ANITAS
ER CENTER

1st Cuneo City Immunotherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2018

CUNEO

May 17-19, 2018

Centro Incontri

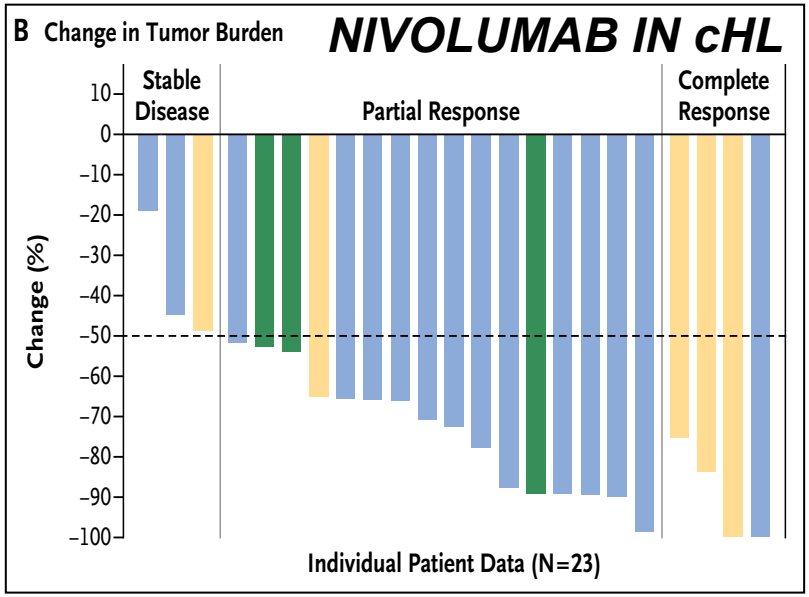
PDI/PDL1 blockade in Hodgkin lymphoma (*Armando Santoro - Rozzano - MI)*

Organized by Prof. Massimo Massaia, SC Ematologia AO S. Croce e Carle, Cuneo, Italy
and Centro Interdipartimentale di Ricerca in Biologia Molecolare (CIRBM), Torino, Italy

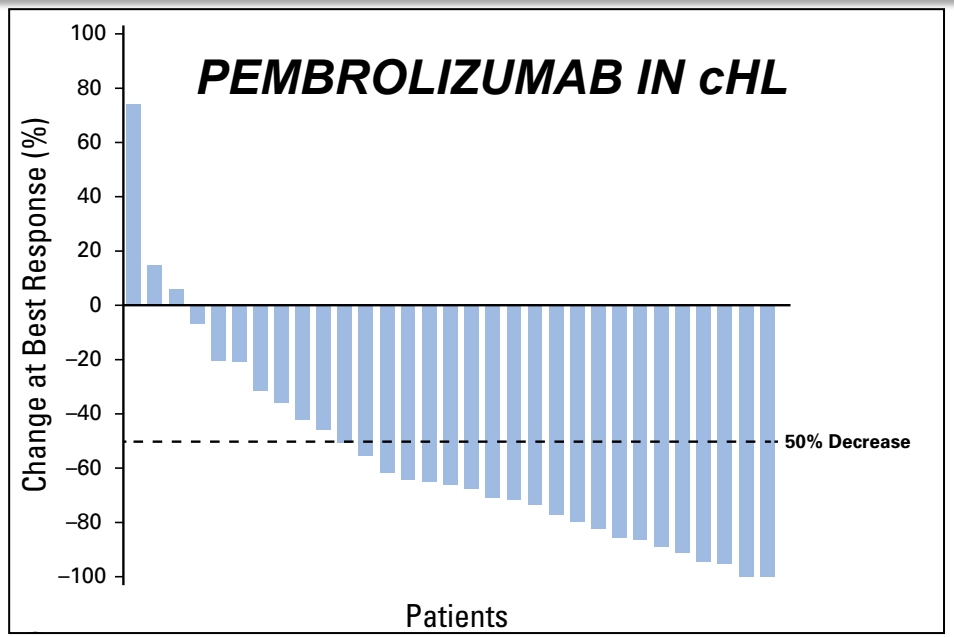
CONFLITTO D'INTERESSI

- ***BMS***
- ***ARQULE***
- ***TAKEDA***
- ***SERVIER***
- ***BAYER***
- ***ASTRA ZENECA***
- ***GILEAD***
- ***MSD***
- ***ROCHE***
- ***LILLY***
- ***NOVARTIS***
- ***SANDOZ***

…….. e altre



Ansell SM et al
NEJM 2015



Armand P et al
JCO 2016

THE SUBSEQUENT STEPS

KEYNOTE-087

Pembrolizumab
200 mg Q3W

Cohort 1 (N = 69)
ASCT and
subsequent BV

Cohort 2 (N = 81)
Salvage chemotherapy
and BV,
ineligible for ASCT

Cohort 3 (N = 60)
ASCT and no BV after
transplantation

CHECKMATE-205

Nivolumab
3 mg/kg IV Q2W

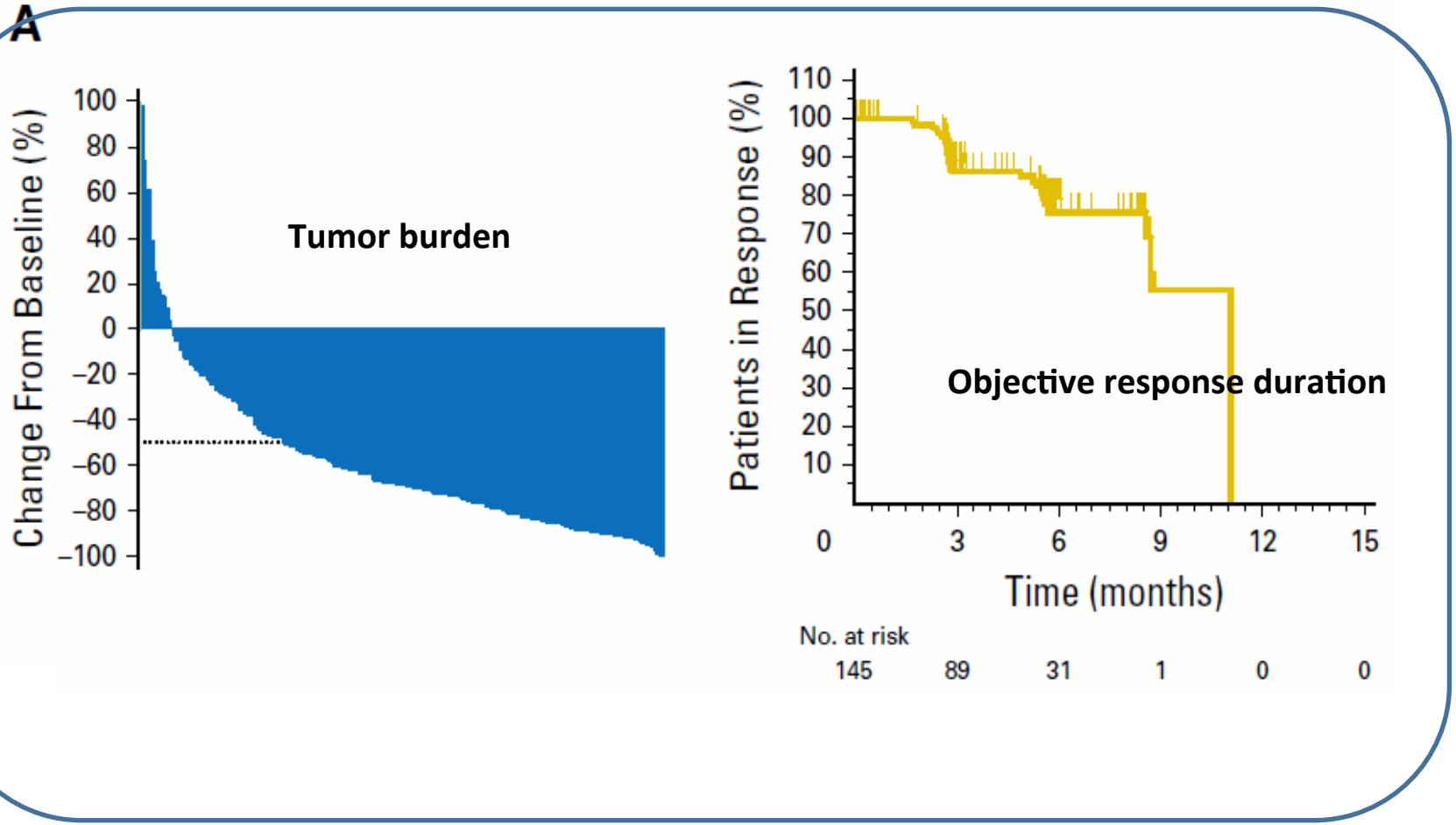
Cohort A:
No BV experience
(n = 63)

Cohort B:
BV after ASCT
(n = 80)

Cohort C:
BV before and/or after
ASCT
(n = 100)

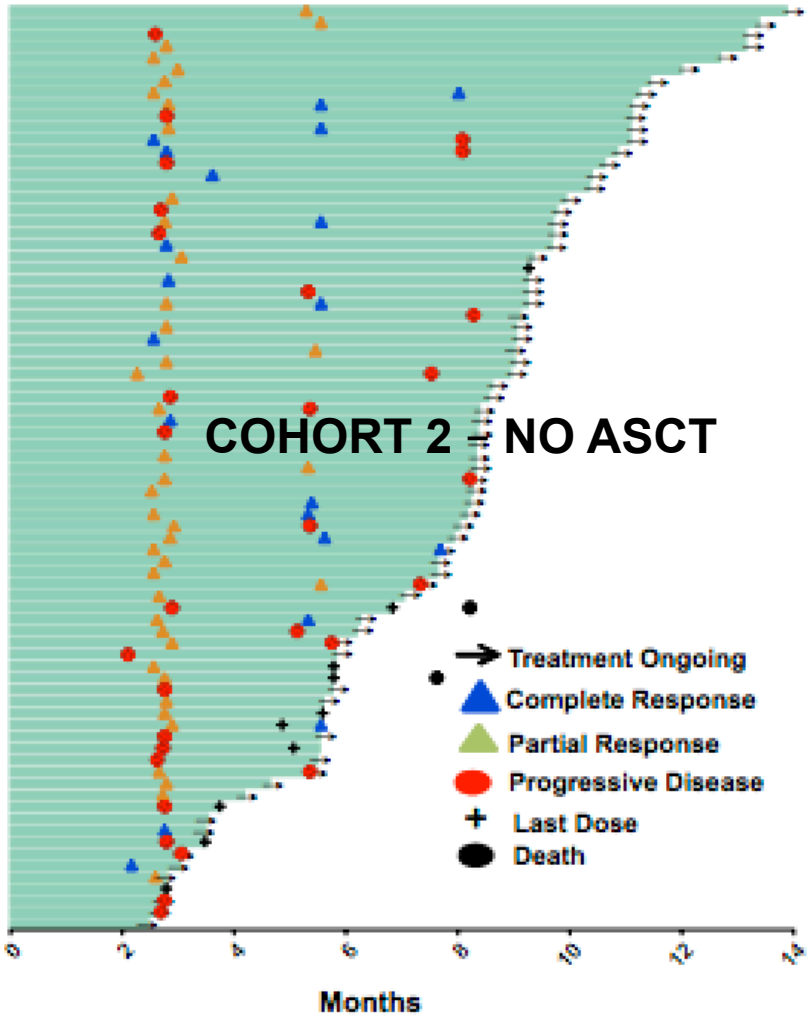
KEYNOTE-087 : PHASE 2 STUDY WITH PEMBROLIZUMAB IN R/R HL

ALL COHORTS (210 PTS)



Chen R, Zinzani PL, Fanale M, et al, JCO 2017

KEYNOTE-087: RESULTS BY COHORT



Cohort 2 After salvage chemo and BV, ineligible for ASCT N = 81		Cohort 3 ASCT and no BV after transplantation N = 60	
N	%	N	%
52	64.2	42	70.0
20	24.7	12	20.0
32	39.5	30	50.0
10	12.3	10	16.7
17	21.0	8	13.3
2	2.5	0	0

Chen R, Zinzani PL, Fanale M, et al, JCO 2017

KEYNOTE-087: SUBGROUP ANALYSIS

	Primary Refractory Disease (n = 73)		Relapsed After ≥3 Lines of Therapy (n = 146)	
	n (%)	95% CI‡	n (%)	95% CI‡
ORR	58 (79.5)	68.4-88.0	99 (67.8)	59.6-75.3
Complete remission	17 (23.3)	14.2-34.6	31 (21.2)	14.9-28.8
Partial remission	41 (56.2)	44.1-67.8	68 (46.6)	38.3-55.0
Stable disease	4 (5.5)	1.5-13.4	24 (16.4)	10.8-23.5
Progressive disease	8 (11.0)	4.9-20.5	20 (13.7)	8.6-20.4
Unable to determine	3 (4.1)	0.9-11.5	3 (2.1)	0.4-5.9

†These subgroups are not mutually exclusive
‡Based on binomial exact confidence interval method

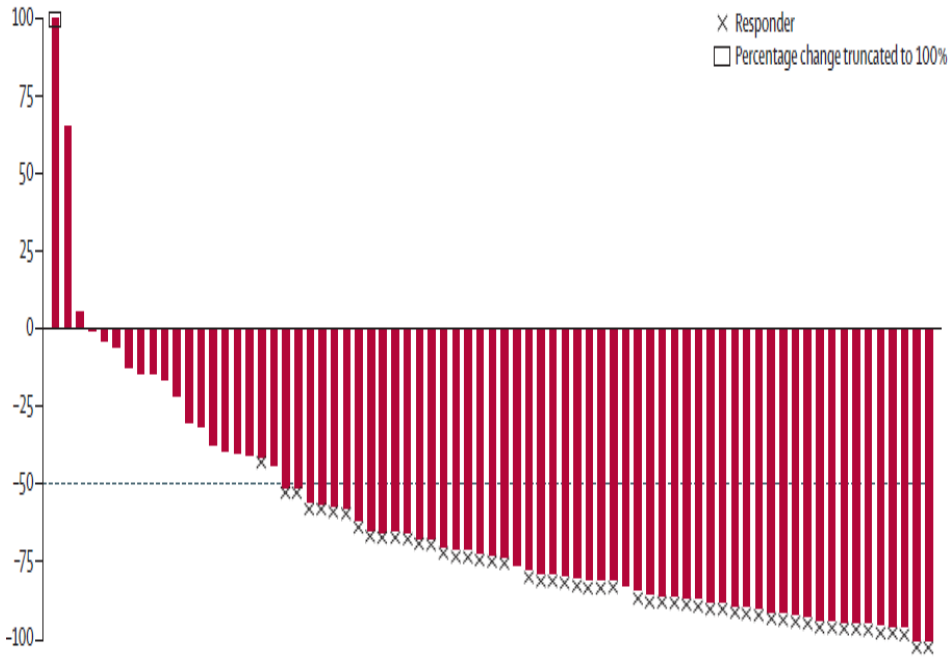
Chen R, Zinzani PL, Fanale M, et al, JCO 2017

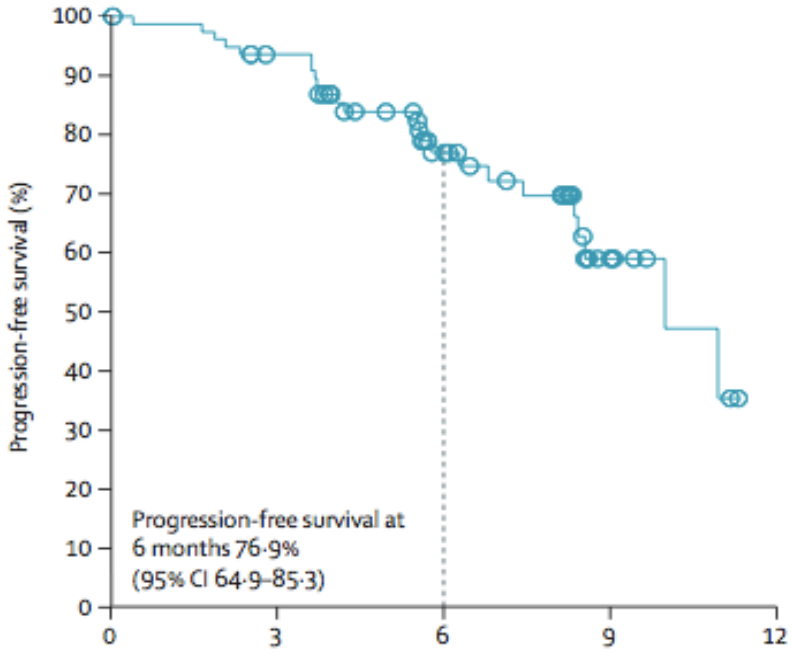
Checkmate 205: COHORT B

NIVO IN ASCT+BV (60 PTS)

OBJECTIVE RESPONSE: 66.3%,

CR 9%, PR 58%





A. Younes, A. Santoro, M. Shipp et al, Lancet Oncol 2016

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

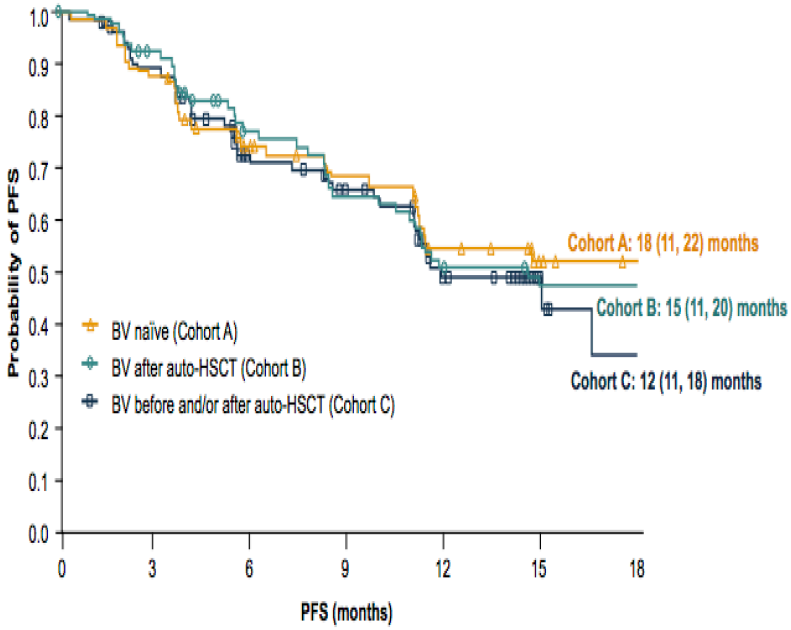
JOURNAL OF CLINICAL ONCOLOGY

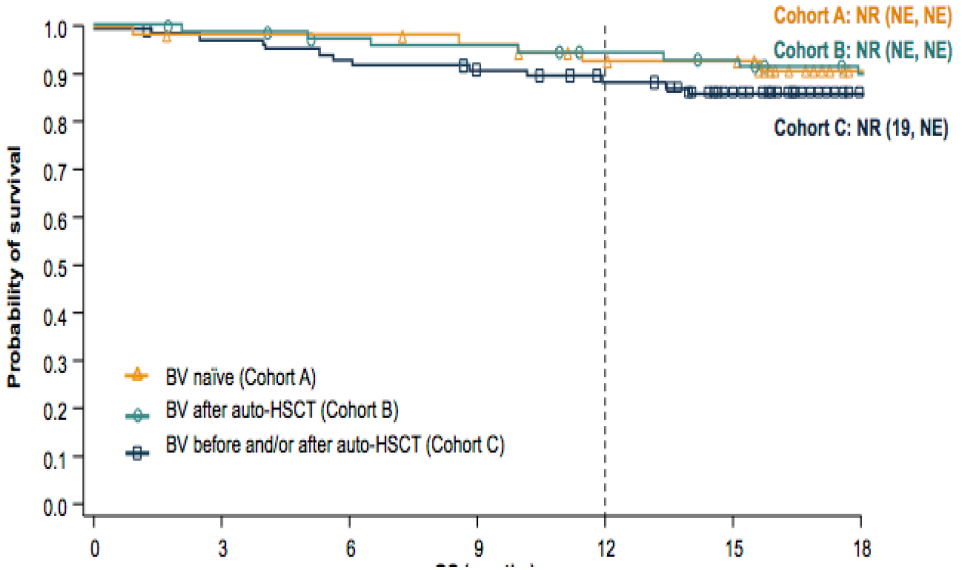
2018

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

	BV naïve (Cohort A) n = 63	BV after auto-HSCT (Cohort B) n = 80	BV before and/or after auto-HSCT (Cohort C) n = 100	Overall N = 243
Objective response per IRC, % (95% CI)	**65 (52, 77)**	**68 (56, 78)**	**73 (63, 81)**	**69 (63, 75)**
Best overall response per IRC, %				
Complete remission[b]	**29**	**13**	**12**	**16**
Partial remission	**37**	**55**	**61**	**53**
Stable disease	**24**	**21**	**15**	**19**
Progressive disease	**11**	**8**	**10**	**9**
Unable to determine	**0**	**4**	**2**	**2**

CHECKMATE 2015: MULTICOHORT RESULTS





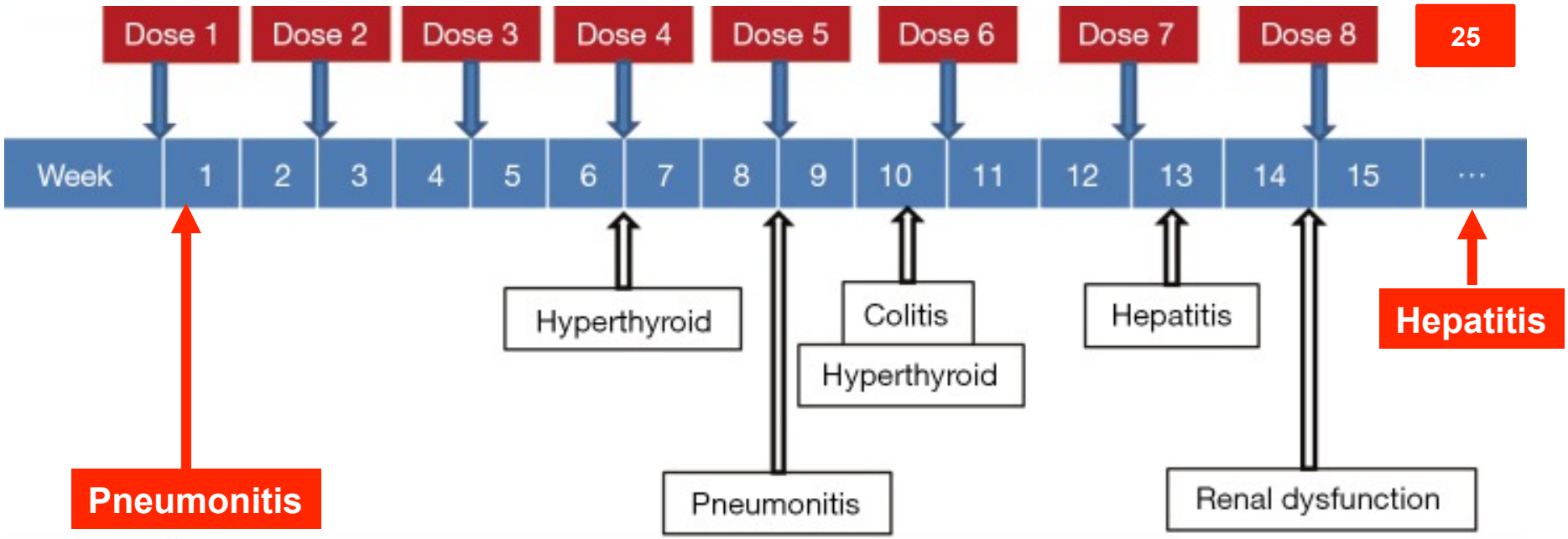
Armand P, Engert A, Younes A, et al, JCO 2018

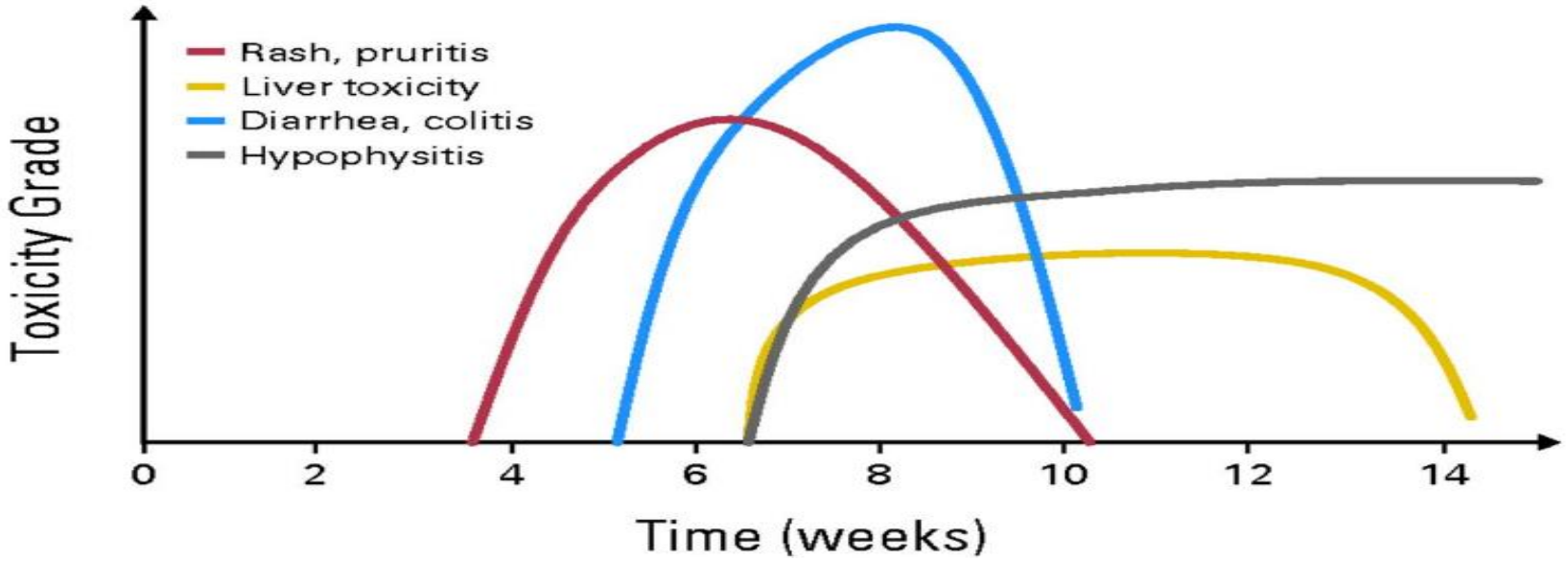
CHECKMATE 205: MULTICOHORT RESULTS ACCORDING TO DISEASE STATUS

	Refractory to first line (n = 142)	Refractory to last line (n = 114)	Refractory to BV after auto-HSCT (n = 70)
Objective response, %	73	68	69
Best overall response, %			
Complete remission	18	13	6
Partial remission	55	54	63
Median DOR in patients with PR, months (95% CI)	13 (9, 18)	17 (9, NE)	17 (8, NE)[a]

Armand P, Engert A, Younes A, et al, JCO 2018

PD1-BLOCKADE: SAFETY PROFILE





FDA APPROVAL OF CHECKPOINT INHIBITORS IN cHL

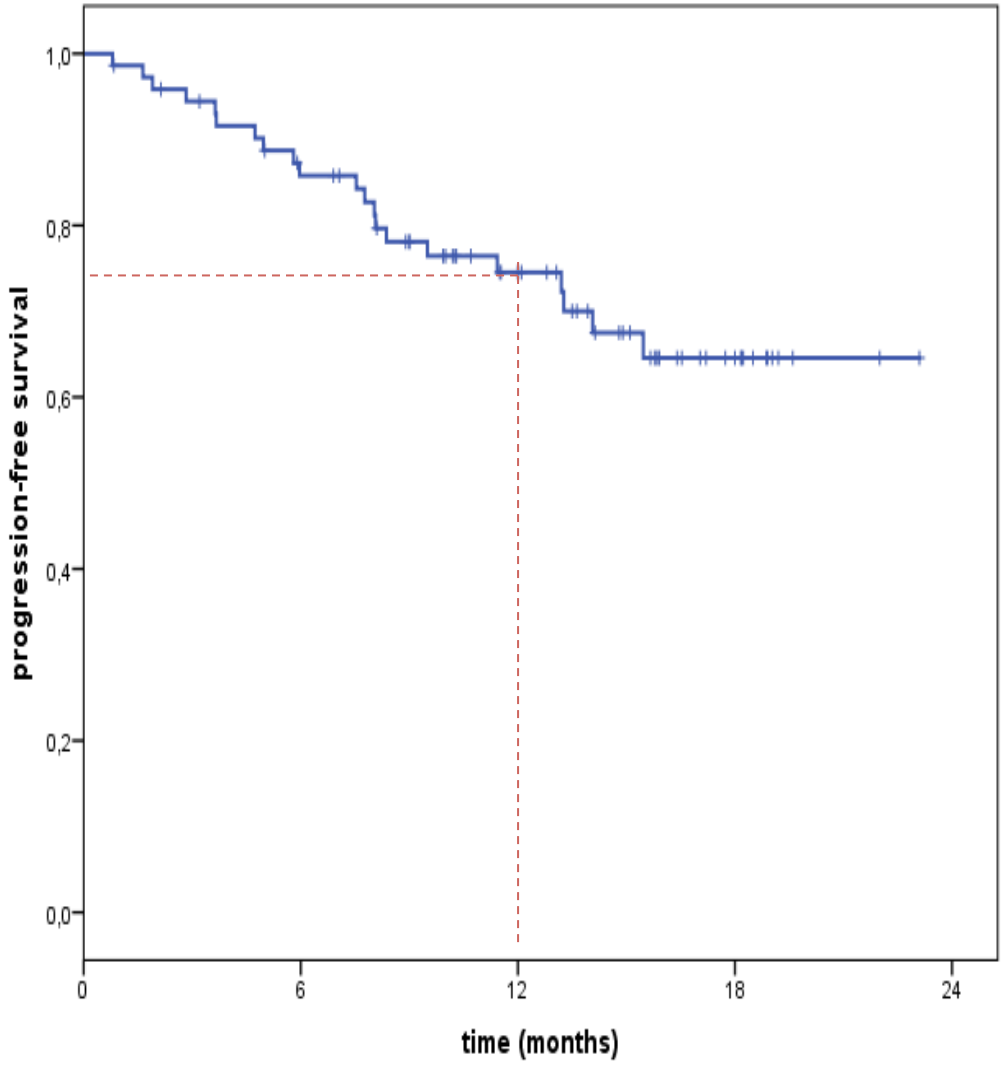
Agent	EU	US
Nivolumab	▪ Adult pts with relapsed/ refractory disease after ASCT and brentuximab vedotin ▪ Dosing: 3 mg/kg Q2W	▪ Adult pts with relapsed/ progressed disease after ASCT and brentuximab vedotin ▪ Adult pts with relapsed/ progressed disease after ≥ 3 lines of systemic therapy including ASCT ▪ Dosing: 3 mg/kg Q2W
Pembrolizumab	▪ Adult pts with relapsed/ refractory disease after ASCT and brentuximab vedotin ▪ Adult pts with relapsed/ refractory disease who failed brentuximab vedotin and are transplantation	▪ Adult or pediatric pts with refractory disease or who have relapsed after ≥ 3 previous lines of therapy ▪ Dosing: 200 mg Q3W (adults) or 2 mg/kg Q3W, up to 200

ITALIAN HL EAP WITH NIVOLUMAB

PFS

PATIENTS 137

1 yr PFS 74.5%
2 yr PFS 64.6%



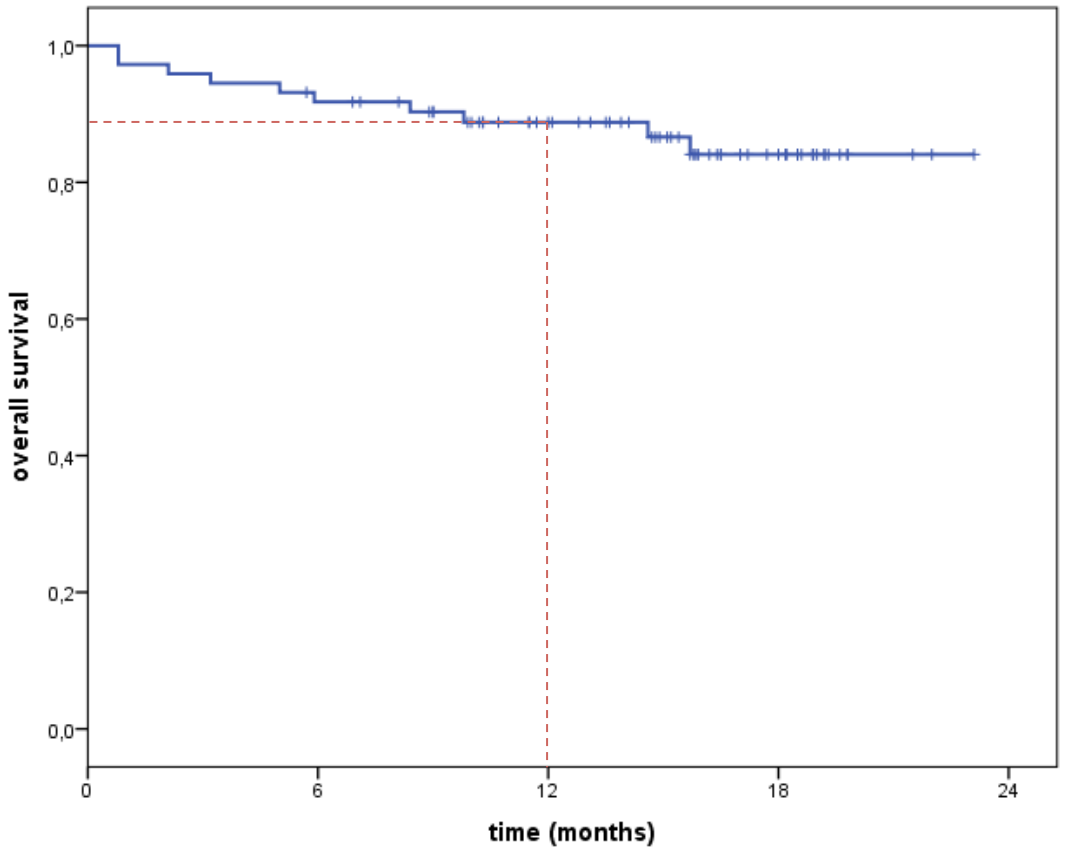
Santoro A et al ASH 2017

ITALIAN HL EAP WITH NIVOLUMAB

OVERALL SURVIVAL

PATIENTS 137

1 year OS 89%
2 year OS 84%



Santoro A et al ASH 2017

RISULTATI ENTUSIASMANTI

SONO D'ACCORDO

VORREI CAPIRE

THE OPEN QUESTIONS

RESPONSE EVALUATION

THERAPY BEYOND PROGRESSION

ALLOTMO: YES OR NOT?

THERAPY DURATION

PREDICTORS OF RESPONSE

LYRIC CRITERIA

LYmphoma
Response to
Immunomodulatory therapy
Criteria

INDETERMINATE RESPONSE CATEGORY

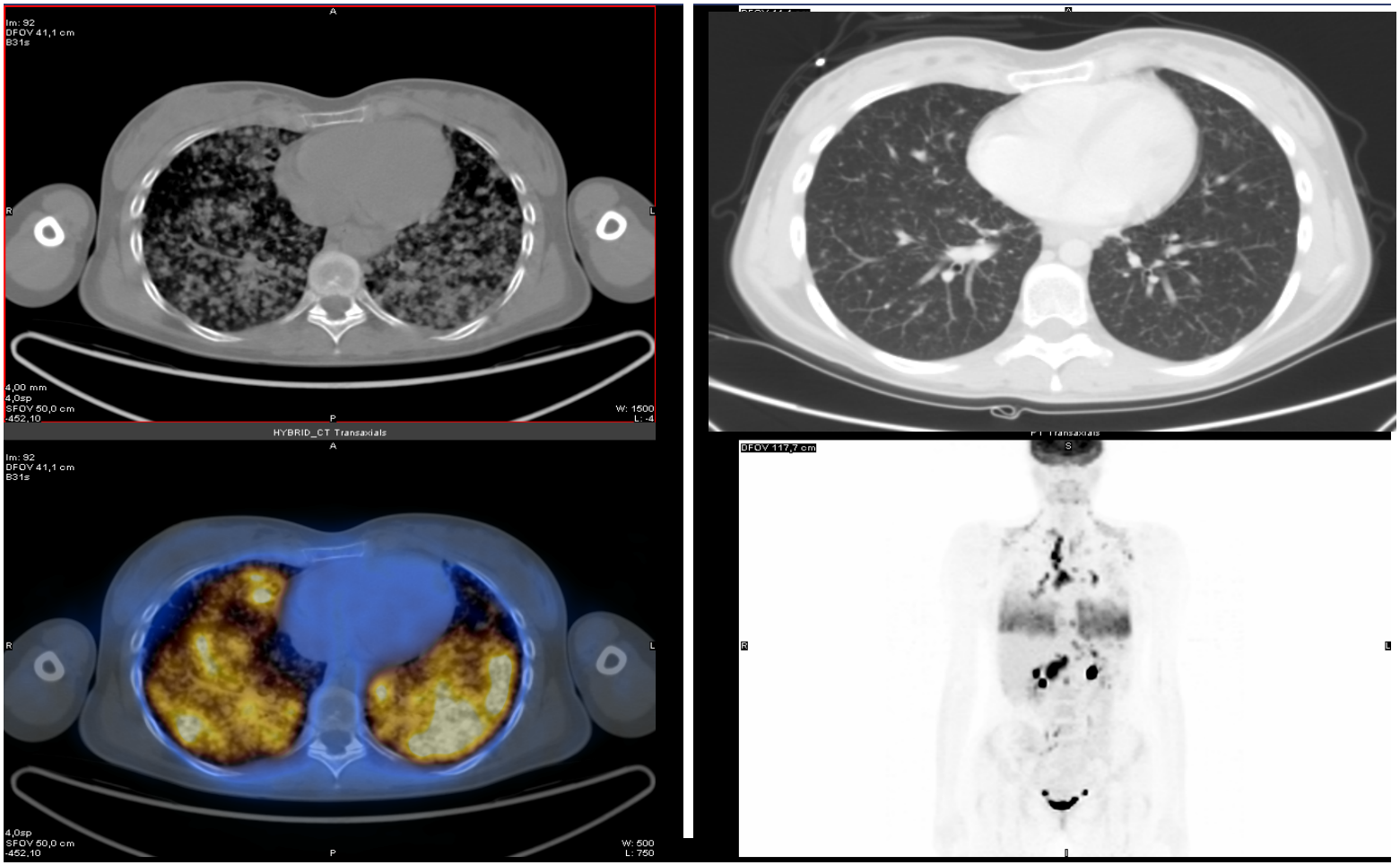
IR	Definition
IR1	*Increase in overall tumor burden (SD)≥50% of up to 6 measurable lesions in the first 12 ws of therapy without clinical deterioration*
IR2	*Appearance of new lesions, or growth of one or more existing lesions ≥50% at any time during treatment, occuring in the context of lack of overall progression of overall tumor burden*
IR3	*Increase in FDG uptake of one or more lesions without a concomitant increase in lesion size or number*

Cheson B et al, Blood 2016

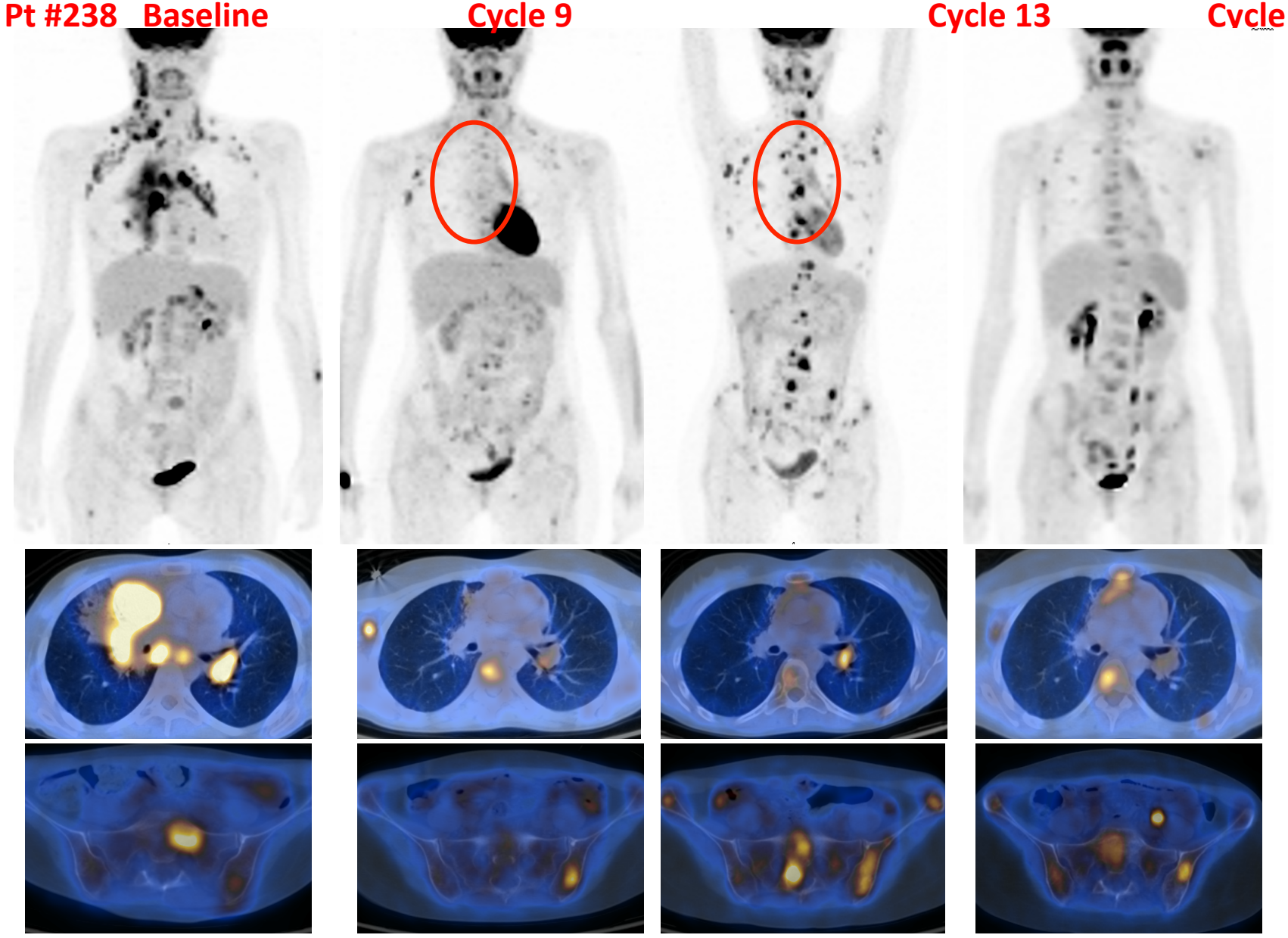
THE OPEN QUESTIONS: RESPONSE EVALUATION

Pt #270 - Baseline

Cycle 3

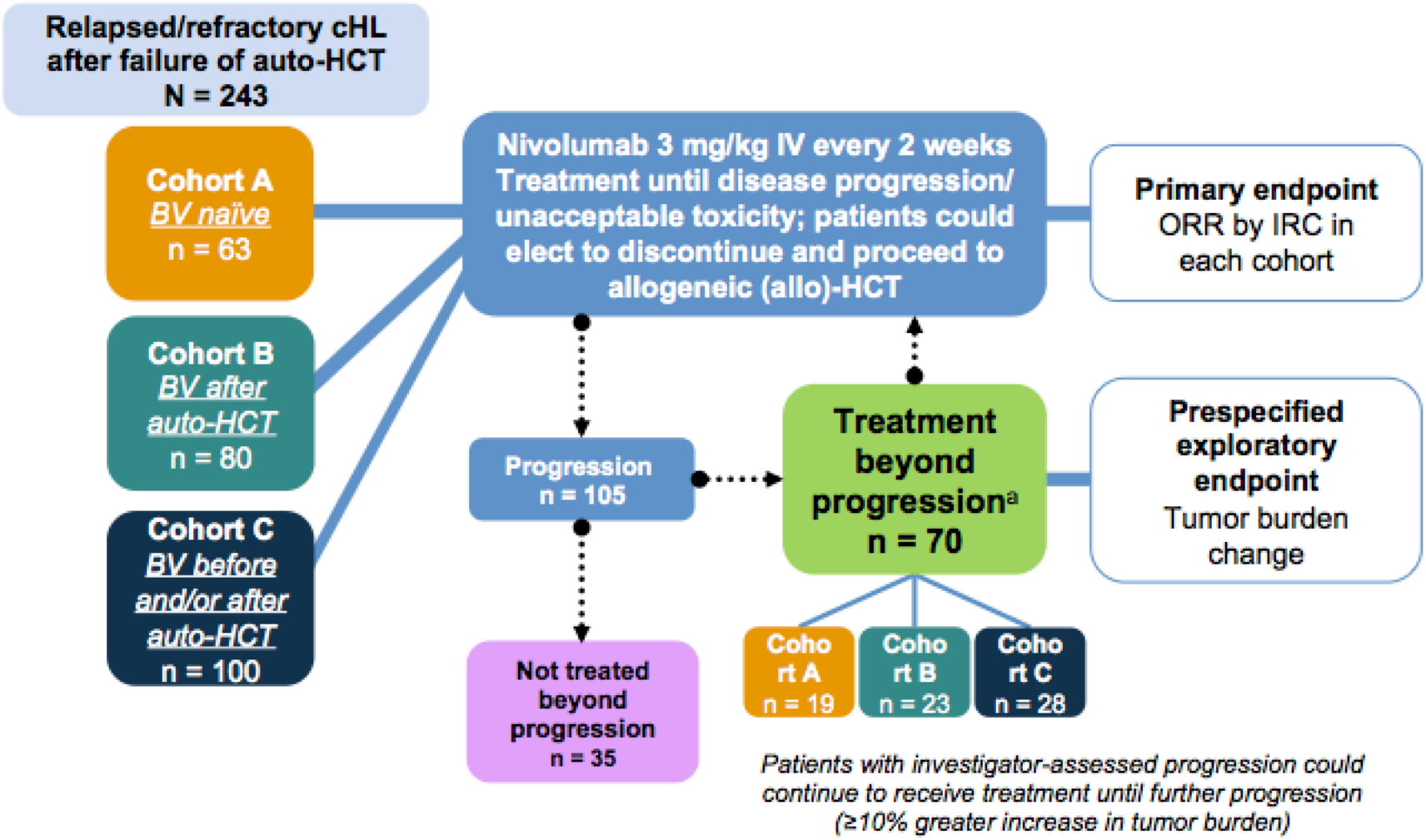


THE OPEN QUESTIONS: RESPONSE EVALUATION



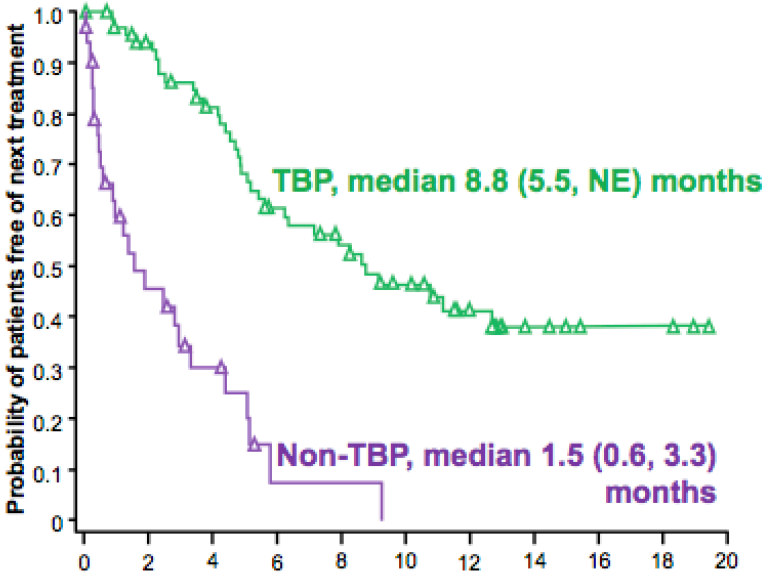
THE OPEN QUESTIONS: WHEN TO STOP TREATMENT

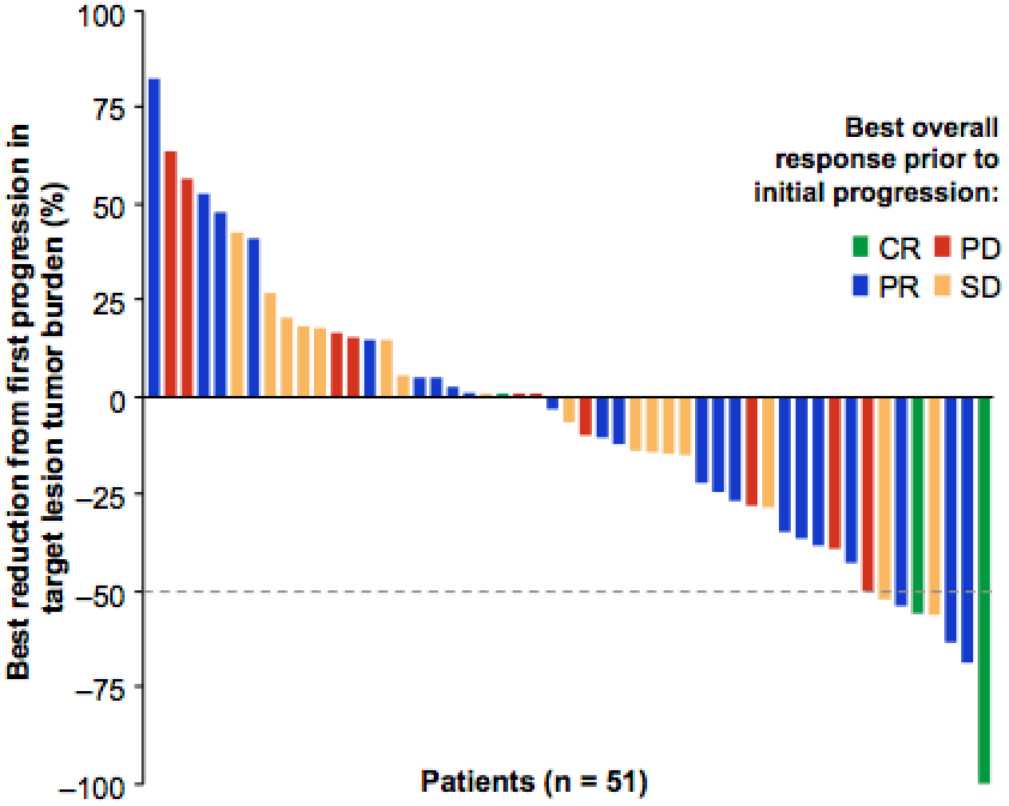
CHECKMATE 205: NIVOLUMAB BEYOND PROGRESSION



CHECKMATE 2015: NIVOLUMAB BEYOND PROGRESSION

TBP n = 70	Non-TBP n = 35
13 (19)	7 (20)
17 (24)	2 (6)
47 (67)	13 (37)



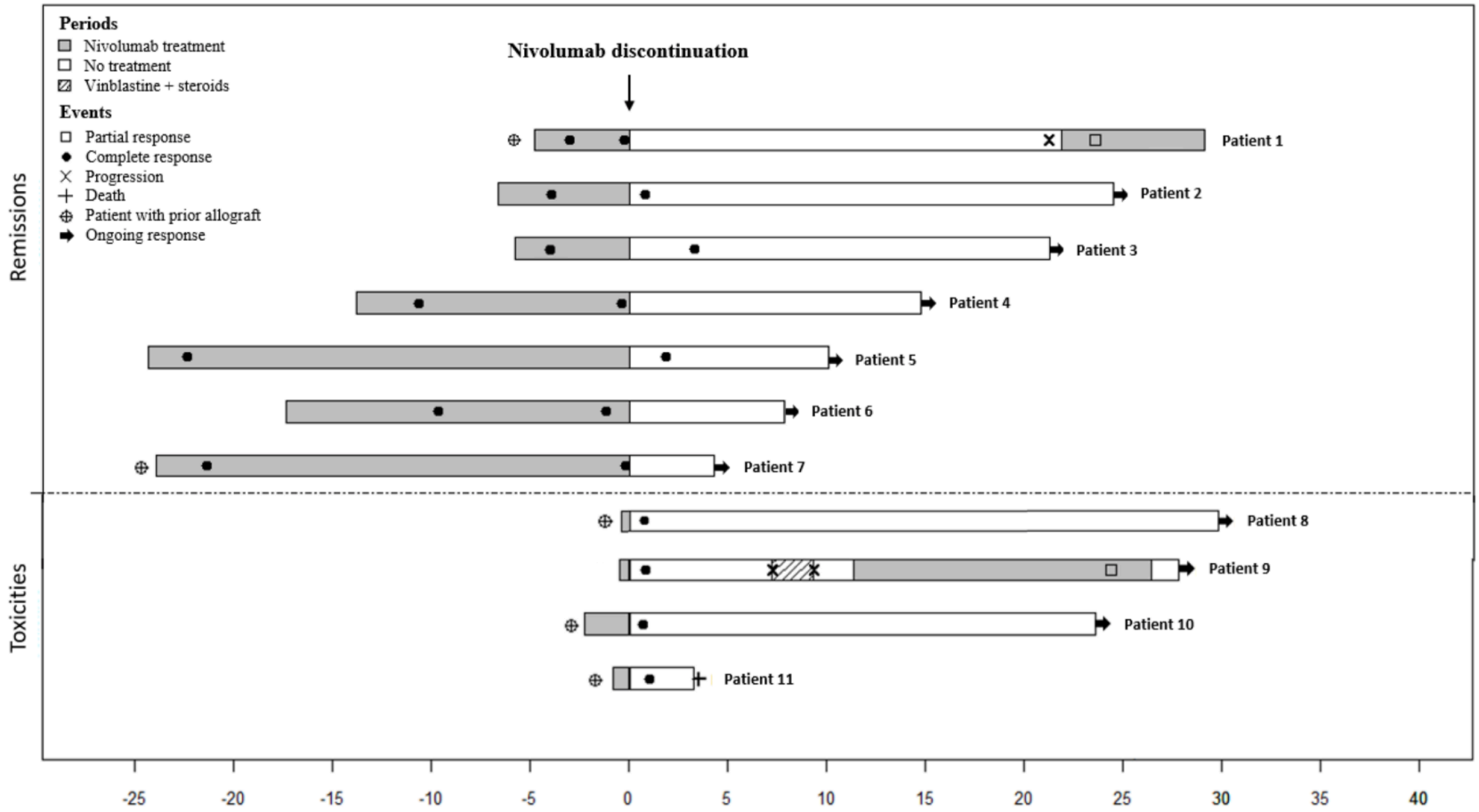


Cohen JB et al, ASH 2017

WHEN TO STOP TREATMENT IN RESPONSIVE PATIENTS

PROLONGED REMISSIONS AFTER ANTI-PD1 DISCONTINUATION

Figure 1. Outcome of patients after nivolumab discontinuation



Manson G et al, BLOOD 2018

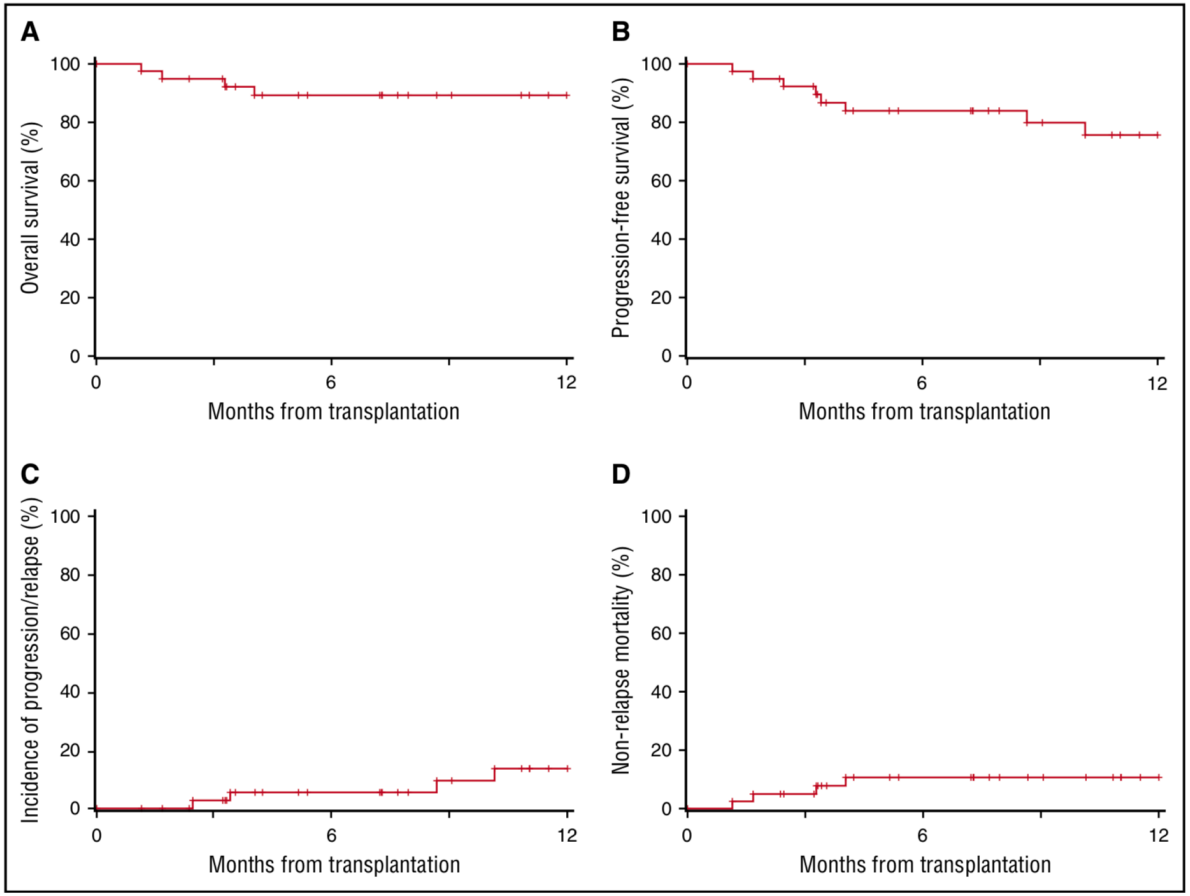
Regular Article

blood

TRANSPLANTATION

Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma

Reid W. Merryman,[1] Haesook T. Kim,[2] Pier Luigi Zinzani,[3] Carmelo Carlo-Stella,[4,5] Stephen M. Ansell,[6] Miguel-Angel Perales,[7] Abraham Avigdor,[8] Ahmad S. Halwani,[9] Roch Houot,[10,11] Tony Marchand,[10] Nathalie Dhedin,[12] Willy Lescaut,[13] Anne Thiebaut-Bertrand,[14] Sylvie François,[15] Aspasia Stamatoullas-Bastard,[16] Pierre-Simon Rohrlich,[17] Hélène Labussière Wallet,[18] Luca Castagna,[4,5] Armando Santoro,[4,5] Veronika Bachanova,[19] Scott C. Bresler,[20] Amitabh Srivastava,[20] Harim Kim,[21] Emily Pesek,[1] Marie Chammas,[1] Carol Reynolds,[1] Vincent T. Ho,[1] Joseph H. Antin,[1] Jerome Ritz,[1] Robert J. Soiffer,[1] and Philippe Armand[1]



CHECKPOINT INHIBITORS: *TREATMENT DURATION*

NO ALLO-TRANSPLANT

2 YEARS?

ALLO- TRANSPLANT

8 COURSES?

THE OPEN QUESTIONS: AFTER ALLO-TMO

CHECKPOINT INHIBITORS AFTER ALLO-TMO

EFFICACY AND TOLERABILITY OF NIVO AFTER ALLO-TMO FOR R-HL

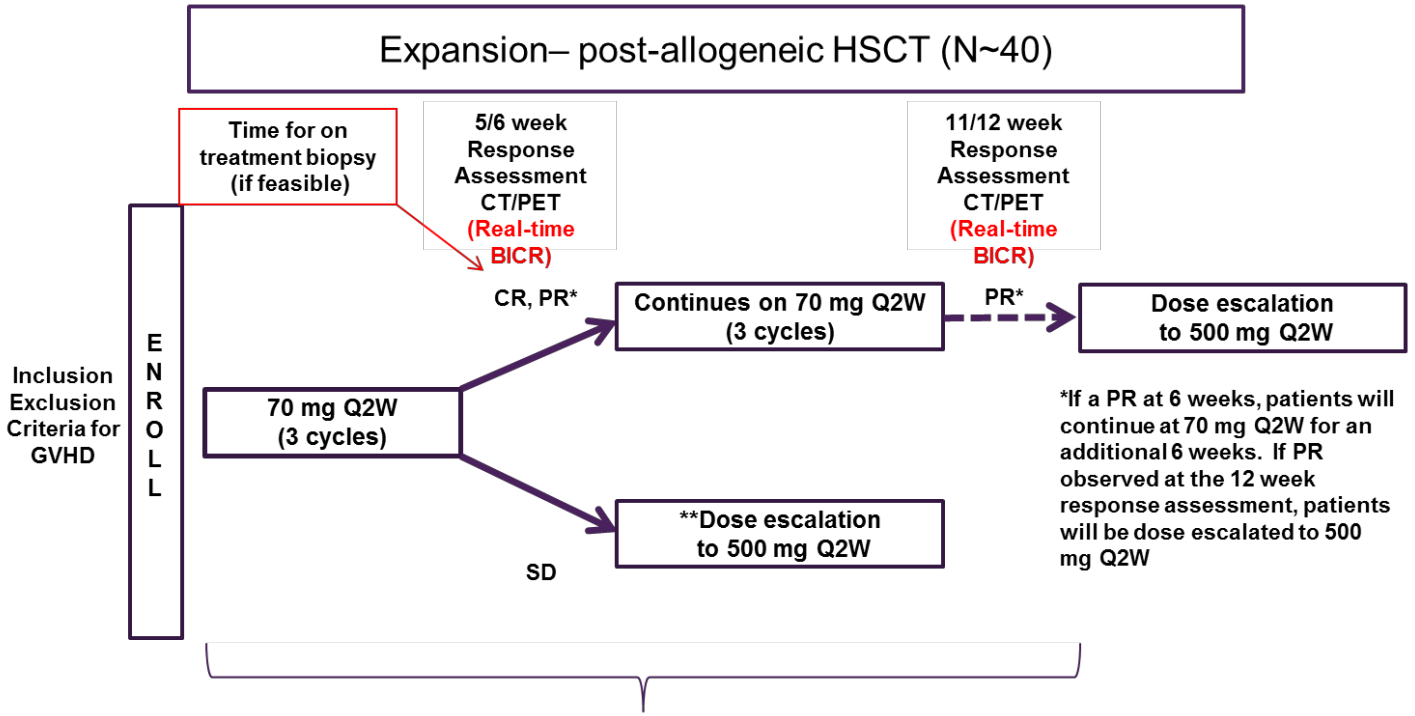
HERBEAUX C ET AL , BLOOD 2017

PD-1 BLOCKADE FOR R-HL POST–ALLO-TMO: HIGH RESPONSE RATE BUT FREQUENT GVHD

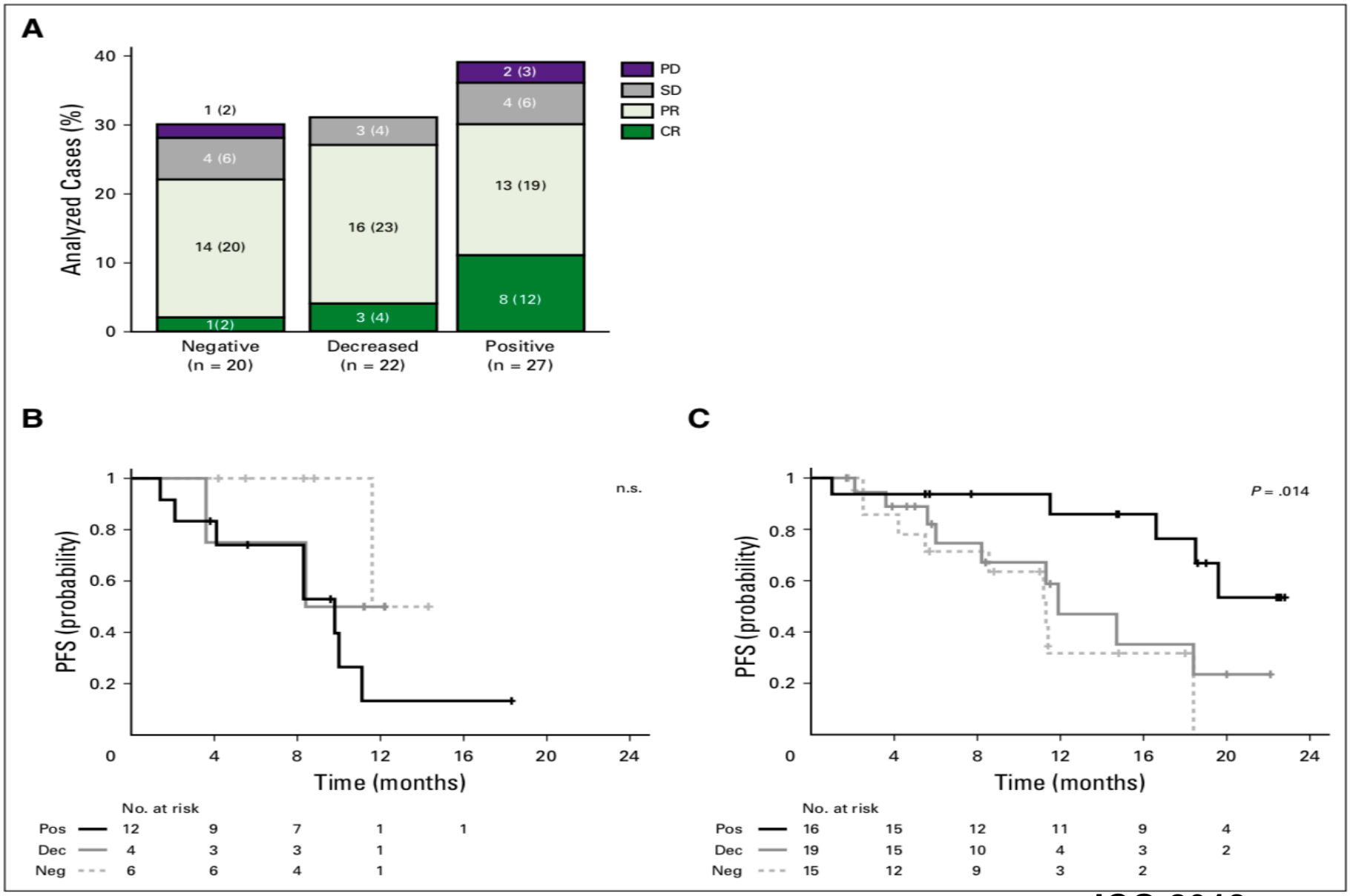
HAVERKOS BM ET AL, BLOOD 2017


HO IMPARATO
COSI' TANTO
DAI MIEI ERRORI
CHE STO
PENSANDO DI
CONTINUARE
A FARNE...
JOE
COOL

Expansion Phase Design

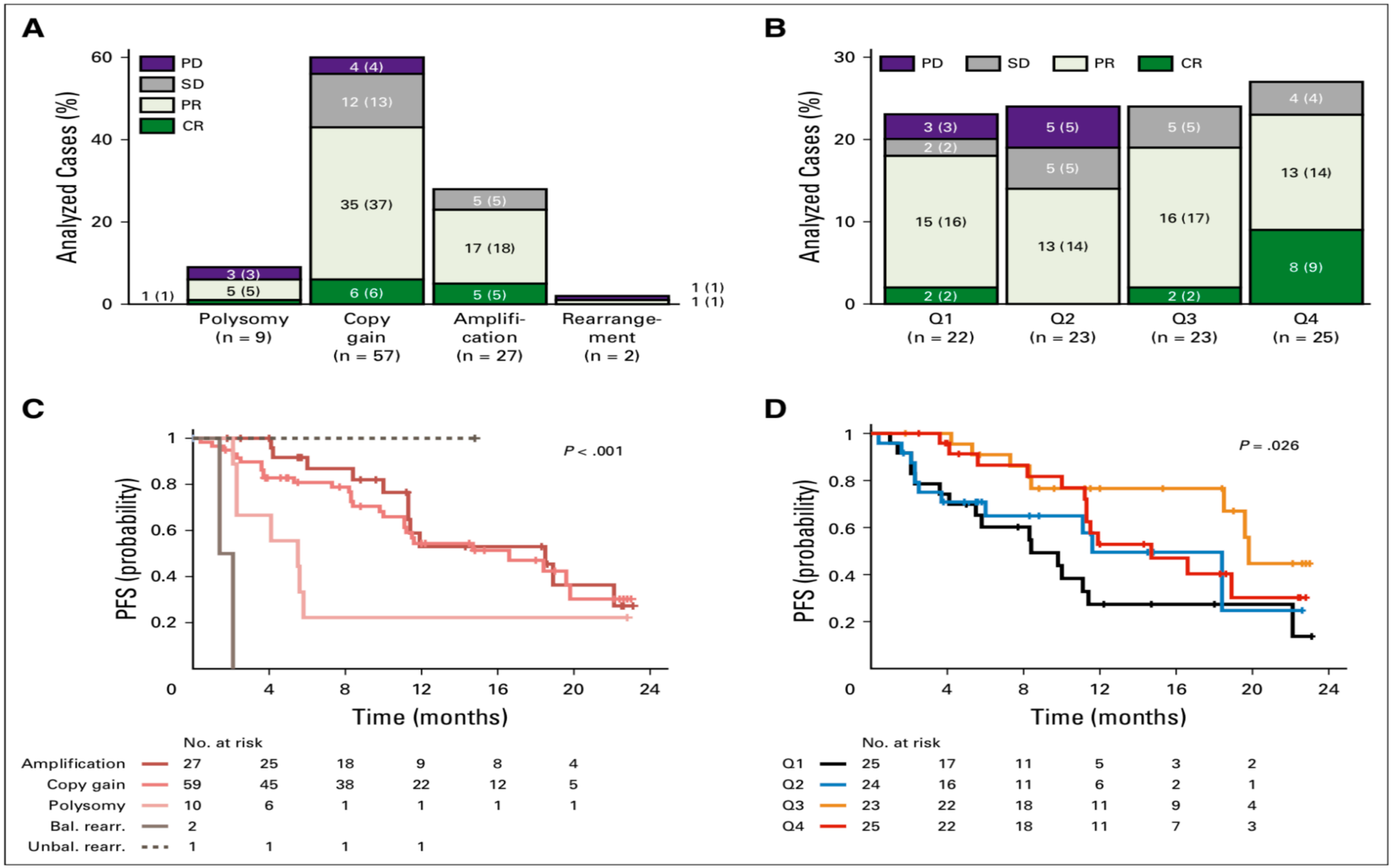


Evaluate for signs/symtpoms of GVHD: Patients who develop GVHD of any grade or treatment related Grade≥2 AEs with a duration of more than 14 days will NOT be dose escalated to 500 mg Q2W
Patients with PD will be discontinued from the treatment


A
Analyzed Cases (%)
40
30
20
10
0
1 (2)
4 (6)
14 (20)
1(2)
3 (4)
16 (23)
3 (4)
2 (3)
4 (6)
13 (19)
8 (12)
PD
SD
PR
CR
Negative (n = 20)
Decreased (n = 22)
Positive (n = 27)
B
PFS (probability)
n.s.
Time (months)
No. at risk
Pos 12 9 7 1 1
Dec 4 3 3 1
Neg 6 6 4 1
C
PFS (probability)
P = .014
Time (months)
No. at risk
Pos 16 15 12 11 9 4
Dec 19 15 10 4 3 2
Neg 15 12 9 3 2

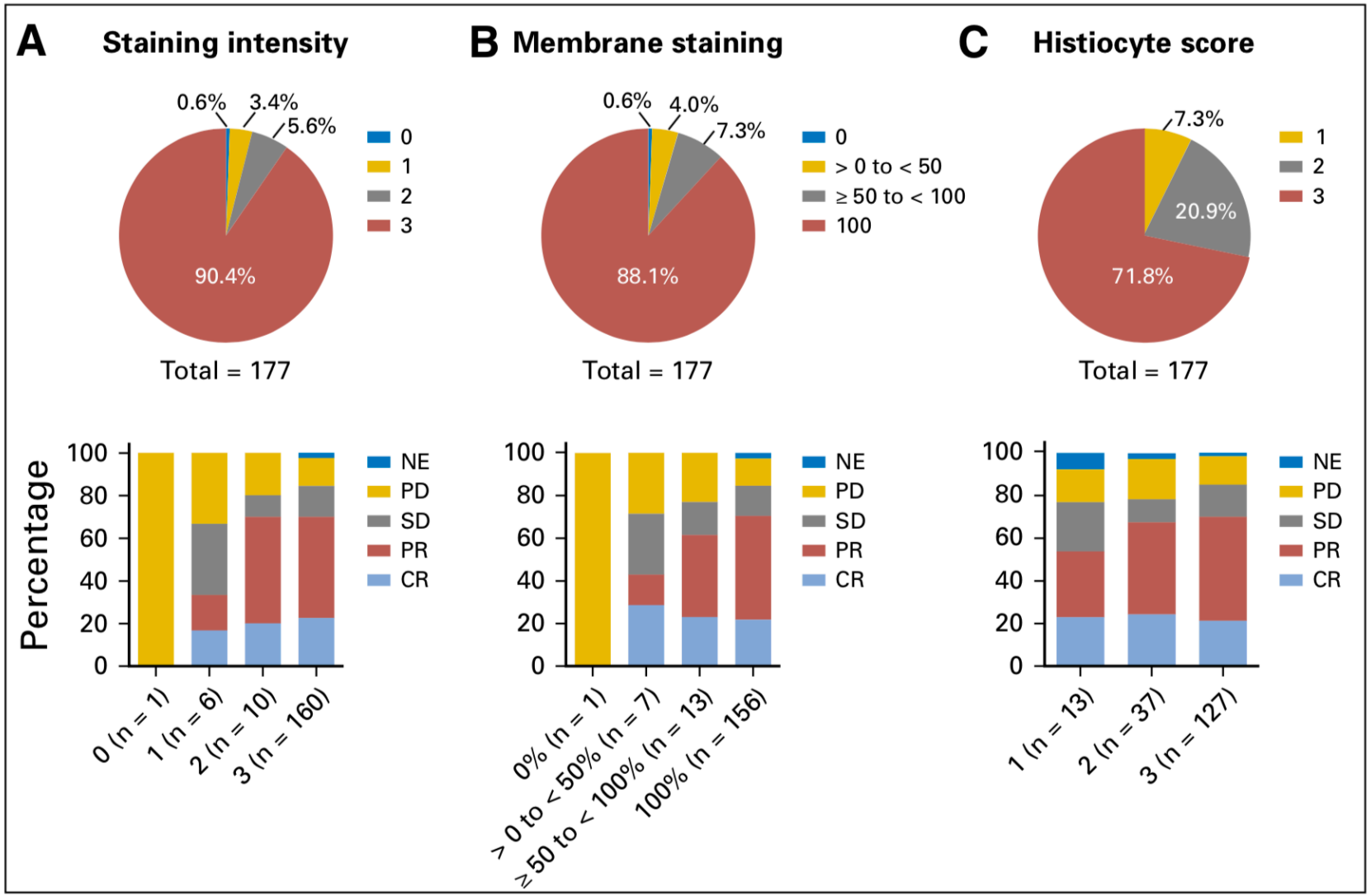
JCO 2018

9p24.1 alterations



JCO 2018

KEYNOTE-087: PDL-1 SCORES and RESULTS



Chen R, Zinzani PL, Fanale M, et al, JCO 2017

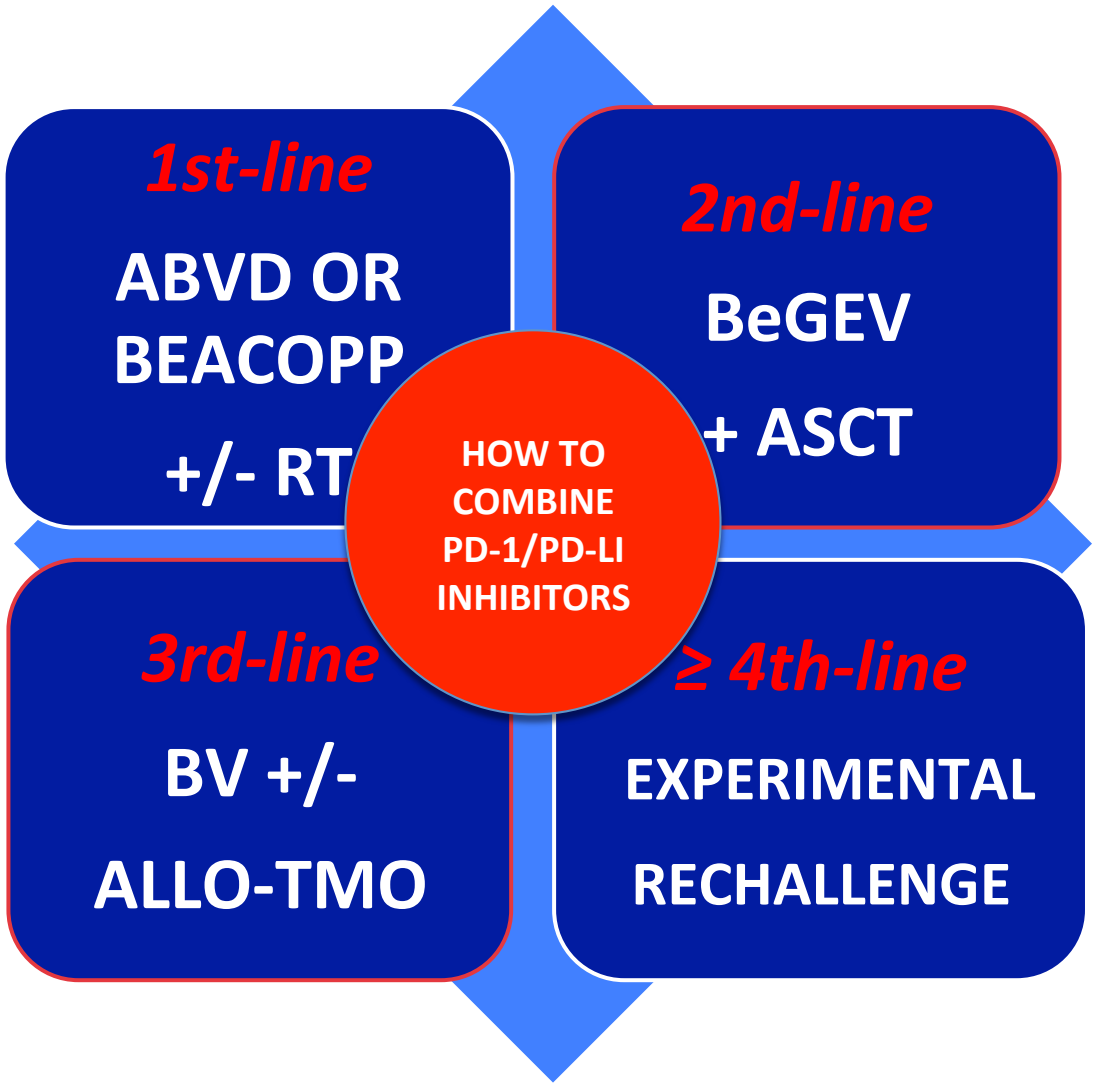
THE NEXT SCENARIOS IN HL TREATMENT

HOW TO FIT CHECKPOINT INHIBITORS IN THE MANAGEMNET OF HL

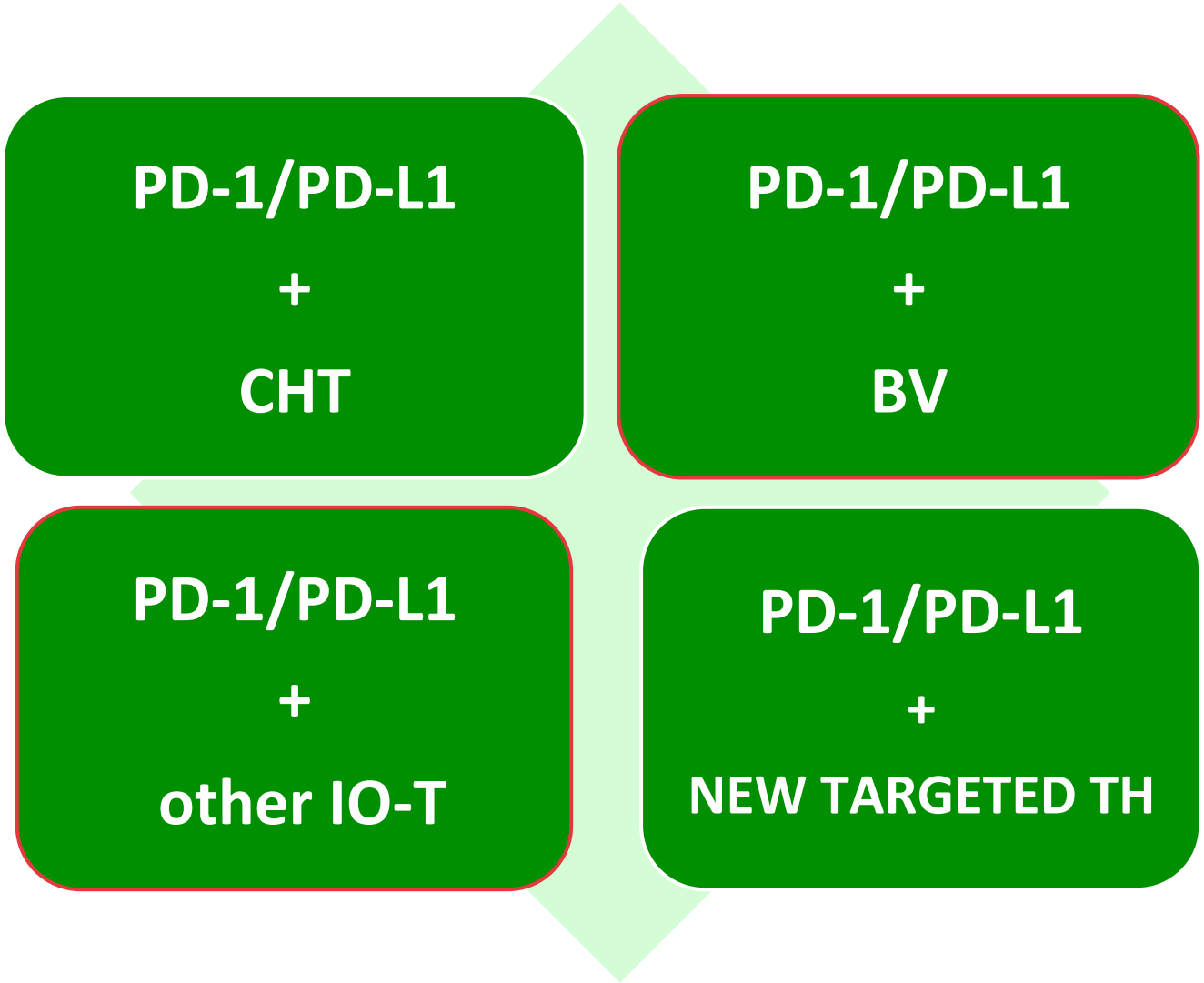
NOVEL SALVAGE REGIMENS FOR R/R HL BEFORE ASCT

Salvage Regimen	N	ORR, %	CR by PET, %
BV + ICE (sequential)	37	86	65
BV + augICE (sequential)	45	82	76
BV + Bendamustine	55	93	74
BV + ESHAP (BRESHAP)	66	94	70
BV + ICE (concurrent)	16	94	69
BeGEV	59	83	73

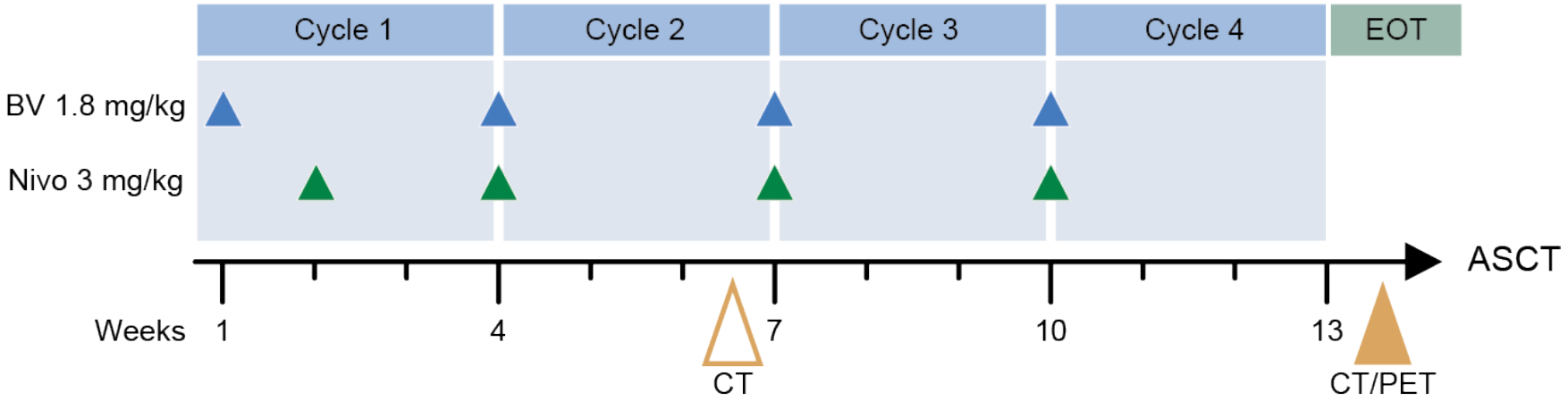
THE NEXT SCENARIOS IN HL TREATMENT



THE NEXT SCENARIOS IN HL TREATMENT



INTERIM RESULTS OF BV IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH R/R HL

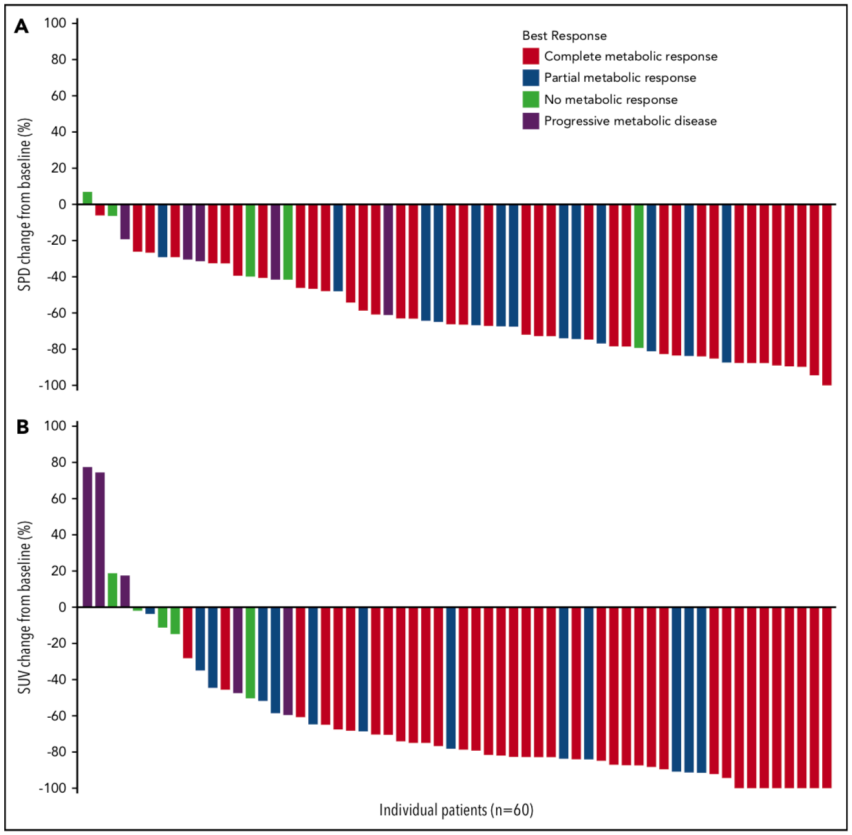


- **PATIENTS RECEIVED TREATMENT (TX) IN 21-DAY CYCLES FOR UP TO 4 CYCLES (12 WEEKS)**
  - **DURING CYCLE 1, BV WAS ADMINISTERED ON DAY 1 AND NIVO ON DAY 8**
  - **DURING CYCLES 2-4, DOSING OF BOTH DRUGS OCCURRED ON DAY 1**
  - **AFTER COMPLETION OF THE EOT RESPONSE ASSESSMENT, PATIENTS WERE ELIGIBLE TO UNDERGO ASCT**
- **RESPONSES WERE ASSESSED USING THE 2014 LUGANO CLASSIFICATION**

Herrera AF, Moskowitz AJ, Bartlett NL, et al BLOOD 2018

INTERIM RESULTS OF BV IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH R/R HL

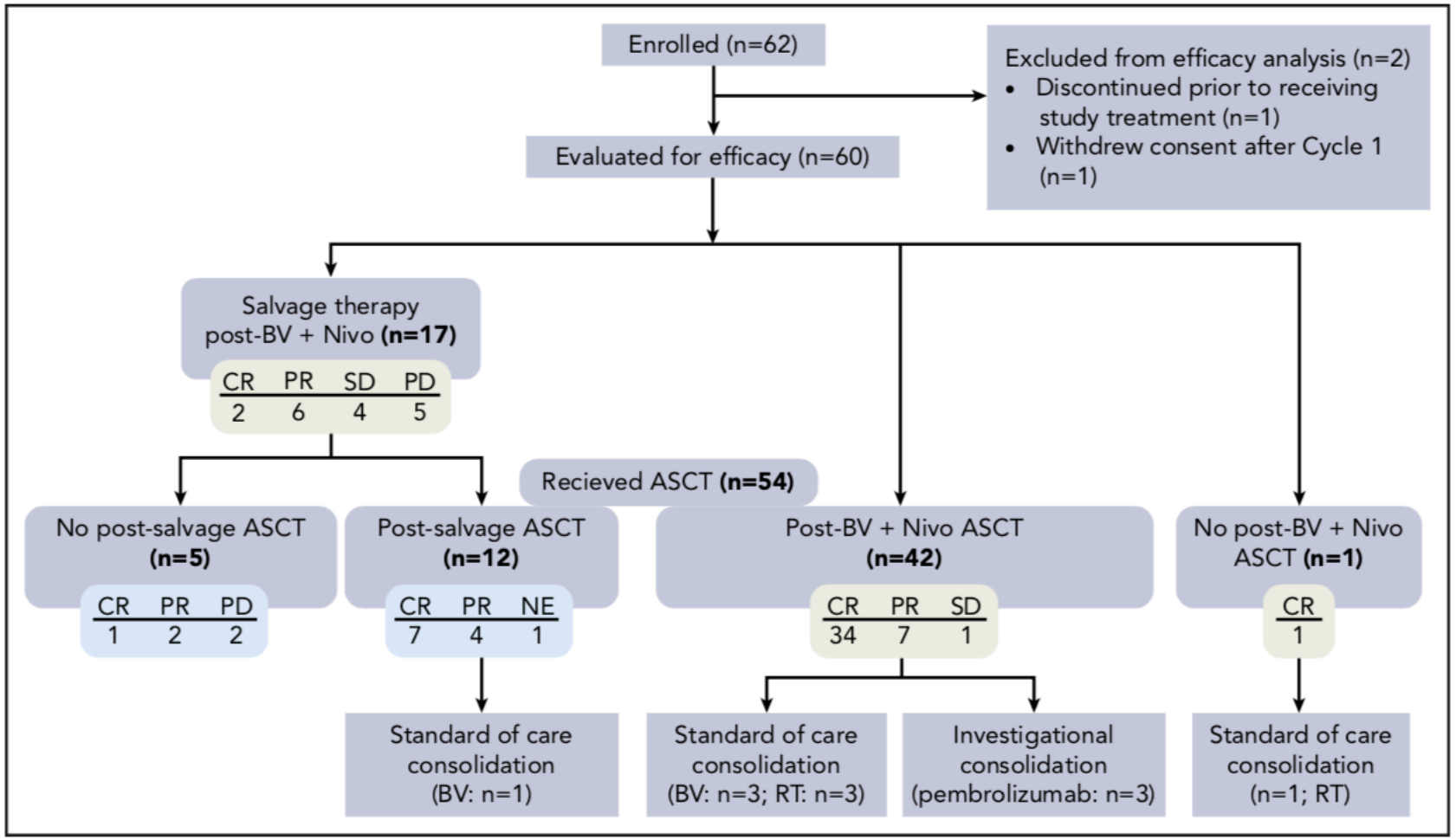
85% OBJECTIVE RESPONSE RATE WITH 63% COMPLETE RESPONSES



	N = 61 %
COMPLETE RESPONSE (CR)	61
PARTIAL RESPONSE (PR)	21
NO METABOLIC RESPONSE (SD)	8
PROGRESSIVE DISEASE (PD)	8
CLINICAL PROGRESSION (CP)	2

Herrera AF, Moskowitz AJ, Bartlett NL, et al BLOOD 2018

INTERIM RESULTS OF BV IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH R/R HL



Herrera AF, Moskowitz AJ, Bartlett NL, et al BLOOD 2018

INTERIM RESULTS OF BV IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH R/R HL

ADVERSE EVENTS

98% of pts with AEs, most of which were low grade
Grade 4 AEs only observed in 2 pts (3%; n = 1 thrombocytopenia, 1 increased lipase enzymes)

25 out of 27 IRRs occurred during BV infusion, most often during cycle 2
IRR severity and frequency not changed by pretreatment with low-dose steroid and antihistamine

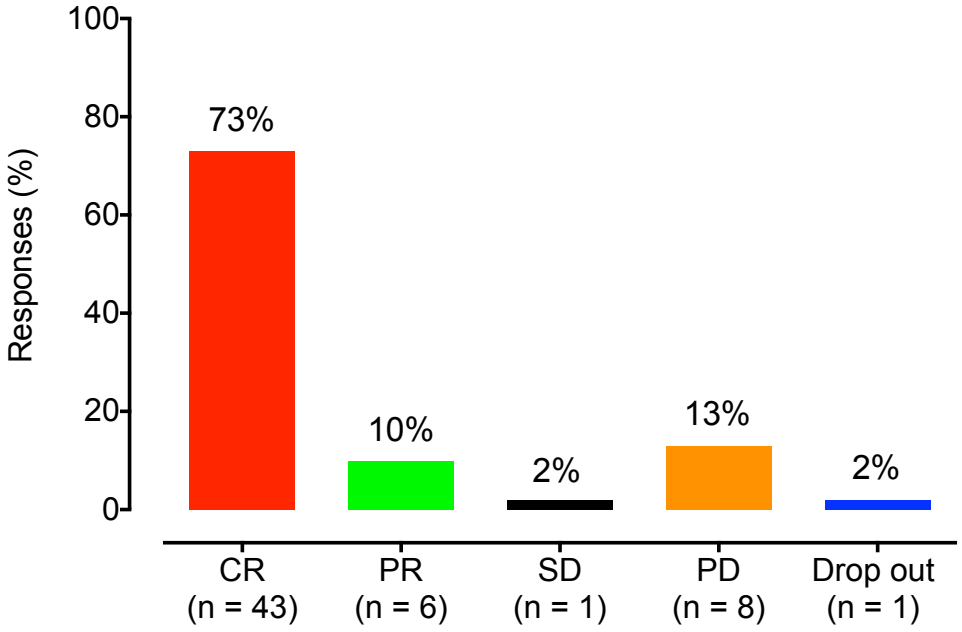
AEs in > 20% of Pts, n (%)	Grade 1/2	Grade 3
Any	40 (66)	17 (28)
Nausea	30 (49)	0
Fatigue	24 (39)	1 (2)
IRRs	25 (41)	2 (3)
Pruritus	18 (30)	1 (2)
Diarrhea	15 (25)	1 (2)
Headache	15 (25)	0
Cough	13 (21)	0
Vomiting	13 (21)	0

Herrera AF, Moskowitz AJ, Bartlett NL, et al BLOOD 2018

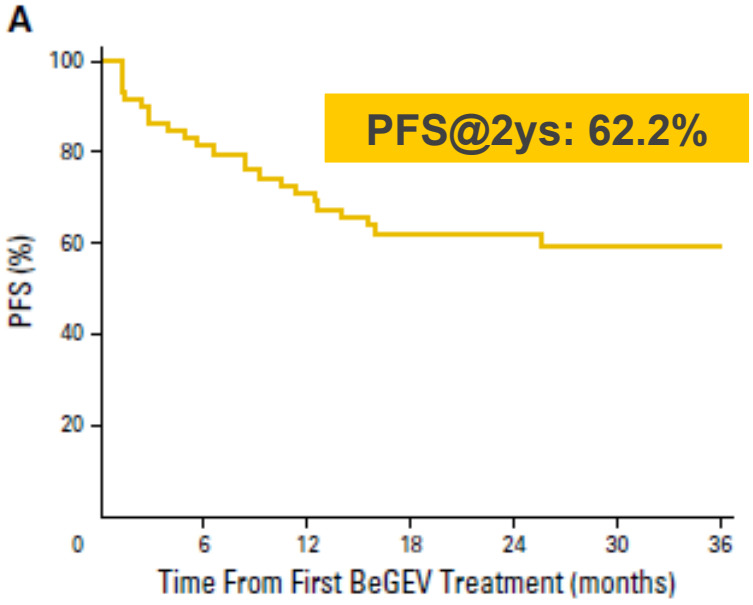
BeGEV

Bendamustine in Combination With Gemcitabine and Vinorelbine Is an Effective Regimen As Induction Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicenter Phase II Study

Bendamustine 90 mg/mq d 2-3, Gemcitabine 800 mg/mq d 1-4, Vinorebine 20 mg/mq d 1



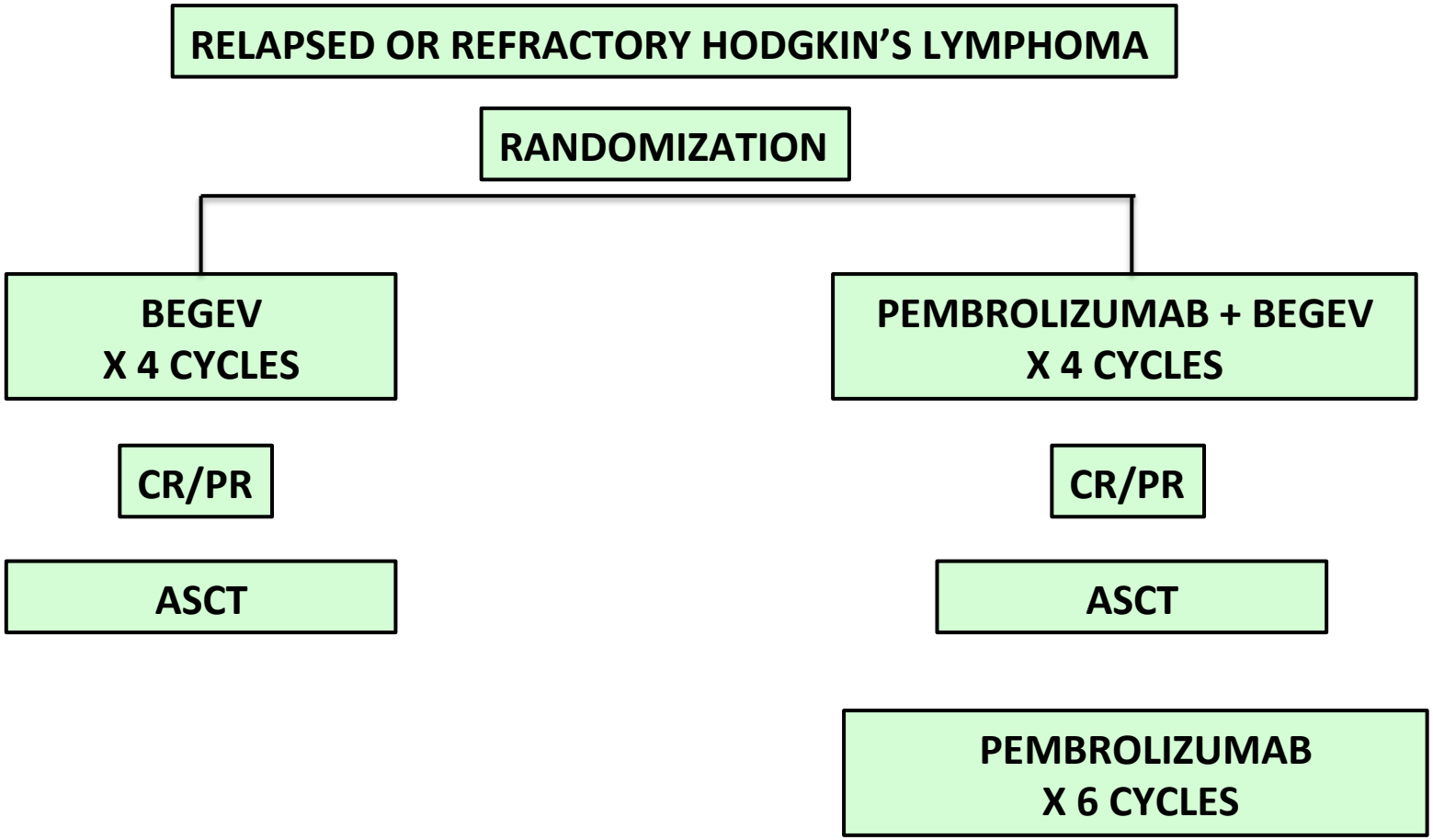
Median CD34+ cells/kg 8.8 x 10^6



Santoro A et al, JCO 2016

PHASE 1-2 STUDY WITH BeGEV PLUS PEMBROLIZUMAB

Bendamustine 90 mg/mq d 2-3, **Ge**mcitabine 800 mg/mq d 1-4, **V**inorebine 20 mg/mq d 1



✔ **CHECKPOINT INHIBITORS CONFIRM:**
- **HIGH ORR WITH LOW CR**
- **TBP SHOULD BE CONSIDERED**
- **ABSENCE OF PREDICTIVE TARGETS IN HL AFTER ASCT +/- BV**

✔ **STANDARD 2° LINE CT (BeGEV, ICE,..) FOLLOWED BY ASCT REMAIN THE GOLD STANDARD FOR R/R HL**

✔ **BY THE MOMENT NO DATA SUPPORT THE ADVANTAGE OF COMBINING CHECKPOINTS WITH BV OR CT VS STANDARD SALVAGE CT**


thanks