbazine; BV, brentuximab vedotin; N, nivolumab; PFS, progression-free survival.View larger

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Hodgkin Lymphoma (Age 18-60 years)

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY[a]
Primary Systemic Therapy Regimens

Classic Hodgkin Lymphoma in Adults 18–60 Years

Primary Systemic Therapy Regimens[b] (Listed In Alphabetical Order)
• ABVD[c,d,e] (doxorubicin, bleomycin, vinblastine, and dacarbazine) ± ISRT[f,1,2,3,4,5]
• ABVD[c,d,e] followed by BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) + G-CSF[g,h] ± ISRT[f,5]
• BrECADD + G-CSF[h] (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) ± ISRT[f,g,6]
• BV-AVD + G-CSF[h] (doxorubicin, vinblastine, and dacarbazine)[g,i,7,9]
• Nivolumab-AVD[c,j,8,10]

PRINCIPLES OF SYSTEMIC THERAPY[a]
Primary Systemic Therapy Regimens

Classic Hodgkin Lymphoma in Adults Age >60 Years or Adults Unfit for Intensive Therapy

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)	
	Age >60 Years and Candidate for Anthracycline
Stage I–II Favorable Disease	• A(B)VD[c,d,e,k] (2 cycles) + ISRT[f,1,11,12] • A(B)VD[c,d,e,k] (3 cycles) ± ISRT[f] (if CR)[1,11,12]
Stage I–II Unfavorable	• A(B)VD[c,d,e,k] (2 cycles) followed by AVD (4 cycles), if FDG-PET scan is negative after 2 cycles of ABVD.[13] ▸ Patients with a positive FDG-PET scan after 2 cycles of ABVD need individualized treatment. • A(B)VD[c,d,e,k] x 4 cycles + ISRT[f,14] • BV x2 cycles followed by AVD x6 cycles, conditionally followed by BV x2 cycles in patients with CR or PR and no neuropathy[i,15] • Nivolumab-AVD x4 cycles + ISRT[d,f,j,10]
Stage III–IV Disease	• BV x2 cycles followed by AVD x6 cycles, conditionally followed by BV x2 cycles in patients with CR or PR and no neuropathy[i,15] (if contraindications to CPI) • Nivolumab-AVD x6 cycles[d,f,j,16,17] (preferred)

Primary Systemic Therapy Regimens (Listed In Alphabetical Order)	
	Any Age and Not a Candidate for Anthracycline
Stage I–IV	• BV-DTIC (dacarbazine) ± ISRT[f,18,19] • BV-nivolumab ± ISRT[f,20] • Nivolumab or pembrolizumab ± ISRT[f] (if contraindications to BV)

PRINCIPLES OF SYSTEMIC THERAPY
Relapsed or Refractory Disease

Classic Hodgkin Lymphoma

- **Consider the following when selecting re-induction or subsequent therapy:**
  - **Clinical trial enrollment**
  - **Referral to a center with expertise**

Primary Refractory Disease or Relapse (within any time frame) (Candidate for or Not a Candidate for HDT/ASCR)		**Additional Considerations for Relapsed/ Refractory CHL (Not a Candidate for HDT/ ASCR)**
Second-Line and Subsequent Therapy[n,o] (in alphabetical order)	**Therapy for Disease Refractory to at Least 3 Prior Lines of Subsequent Therapy (in alphabetical order)**	• Individualized treatment is necessary. • For localized relapse, consolidative ISRT should be strongly considered. • Refer to or consult a center with expertise. • Single-agent palliative therapy options include: ▸ CPI: ◊ Nivolumab[27,28] ◊ Pembrolizumab[29,30] ▸ Non-CPI containing regimen: ◊ Bendamustine[15] ◊ BV[5] ◊ Everolimus[20] ◊ ISRT[f] ◊ Gemcitabine[31] ◊ Lenalidomide[23] ◊ Vinblastine[24]
CPI-containing regimens • BV-Nivolumab[1] • GVD-Pembrolizumab[2] • ICE-Nivolumab[3] • ICE-Pembrolizumab[4] <u>Non-CPI-containing regimens</u> • BV[5] • BV-bendamustine[6] • DHAP (dexamethasone, cisplatin, high-dose cytarabine)[7,8] • Gemcitabine/bendamustine/vinorelbine[9] • GVD (gemcitabine, vinorelbine, liposomal doxorubicin)[10] • ICE (ifosfamide, carboplatin, etoposide)[8,11,12] • ICE-BV[13] • IGEV (ifosfamide, gemcitabine, vinorelbine)[14]	• Bendamustine[15] • Bendamustine-carboplatin-etoposide[16] • Decitabine-pembrolizumab[17,18,19] • GCD (gemcitabine, cisplatin, dexamethasone)[21] • GEMOX (gemcitabine, oxaliplatin)[22] • ISRT[d] • Vorinostat-pembrolizumab[25]	

Combination Therapy(NCCN)

Nivolumab given with brentuximab vedotin as a first salvage treatment for up to four cycles resulted in a CR rate of 61% and an ORR of 82% in 61 patients with relapsed or refractory classic Hodgkin lymphoma

In a phase II study of 30 patients who had been unsuccessfully treated with nivolumab monotherapy, patients were given nivolumab with bendamustine. The addition of bendamustine resulted in a CR rate of 57% and an ORR of 87%; however, the duration of response was short at 6.6 months

radiation and checkpoint inhibitors

2 patients with relapsed or refractory classic Hodgkin lymphoma who received nivolumab with radiation therapy after undergoing autologous stem-cell transplantation and treatment with brentuximab vedotin; both patients had a CR.

Multiple mechanisms likely contribute to the synergistic benefits of combining a checkpoint inhibitor and radiation therapy for the treatment of relapsed or refractory classic Hodgkin lymphoma

PD-1 blockade maintenance

A multicenter study administered pembrolizumab 200 mg intravenously every three weeks for up to eight cycles beginning within 21 days post autologous HCT hospital discharge.

At 18 months, the PFS was 82 percent and OS was 100 percent among 28 evaluable patients.

Toxicity was manageable, with 30 percent experiencing ≥1 grade 3 adverse event (AE) and 40 percent ≥1 grade 2 immune-related AE.

While promising, maintenance therapy with PD-1 blockade must be validated in other studies before suggesting its use.

GVHD with PD-1 blockade and allogeneic HCT

Patients treated with nivolumab or pembrolizumab who proceed to allogeneic HCT have a high rate of transplant-related complications, such as

hyperacute graft-versus-host disease (GVHD),

severe acute GVHD,

steroid-requiring febrile syndrome,

hepatic sinusoidal obstruction syndrome,

other immune-related adverse reactions.

- Conversely, there are reports of acute GVHD developing with nivolumab treatment in patients who had previously undergone allogeneic HCT.
- GVHD began within one week after the first infusion of nivolumab .
- All patients had a prior history of acute GVHD.
- The OR to nivolumab was 95 percent and median PFS was not reached after more than one year of observation.

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722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION | NOVEMBER 2, 2023

Checkpoint Inhibitors and Allo-SCT in Hodgkin Lymphoma: A Matter of Time - a Study By the SFGM-TC

Conclusion: CPI use before allo-SCT within 60 days before allo-SCT can lead to significant severe aGVHD,

persisting higher risk of aGVHD grade ≥II even after 60 days of delay.

This highlights the importance of exercising caution when administering CPI injections within 60 days before allo-SCT.

There is need to develop GVHD prophylaxis strategies in this population at risk.

Indications for allogeneic HCT

limit allogeneic HCT to medically-eligible patients who were previously treated with brentuximab vedotin (BV) and autologous HCT and who had only a partial response or progressive disease after immune checkpoint inhibition (ICI).

do not proceed with allogeneic HCT for patients who had a complete response (CR) with ICI.


سپاس
از توجه شما