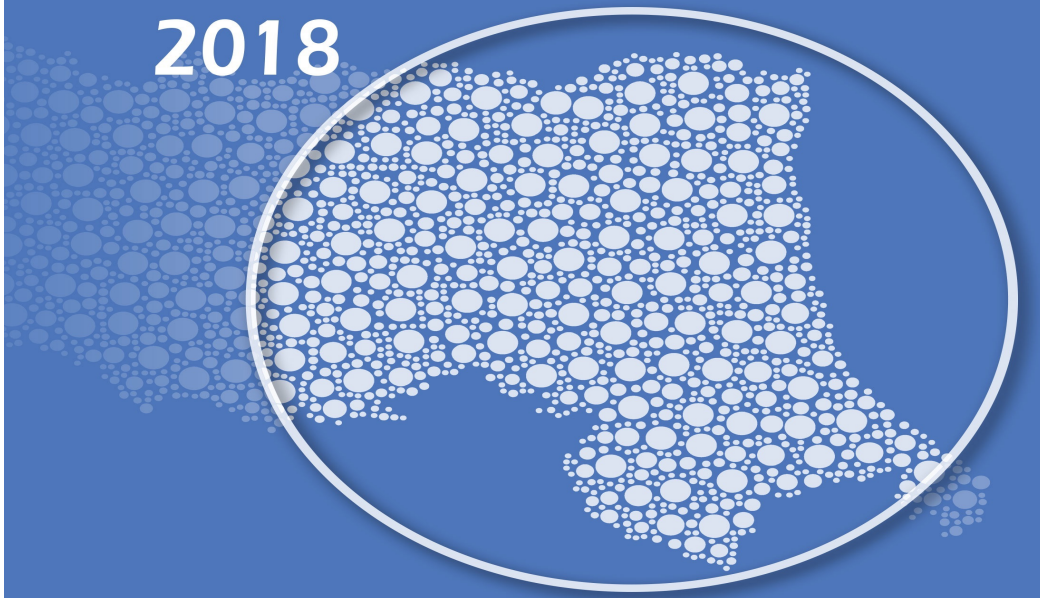


Progetto Ematologia Romagna

Linfoma di Hodgkin: Nuovi Approcci Terapeutici con Immunomodulatori

HUMANITAS UNIVERSITY

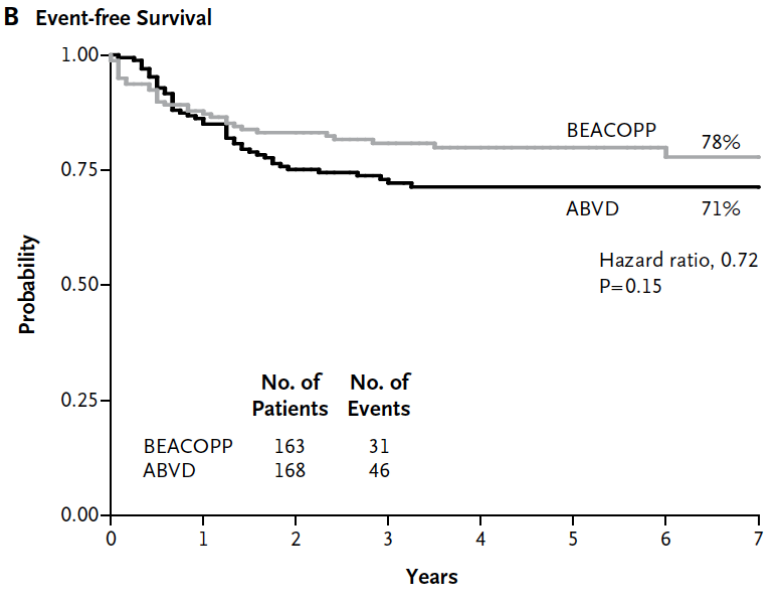
Carmelo Carlo-Stella
Dipartimento di Scienze Biomediche, Università Humanitas, Rozzano
Dipartimento di Oncologia ed Ematologia, Istituto Humanitas IRCCS, Rozzano

HUMANITAS CANCER CENTER

Advanced-Stage HL

First-Line Therapy

- 25 to 30% of these patients are not cured with ABVD
  - *Primary refractory* to chemotherapy (disease progression during or within 3 months of doxorubicin-based chemotherapy)
  - *Early relapsing* (i.e., within 12 months after first-line treatment)
  - *Late relapsing* (i.e., beyond 12 months after first-line treatment)

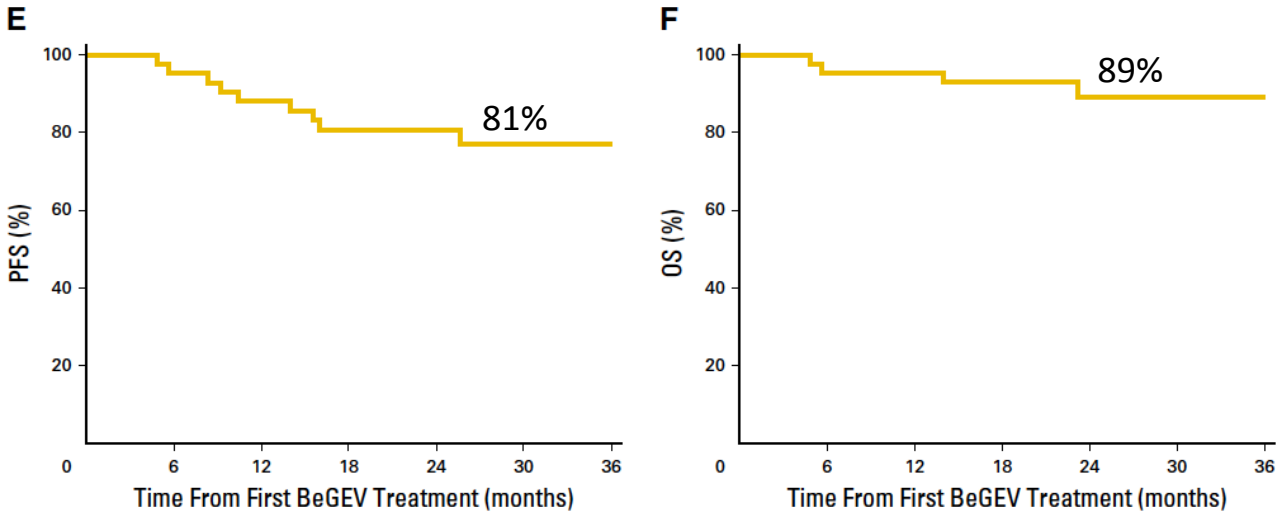


Viviani et al, NEJM, 2011

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

Armando Santoro, Rita Mazza, Alessandro Pulsoni, Alessandro Re, Maurizio Bonfichi, Vittorio Ruggero Zilioli, Flavia Salvi, Francesco Merli, Antonella Anastasia, Stefano Luminari, Giorgia Annechini, Manuel Gotti, Annalisa Peli, Anna Marina Liberati, Nicola Di Renzo, Luca Castagna, Laura Giordano, and Carmelo Carlo-Stella

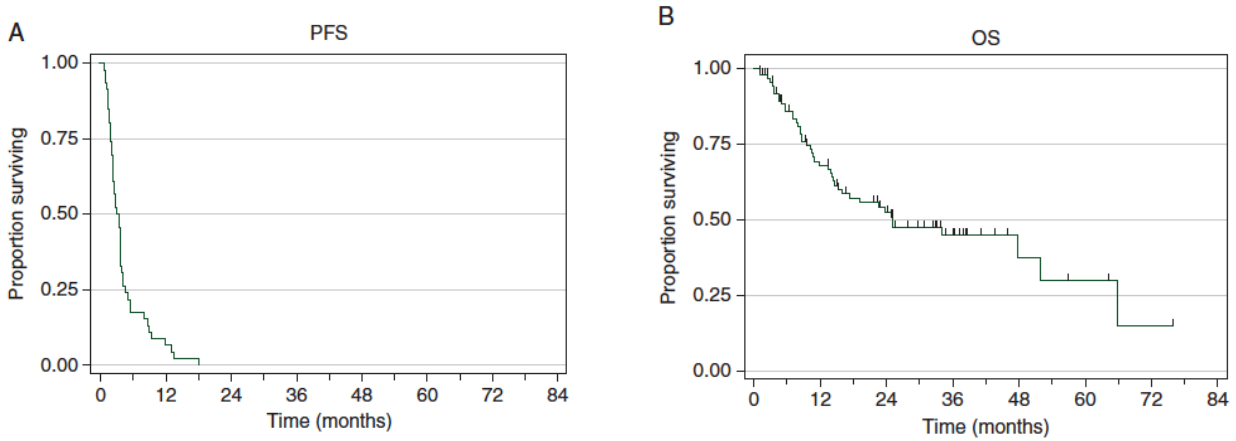
J Clin Oncol, 2016



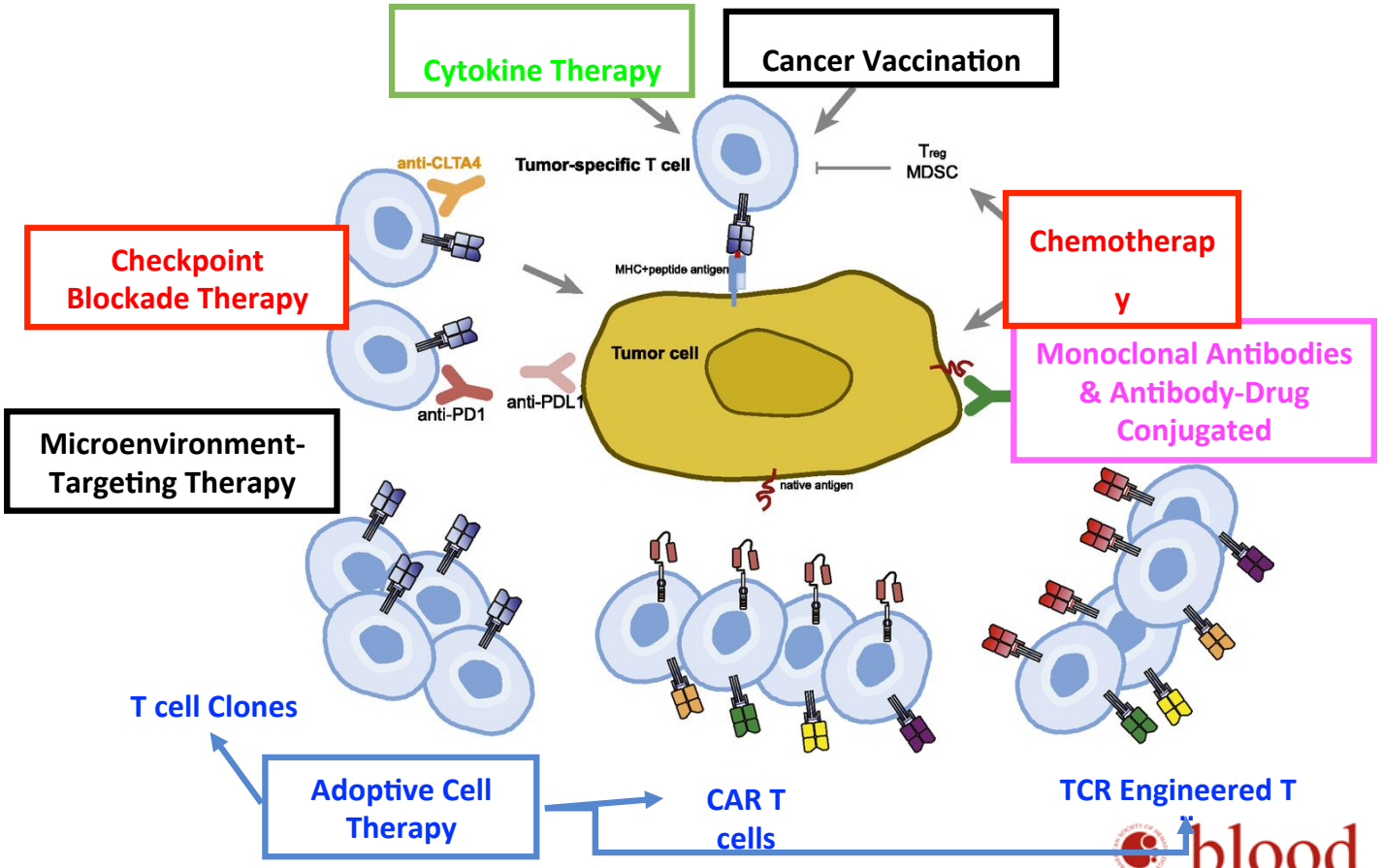
By ITT, 73% proceeded to ASCT

Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes

Cheah CI et al, Ann Oncol, 27:1317, 2016

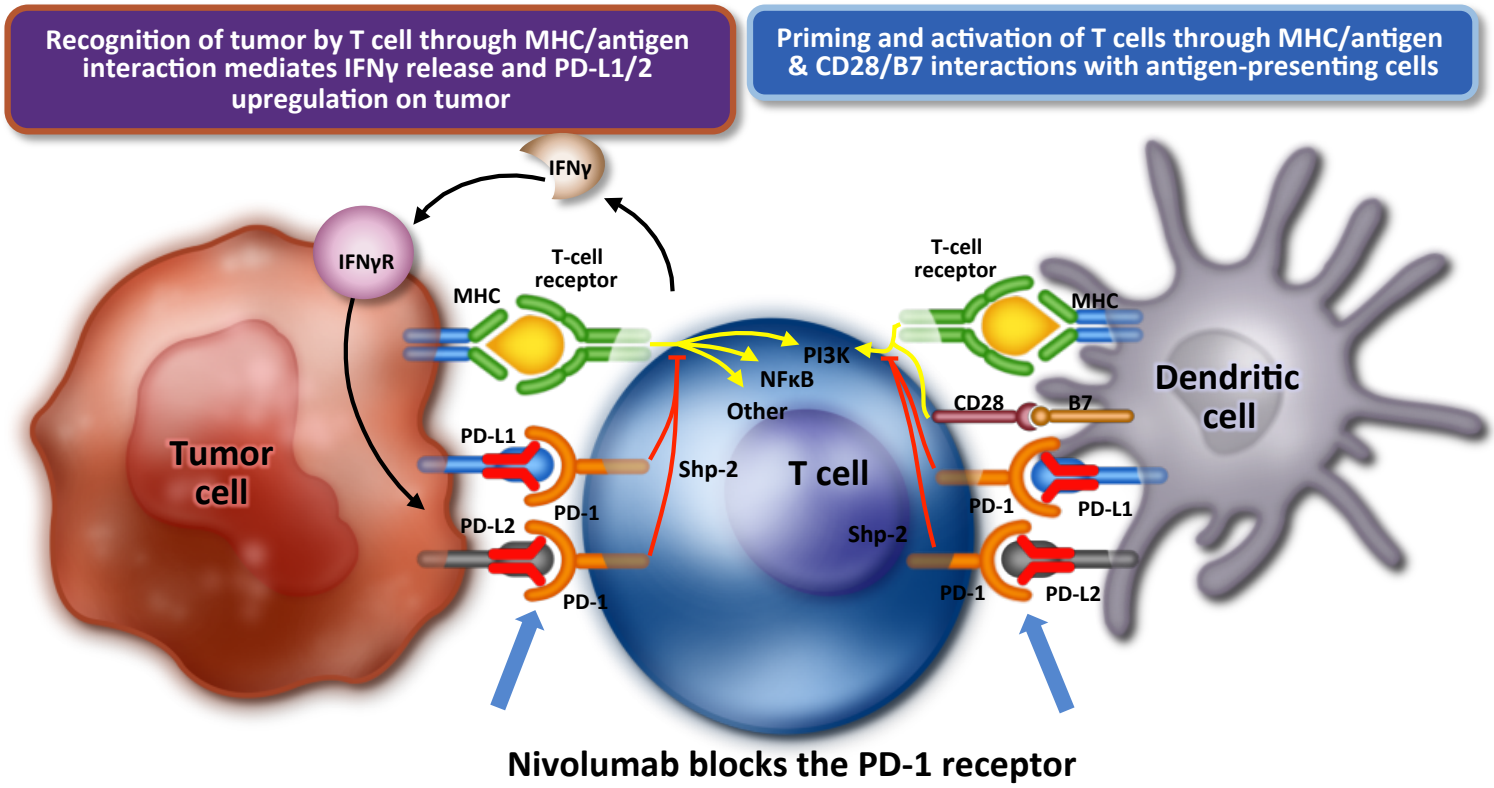


Cancer Immunotherapy



Marcela V. Maus et al. Blood 2014;123:2625-2635

Nivolumab: Mechanism of Action



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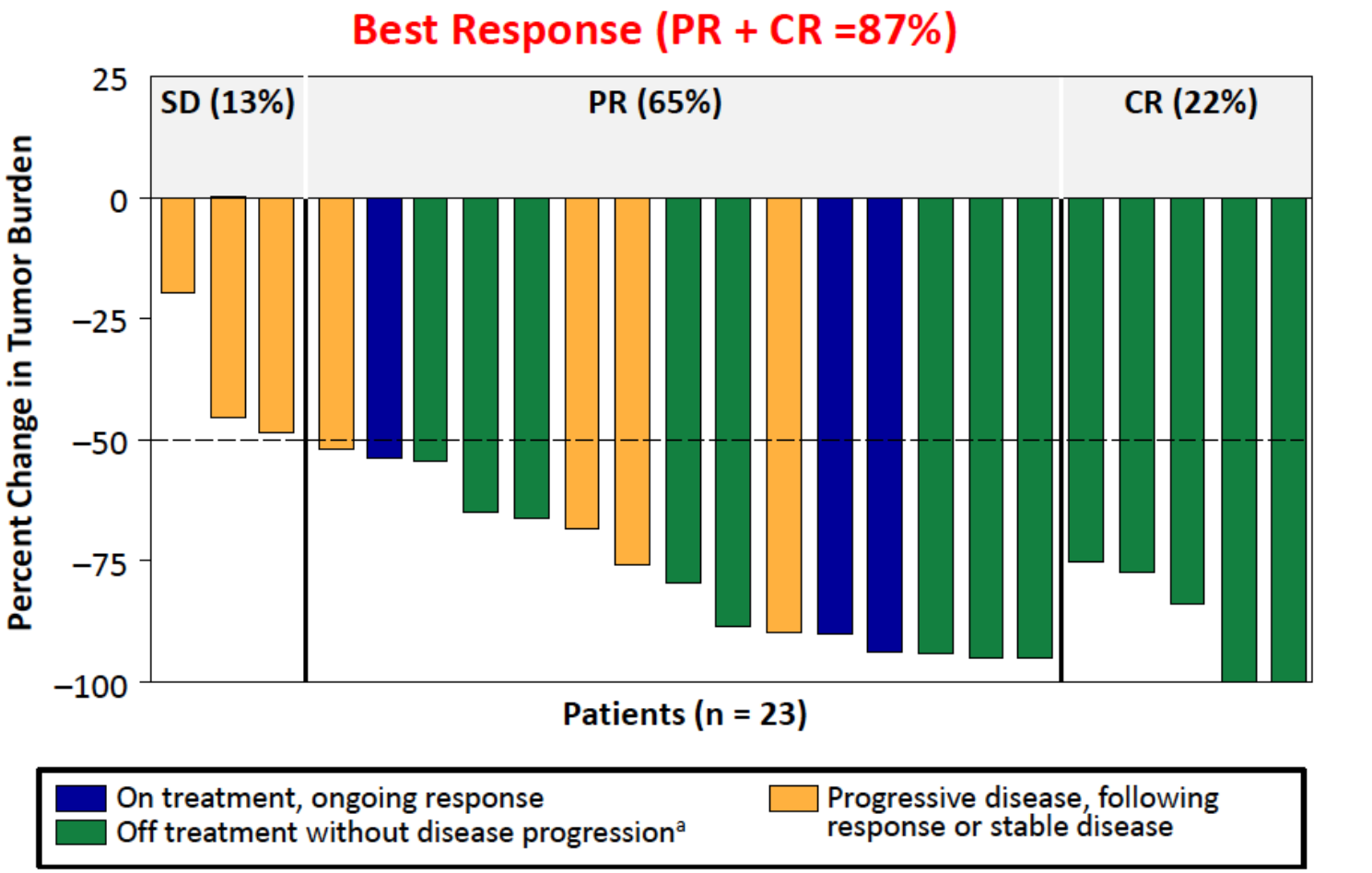
ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

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.

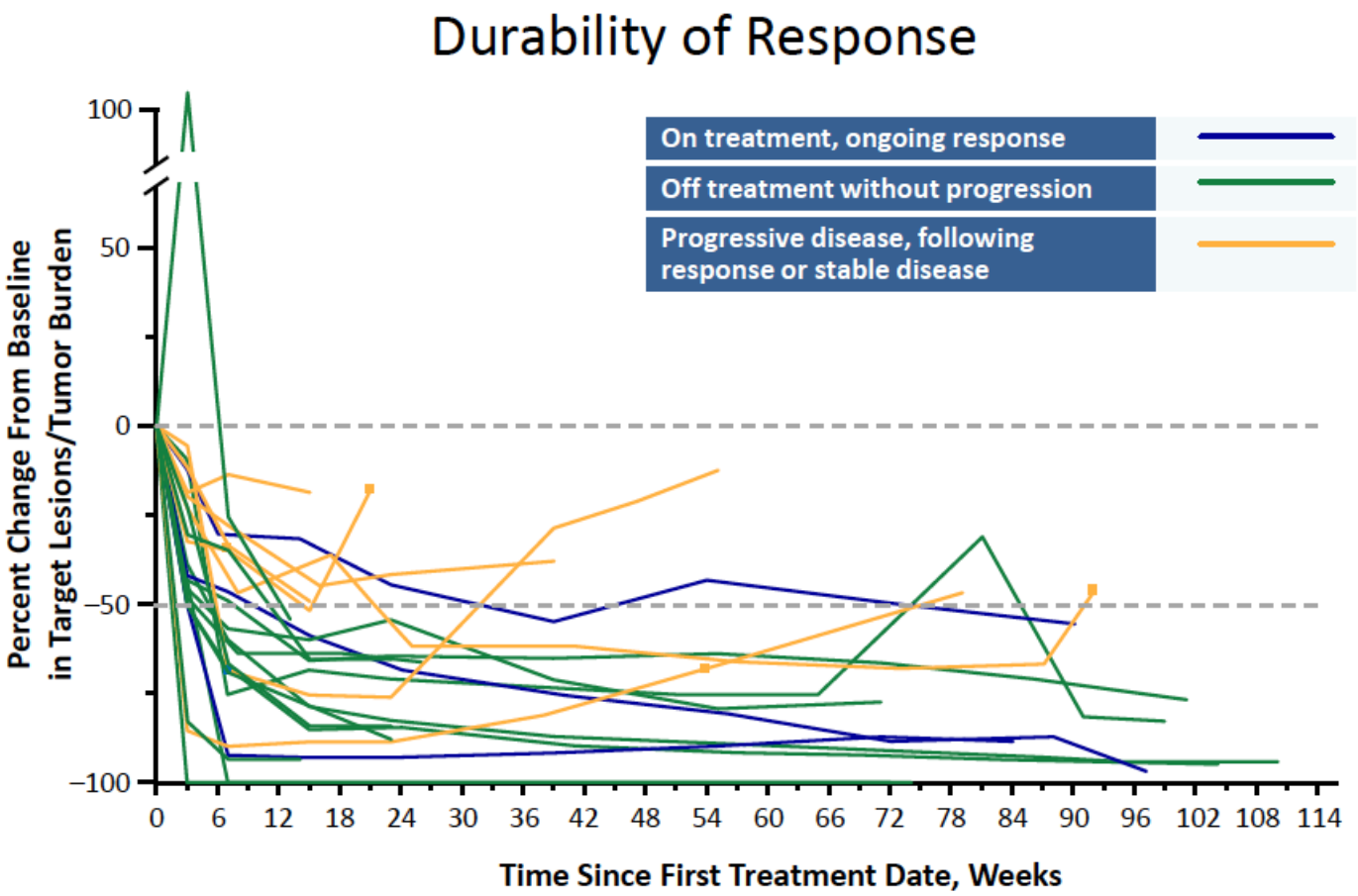
Nivolumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma



[a]Maximum clinical benefit, transplant, or toxicity

Ansell et al , ASH 2015

Nivolumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma

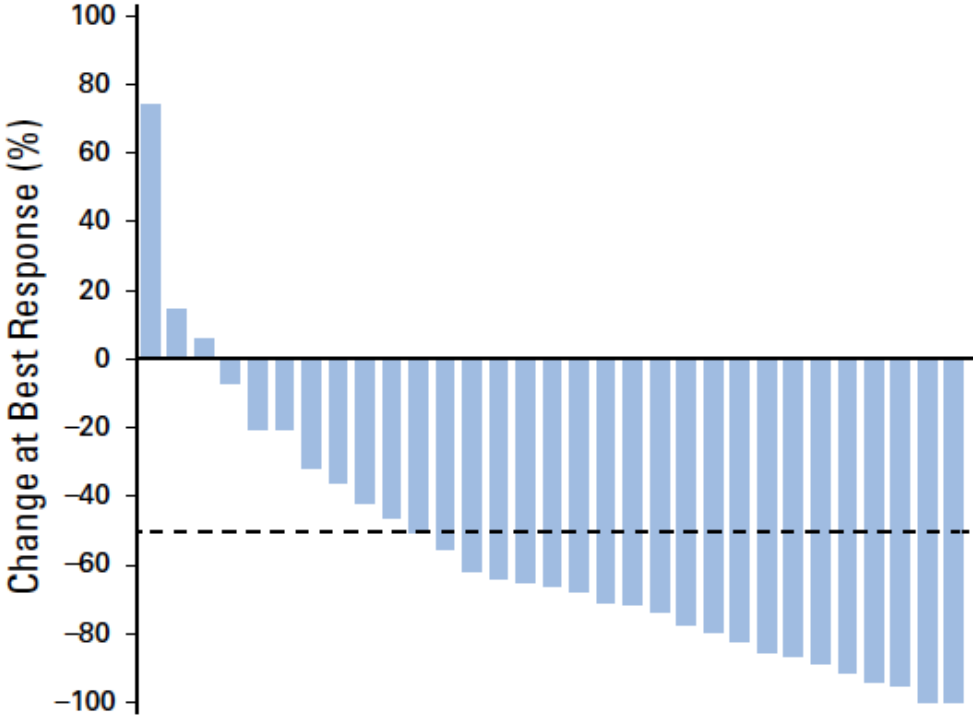


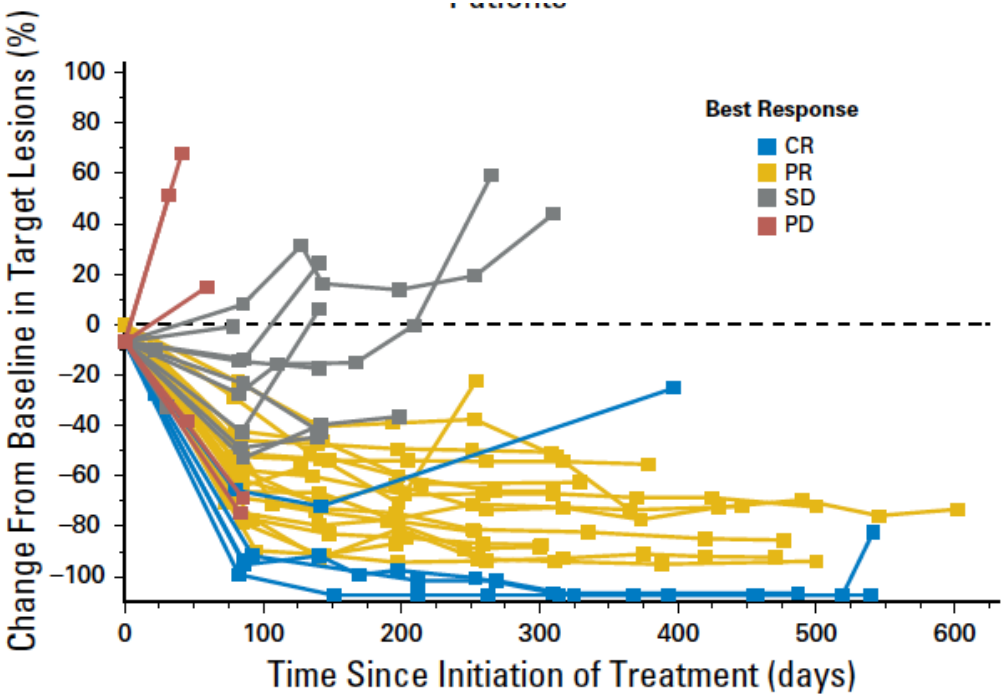
- First occurrence of new lesion

Ansell et al ASH 2015

Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure

Philippe Armand, Margaret A. Shipp, Vincent Ribrag, Jean-Marie Michot, Pier Luigi Zinzani, John Kuruvilla, Ellen S. Snyder, Alejandro D. Ricart, Arun Balakumaran, Shelonitda Rose, and Craig H. Moskowitz





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

J Clin Oncol, 2018

Table 2. Objective and Best Overall Response per IRC

Response	Protocol-Specified Analysis by Cohort			All patients (N = 243)
	BV Naïve: Cohort A (n = 63)	BV After Auto-HCT: Cohort B (n = 80)	BV Before and/or After Auto-HCT: Cohort C (n = 100)	
ORR, % (95% CI)	65 (52-77)	68 (56-78)	73 (63-81)	69 (63-75)
Best overall response				
Complete remission	18 (29)	10 (13)	12 (12)	40 (16)
Partial remission	23 (37)	44 (55)	61 (61)	128 (53)
Stable disease	15 (24)	17 (21)	15 (15)	47 (19)
Progressive disease	7 (11)	6 (8)	10 (10)	23 (9)
Unable to determine	0	3 (4)	2 (2)	5 (2)

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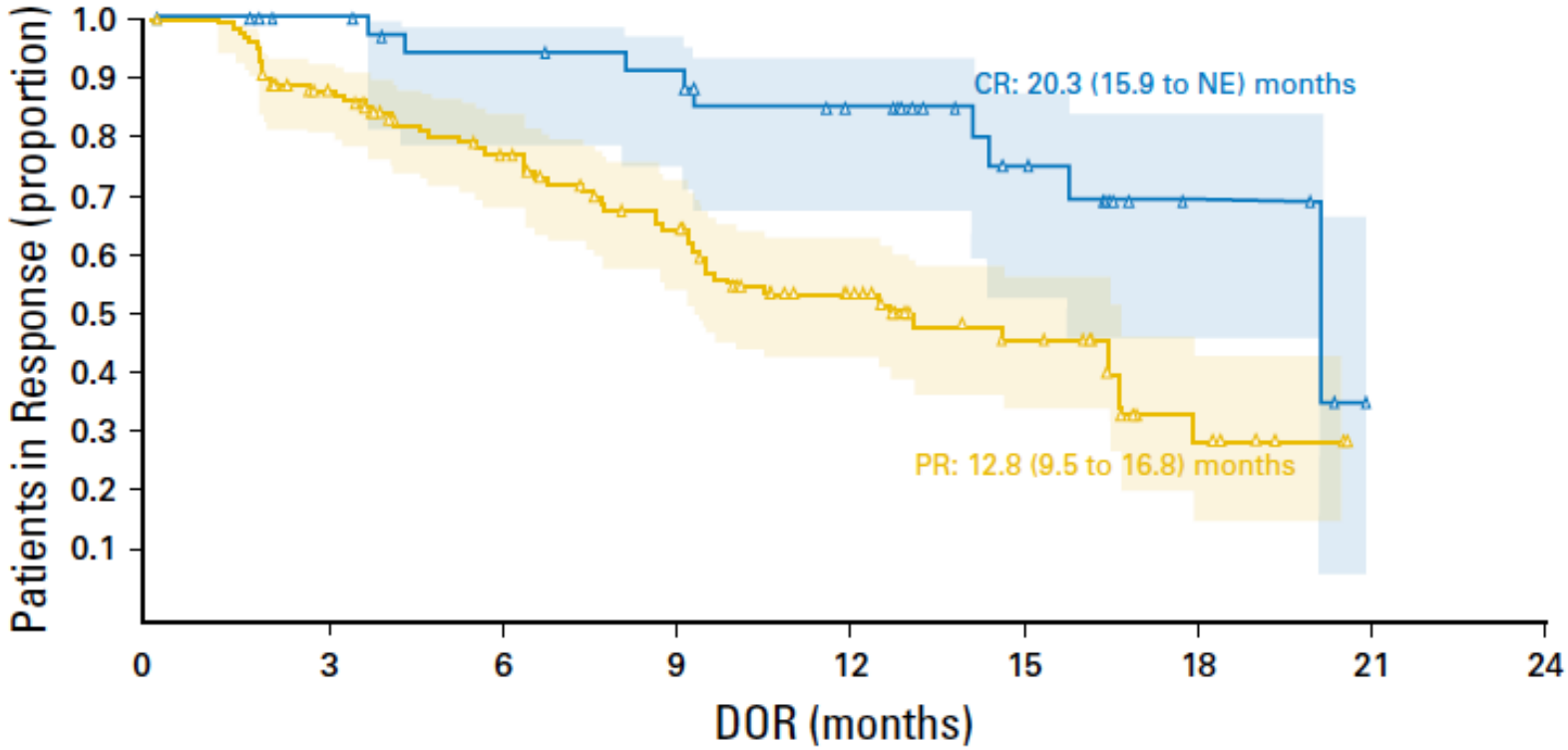

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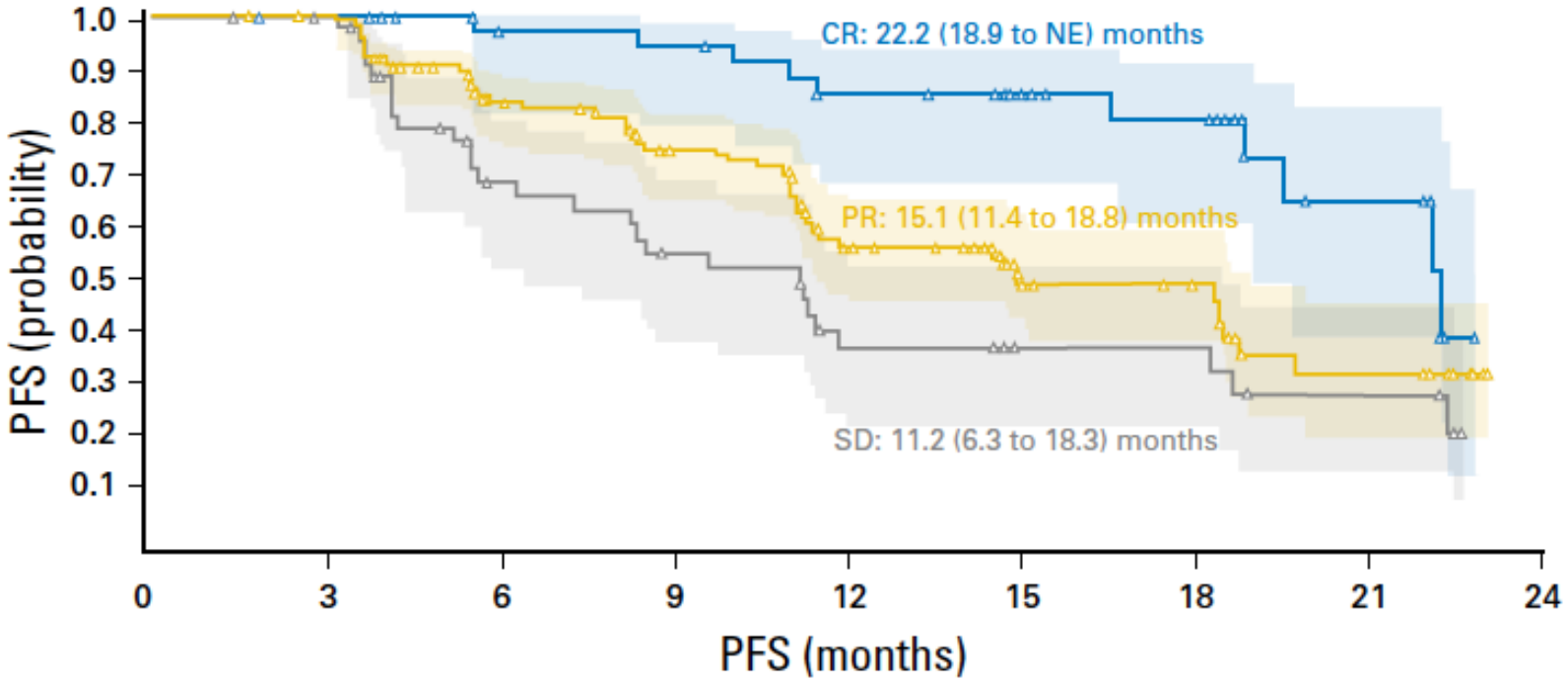

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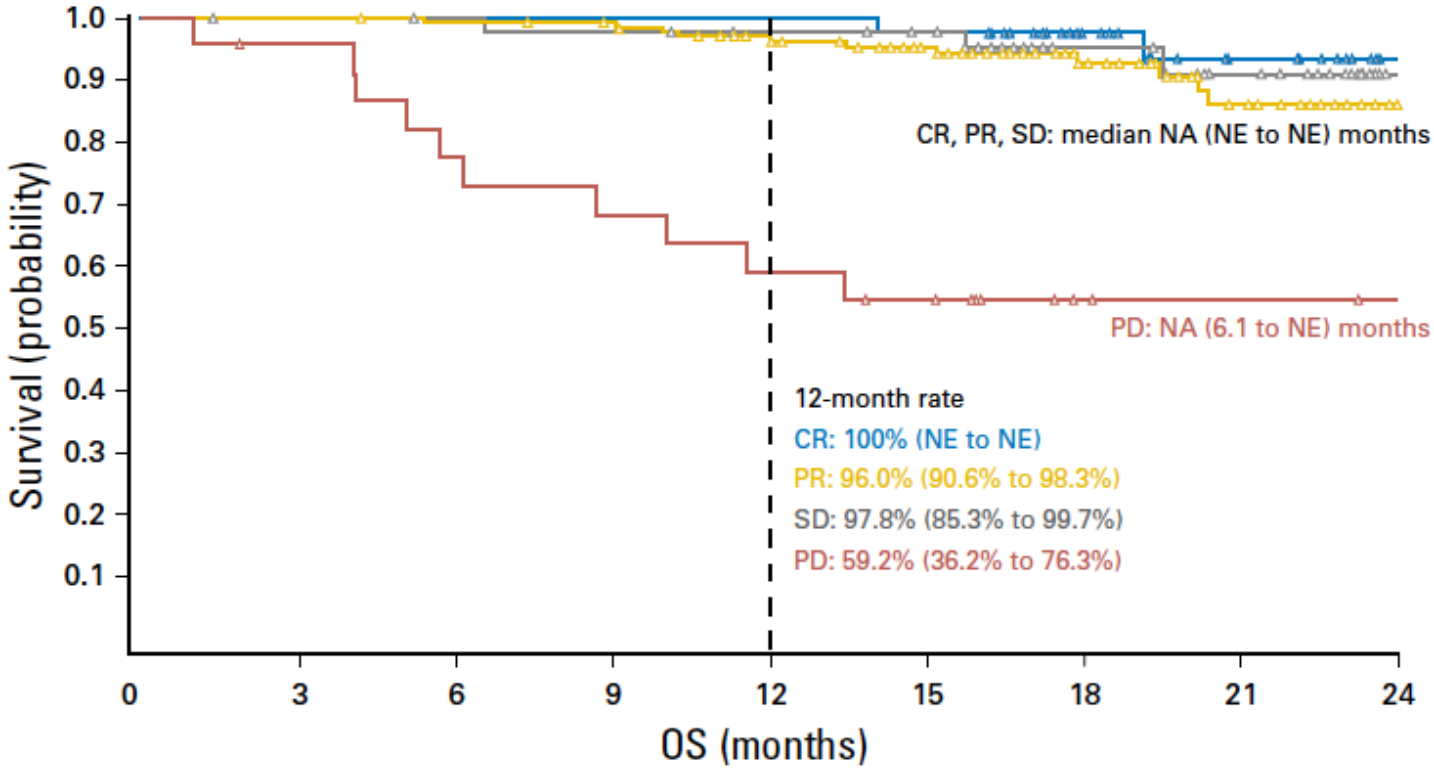

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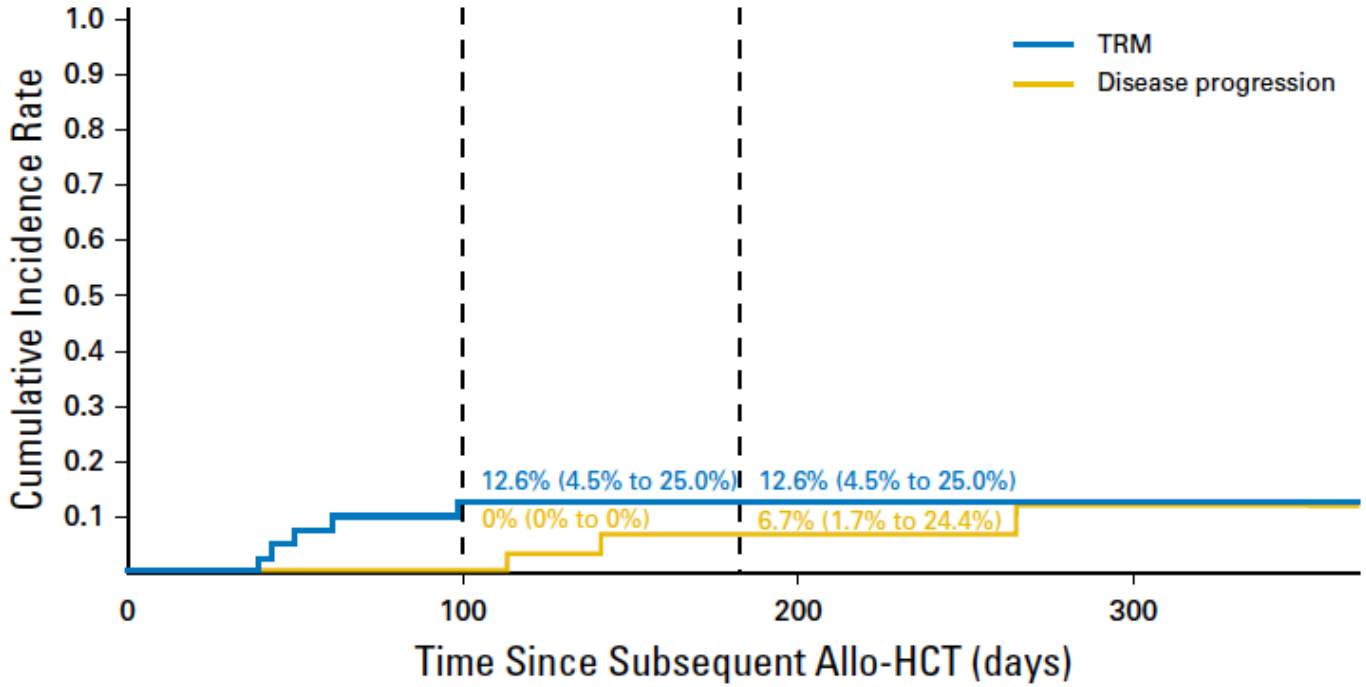

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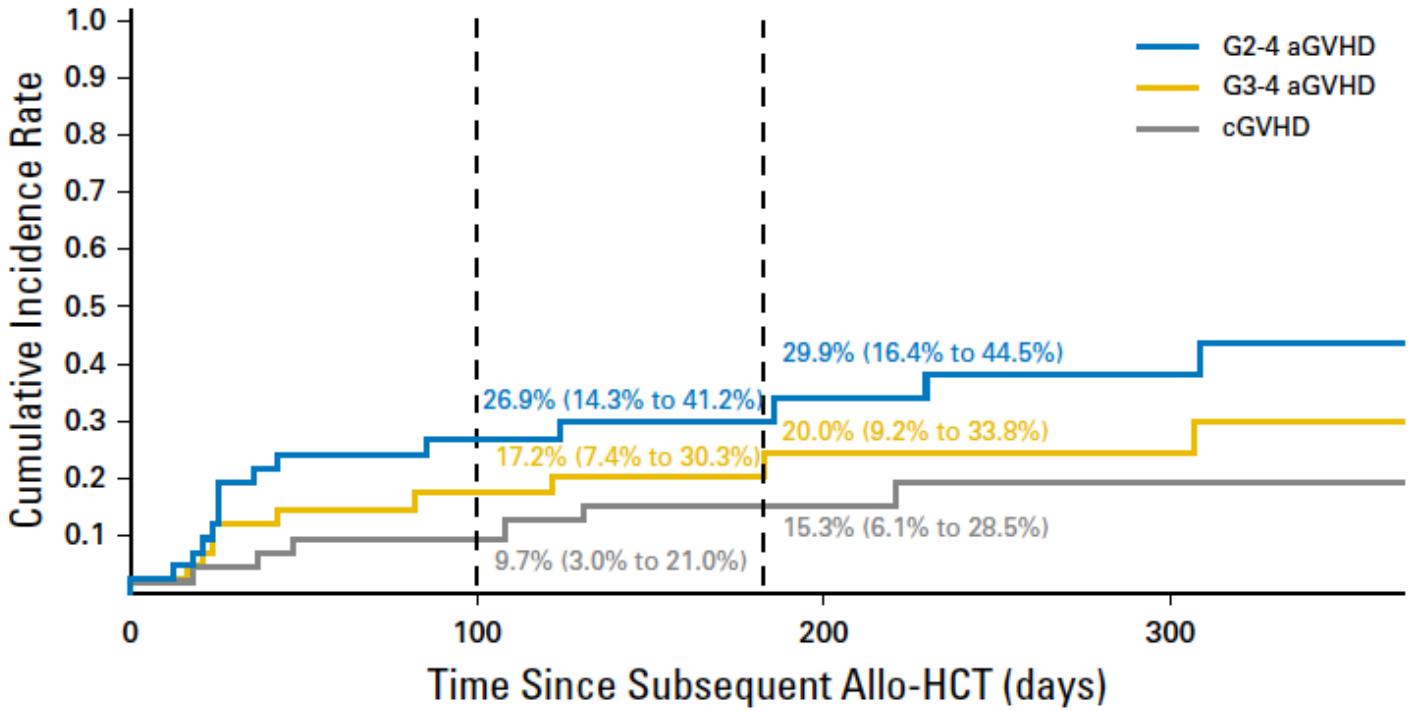

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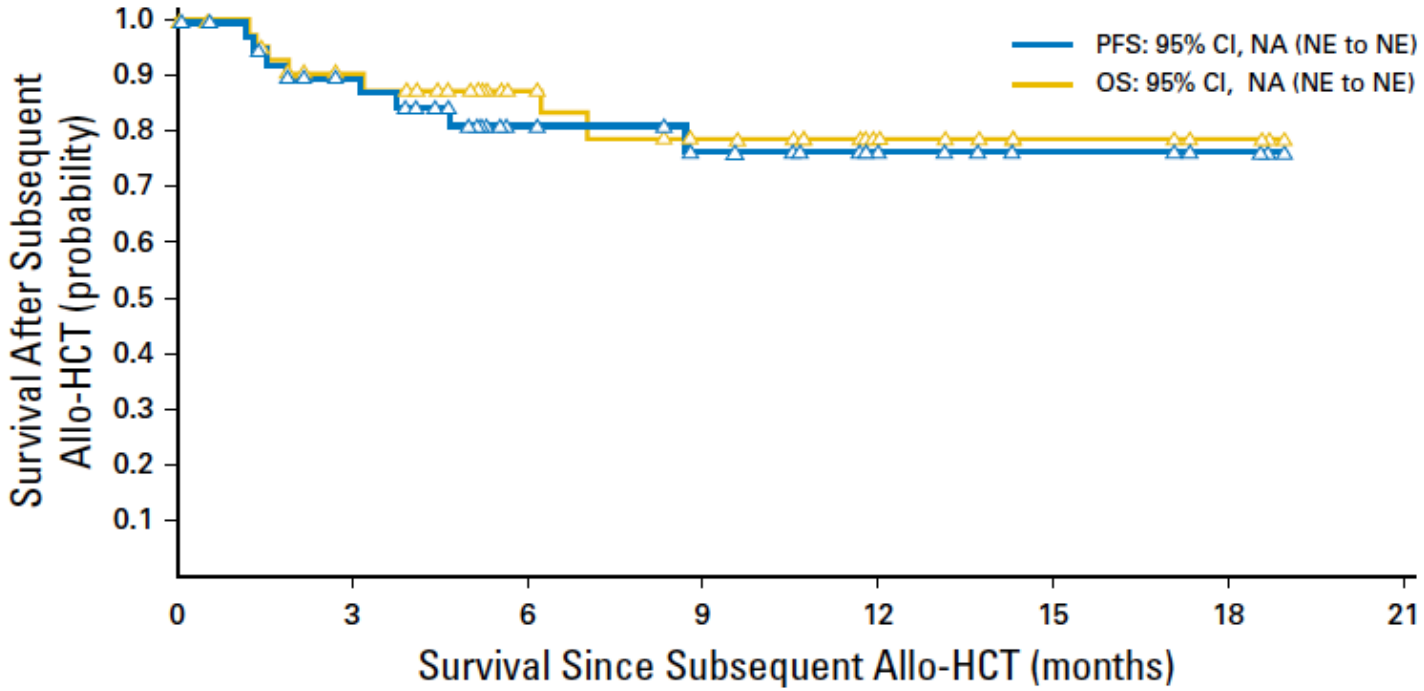

Conclusions

- Anti-PD-1/PD-L1 therapy induces an unprecedented clinical efficacy in rel/ref HL
- Results achieved with PD-1 blockade hint at a potential *paradigm shift* in cHL therapy
- Combining PD-1 blockade with Allo-SCT is an optimal therapeutic strategy

Challenging Issues

- Response assessment by PET
- Mechanisms of acquired resistance to Nivo

Translational Approach to Improve Response Assessment

- PET scan (A. Chiti)
  - Radiomic approach
- Repeated Biopsy (S. Pileri)
  - Persistance of PD-1/PD-L1 axis
  - Presence/absence of disease
- Circulating chemokine analysis (P. Allavena)
- Circulating tumor DNA genotyping (D. Rossi)
  - To monitor disease eradication
  - To identify treatment-emergent mutations associated with resistance

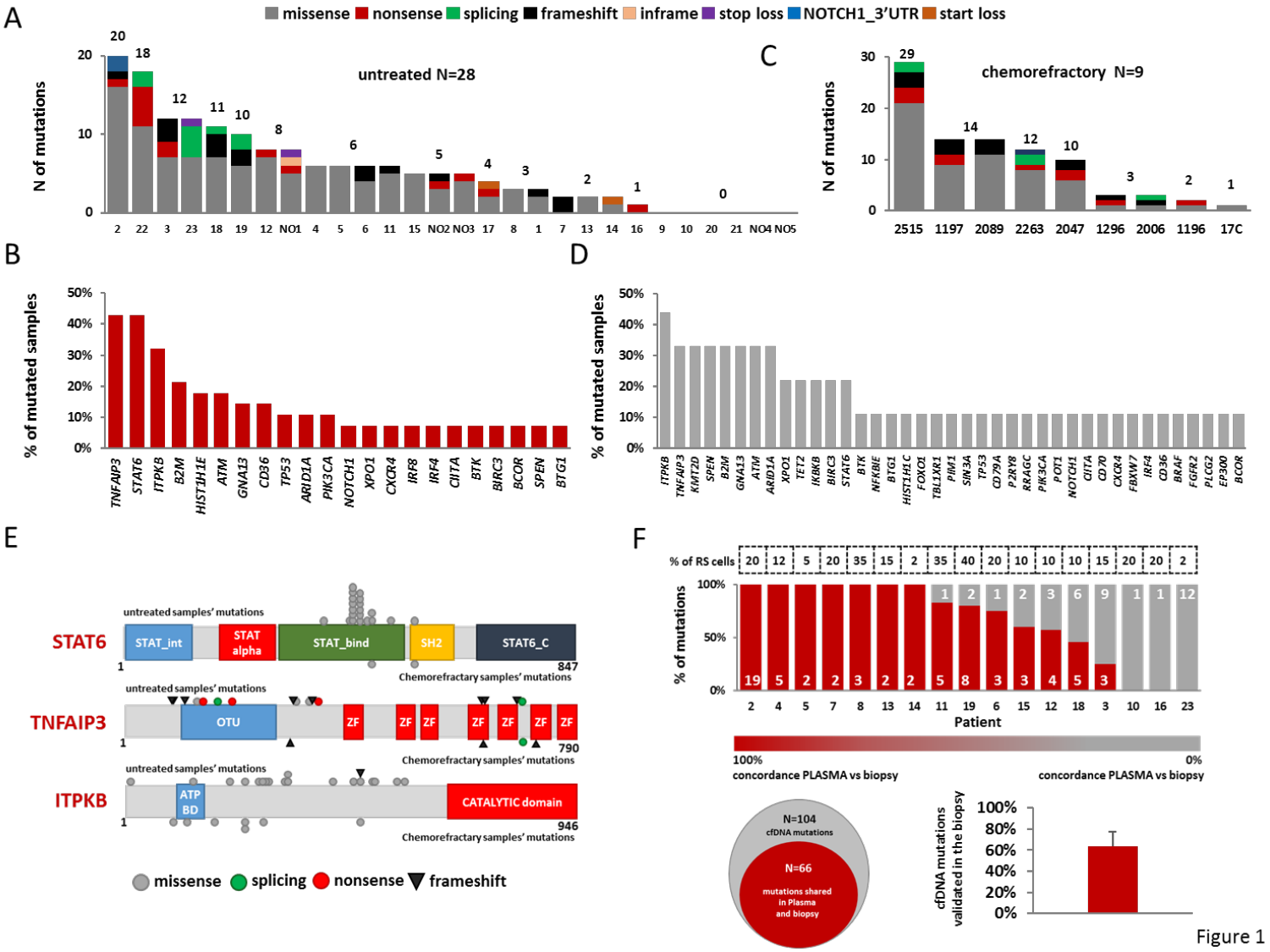
A
missense nonsense splicing frameshift inframe stop loss NOTCH1_3'UTR start loss
untreated N=28
N of mutations
20 18 12 11 10 8 6 5 4 3 2 1 0
2 22 3 23 18 19 12 NO1 4 5 6 11 15 NO2 NO3 17 8 1 7 13 14 16 9 10 20 21 NO4 NO5
C
chemorefractory N=9
N of mutations
29 14 12 10 3 2 1
2515 1197 2089 2263 2047 1296 2006 1196 17C
B
% of mutated samples
TNFAIP3 STAT6 ITPKB B2M HIST1H1E ATM GNA13 CD36 TP53 ARID1A PIK3CA NOTCH1 XPO1 CXCR4 IRF8 IRF4 CIITA BTK BIRC3 BCOR SPEN BTG1
D
% of mutated samples
ITPKB TNFAIP3 KMT2D SPEN B2M GNA13 ATM ARID1A XPO1 TET2 IKBKB BIRC3 STAT6 BTK NFKBIE BTG1 HIST1H1C FOXO1 TBL1XR1 PIM1 SIN3A TP53 CD79A P2RY8 RRAGC PIK3CA POT1 NOTCH1 CIITA CD70 CXCR4 FBXW7 IRF4 CD36 BRAF FGFR2 PLCG2 EP300 BCOR
E
STAT6
untreated samples' mutations
STAT_int STAT alpha STAT_bind SH2 STAT6_C
1 847
Chemorefractary samples' mutations
TNFAIP3
untreated samples' mutations
OTU ZF ZF ZF ZF ZF ZF ZF
1 790
Chemorefractary samples' mutations
ITPKB
untreated samples' mutations
ATP BD CATALYTIC domain
1 946
Chemorefractary samples' mutations
missense splicing nonsense frameshift
F
% of RS cells 20 12 5 20 35 15 2 35 40 20 10 10 10 15 20 20 2
% of mutations
100% 50% 0%
19 5 2 2 3 2 2 5 8 3 3 4 5 3
1 2 1 2 3 6 9 1 1 12
2 4 5 7 8 13 14 11 19 6 15 12 18 3 10 16 23
Patient
100% concordance PLASMA vs biopsy
0% concordance PLASMA vs biopsy
N=104
cfDNA mutations
N=66
mutations shared in Plasma and biopsy
cfDNA mutations validated in the biopsy
100% 80% 60% 40% 20% 0%

Figure 1

Acknowledgements

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P. De Nittis, MD

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