"Farmaci Innovativi, Biotecnologie e Terapie Staminali: Farmacologia, Farmacoterapia e Normative"

"L'innovazione nella target-therapy: Brentuximab Vedotin"

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Roma

Roma, 14 aprile 2015

Ifo Istituti Fisioterapici Ospitalieri

IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA

S.C. di Ematologia e Trapianti

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B. B. case report, 02-06-1971, female, kg 57, BSA 1,7 m^2.

18-07-2007 Diagnosis of anaplastic large cell lymphoma (ALCL) T phenotype, CD30+, fusion protein Alk- (according to WHO 2001). Stage II according to Ann-Arbor classification with 6 cm diameter right laterocervical lymphoadenopathy (PET/CT and CT scan). LDH normal value. Karnofsky performance status 100. No involvement of bone marrow and CNS.

30-07-2007→20-02-2008 Six cycles of CEVOP-B enhanced: CTX 1 gr/m^2 day 1, EPI 100 mg/m^2 c.i. 96h (day 1→4), VP16 360 mg/m^2 c.i. 96h (day 1→4), VCR 2 mg t.d. day 1, BLM 15 mg t.d. day 5, PDN 60 mg/m2 day 1→5, MTX 2 gr/m^2 day 8 only fourth and fifth cycle.

02-04-2008 Restaging: CT scan negative, PET/CT positive on the right side of the neck.

09-04-2008 Radical right laterocervical lymphoadenectomy (confirmed diagnosis of ALCL CD30+ Alk-.)

18-04-2008 Appearance of fever and peripheral pancytopenia.

24-04-2008 Involvement of bone marrow from ALCL CD30+ documented by biopsy.

29-04-2008 CNS liquor negative.

30-04-2008 CT scan: 15 mm diameter right inframandibular and carinal lymphoadenopathy, multiple ipodense splenic solid lesions (maximum diameter 2,5 cm).

01-05-2008 MAD first cycle: MITOXANTRONE 8 mg/m^2 day 1→3, ARA-C 2 gr/m2 bid day 1→3, DXM 40 mg t.d. day 1→4. Tumor lysis syndrome with acute toxic hepatitis requiring intensive medical therapy.

19-05-2008 No HLA suitable family donor.

29-05-2008 Bone marrow negative by bilateral biopsy.

06-06-2008 MAD second cycle with failed PBSC mobilization.

01-07-2008 Appearance of fever and peripheral pancytopenia.

04-07-2008 CNS negative (MRI and liquor), bilateral bone marrow biopsy positive for focal ALCL CD30+ involvement, 10% of lymphoma blast cells at bone marrow cytosmear morphological examination, PET/CT positive for massive progression at hepatic, splenic, supra and infradiaphragmatic lymphonodal levels.

10-07-2008 Unrelated donor research paper forms sent from CTMO Rome Ø4 to Italian Bone Marrow Donor Registry.

From 13-07-2008 in therapy with HD-DXM

SGN-35 (plus gemcitabine?) may be the only chance to control the disease (eventually waiting for an allogeneic transplant).

Rome, 17-07-2008

Dott. Andrea Mengarelli

IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

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Relazione clinica del paziente M. G., nato il 24/06/1959.

Settembre 2013 diagnosi di Linfoma non Hodgkin Anaplastico a grandi cellule, fenotipo T, CD 30+, ALK Neg, IV stadio per localizzazioni cutanee con estensione ai tessuti molli e linfonodi sovra e sottodiaframmatici, BOM e Liquor neg. PS 0. IPI intermedio-alto.

In data 04/11/2013: inizia terapia secondo lo schema CHOEP / DHAP. PL di profilassi con MTX.
Post 2°ciclo DHAP staminoaferesi in data 11/02/201 4.

Post 4°ciclo di chemioterapia progressione di mala ttia livello cutaneo e viscerale (PET). Biopsia della lesione cutanea ascella destra del 17/03/2014: conferma ALCL fenotipo T, CD30+, Alk neg., Ki67 90%.

In data 04/04/2014 ha iniziato 2°linea del trattamento con Brentuximab vedotin 180 mg ogni 21 giorni di cui ha eseguito 5 cicli (ultimo 16/07/2014).
In data 07/04/2014 - studio HLA del nucleo familiare (sorella e figlio): il paziente non dispone di donatori HLA identici.

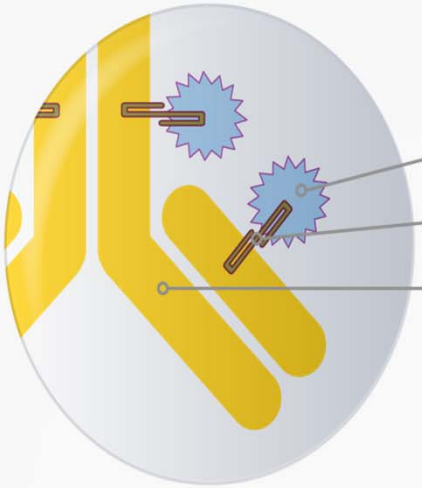
Rivalutazione della malattia post 4 cicli di terapia: RP > 50% viscerale (PET, TC neg.) e cutanea.

In data 08/08/2014: ASCT, condizionamento BEAM.
Complicanze sepsi da st. haemolyticus, ileotiflite, riattivazione CMV.
Restaging a 60 giorni: RC

Si invia per Trapianto allogenico da MUD.

Il 09/10/2014

In fede
Dott.ssa Svitlana Gumenyuk

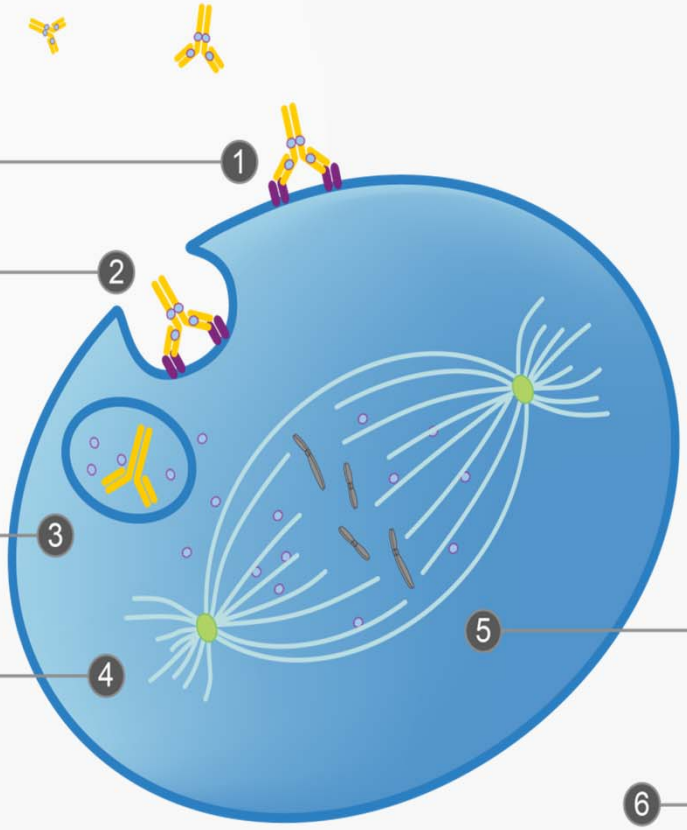


Brentuximab Vedotin Antibody-Drug Conjugate (ADC)

Monomethyl auristatin E (MMAE), microtubule-disrupting agent

Protease-cleavable linker

Anti-CD30 monoclonal antibody



anti-CD30 come target therapy...

VOLUME 25 · NUMBER 19 · JULY 1 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Lancet. 1992 May;339(8803):11

bjh research paper

Phase I/II Study of an Anti-CD30 Monoclonal Antibody (MDX-060) in Hodgkin's Lymphoma and Anaplastic Large-Cell Lymphoma

Stephen M. Ansell, Steven M. Horwitz, Andreas Engert, Khuda Dad Khan, Thomas Lin, Roger Strair, Tibor Keler, Robert Graziano, Diann Blanset, Michael Yellin, Steven Fischkoff, Albert Assad, and Peter Borchmann

A Phase II study of SGN-30 (anti-CD30 mAb) in Hodgkin lymphoma or systemic anaplastic large cell lymphoma

Andres Forero-Torres,[1] John P. Leonard,[2] Andrei [illegible],[3] Stephen Shibata,[4] Pauline Brice,[5] Nancy L. Bartlett,[6] Andre Bosly,[7] Lauren Pinter-Brown,[8] Dana Kennedy,[9] Eric D. Stevens[9] and Ajay K. Gopal[10]

[1]University of Alabama at Birmingham, Birmingham, AL, [2]Weill Cornell Medical College, New York, NY, [3]MD Anderson Cancer Center, University of Texas, Houston, TX, [4]Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, FL, USA, [5]Hospital Saint Louis, Paris, France, [6]Washington University School of Medicine, St. Louis, MO, USA, [7]Mont-Godinne University Hospital, Yvoir, Belgium, [8]Department of Medicine, Geffen School of Medicine at UCLA, Los Angeles, CA, [9]Seattle Genetics, Inc., Seattle, WA, and [10]Department of Medical Oncology, University of Washington, Seattle, WA, USA

Received 19 February 2009; accepted for publication 15 April 2009

Summary

SGN-30, a chimeric anti-CD30 monoclonal antibody, has demonstrated potent preclinical antitumour activity in both Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL). We conducted an open-label, Phase II study to determine the safety and objective response rate of SGN-30 in 79 patients with refractory or relapsed HL (n = 58) or systemic ALCL (n = 21). Each course of SGN-30 comprised 6 weekly intravenous infusions, followed by a 2-week treatment-free period. Patients had received a median of 3 (range 1–5) prior regimens of chemotherapy or systemic therapy. The initial 40 patients received 6 mg/kg weekly; the latter 39 patients received 12 mg/kg weekly. In the ALCL group, two patients achieved a complete response and five additional patients achieved a partial response, with response durations ranging from 27 to 1460+ d. No objective responses were observed in the HL group; however, 11 patients (29%) had stable disease (duration 62–242 days). Although adverse events were common, most were mild or moderate, and no specific pattern of adverse events was observed in either disease group. These results demonstrate that weekly administration of SGN-30 is safe, with modest clinical activity in patients with ALCL.

Keywords: Hodgkin lymphoma, anaplastic large cell lymphoma, monoclonal antibody, anti-CD30 antibody, anaplastic lymphoma kinase.

CD30

Membro della superfamiglia dei recettori del TNF (TNF-R).

Glicoproteina transmembrana normalmente espressa sulla superficie di cellule T attivate implicata nei meccanismi di apoptosi via NFkB.

Fortemente espresso sulla cellula di Reed-Sternberg nel HL e sulla cellula T nel sALCL.

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SG035-0001: Phase 1 dose-escalation study in patients with rel/ref CD30+ lymphoma

Case study

MTD: 1.8 mg/kg

- **37-yr-old male diagnosed with HL**

NEOPLASIA

Blood 2003

cAC10-vcMMAE, an anti-CD30–monomethyl auristatin E conjugate with potent and selective antitumor activity

Joseph A. Francisco, Charles G. Cerveny, Damon L. Meyer, Bruce J. Mixan, Kerry Klussman, Dana F. Chace, Starr X. Rejniak, Kristine A. Gordon, Ron DeBlanc, Brian E. Toki, Che-Leung Law, Svetlana O. Doronina, Clay B. Siegall, Peter D. Senter, and Alan F. Wahl

- **Rituximab**
- **Cycle 2 restaging: CR**

From New England Journal of Medicine, Younes A, et al. Brentuximab Vedotin (SGN-35) for Relapsed CD30 Positive Lymphomas, 363;1812–21;Suppl Appendix.

Indicazioni terapeutiche approvate

FDA 2011
EMA 2012
AIFA L.648/96 2012, determinazione di Prezzo e Rimborso G.U. n. 143 del 23 giugno 2014
PTOTR Lazio novembre 2014

Adcetris® è indicato per il trattamento di pazienti adulti affetti da linfoma di Hodgkin (HL) CD30+ recidivante o refrattario:

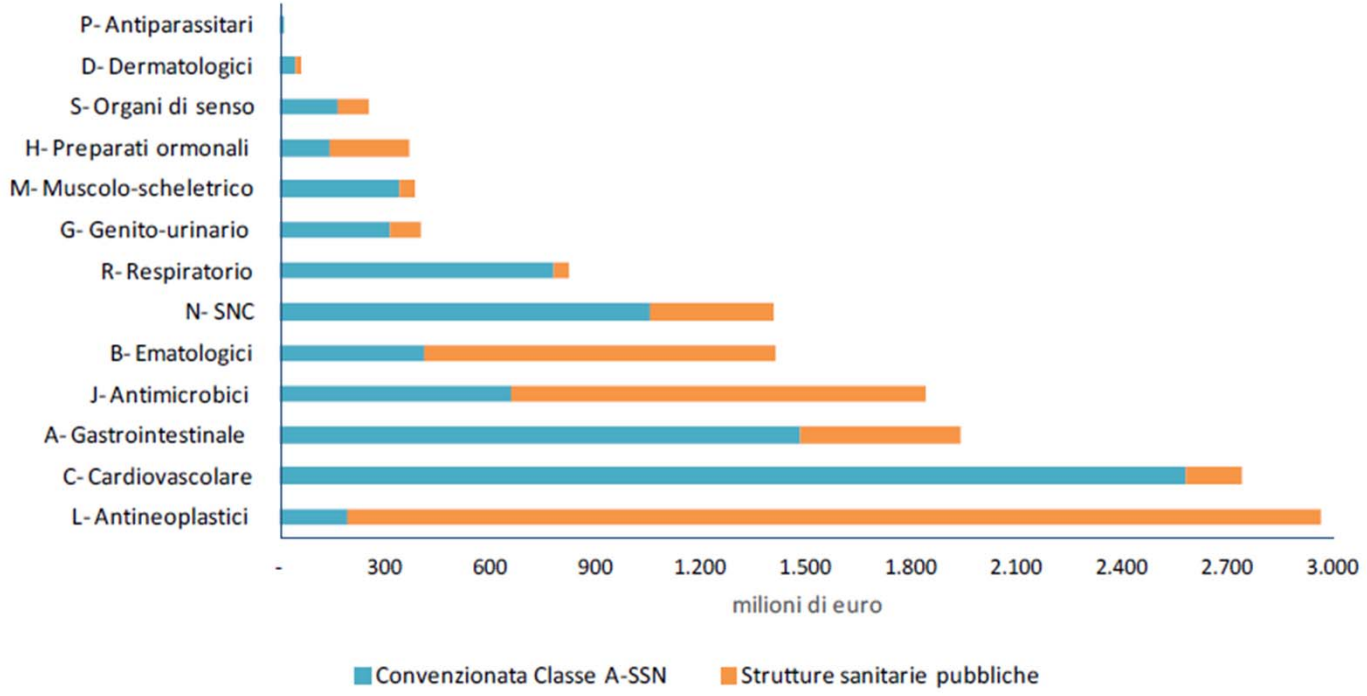
- **in seguito a trapianto autologo di cellule staminali (ASCT) *oppure***
- **in seguito ad almeno due precedenti regimi terapeutici, quando ASCT o la poli-chemioterapia non sono un'opzione terapeutica.**

Adcetris® è indicato per il trattamento di pazienti adulti affetti da linfoma anaplastico a grandi cellule sistemico (sALCL) recidivante o refrattario.

Place in therapy: per la popolazione a cui Adcetris® è indirizzato non esistono alternative terapeutiche di provata efficacia. RCP

Valutazione farmaco-economica e budget impact

I farmaci antineoplastici diventano nel 2014 i primi per spesa pubblica



Agenzia Italiana del Farmaco
AIFA

- **Costo delle singole confezioni**

1 confezione: 1 flaconcino da 50 mg.

Cicli di terapia	Prezzo al pubblico	Prezzo ex-factory	Sconto applicato	Prezzo applicato alle strutture del SSN
Dal 1° al 9°	€ 5.500,83	€ 3.333,00	13%	**€ 2.899,72**
Dal 10° al 12°	€ 5.500,83	€ 3.333,00	23%	**€ 2.566,41**
Dal 13° al 16°	€ 5.500,83	€ 3.333,00	50%	**€ 1.666,50**

- **Costo dei farmaci di documentata similarità o equivalenza clinica/terapeutica**

Non applicabile in quanto Adcetris® si propone per pazienti per i quali non esiste una valida alternativa terapeutica.

- **Non esistono al momento pubblicazioni di HTA disponibili**

Regione Lazio – stima n. nuovi casi anno

	n. pazienti		n. pazienti
HL	196	NHL	800
Refrattari o recidivati	49 (25%)	sALCL	16 (2%)
Ricaduti dopo terapia di salvataggio o ASCT	25 (50%)	Ricaduti dopo terapia di prima linea	4 (25%)
Eleggibili a BV	**25**	**Eleggibili a BV**	**4**

HL	#	n. fiale/anno	Costo per il SSR al netto degli sconti negoziati	sALCL	#	n. fiale/anno	Costo per il SSR al netto degli sconti negoziati
8 cicli 24 fl Sconto 13%	16,75 (67%)	402	€ 1.165.687	8 cicli 24 fl Sconto 13%	2,96 (74%)	71	€ 205.996
4 cicli (progressione) 12 fl Sconto 13%	3,75 (15%)	45	€ 130.487	4 cicli (progressione) 12 fl Sconto 13%	0,36 (9%)	4	€ 12.527
16 cicli 48 fl Sconto 13% x 27 fl Sconto 23% x 9 fl Sconto 50% x 12 fl	4,5 (18%)	216	€ 546.247	16 cicli 48 fl Sconto 13% x 27 fl Sconto 23% x 9 fl Sconto 50% x 12 fl	0,68 (17%)	33	€ 82.544

Costo complessivo effettivo di acquisto al netto delle condizioni di sconto negoziate (sconto progressivo 13 - 23 - 50%): € 2.143.488

AIRTUM

Istat

Tabella 22. Composizione per classe di rimborsabilità della spesa regionale per medicinali erogati nell'ambito dell'assistenza farmaceutica ospedaliera ed ambulatoriale

Regione	Classe A (*euro*)	Classe C (*euro*)	Classe H (*euro*)	Totale (*euro*)	Inc% A	Inc% C	Inc% H
Lazio	18.930.453	24.760.517	122.744.553	166.435.523	11,4%	14,9%	73,7%

7.6 Assistenza farmaceutica ospedaliera

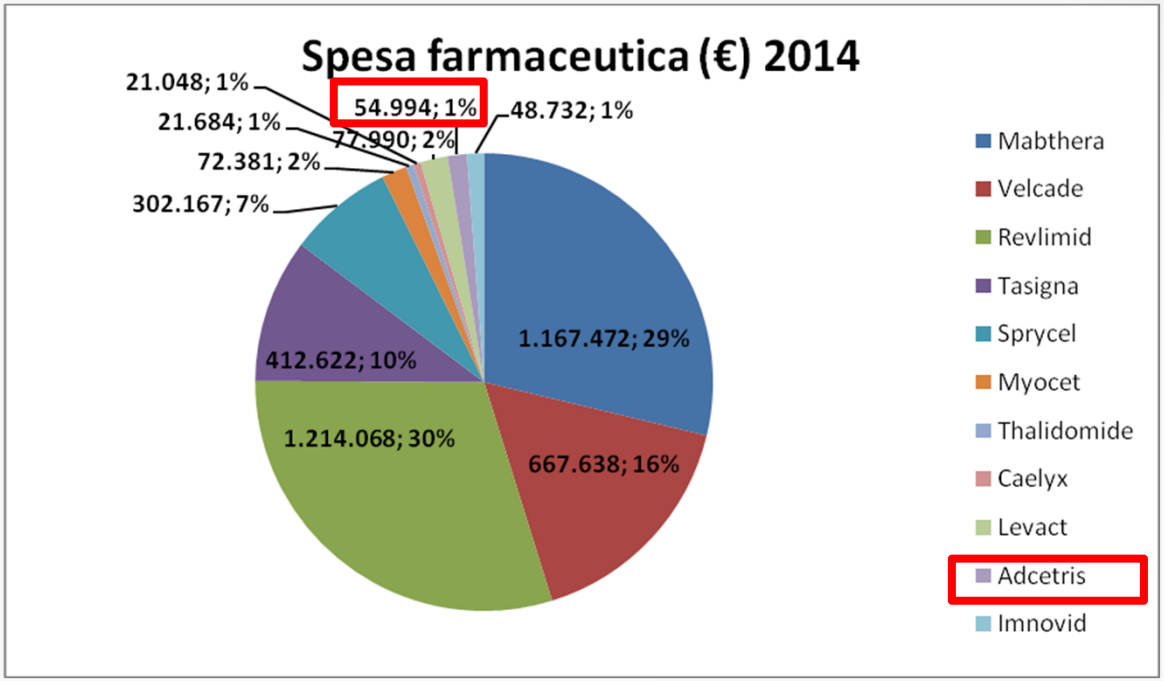
Tabella 7.6.1. Composizione per classe di rimborsabilità della spesa regionale per medicinali erogati nell'ambito dell'assistenza farmaceutica ospedaliera

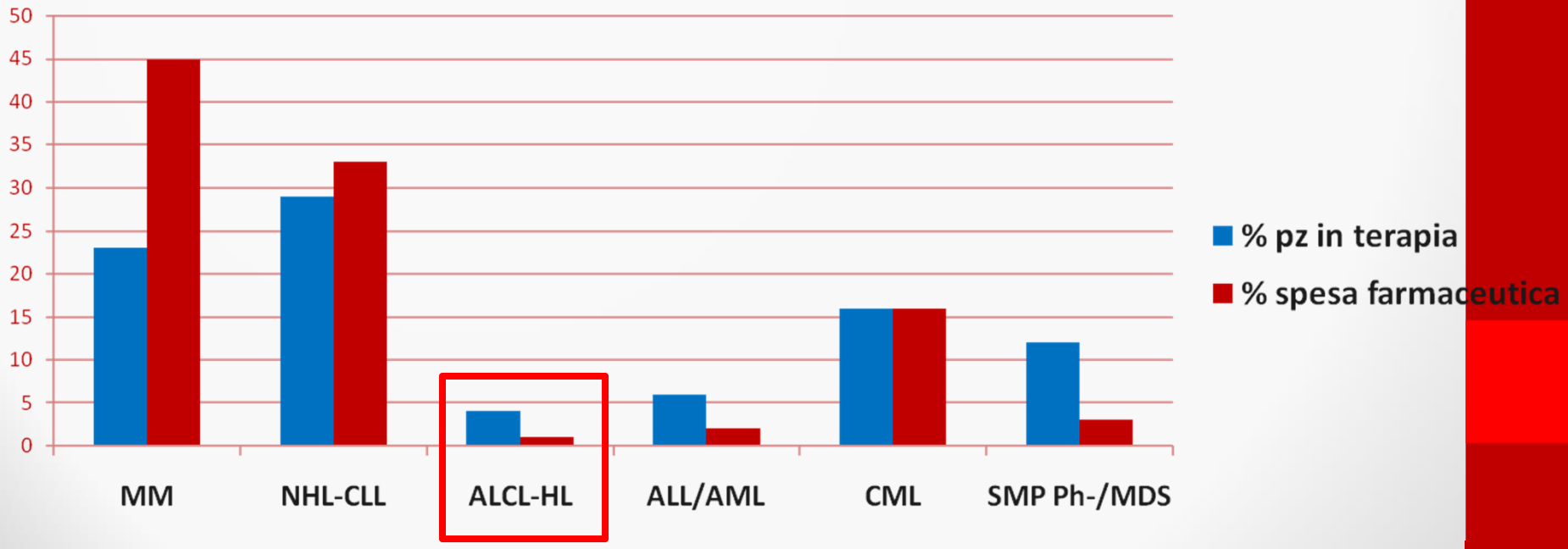
Regione	Classe A (*euro*)	Classe C (*euro*)	Classe H (*euro*)	Totale (*euro*)	Inc% A	Inc% C	Inc% H
Lazio	28.890.973	35.795.281	205.630.095	270.316.348	10,7%	13,6%	75,7%

Considerata la spesa della Regione Lazio per medicinali erogati nell'ambito dell'assistenza farmaceutica ospedaliera nel 2013 e nel gennaio-settembre 2014, Adcetris® impatta per circa lo 0.8 % annuo

EMA-IRE

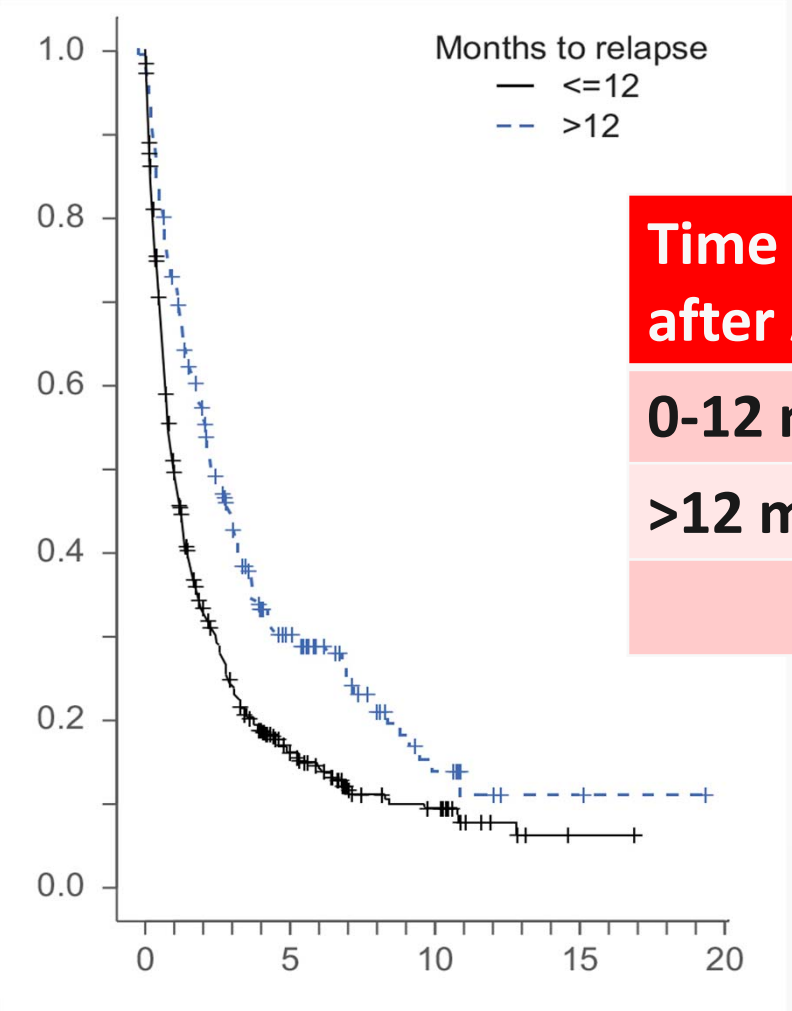
Budget impact 1,1%





Clinical Data in Hodgkin Lymphoma

Patients who fail ASCT have a poor prognosis

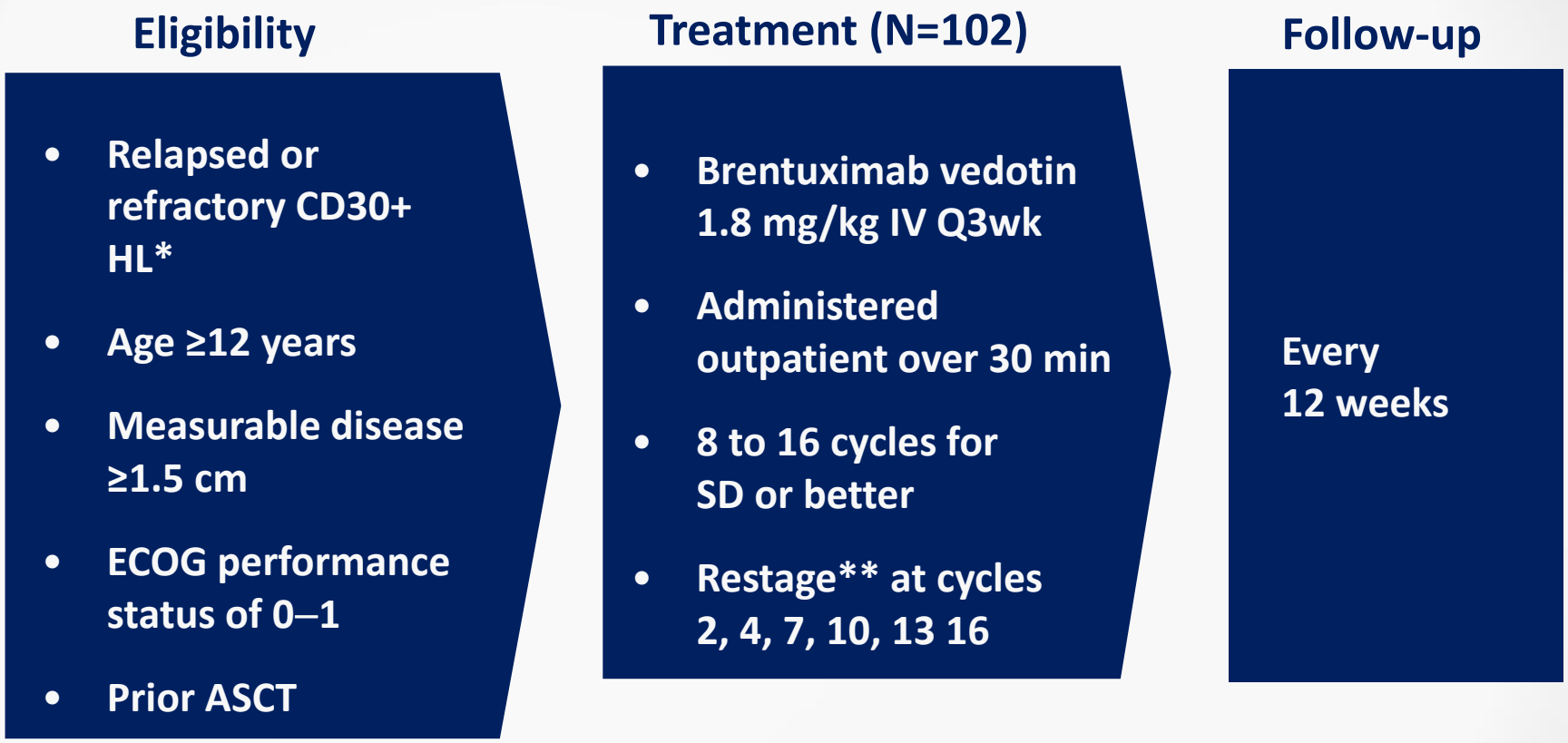


Time to relapse after ASCT	N	Median PPS (yr)
0-12 months	542	0.98
>12 months	214	2.26
		P<0.0001

Post-progression survival PPS (yrs)

Arai S et al. Leukemia & Lymphoma 2013; doi:10.3109/10428194.2013.798868.

SG035-0003: Phase 2 pivotal study of brentuximab vedotin in patients with rel/ref HL post ASCT: overview



Primary Endpoint: objective response rate (ORR; CR+PR) by Independent Review Facility (IRF)

* Histologically documented CD30-positive HL by central pathology review

** Revised response criteria for malignant lymphoma (Cheson 2007)

Younes A, et al. J Clin Oncol 2012;30: 2183-2189.

SG035-0003: Phase 2 pivotal study of brentuximab vedotin in patients with rel/ref HL post ASCT

Response

% (95% CI)	IRF (N=102)
ORR	75 (65, 83)
CR	34 (25, 44)
PR	40
SD	22
PD	3
Not evaluable	1

Median time to OR (range)	5.7 wks (5.1–56)
Median duration of OR (95% CI)	6.7 months (3.6–14.8)
Median time to CR (range)	12 wks (5.1–56)
Median duration of CR (95% CI)	20.5 months (10.8, –)
Median PFS (95% CI)	5.6 months (5.0, 9.0)

Median (range) cycles of treatment: 9 (1–16)

- Assessment of OR was concordant between IRF and investigators for 87% of patients. The κ coefficient was 0.68, suggesting good concordance between assessors

Younes A, et al. J Clin Oncol 2012;30: 2183-2189.

SG035-0003: Phase 2 pivotal study of brentuximab vedotin in patients with rel/ref HL post ASCT

Treatment-related grade ≥3 AEs (20% of patients discontinued due to AEs)

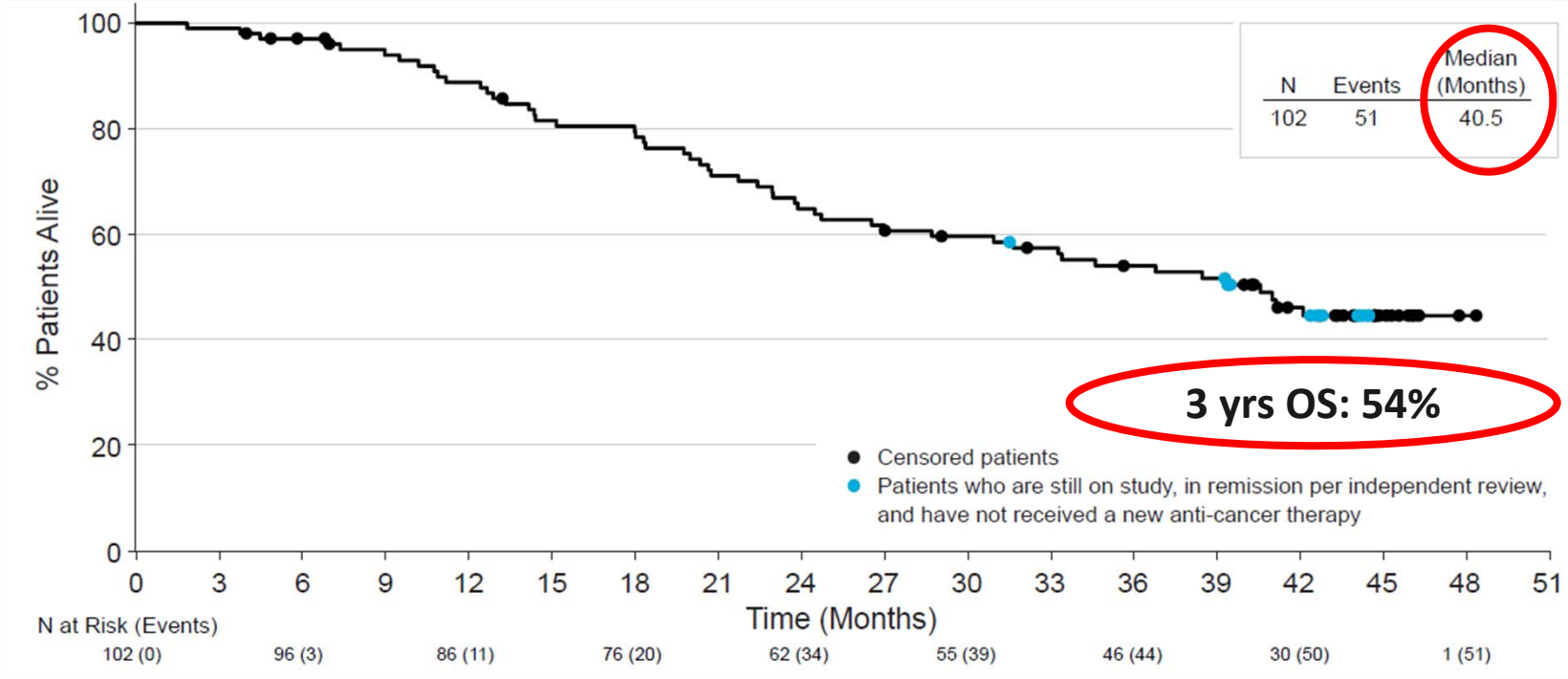
Preferred Term	Grade ≥3 AEs
Neutropenia	20%
Peripheral sensory neuropathy	8%
Thrombocytopenia	8%
Anemia	6%
Fatigue	2%
Pyrexia	2%
Diarrhea	1%
Peripheral motor neuropathy	1%

- Total patients with any grade ≥3 AE: 55%
- Dose delays due to AEs in 47% of patients; dose reductions in 11 patients
- No deaths within 30 days of last drug administration; no deaths attributed to brentuximab vedotin

Younes A, et al. J Clin Oncol 2012;30: 2183-2189.

SG035-0003: Updated (ASH 2013) Overall Survival

- **Median follow up since first dose of brentuximab vedotin: 32.7 mos (1.8 – 48.3 mos)**
- **18 patients remain in remission per investigator review/14 patients remain in remission per independent review**

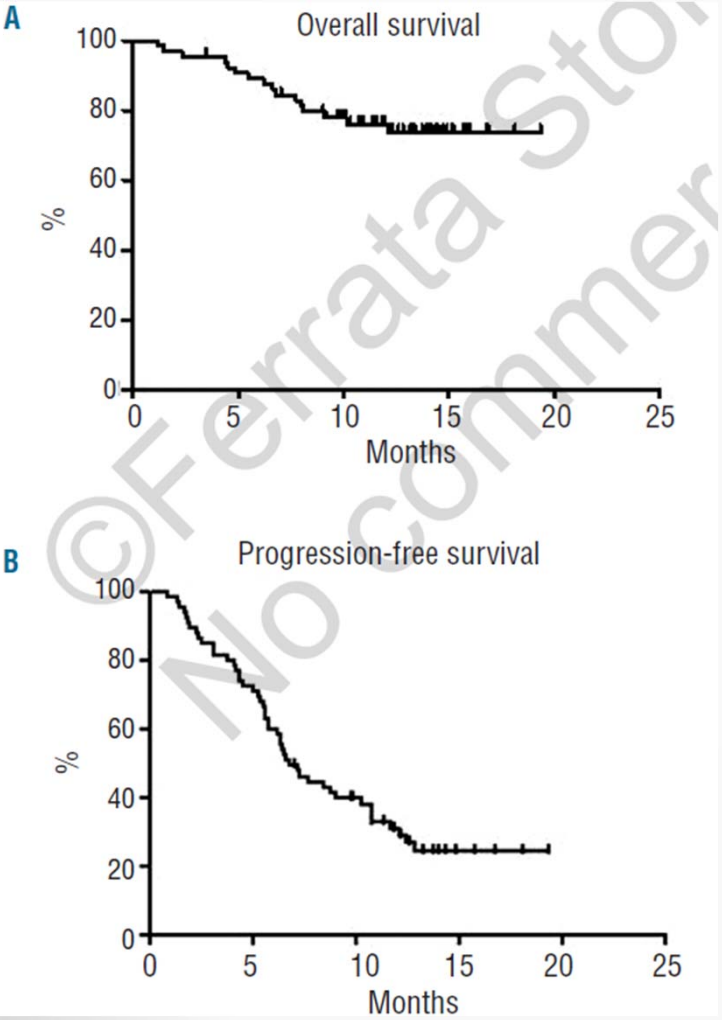


Gopal A, et al. ASH 2013, New Orleans, LA, USA (Abstract 4382).

blood

Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials

Pier Luigi Zinzani,[1] Simonetta Viviani,[2] Antonella Anastasia,[3] Umberto Vitolo,[4] Stefano Luminari,[5] Francesco Zaja,[6] Paolo Corradini,[7] Michele Spina,[8] Ercole Brusamolino,[9] Alessandro M. Gianni,[2] Armando Santoro,[3] Barbara Botto,[4] Enrico Derenzini,[1] Cinzia Pellegrini,[1] and Lisa Argnani[1]



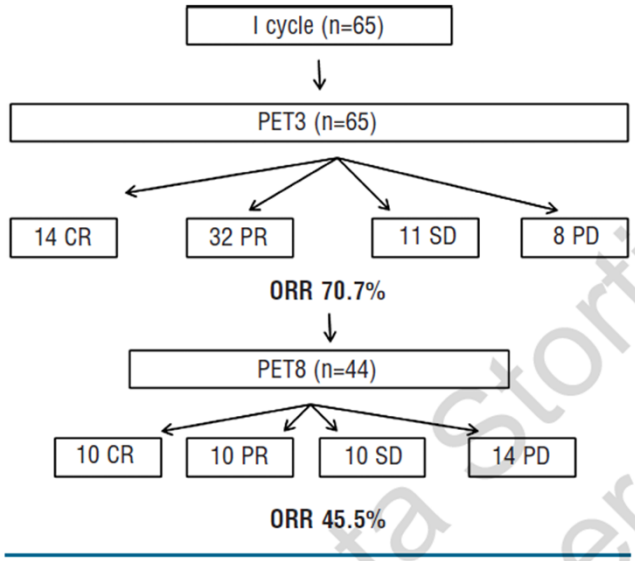


Figure 1. Algorithm of the responses at the PET3 and PET8 evaluations. CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate.

Table 3. Results of the pivotal study and NPP experiences.

Study	N. pts	ORR%	CR%
Pivotal[11]	102	73	32
German NPP[14]	45	60	22
UK NPP[15]	18	72	17
Italian NPP	65	70.7	21.5

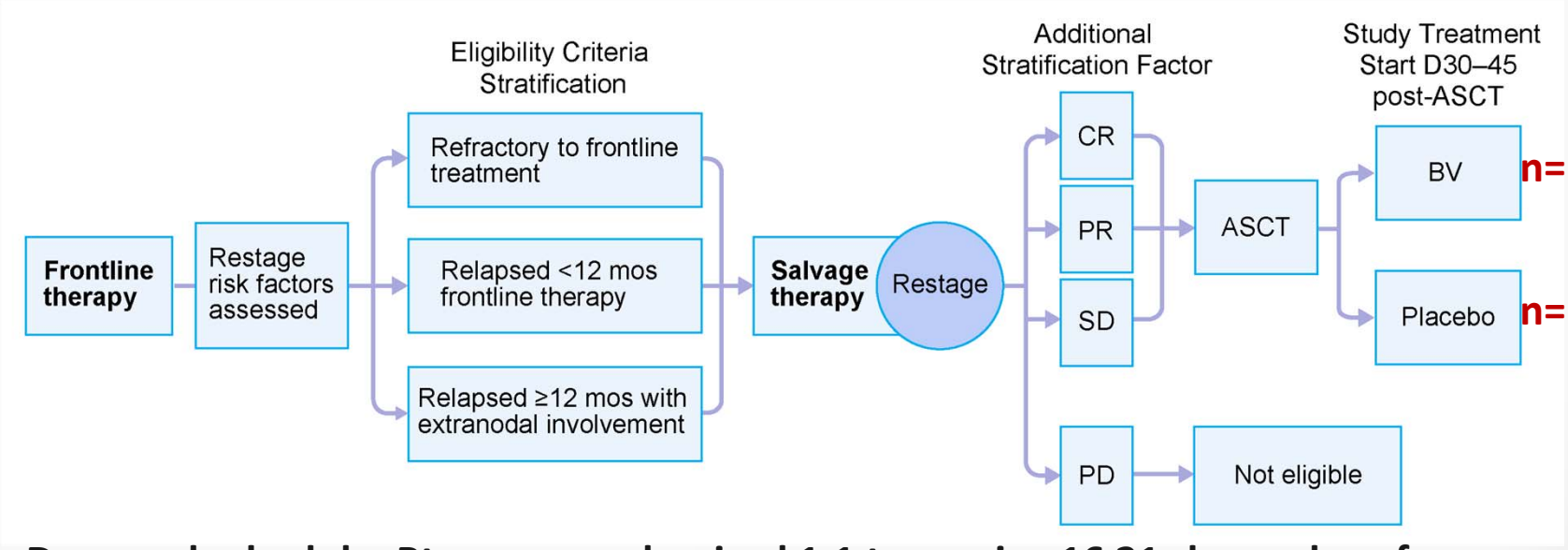
NPP: Named Patient Program; pts: patients; ORR, overall response rate; CR: complete response.

In the "real world" setting response rates to BV are similar to those reported in phase 2 trial. BV is generally well tolerated.

Zinzani P, et al. Haematologica 2013; 98: 1232-1236.

SGN35-005: AETHERA phase 3 trial of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of relapse post ASCT

- **Design: Phase 3 randomized, double-blind, placebo-controlled, multicenter study of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of progression following ASCT**
- **Objectives: *Primary:* PFS per IRF; *Secondary:* OS, safety/tolerability**



Dose and schedule: Pts were randomized 1:1 to receive 16 21-day cycles of brentuximab vedotin 1.8 mg/kg IV day 1 or placebo

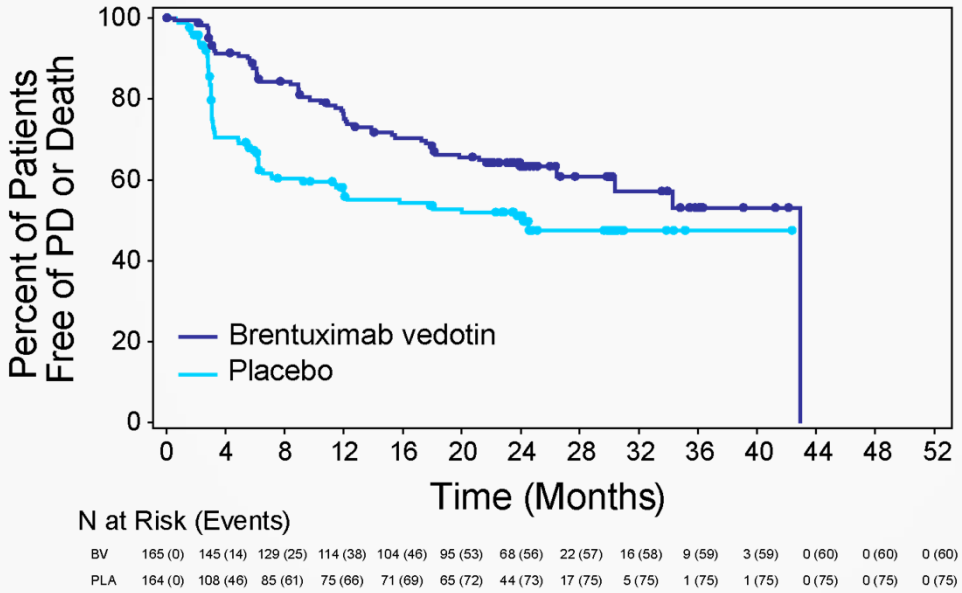
- **Pts who progressed on placebo could receive brentuximab vedotin in another trial**

Craig H, et al. 2014 ASH Meeting, Oral Presentation
Blood 2014, 124:673.

blood

SGN35-005: AETHERA phase 3 trial of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of relapse post ASCT

PFS per IRF



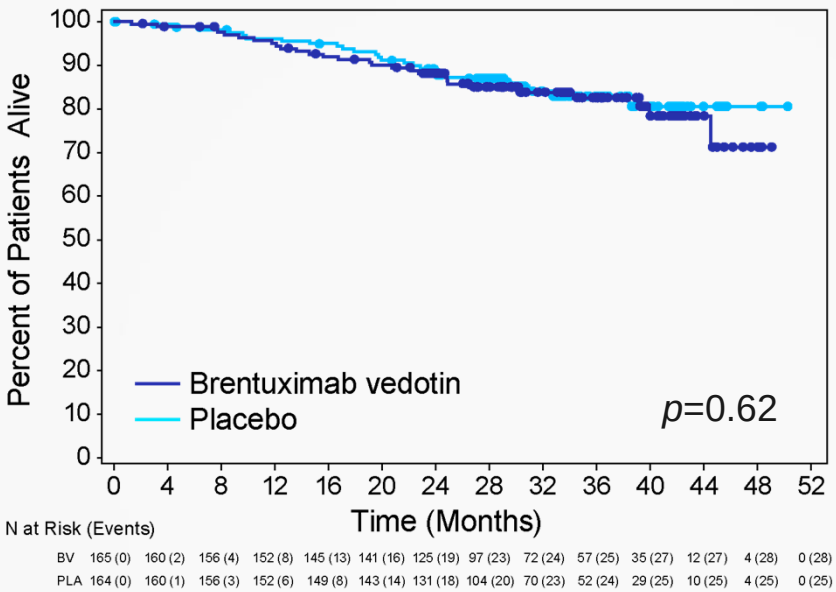
PFS outcome	Brentuximab vedotin (n=165)	Placebo (n=164)
Median PFS	43 mos	24 mos
HR (95% CI)	0.57 (0.40, 0.81) *p*=0.001	
2-year PFS	63%	51%

Craig H, et al. 2014 ASH Meeting, Oral Presentation
Blood 2014, 124:673.

blood

SGN35-005: AETHERA phase 3 trial of brentuximab vedotin vs placebo in relapsed or refractory HL pts at risk of relapse post ASCT

OS



PFS and OS by no. of risk factors

No. of risk factors	n	PFS per IRF HR (95% CI)	OS HR (95% CI)
≥1	329	0.57 (0.40, 0.81)	1.15 (0.67, 1.97)
≥2*	280	0.49 (0.34, 0.71)	0.94 (0.53, 1.67)
≥3*	166	0.43 (0.27, 0.68)	0.92 (0.45, 1.88)

* Ad hoc analysis

Risk factors

- Relapsed <12 mos or refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- ≥2 prior salvage therapies

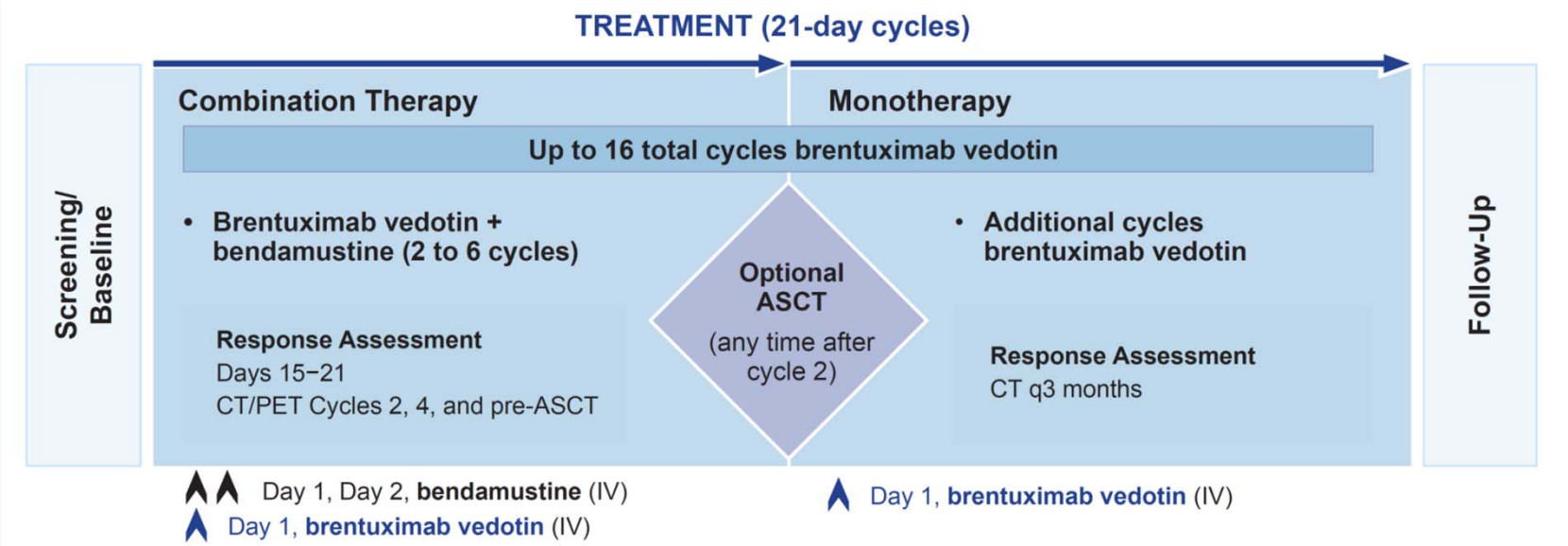
1 death occurred within 30 days of brentuximab vedotin treatment
Drug-related ARDS associated with pneumonitis
1 death occurred on day 40 (brentuximab vedotin arm)
ARDS following drug-related acute pancreatitis, which had resolved at the time of death

Craig H, et al. 2014 ASH Meeting, Oral Presentation
Blood 2014, 124:673.

Phase 1/2 trial of brentuximab vedotin combined with bendamustine in RR HL after front-line therapy

Design: Phase 1/2, single-arm, two-stage trial of brentuximab vedotin plus bendamustine in RR HL

- **Phase 1 objectives: dose level of bendamustine, safety/tolerability**
- **Phase 2 objectives: best response, DOR, PFS**



Dose and schedule: BV 1.8 mg/kg IV day 1 + bendamustine 90 mg/m^2 days 1, 2

LaCasce A, et al. 2014 ASH Meeting, Oral Presentation
Blood 2014, 124:293.

blood

Phase 1/2 trial of brentuximab vedotin combined with bendamustine in RR HL after front-line therapy

	N=54
Median age, (range)	37 years (27–51)
Gender (% male/female)	57/43
ECOG status, n (%)	
0	35 (65)
1	18 (33)
2	1 (2)
Median time since HL diagnosis, (range)	13.8 months (8.8–20.4)
Stage III/IV at diagnosis, n (%)	29 (54)
Baseline disease status, n (%)	
Primary refractory	27 (50)
Relapsed	27 (50)
No. of patients with remission duration >1 yr	17
No. of patients with remission duration ≤ 1 yr	10

- Majority of patients received ABVD as their frontline therapy

Best clinical response	N=48
ORR, n (%; [95% CI])	46 (96; [86, 100])
CR rate, n (%; [95% CI])*	40 (83; [70, 93])
PR rate, n (%)	6 (13)

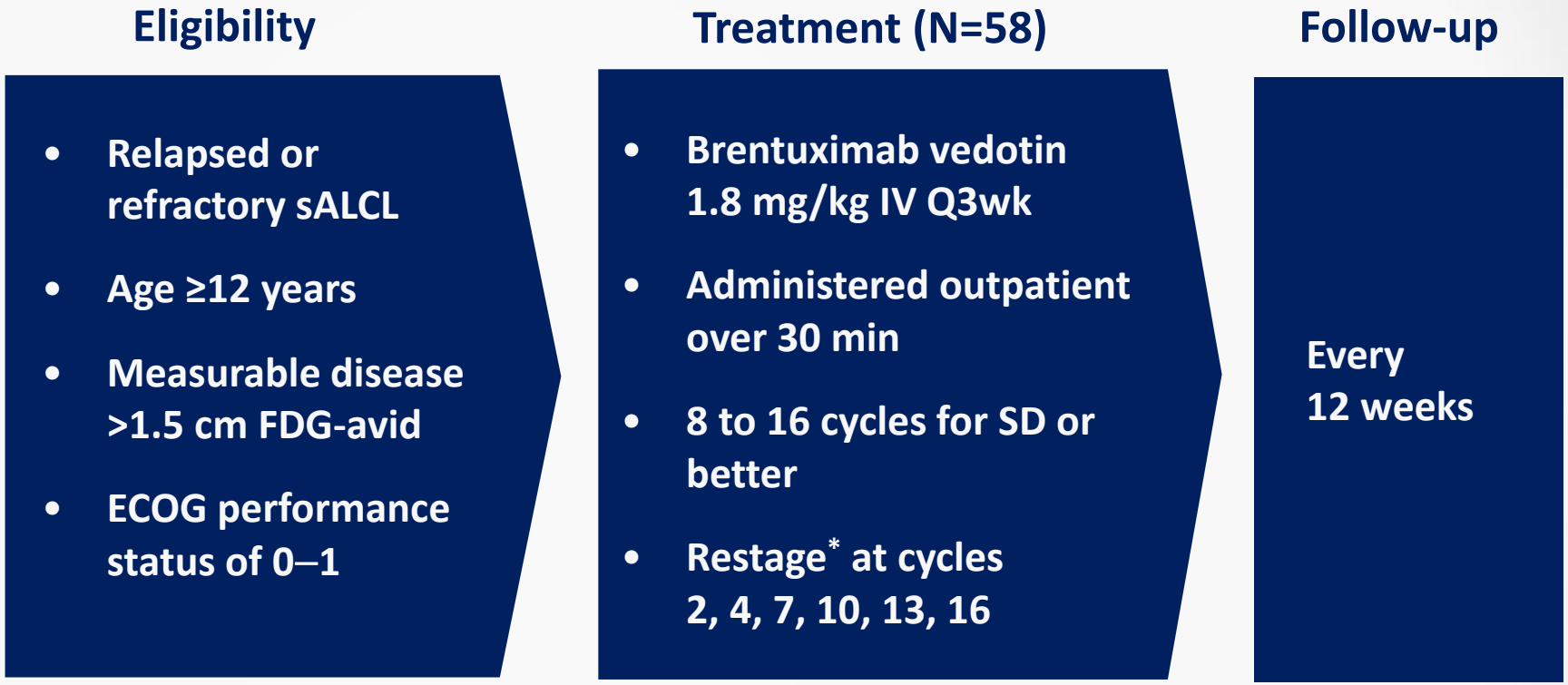
*34/40 CR achieved at cycle 2 restage

LaCasce A, et al. 2014 ASH Meeting, Oral Presentation
Blood 2014, 124:293.

blood

Clinical Data in sALCL

SG035-0004: Phase 2 study of brentuximab vedotin in patients with rel/ref sALCL: overview



Primary endpoint: ORR by IRF

* Revised response criteria for malignant lymphoma (Cheson 2007)

Pro B, et al. J Clin Oncol 2012; 30:2190–6.

FDG = fluorodeoxyglucose

SG035-0004: Phase 2 study of brentuximab vedotin in patients with rel/ref sALCL

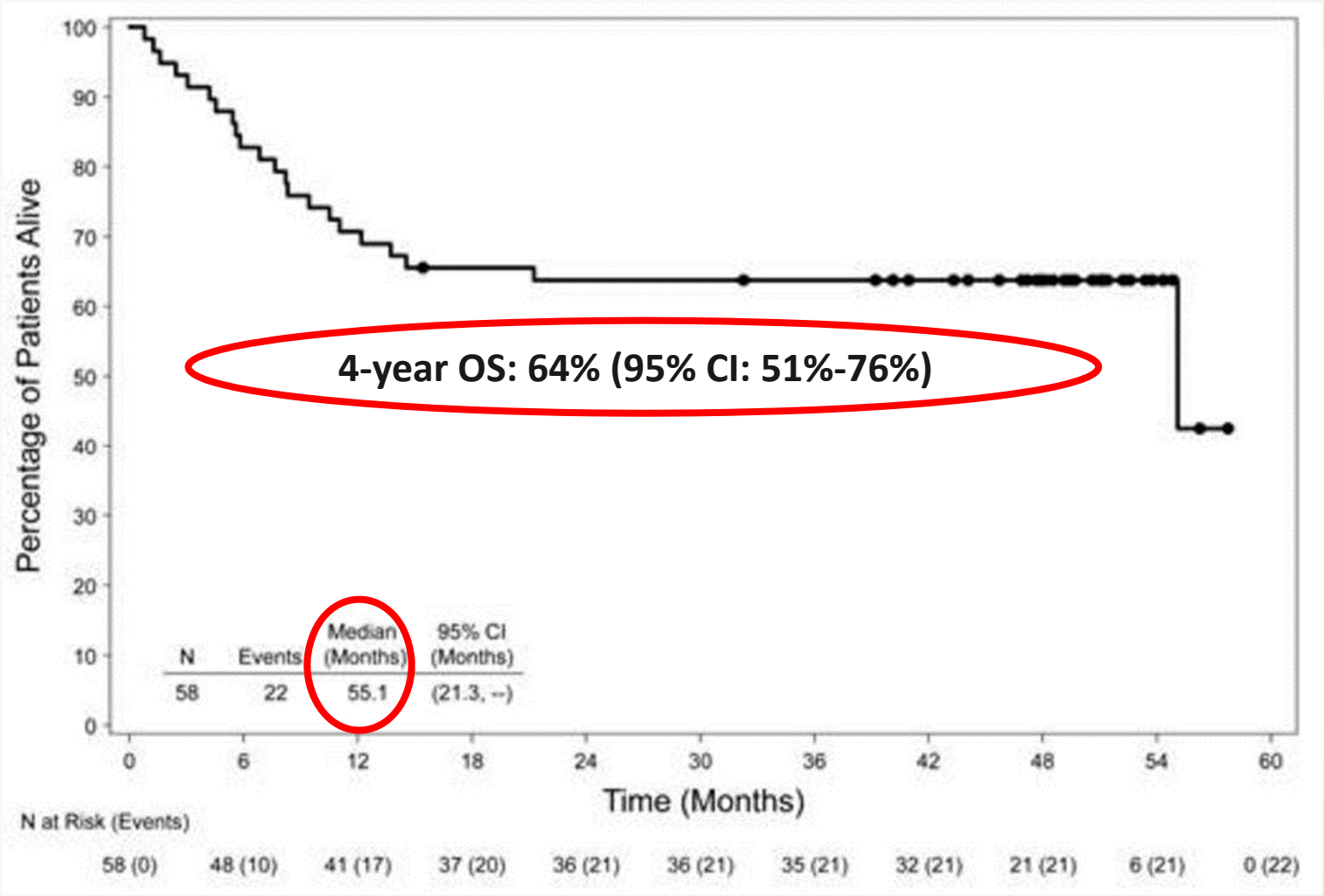
Response and outcomes
(data cut off: Jan 2011)

	IRF (N=58)
ORR, % (95% CI)	86 (74.6, 93.9)
CR, % (95% CI)	57 (43.2, 69.8)
PR, %	29
SD, %	3
PD, %	5
Histologically ineligible, %	3
NE, %	2
Median duration of OR, months (95% CI)	12.6 (5.7, NE)
Median duration of response in patients with CR, months (95% CI)	13.2 (10.8, NE)
Median PFS, months (95% CI)	13.3 (6.9, NE)
Median OS, months (95% CI)	NR (14.6, NE)
12-mo OS, %	70

NE = not estimable

Pro B, et al. J Clin Oncol 2012; 30:2190–6.

SG035-0004: Updated data from pivotal phase 2 trial in RR CD30+ sALCL: results



Pro B, et al. Blood 2014;124:3095.

blood