HODGKİN LENFOMA-İMMÜNOTERAPİ

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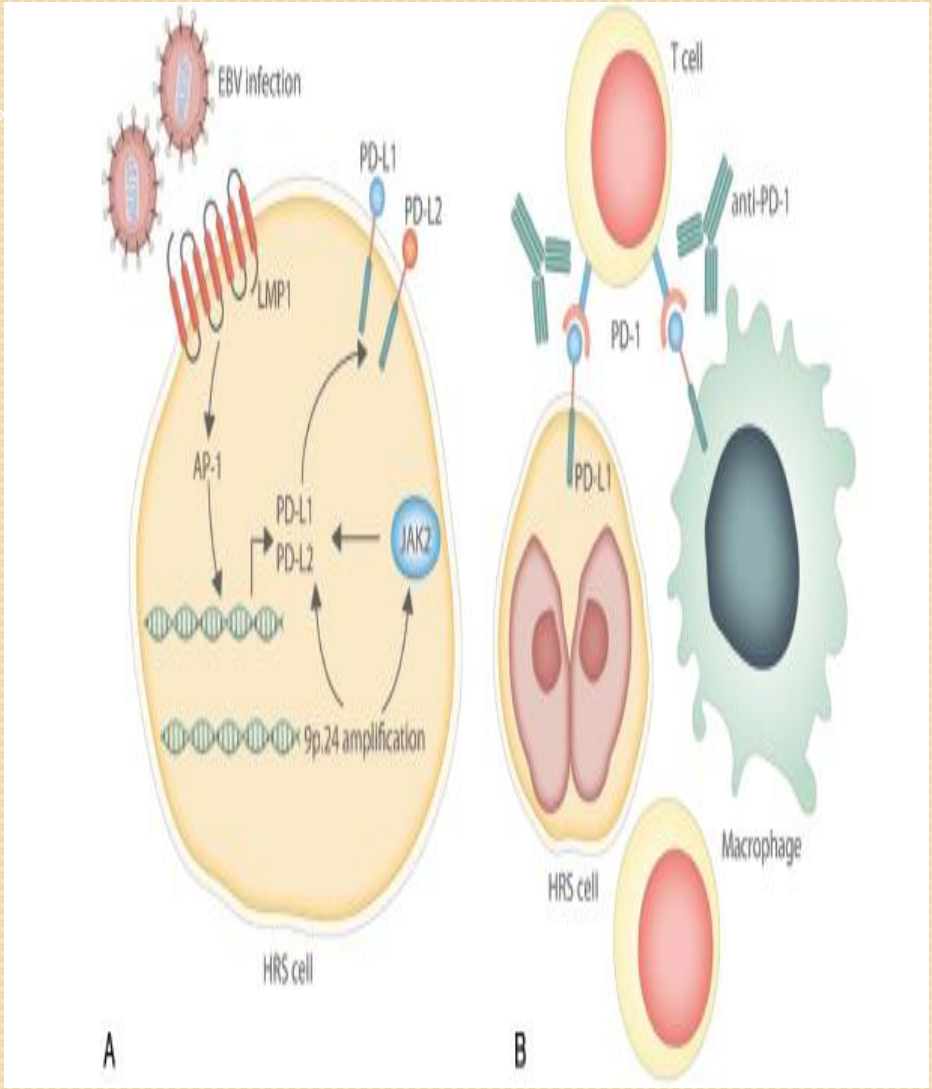


Key points

- Patients with early-stage cHL are risk stratified according to a number of factors, including the presence of bulky disease, ESR, and number of nodal sites of involvement.
- More than 90% of patients with favorable disease and 85% of patients with unfavorable disease are cured with initial therapy.
- Therapeutic options include combined modality therapy: two to four cycles of ABVD (favorable), four to six cycles of ABVD (unfavorable), or the Stanford V regimen plus IFRT.
- Chemotherapy alone with ABVD in patients without bulky disease is an alternative in selected cases.

Table 20-4 International Prognostic Score in advanced-stage HL

Number of risk factors*	5-year FFP (%)	5-year OS (%)
0	84 ± 4	89 ± 2
1	77 ± 3	90 ± 2
2	67 ± 2	81 ± 2
3	60 ± 3	78 ± 3
4	51 ± 4	61 ± 4
>5	42 ± 5	56 ± 5

From Hasenclever D, Diehl V. *N Engl J Med.* 1998;339:1506-1514.
FFP = freedom from progression, OS = overall survival.
* The IPS is derived from a retrospective analysis of 5,141 patients treated at 25 centers from 1983-1992 with advanced-stage HL. Risk factors identified in this retrospective study included age >45 years, male gender, WBC >15,000/mm^3, Hb <10.5 g/dL, absolute lymphocyte count <600/mm^3 or <8% of WBC, albumin <4.0 g/dL, and stage IV disease. More recent data on the value of IPS suggest that the impact might have narrowed in the modern treatment era (Moccia et al., 2012).

Table 20-3 Frontline chemotherapy regimens in HL

Regimen	Drugs	Method of administration	When administered	Cycle
ABVD	Doxorubicin 25 mg/m^2	IV	Days 1 and 15	Q28 days
	Bleomycin 10 units/m^2	IV	Days 1 and 15	
	Vinblastine 6 mg/m^2	IV	Days 1 and 15	
	Dacarbazine 375 mg/m^2	IV	Days 1 and 15	
BEACOPP (baseline)	Bleomycin 10 mg/m^2	IV	Day 8	Q21 days
	Etoposide 100 mg/m^2	IV	Days 1-3	
	Doxorubicin 25 mg/m^2	IV	Days 1	
	Cyclophosphamide 650 mg/m^2	IV	Day 1	
	Vincristine 1.4 mg/m^2 (capped at 2.0 mg)	IV	Day 8	
	Procarbazine 100 mg/m^2	IV	Days 1-7	
	Prednisone 40 mg/m^2	IV	Days 1-14	
BEACOPP (escalated)	Bleomycin 10 mg/m^2	IV	Day 8	Q21 days
	Etoposide 200 mg/m^2	IV	Days 1-3	
	Doxorubicin 35 mg/m^2	IV	Days 1	
	Cyclophosphamide 1,250 mg/ m^2	IV	Day 1	
	Vincristine 1.4 mg/m^2 (capped at 2.0 mg)	IV	Day 8	
	Procarbazine 100 mg/m^2	IV	Days 1-7	
	Prednisone 40 mg/m^2	IV	Days 1-14	
Stanford V	Doxorubicin 25 mg/m^2	IV	Weeks 1, 3, 5, 7, 9, 11	
	Vinblastine 6 mg/m^2	IV	Weeks 1, 3, 5, 7, 9, 11	
	Vincristine 1.4 mg/m^2 (capped at 2.0 mg)	IV	Weeks 2, 4, 6, 8, 10, 12	
	Bleomycin 5 U/m^2	IV	Weeks 2, 4, 6, 8, 10, 12	
	Mustard 6 mg/m^2	IV	Weeks 1, 5, 9	
	Etoposide 60 mg/m^2	IV	Weeks 3, 7, 11	
	Prednisone 40 mg/m^2	PO QOD	Weeks 1-9; taper by 10 mg QOD weeks 10 and 11	

IV= intravenous; PO = per os (by mouth); Q = every; QOD = every other day.

Standards of care

- ABVD x 6
  - Cures the majority of patients with acceptable toxicity
  - 30-35% of patients fail treatment, app. 50% are cured with HD+ASCT
  - Undertreatment of 1/3 of patients

- BEACOPPesc x 6
  - Cures more patients
  - HR for PFS app. 0.5
  - OS benefit app. 5 % (NNT ~ 20)
  - More acute and late toxicity
  - Overtreatment of 2/3 or patients

Borchmann P and Engert A. JCO 2016; 34(17): 1975-77.

Acute + late toxicity of ABVD vs. BEACOPPesc

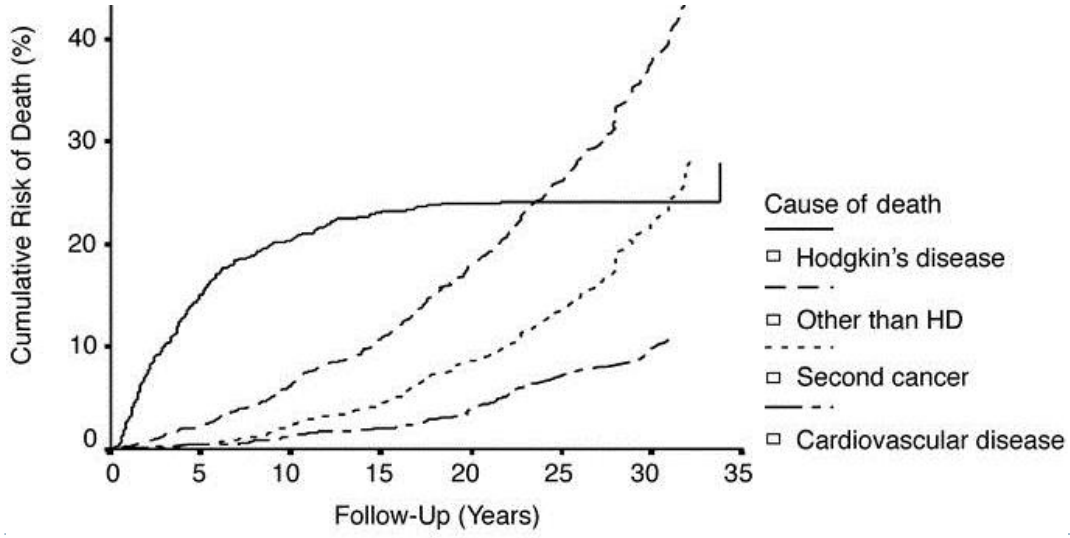
Adverse effects of ABVD versus BEACOPPesc	**ABVD**	**BEACOPPesc**
Acute		
Grade 3-4 neutropenia	+	+++
Serious infections during treatment	+	++
Serious adverse events during treatment	+	+++
Hospitalisation during treatment	+	+++
Acute treatment-related death	+	+
Late		
Secondary leukemia/MDS	-/+	++
Infertility	-	+++
Pulmonary disease	++	+
Cardiovascular disease	++	+

What are the challenges of early stage HL?

- The large majority of patients are cured although not 100%
- Late effects of treatment include second cancers, cardiovascular disease, chronic fatigue, muscle weakness, psychosocial problems etc.

- Radiotherapy is the dominant cause of the late treatment-related morbidity and mortality seen today in survivors of HL treated 15-50 years ago
  - Since then, both radiotherapy doses and field sizes have been reduced dramatically along with fundamental improvements in radiotherapy techniques

- But chemotherapy also has late effects, serious and potentially fatal:
  - Cardiovascular disease, chronic muscle weakness and fatigue (dose-dependent effects of doxorubicin)
  - Pulmonary disease (bleomycin)



Aleman et al. J CO 2003; 21(18): 3431-39

Table 20-6 Salvage combination chemotherapy regimens utilized for relapsed or refractory Hodgkin lymphoma

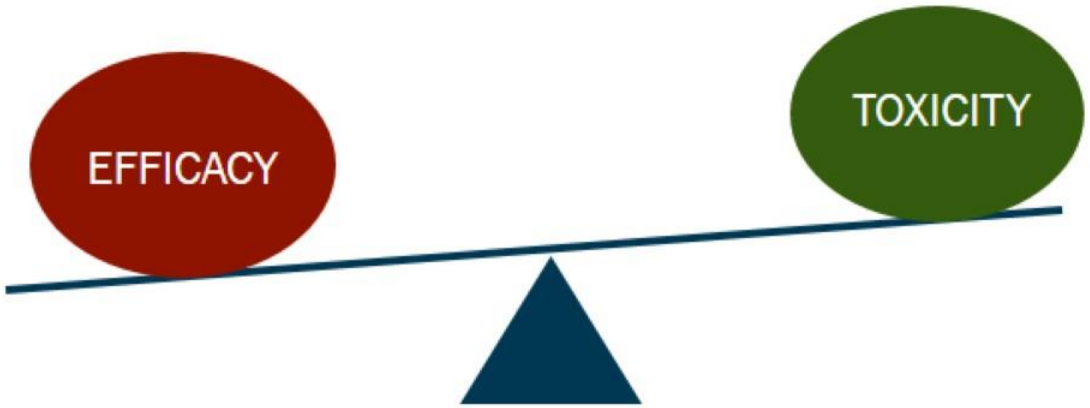
Regimen	Drugs	Method of administration	When administered	Cycle
GVD (not previously transplanted)	Gemcitabine 1,000 mg/m^2	IV	Days 1 and 8	Q21 days
	Vinorelbine 20 mg/m^2	IV	Days 1 and 8	
	Liposomal doxorubicin 15 mg/m^2	IV	Days 1 and 8	
GVD (previously transplanted)	Gemcitabine 800 mg/m^2	IV	Days 1 and 8	Q21 days
	Vinorelbine 15 mg/m^2	IV	Days 1 and 8	
	Liposomal doxorubicin 10 mg/m^2	IV	Days 1 and 8	
ICE	Ifosfamide 5,000 mg/m^2	IV over 24 h	Day 2	Q14 days
	Mesna 5,000 mg/m^2	IV over 24 h	Day 2	
	Etoposide 100 mg/m^2	IV	Days 1-3	
	Carboplatin AUC = 5 (maximum dose of 800 mg)	IV	Day 2	
DHAP	Dexamethasone 40 mg	IV/PO	Days 1-4	Q21 days
	Cisplatin 100 mg/m^2	IV over 24 h	Day 1	
	Cytarabine 2,000 mg/m^2	IV every 12 h	Day 2	
ESHAP	Etoposide 40 mg/m^2	IV	Days 1-4	Q21 days
	Methylprednisolone 500 mg	IV	Days 1-5	
	Cytarabine 2,000 mg/m^2	IV	Day 5	
	Cisplatin 25 mg/m^2	CIV	Days 1-4	
Mini-BEAM	BCNU (carmustine) 60 mg/m^2	IV	Day 1	Q21-28 days
	Etoposide 75 mg/m^2	IV	Days 2-5	
	Cytarabine 100 mg/m^2	IV every 12 h	Days 2-5	
	Melphalan 30 mg/m^2 (maximum of 50 mg)	IV	Day 5	
Dexa-BEAM	Dexamethasone 24 mg	PO	Days 1-10	Q28 days
	BCNU (carmustine) 60 mg/m^2	IV	Day 2	
	Melphalan 20 mg/m^2	IV	Day 3	
	Etoposide 200 mg/m^2	IV every 12 h	Days 4-7	
	Cytarabine 100 mg/m^2	IV every 12 h	Days 4-7	
	G-CSF 300-480 µg	SQ	Day 9 until WBC > 2,500/µL	
IGEV	Ifosfamide 2,000 mg/m^2	IV	Days 1-4	Q21 days
	Gemcitabine 800 mg/m^2	IV	Days 1 and 4	
	Vinorelbine 20 mg/m^2	IV	Day 1	
	Prednisolone 100 mg	PO	Days 1-4	
GDP	Gemcitabine 1,000 mg/m^2	IV	Days 1 and 8	Q21 days
	Cisplatin 75 mg/m^2	IV	Days 1 and 8	
	Dexamethasone 40 mg	PO	Days 1-4	
ChlVPP	Chlorambucil 6 mg/m^2	PO	Days 1-14	Q28 days
	Vinblastine 6 mg/m^2	IV	Days 1 and 8	
	Procarbazine 100 mg/m^2	PO	Days 1-14	
	Prednisone 40 mg	PO	Days 1-14	

Optimal Treatment in HL

Table 20-2 Risk factors in early-stage Hodgkin lymphoma

Organization	Risk factors
EORTC	Age <50
	No LMA (less than one-third maximum intrathoracic diameter)
	ESR <50 without B sx
	ESR <30 with B sx
	<4 lymph node groups
GHSG	No LMA (less than one-third maximum intrathoracic diameter)
	ESR <50 without B sx
	ESR <30 with B sx
	No extranodal extension
	<3 lymph node groups

B sx = fevers, drenching night sweats, unexplained weight loss; EORTC = European Organization for Research and Treatment of Cancer; ESR = erythrocyte sedimentation rate; GHSG = German Hodgkin Study Group; LMA = large mediastinal mass.



Traditionally: prognostic factors
for response to treatment (stage, bulky disease, etc)

PET era: treatment adapted to response

How can we apply interim PET-based therapy to early favourable HL?

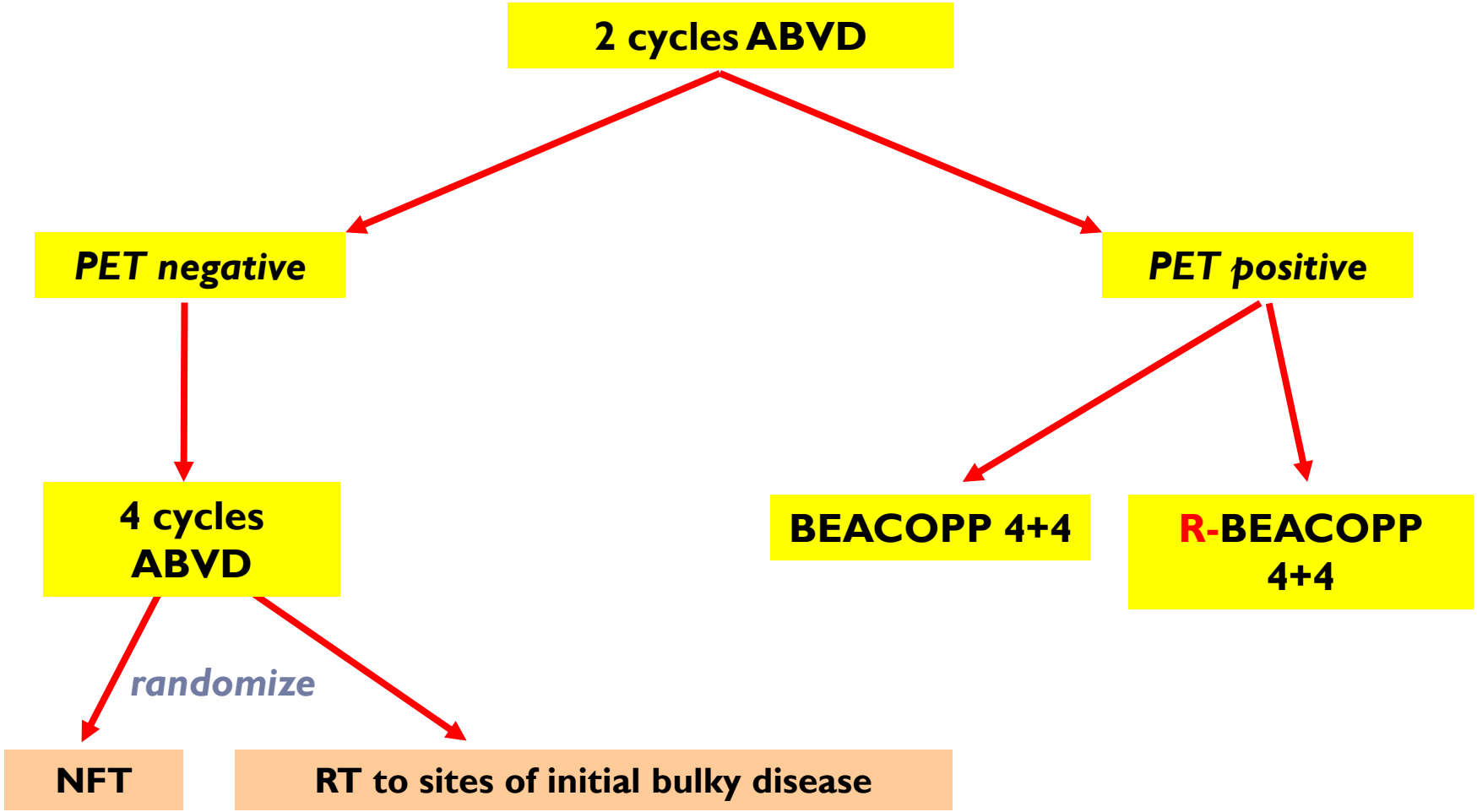
- Probably in a large number of ways, but so far there is available evidence to inform us about

- 1. Omission of radiotherapy in early PET-negative patients
- 2. Escalation of therapy in early PET-positive patients

Early stage HL: Can a negative early PET/CT select patients who do not need radiotherapy?

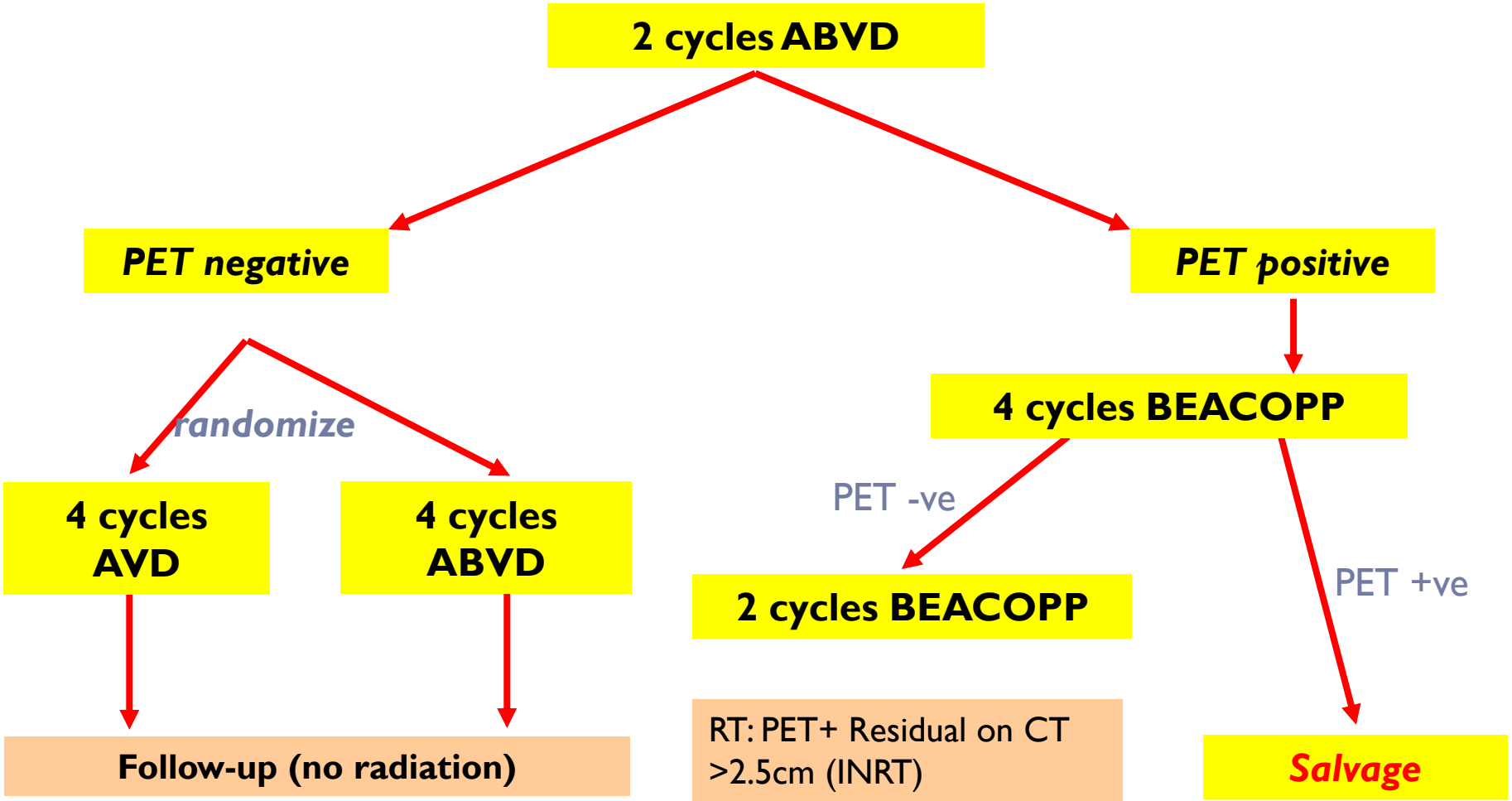
Study	Patients	Main PET-driven intervention	Phase
UK NCRI RAPID	Early stage HL	If PET-negative after 3xABVD randomization to RT vs. no RT	III
EORTC/GELA/FIL H10	Early stage HL	Experimental arm: No radiotherapy if PET-neg after 2xABVD BEACOPPesc + radiotherapy if PET-pos after 2xABVD	III
CALGB 50604	Early stage HL non-bulky	Additional ABVDx2 and no radiothrapy if PET-neg after 2xABVD BEACOPPesc + radiotherapy if PET-pos after 2xABVD	II
GATLA HL05	All stages HL	No further treatment if PET-negative after 3 x ABVD	II
GHSG HD16	Early stage HL no risk factors	No radiotherapy in experimental arm if PET-negative after 2xABVD	III
CALGB 50801	Early stage HL bulky	Additional ABVDx4 and no radiothrapy if PET-neg after 2xABVD BEACOPPesc + radiotherapy if PET-pos after 2xABVD	II
ECOG 2410	Early stage HL bulky	4xBEACOPPesc + RT if PET-positive after 2xABVD	II

GITIL HD0607



PI: Andrea Gallamini, Cuneo IT

RATHL



PI: Prof. Peter Johnson, Southampton

HODGKİN LENFOMA-İMMÜNOTERAPİ PERSPEKTİFLERİ

İlk basamak

- ✓ **Erken evre**
  - ❖ Radyoterapisiz kür arayışı
- ✓ **İleri evre**
  - ❖ Yüksek riskli hastalarda artmış yanıt arayışı
- ✓ **Yaş ≥ 60**
  - ❖ Anti-neoplastik etkinliği arttırırken toksik organ hasarlarından kaçınmak

İkinci basamak

- ✓ «pre-transplant PET negatif» oranını geliştirmek

Otolog nakil sonrası (remisyonda)

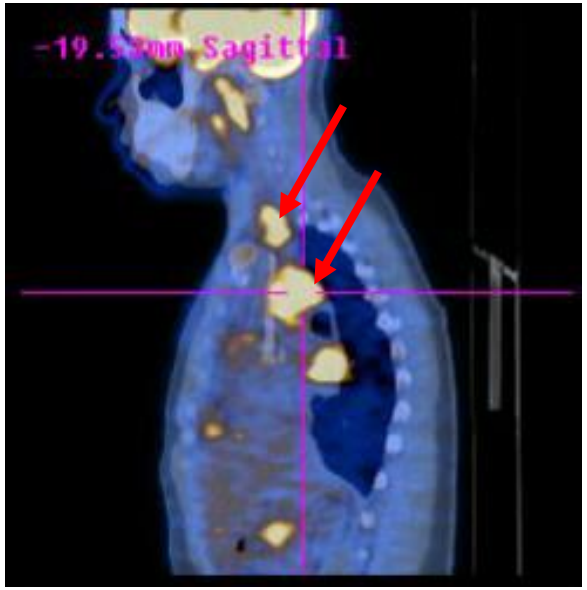
- ✓ Transplant sonrası nüks riskinden kaçınmak

Otolog nakil sonrası (relaps/refrakter)

- ✓ Palyasyon, allojeneik nakil için köprü tedavisi

PET/CT scans before and after ABVD x 2

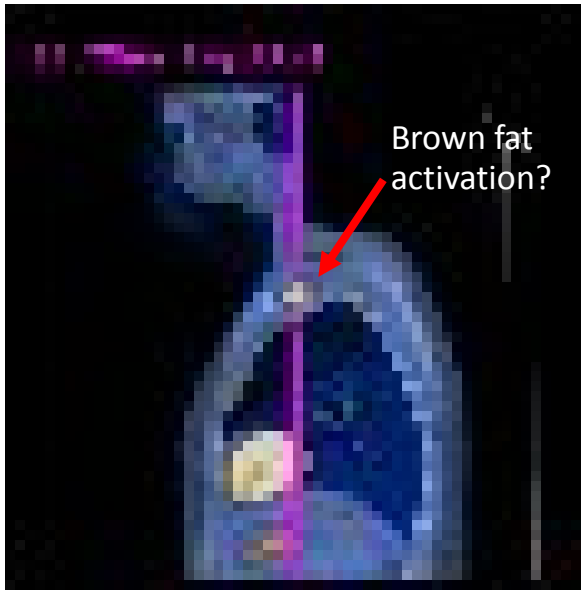
Baseline: Before ABVD

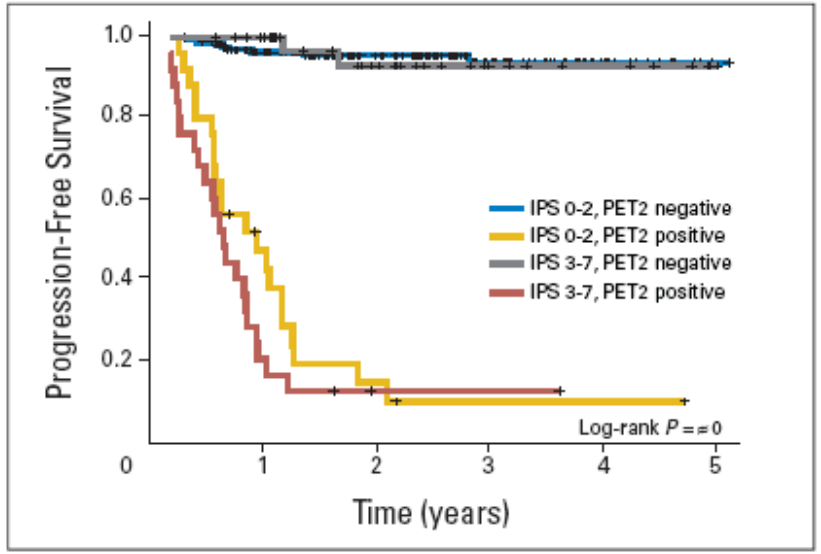


Cervical LAD

Mediastinal LAD

After ABVD x 2: PET-negative





EARLY RESPONSE is predictive of outcome

Interim PET/CT response adapted strategies after ABVD x 2

(Gallamini A. et al. JCO 2007)

Immune Checkpoint Inhibition in Hodgkin Lymphoma

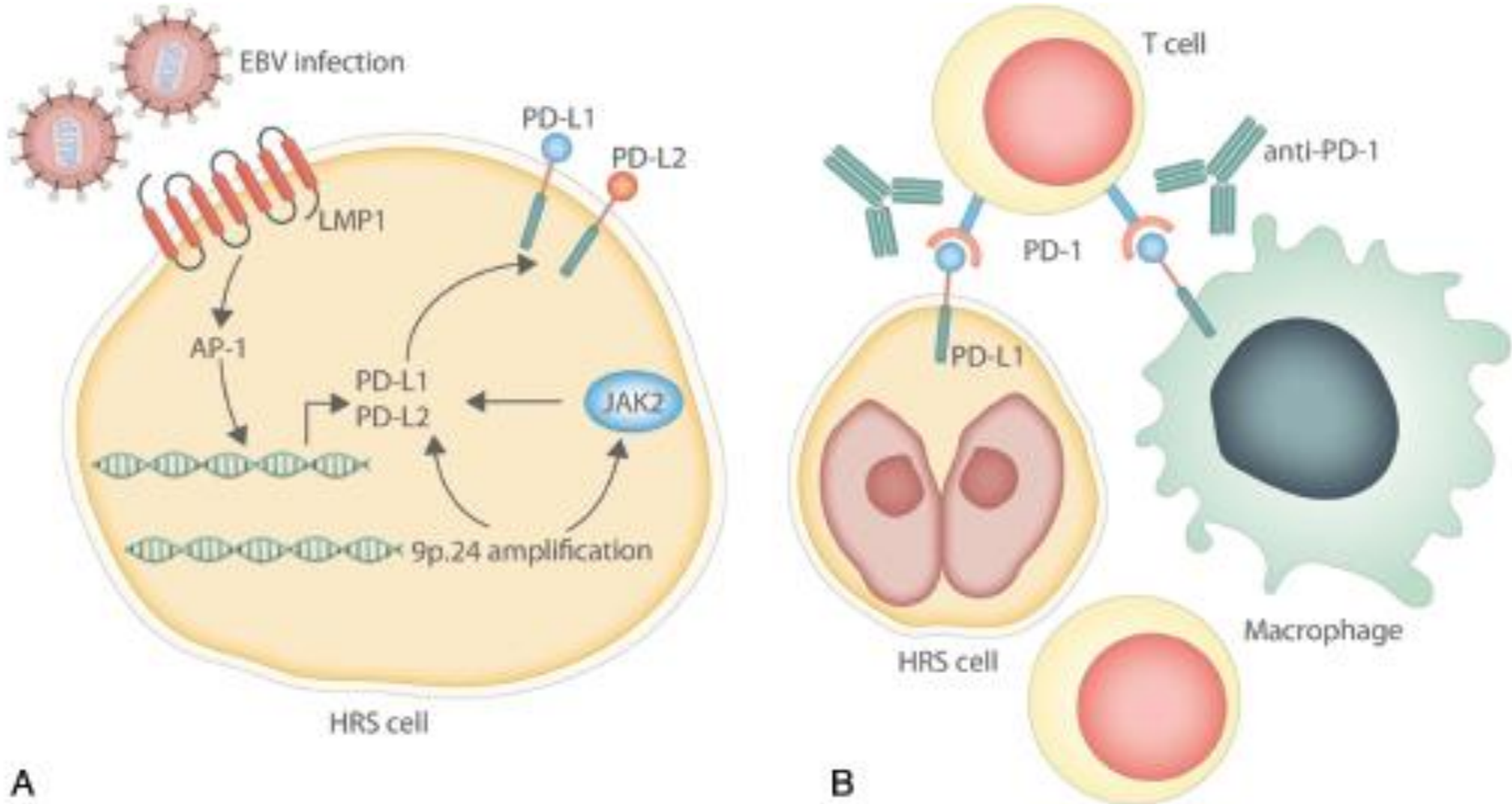
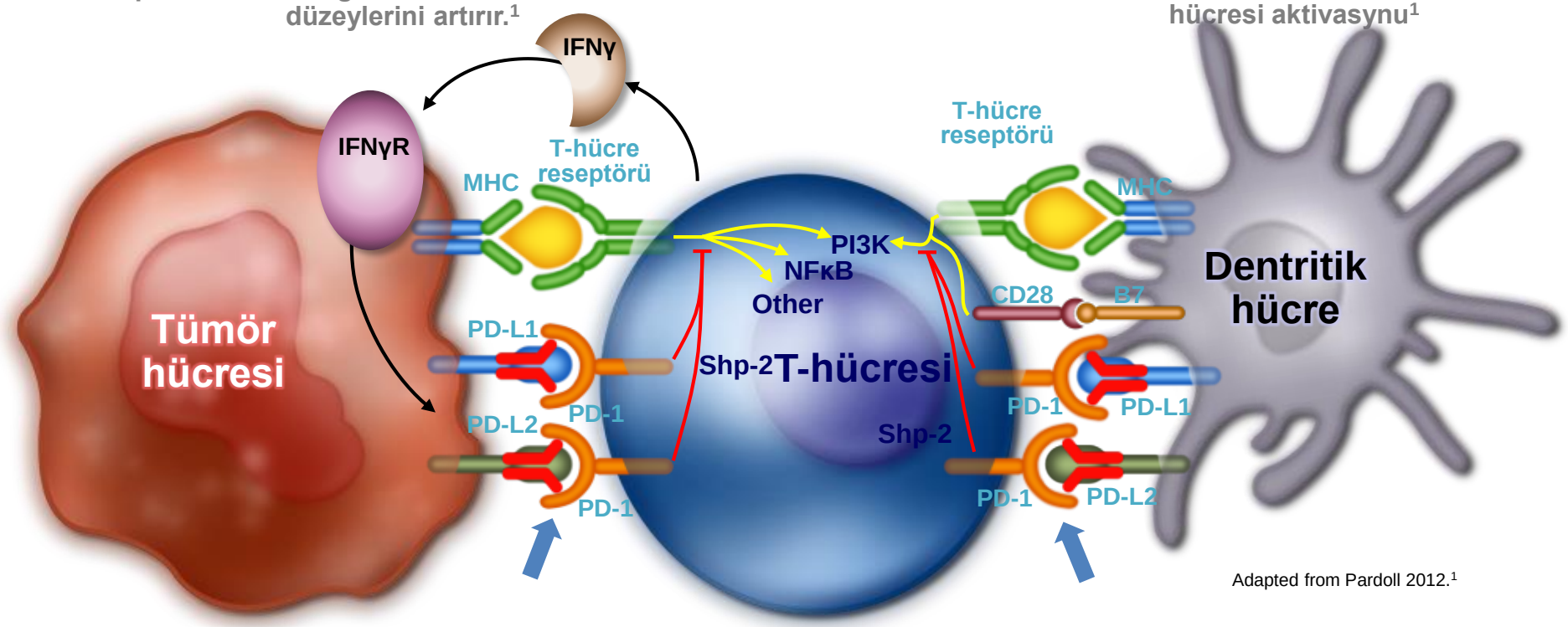


Figure 1. **PD-1 blockade in Hodgkin lymphoma. (A) PD-L1 and PD-L2 are upregulated in Hodgkin Reed-Sternberg (HRS) cells through several mechanisms, including amplification of chromosome 9p.24 which encodes the *PDL1* and *PDL2* loci.** JAK2 is also encoded on chromosome 9p.24, and

Nivolumab Etki Mekanizması

MHC/antijen etkileşimi üzerinden tümörün tanınması IFNγ salınmasını sağlar ve bu da tübörde PD-L1/2 düzeylerini artırır.[1]

Priming and activation of T-cells through MHC/antijen ve CD28/B7 üzerinden T-hücresi/dentritik hücre etkileşmi T-hücresi aktivasynu[1]



Adapted from Pardoll 2012.[1]

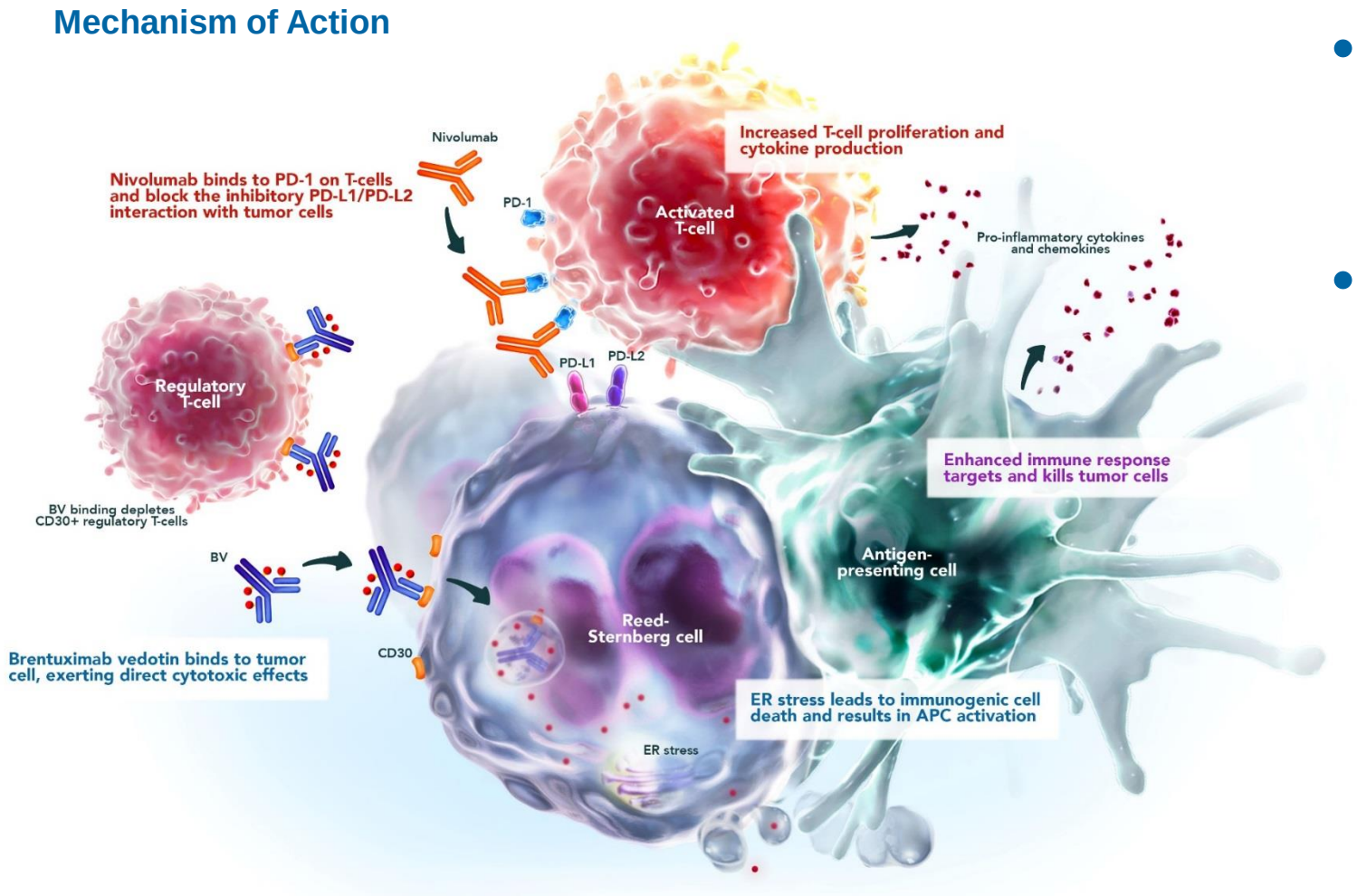
Nivolumab PD-1 reseptörünü bloklar

- Nivolumab PD-1 reseptör blokajı yapan IgG4 yapısında tamamıyla insan monoklonal antikorudur-blocking monoclonal antibody[2-4]
- Nivolumab PD-1 reseptörüne bağlanır ve PD-L1/2 ile olan etkileşimini bloklar.[5]

CD, cluster of differentiation; IFN, interferon; MOA, mechanism of action; MHC, major histocompatibility complex; NFκB, nuclear factor kappa B; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PD-L2 programmed cell death ligand 2; PI3K, phosphatidylinositol-4,5-hisphosphate 3-kinase;Shp-2, Src-Homology domain 2 containing protein tyrosine phosphatase 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12(4):252-264. 2. Brahmer JR et al. *J Clin Oncol*. 2010;28(19):3167-31751. 3. Menzies AM, Long GV. Ther Adv Med Oncol. 2013;5(5):278-285. 4. Brahmer JR et al. Oral presentation at ASCO 2013. 8030. 5. OPDIVO (nivolumab). US Prescribing Information. 2015.

Nivolumab Yapı ve Etki Mekanizması



Brentuximab vedotin plus nivolumab is an investigational drug combination; the safety and efficacy of this combination has not been established.

- **Nivolumab: IgG yapısında tamamıyla insan monoklonal antikor**
- **PD-1 reseptör blokajı üzerinden etki**

*Gardai et al., Cancer Res 75: Abstract 2469; 2015

PD-1 – a negative regulator of T-cells

Like CTLA-4, PD-1 is activated by CD4+ and CD8+ T-cells and antigen presenting cells (APCs)

PD-1 has two ligands – PD-L1 and PD-L2. PD-L1 is expressed by APCs, T-Cells, B-cells and tumour cells, whereas PD-L2 is produced only by APCs

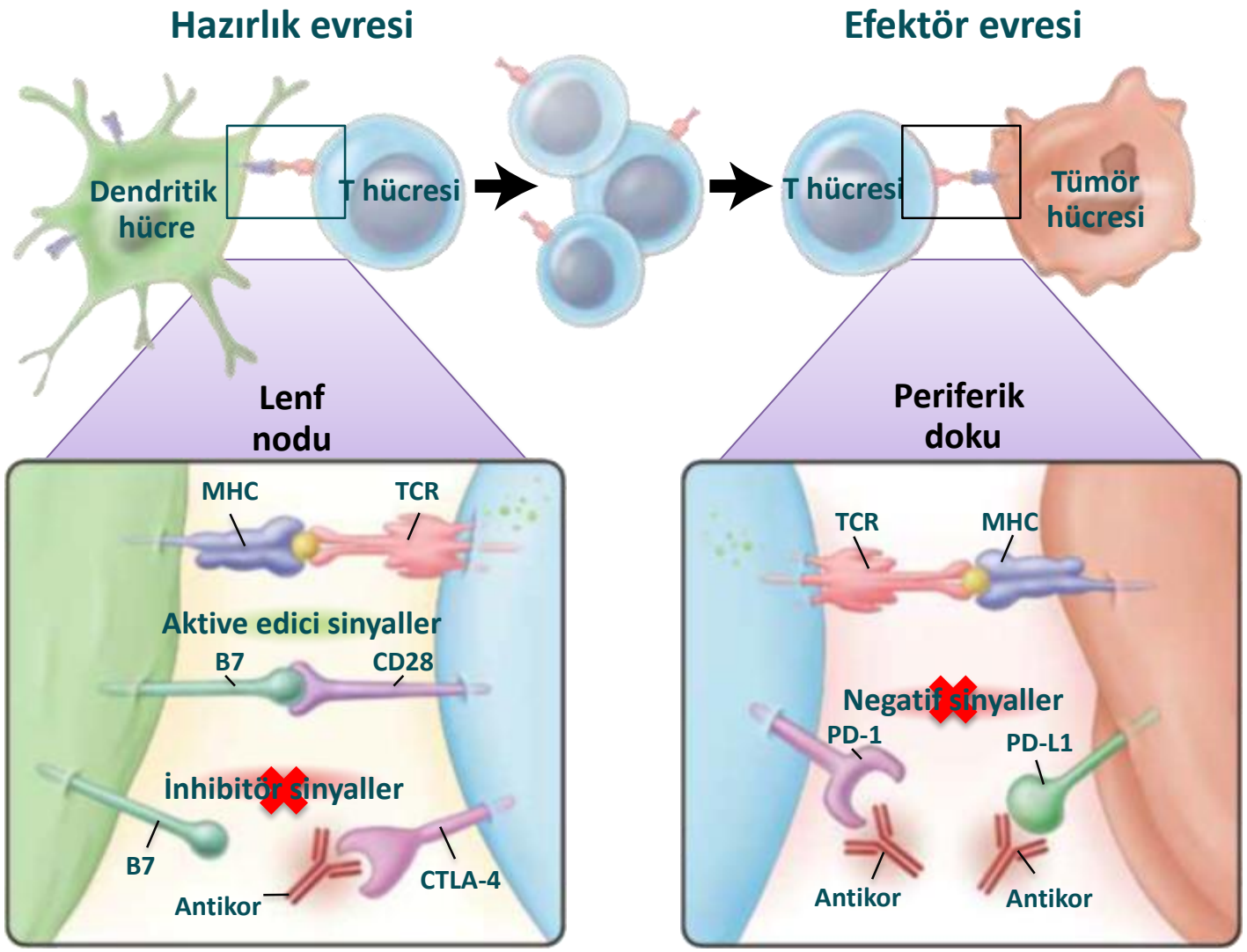
Binding of PD-1 to its ligands causes a negative T-cell response

Blocking PD-1 or its ligands can activate T-cell responses leading to reduced metastasis and tumour growth

Immune Checkpoint Inhibition in Hodgkin Lymphoma

1. Lizée G et al. Annu Rev Med 2013;64:71-90.

Nivolumab Yapı ve Etki Mekanizması



TCR = T-hücresi reseptörü; PD-L1 = programlı ölüm-ligand 1.

Ribas A. *N Engl J Med.* 2012;366:2517–2519.

Optimal role of PD-1 blockade in HL: can we enhance PD-1 blockade?

- Anti-PD-1 monotherapy a major advance in HL therapy
- However, there is room for improvement!
  - Low CR rate, depth of response ≈ duration of response
  - Ongoing risk of relapse - curative potential of monotherapy appears low
- Many potentially rational combination targets
  - Chemotherapy, radiation therapy
  - Immunomodulators: iMiDs, ibrutinib, HDACi, PI3K
  - Combination checkpoint therapy: CTLA-4, LAG-3, 4-1-BB
  - Combination immunotherapy: AFM13, CAR T-cells?

Otolog nakil sonrası (relaps/refrakter)

- ✓ Palyasyon, allojeneik nakil için köprü tedavisi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

BACKGROUND

Preclinical studies suggest that Reed–Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection. In classic Hodgkin's lymphoma, alterations in chromosome 9p24.1 increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and promote their induction through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling. We hypothesized that nivolumab, a PD-1–blocking antibody, could inhibit tumor immune evasion in patients with relapsed or refractory Hodgkin's lymphoma.

Otolog nakil sonrası (relaps/refrakter)

- ✓ Palyasyon, allojeneik nakil için köprü tedavisi

METHODS

In this ongoing study, 23 patients with relapsed or refractory Hodgkin's lymphoma that had already been heavily treated received nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks until they had a complete response, tumor progression, or excessive toxic effects. Study objectives were measurement of safety and efficacy and assessment of the *PDL1* and *PDL2* (also called *CD274* and *PDCD1LG2*, respectively) loci and PD-L1 and PD-L2 protein expression.

Otolog nakil sonrası (relaps/refrakter)

- ✓ Palyasyon, allojeneik nakil için köprü tedavisi

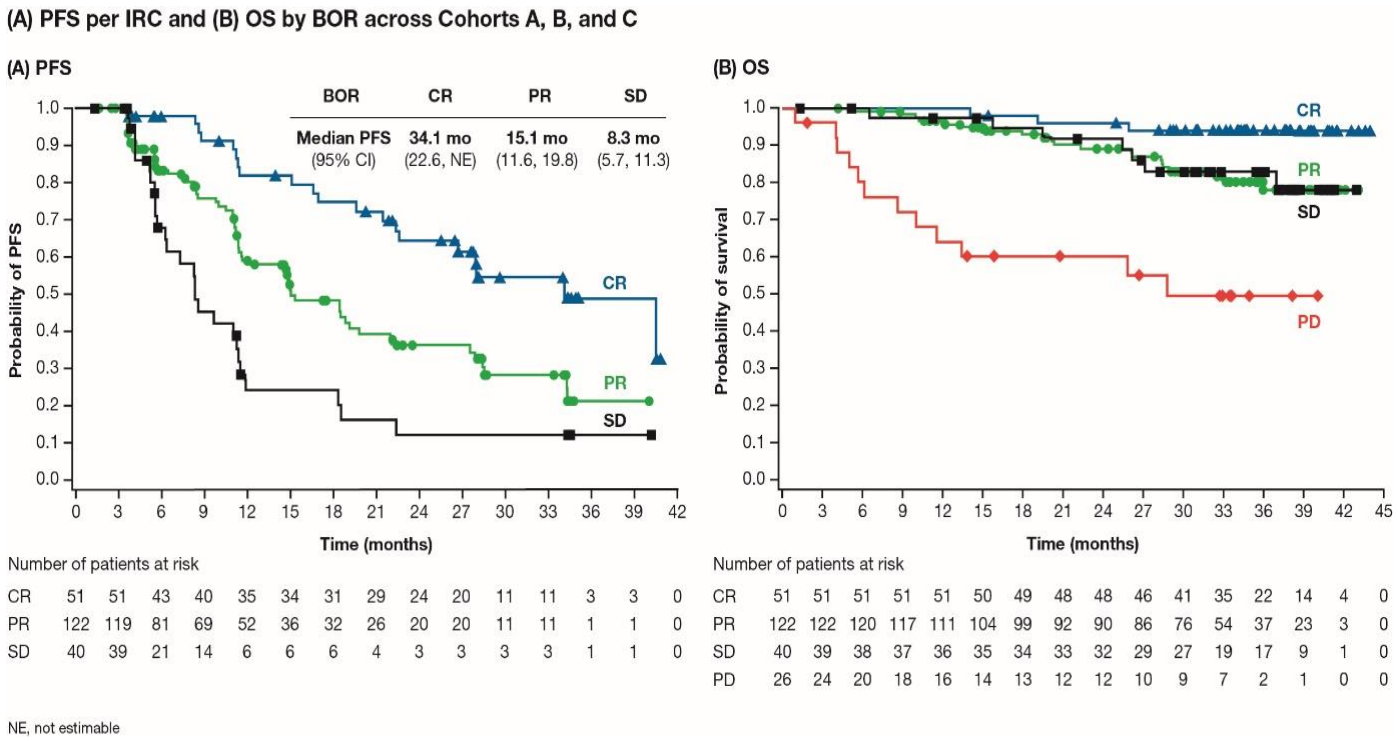
RESULTS

Of the 23 study patients, 78% were enrolled in the study after a relapse following autologous stem-cell transplantation and 78% after a relapse following the receipt of brentuximab vedotin. Drug-related adverse events of any grade and of grade 3 occurred in 78% and 22% of patients, respectively. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of progression-free survival at 24 weeks was 86%; 11 patients were continuing to participate in the study. Reasons for discontinuation included stem-cell transplantation (in 6 patients), disease progression (in 4 patients), and drug toxicity (in 2 patients). Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in *PDL1* and *PDL2* and increased expression of these ligands. Reed–Sternberg cells showed nuclear positivity of phosphorylated STAT3, indicative of active JAK-STAT signaling.

Table 3. Clinical Activity in Nivolumab-Treated Patients.*

Variable	All Patients (N=23)	Failure of Both Stem-Cell Transplantation and Brentuximab (N=15)	No Stem-Cell Transplantation and Failure of Brentuximab (N=3)	No Brentuximab Treatment (N=5)†
Best overall response — no. (%)				
Complete response	4 (17)	1 (7)	0	3 (60)
Partial response	16 (70)	12 (80)	3 (100)	1 (20)
Stable disease	3 (13)	2 (13)	0	1 (20)
Progressive disease	0	0	0	0
Objective response				
No. of patients	20	13	3	4
Percent of patients (95% CI)	87 (66–97)	87 (60–98)	100 (29–100)	80 (28–99)
Progression-free survival at 24 wk — % (95% CI)‡	86 (62–95)	85 (52–96)	NC§	80 (20–97)
Overall survival — wk				
Median	NR	NR	NR	NR
Range at data cutoff¶	21–75	21–75	32–55	30–50

Nivolumab for Relapsed or Refractory Classical Hodgkin Lymphoma (cHL) after Autologous Hematopoietic Cell Transplantation (auto-HCT): Extended Follow-up of the Phase 2 Single-Arm CheckMate 205 Study ,



Otolog nakil sonrası (relaps/refrakter)

✓ Palyasyon, allojeneik nakil için köprü tedavisi

243 pts

follow-up was 31 mo

ORR per IRC was 71%

Median duration of Tx was 14 mo

Median DOR was 18 mo overall, and was 34 and 15 mo in pts with a BOR of CR and PR, respectively.

Philippe Armand et al Blood 2018:132,2897

İkinci basamak

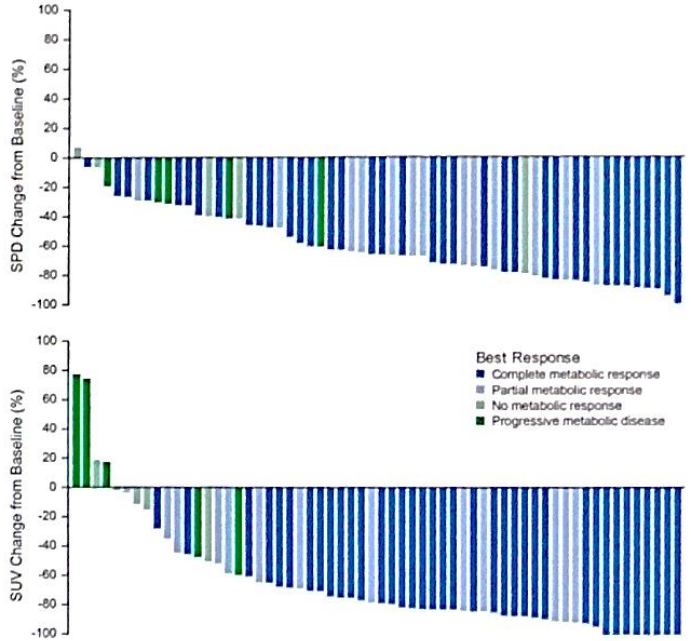
- ✓ «pre-transplant PET negatif» oranını geliştirmek

BV + Nivo as 2nd line therapy for HL

83% ORR, 62% CR among efficacy evaluable patients (n=60)

(82% ORR, 61% CR among all treated patients, n=61)

	n (%)
Objective response rate (CR + PR)	50 (83)
Complete response	37 (62)
Partial response	13 (22)
Stable disease	5 (8)
Progressive disease	4 (7)
Clinical progression	1 (2)



the MIRACLE of SCIENCE with SOUL City of Hope

Herrera AF, et al. Blood 2018

Part 1 and 2: BV 1.8 mg/kg day 1,
Nivo 3 mg/kg day 8

Nivolumab Türkiye Verisi

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2496–2502, 2017
doi:10.1093/annonc/mdx341
Published online 30 June 2017

ORIGINAL ARTICLE

Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience

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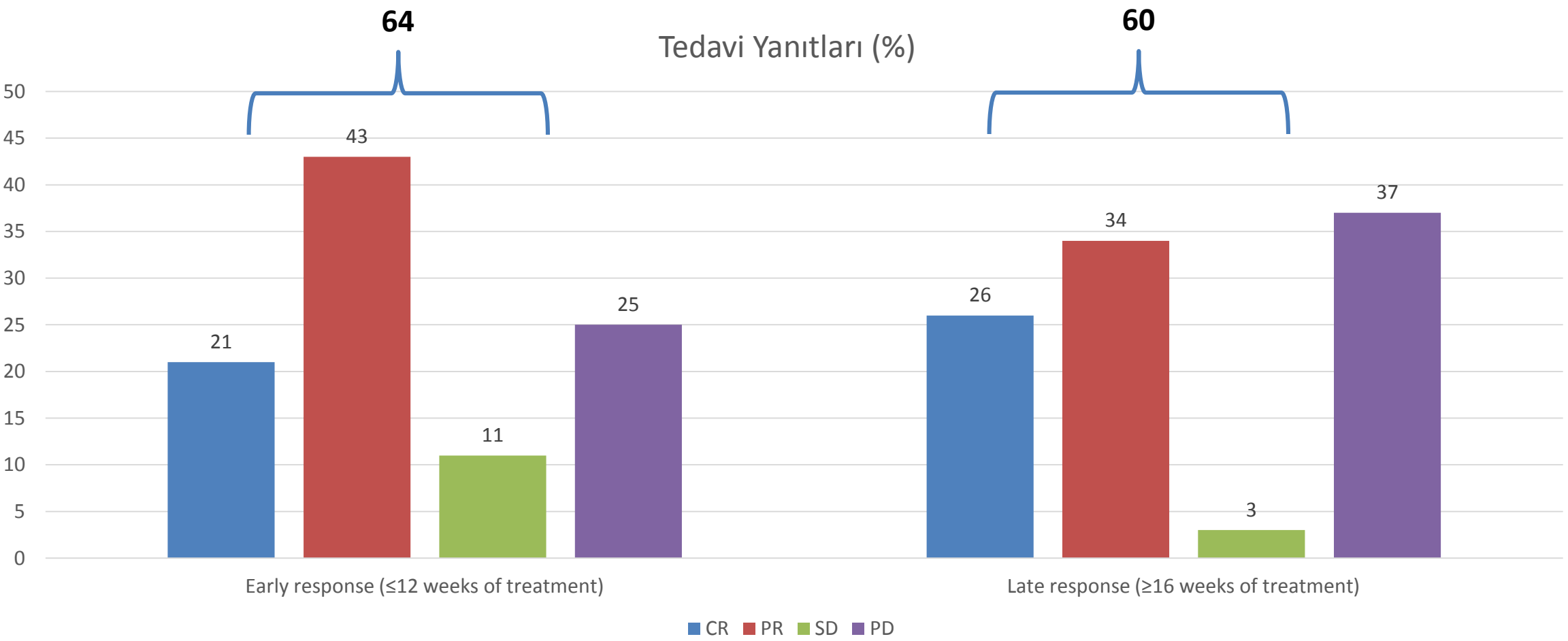
- Medyan 5(2-11) sıra tedavi almış olan hastalar
- 24 merkez, 82 hasta
- Nivolumab 3 mg/kg IV iki haftada bir
- 12/16 haftalık Nivolumab tedavisi sonrasında değerlendirme

Annals of Oncology 28: 2496–2502, 2017 doi:10.1093/annonc/mdx341 Published online 30 June 2017

Erken ve Geç Dönem Tedavi Yanıtları



- Alınan medyan nivolumab siklus sayısı: 12 (1–40)

Annals of Oncology 28: 2496–2502, 2017 doi:10.1093/annonc/mdx341 Published online 30 June 2017

Takip Sürecindeki Advers Olaylar

Adverse event	Grade 1	Grade 2	Grade 3
Fatigue	20 (25%)	4 (5%)	1 (1.2%)
Pruritus	5 (6%)	2 (2.5%)	1 (1.2%)
Fever	5 (6%)	3 (3.7%)	
Rash	5 (6%)	1 (1.2%)	
Autoimmune pneumonitis		6 (7.4%)	1 (1.2%)
Anemia	5 (6%)	2 (2.5%)	
Poor appetite	3 (3.7%)	1 (1.2%)	1 (1.2%)
Nausea	4 (5%)	1 (1.2%)	
Pneumonia	5 (6%)		
Upper respiratory tract Inf	5 (6%)		
Pain (all pains included)	5 (6%)		
Stomatitis	1 (1.2%)	1 (1.2%)	2 (2.5%)
Hypothyroidism	2 (2.5%)	2 (2.5%)	
Tumor pain		1 (1.2%)	2 (2.5%)
Neutropenia	3 (3.7%)	1 (1.2%)	
Diarrhea	1 (1.2%)	2 (2.5%)	
Lymphopenia	2 (2.5%)	1 (1.2%)	
Transaminase elevation	3 (3.7%)		
Thrombocytopenia	1 (1.2%)		1 (1.2%)

Adverse event	Grade 1	Grade 2	Grade 3
Cramps	2 (2.5%)		
Creatinine elevation	2 (2.5%)		
Hypophosphatemia	2 (2.5%)		
Hypocalcemia	2 (2.5%)		
Edema	2 (2.5%)		
Encephalitis			1 (1.2%)
GVHD aggravation			2 (2.5%)
Pancreatitis			1 (1.2%)
Infusion hypersensitivity	1 (1.2%)		
Hypercalcemia	1 (1.2%)		
Scrotal pain	1 (1.2%)		
Headache	1 (1.2%)		
Abdominal pain	1 (1.2%)		
Gynecomastia	1 (1.2%)		
Visual problem	1 (1.2%)		
Peripheral neuropathy	1 (1.2%)		
Arthritis	1 (1.2%)		

- 6 hastada advers olay nedeniyle tedavi sonlandırılmıştır.

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İlk basamak

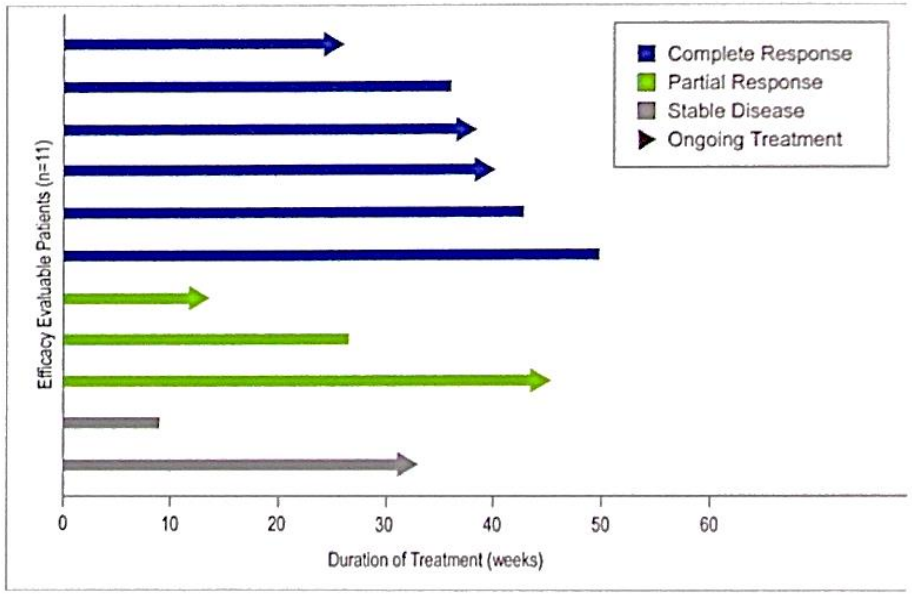
- ✓ **Erken evre**
  - ❖ Radyoterapisiz kür arayışı
- ✓ **İleri evre**
  - ❖ Yüksek riskli hastalarda artmış yanıt arayışı
- ✓ **Yaş ≥ 60**
  - ❖ Anti-neoplastik etkinliği arttırırken toksik organ hasarlarından kaçınmak

Nivolumab+BV as frontline therapy in elderly pts with HL

82% ORR, 55% CR among efficacy evaluable patients (n=11)

Best Responses Evaluable Patients (n=11)	N (%)
Complete response	6 (55)
Partial response	3 (27)
Stable disease	2 (18)
Progressive disease	0
Overall response rate (CR+PR)	9 (82)
Disease control rate (CR+PR+SD)	11 (100)

Median follow-up: 8 months



the MIRACLE of SCIENCE with SOUL City of Hope.

Friedberg J., et al. ISHL 2018

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MOA of Checkpoint Inhibitors

Pseudo-Progression as Response to Immuno-Oncology Therapies

Nivolumab: Ongoing BMS-Sponsored Clinical Trials

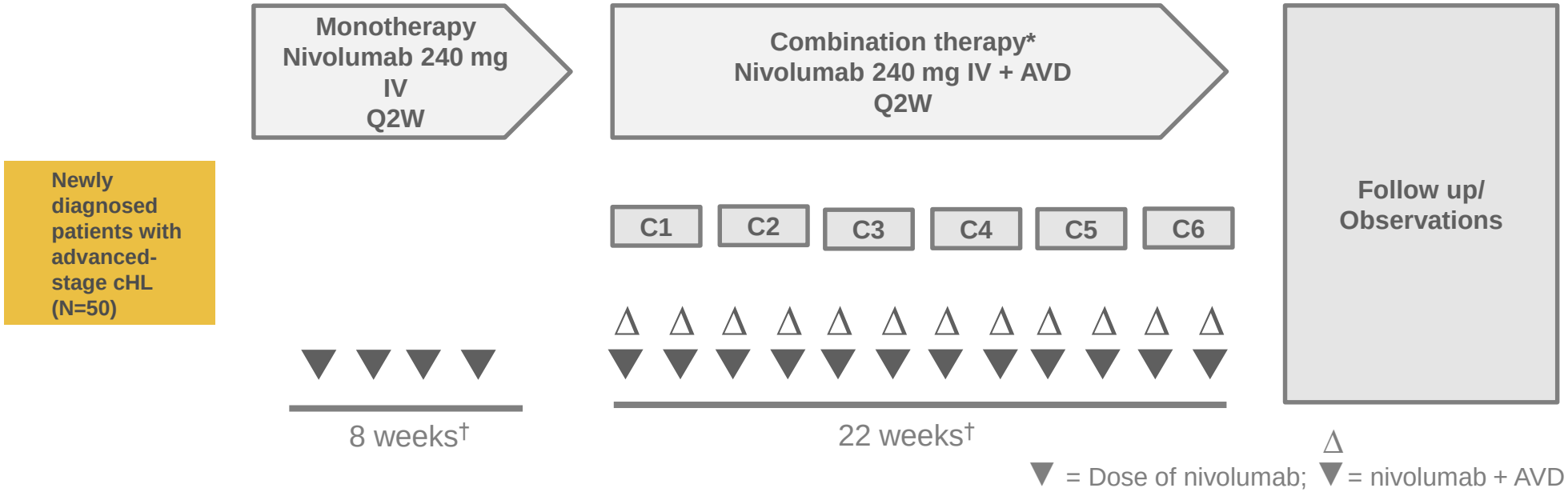
Nivolumab: Flat dosing

Nivolumab: ISRs

Summary

CheckMate 205 (Cohort D): Nivolumab in Newly Diagnosed Advanced Stage cHL

NCT02181738: Cohort D is evaluating nivolumab in newly diagnosed, treatment naïve patients with cHL



Start Date: July 2014
Actual Primary Completion Date: August 2017
Estimated Study Completion Date: October 2020
Sponsor: BMS
Status: Ongoing, but not recruiting participants

Primary endpoint: Safety/tolerability

Secondary endpoint: CR (PFS, exploratory)

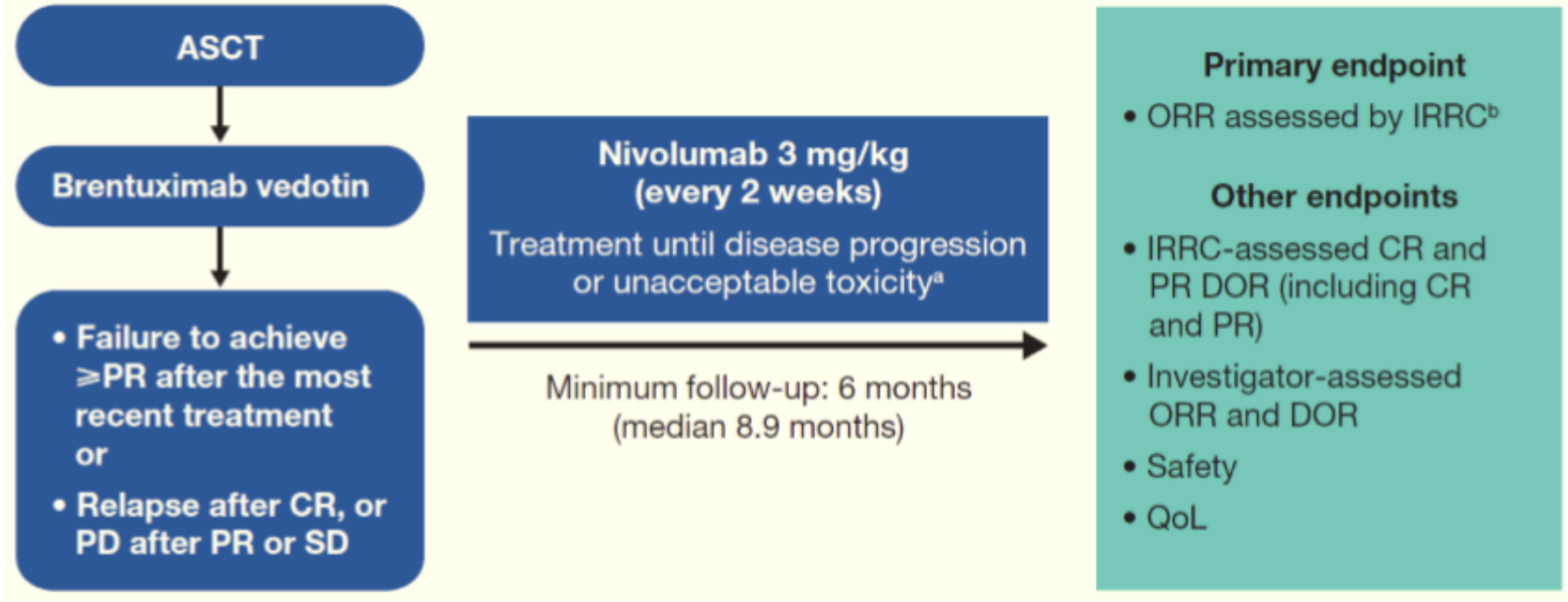
*AVD without nivolumab is permitted if criteria met. †Approximate duration.
AVD, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2; C, cycle (dose on Day 1 and Day 15); every 28 days of therapy; cHL, classical Hodgkin lymphoma; CR, complete response; IV, intravenous; PFS, progression-free survival, Q2W, every 2 weeks.
1. Clinicaltrials.gov. NCT02181738. 2. Armand P et al. Poster presentation at ASCO 2016. Abstract TPS7573.

Slide last updated March 6, 2019.

Bristol-Myers Squibb

CheckMate 205 Çalışma Tasarımı (Cohort B)

Figure 1. Study Design



[a]Patients could elect to discontinue nivolumab and proceed to hematopoietic SCT

[b]ORR per the 2007 IWG criteria

CR = complete remission; DOR = duration of response; IRRC = independent radiologic review committee; IWG = International Working Group; ORR = objective response rate; PD = progressive disease; PR = partial remission; SCT = stem cell transplantation; SD = stable disease

Başlangıç Hasta Özellikleri

Characteristics	Value
Age (years), median (range)	37 (18–72)
Age <65 years	77 (96)
Male sex	51 (64)
Previous lines of therapy,[a] median (range)	4 (3–15)
⩾5 lines of therapy	39 (49)
Previous radiation therapy	59 (74)
Previous ASCT	80 (100)
1 prior ASCT	74 (93)
⩾2 prior ASCTs	6 (8)

Data shown as n (%) unless indicated otherwise

[a]Excluding high-dose preparative regimen prior to ASCT

CheckMate 205 Çalışması Sonuçları

Cevap	*Araştırmacı (n = 80)*	*IRRC (n = 80)*
ORR, n (%) **95% CI**	58 (72.5%), 61.4–81.9	53 (66.3%), 54.8–76.4
En iyi genel cevap, n (%)		
CR	**22 (28%)**	**7 (9%)**
PR	**36 (45%)**	**46 (58%)**
SD	18 (23%)	18 (23%)
PD	3 (4%)	6 (8%)
Belirlenmemiş	1 (1%)±	3 (4%)*

- İlk cevaba dek geçen ortanca süre: 2.1 ay (aralık 1.6–5.7)
- **Medyan cevap süresi: 7.8 ay (95% CI, 6.6 – ulaşılmadı)**
  - **Medyan CR süresi: 8.7 ay (95% CI, NA)**
  - Medyan PR süresi: 7.8 ay (95% CI, 6.7 – 7.8)

±No radiographic assessment was done after the first dose of nivolumab.

*Two patients had no post-baseline tumor assessment available before or on the day of subsequent therapy (if any); for one patient, all post-baseline tumor assessments before or on the day of subsequent therapy (if any) are unknown.

- BV, brentuximab vedotin; CI, confidence interval; IRRC, independent radiologic review committee; OR, objective response; ORR, objective response rate.
- 1. Younes A et al. *Lancet Oncol.* 2016.

CheckMate 205 Çalışması Advers Olaylar (≥10% of N: 80)

	Any grade	Grade 3–4
Patients with a drug-related event	72 (90)	20 (25)
Fatigue	20 (25)	0
Infusion-related reaction	16 (20)	0
Rash	13 (16)	1 (1)
Pyrexia	11 (14)	0
Arthralgia	11 (14)	0
Nausea	10 (13)	0
Diarrhea	8 (10)	0
Pruritus	8 (10)	0

Data shown as n (%)

[a]AEs occurring between first dose and 30 days after last dose

Sonuçlar

- Otolog nakil ve BV sonrası relaps hastalarda nivolumab;
  - %66 ORR sağladı
  - Data cut-off sırasında 7.8 ay medyan yanıt süresi ve 10 ay PFS sergiledi

- Bir anti-PD1 ajan olan nivolumab otolognakil ve BV kullanımı sonrası relaps olan hasta grubundaki karşılanmamış ihtiyacı karşılamaya aday bir ajandır.

CheckMate 205 Devam Çalışması

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

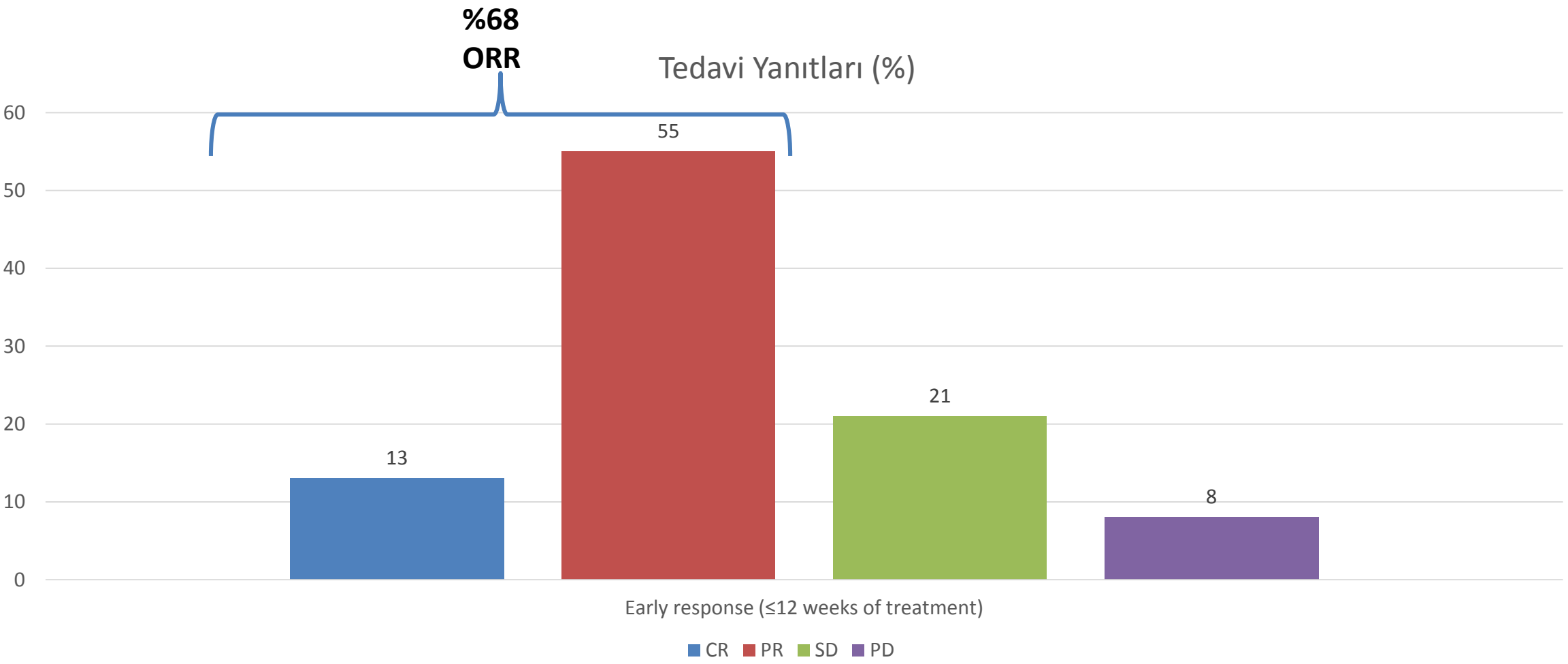
Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial

Philippe Armand, Andreas Engert, Anas Younes, Michelle Fanale, Armando Santoro, Pier Luigi Zinzani, John M. Timmerman, Graham P. Collins, Radhakrishnan Ramchandren, Jonathon B. Cohen, Jan Paul De Boer, John Kuruvilla, Kerry J. Savage, Marek Trneny, Margaret A. Shipp, Kazunobu Kato, Anne Sumbul, Benedetto Farsaci, and Stephen M. Ansell

- Kohort A:63, B:80 C:100 n: 243

Published at jco.org on March 27, 2018. https://doi.org/10.1200/JCO.2017. 76.0793

Uzun Dönem Tedavi Yanıtları



- Medyan takip süresi kohort B için 23 aydır

Published at jco.org on March 27, 2018. https://doi.org/10.1200/JCO.2017. 76.0793

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Summary of Nivolumab in Hodgkin Lymphoma

- Nivolumab binds to PD-1, allowing disruption of PD-L1 and PD-L2 interactions[1]
- Nivolumab has demonstrated clinical activity in patients with relapsed/refractory cHL[2,3] and has the following indications in HL:
  - **US[1]**
    - cHL that has relapsed or progressed after auto-HSCT and brentuximab vedotin or ≥3 lines of systemic therapy that includes auto-HSCT
  - **EU[4]**
    - Adult patients with relapsed or refractory cHL after autologous stem cell transplant and treatment with brentuximab vedotin
- Research is ongoing into the use of nivolumab in earlier lines of therapy, or as part of combination regimens[5]

Slide last updated March 6, 2019.

auto-HSCT, autologous hematopoietic stem cell transplantation; cHL, classical Hodgkin lymphoma; EU, European Union; HL, Hodgkin lymphoma; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; US, United States.

1. Opdivo (nivolumab). US Prescribing Information. Bristol Myers Squibb. February 2019. 2. Ansell SM et al. Oral Presentation at ASH 2015. Abstract 583. 3. Armand P et al. Oral Presentation at ASH 2015. Abstract 584. 4. Opdivo (nivolumab), SMPC. Bristol Myers Squibb. January 2019. 5. Clinicaltrials.gov. Accessed December 11, 2018.

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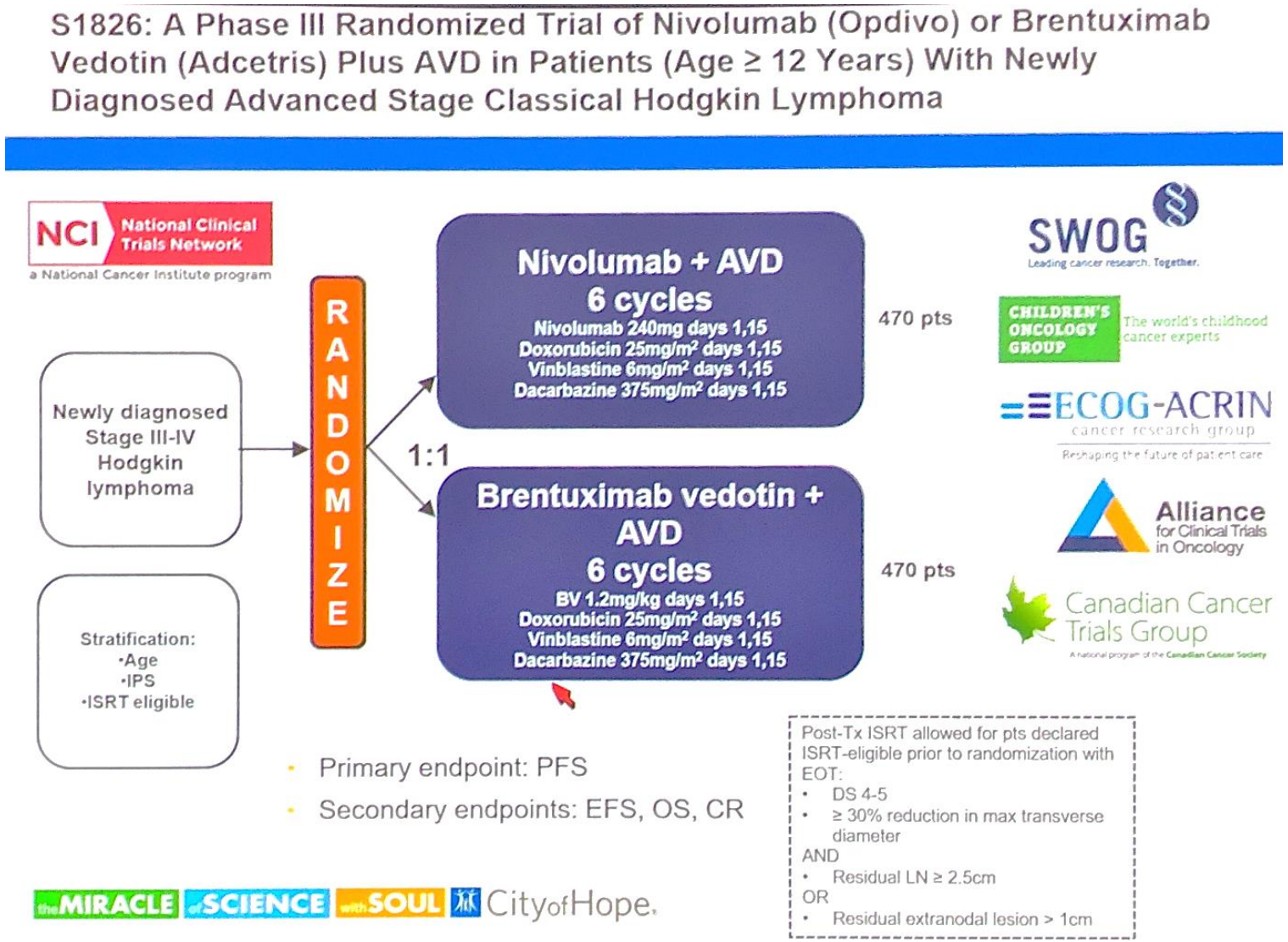

Table 4

Ongoing Clinical Trials of PD-1 Inhibitor Combination Therapy

Trial Intervention	Phase	Status; Estimated Completion Date	ClinicalTrials.gov NCT Reference
Combined with chemotherapy			
Nivolumab and AVD in early-stage unfavorable HL	II	Recruiting; December 2020	NCT03004833
A(B)VD followed by nivolumab as frontline therapy	II	Recruiting; January 2020	NCT03033914
Nivolumab with ICE as second-line therapy	II	Recruiting; April 2019	NCT03016871
Pembrolizumab with ICE as second-line therapy	II	Recruiting; February 2020	NCT03077828
Pembrolizumab and combination chemotherapy in untreated patients	II	Not yet recruiting	NCT03226249
Combined with brentuximab vedotin			
Nivolumab plus brentuximab vedotin vs brentuximab alone in relapsed/refractory HL	III	Recruiting; July 2023	NCT03138499
Nivolumab and brentuximab vedotin with or without ipilimumab in relapsed/refractory HL	I/II	Recruiting; June 2018	NCT01896999
Nivolumab and brentuximab vedotin in older patients with untreated HL	II	Recruiting; May 2024	NCT02758717
Nivolumab and brentuximab vedotin after SCT in patients with relapsed/refractory HL	II	Recruiting; April 2019	NCT03057795
Combined with BTK inhibitors			
Ibrutinib and nivolumab in relapsed or refractory HL	II	Recruiting; May 2020	NCT02940301
ACP-196 (acalabrutinib) with pembrolizumab	Ib/II	Ongoing; April 2021	NCT02362035
Combined with immunodulatory agents			
Nivolumab and lenalidomide in relapsed or refractory NHL or HL	I/II	Suspended; April 2020	NCT03015896
Pembrolizumab and lenalidomide in relapsed NHL and HL	I/II	Recruiting; August 2023	NCT02875067
Combined with HDAC inhibitors			
Pembrolizumab and vorinostat in relapsed or refractory DLBCL, FL, or HL	I	Recruiting; July 2019	NCT03150329
Combined with radiotherapy			
Pembrolizumab and ISRT for early-stage relapsed or primary refractory HL	II	Recruiting; June 2020	NCT03179917

ABVD = adriamycin, bleomycin, vinblastine, dacarbazine, AVD = doxorubicin, vinblastine, and dacarbazine, BTK = Bruton tyrosine kinase, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, HDAC = histone deacetylase, HL = Hodgkin lymphoma, ICE = ifosfamide, carboplatin, etoposide, ISRT = involved-site radiation therapy, NHL = non-Hodgkin lymphoma, SCT = stem cell transplant.