

2018



# Progetto Ematologia Romagna

**Il problema dei HL resistenti refrattari:  
identikit alla diagnosi del candidato a  
diventare resistente refrattario**

Simonetta Viviani

## Premesse



**Sopravvivenza a 5 anni**  
**86.6%**

Report SEER 2018: 2008-2014

Incidenza in Italia: 1584 nuovi casi/anno; Mortalità: 422 casi/anno

Refrattarietà: mancato ottenimento della CR o ricaduta  $\leq 3$  mesi da fine terapia di 1 linea

Ricadute precoci:  $> 3$  mesi  $\leq 12$  mesi da fine terapia di 1 linea

Ricadute tardive:  $> 12$  mesi da fine terapia di 1 linea

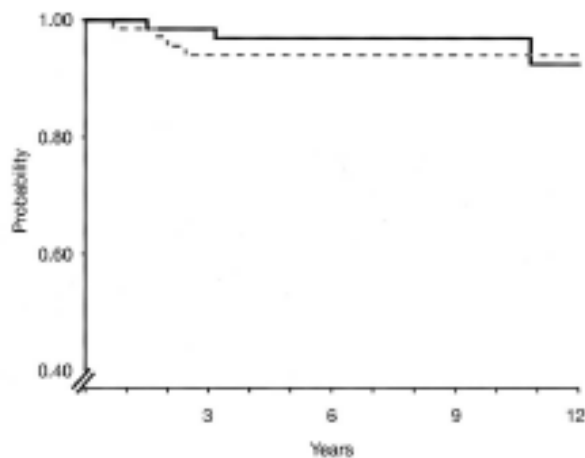
Ricadute molto tardive:  $> 60$  mesi da fine terapia di 1 linea



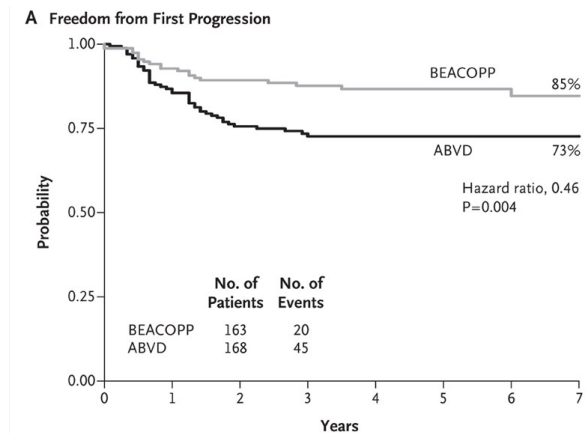
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# Quanti sono i R/R dopo terapia di prima linea ?

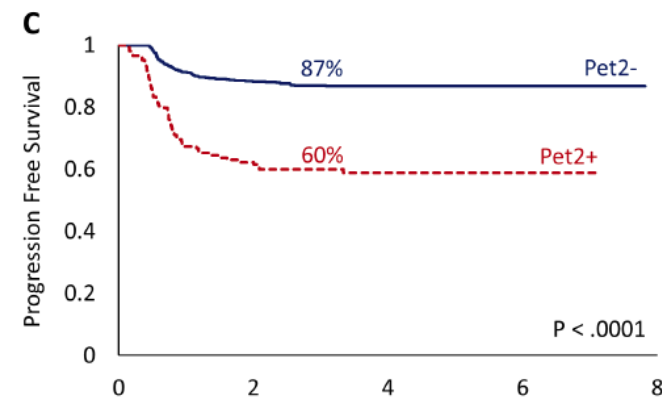
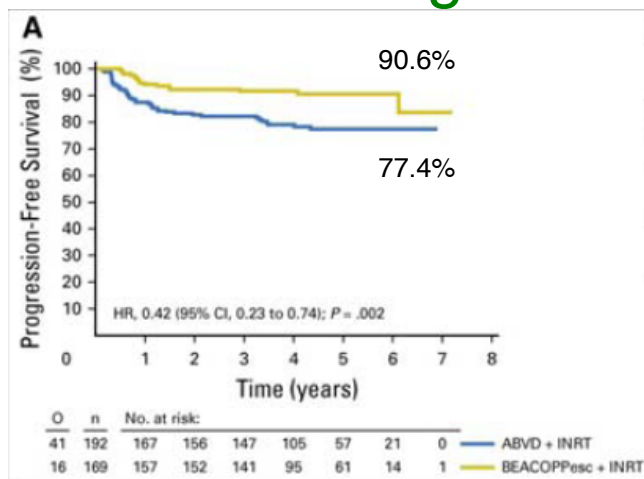
## Stadi iniziali



## Stadi avanzati



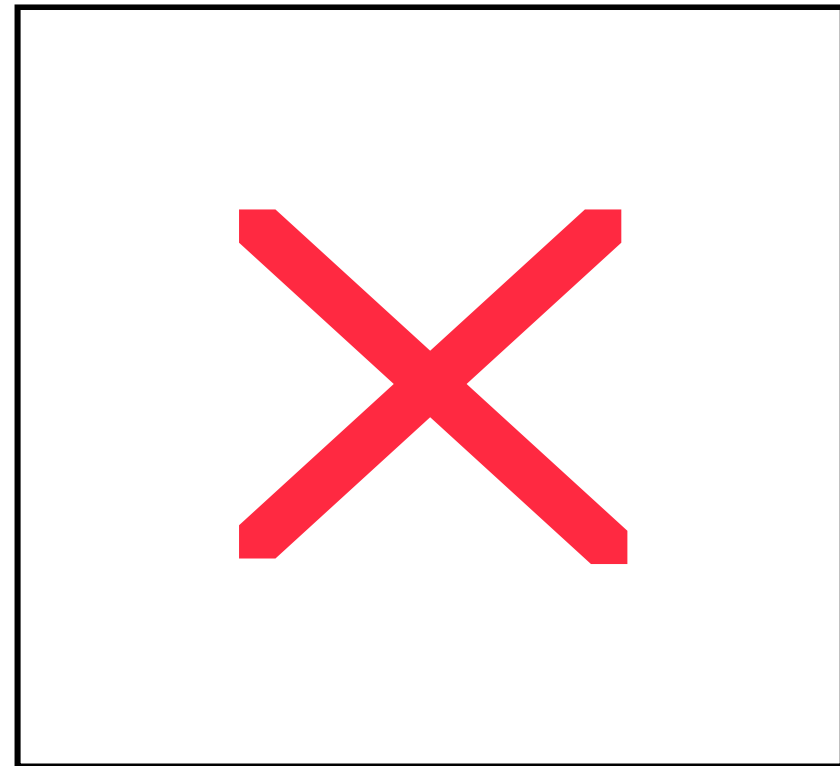
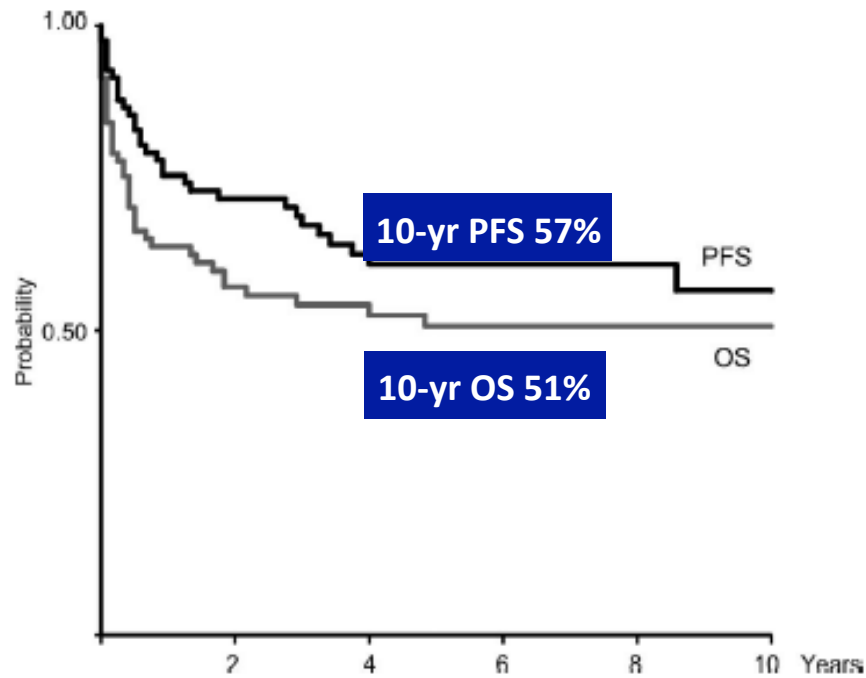
## Strategie modulate sulla interim PET



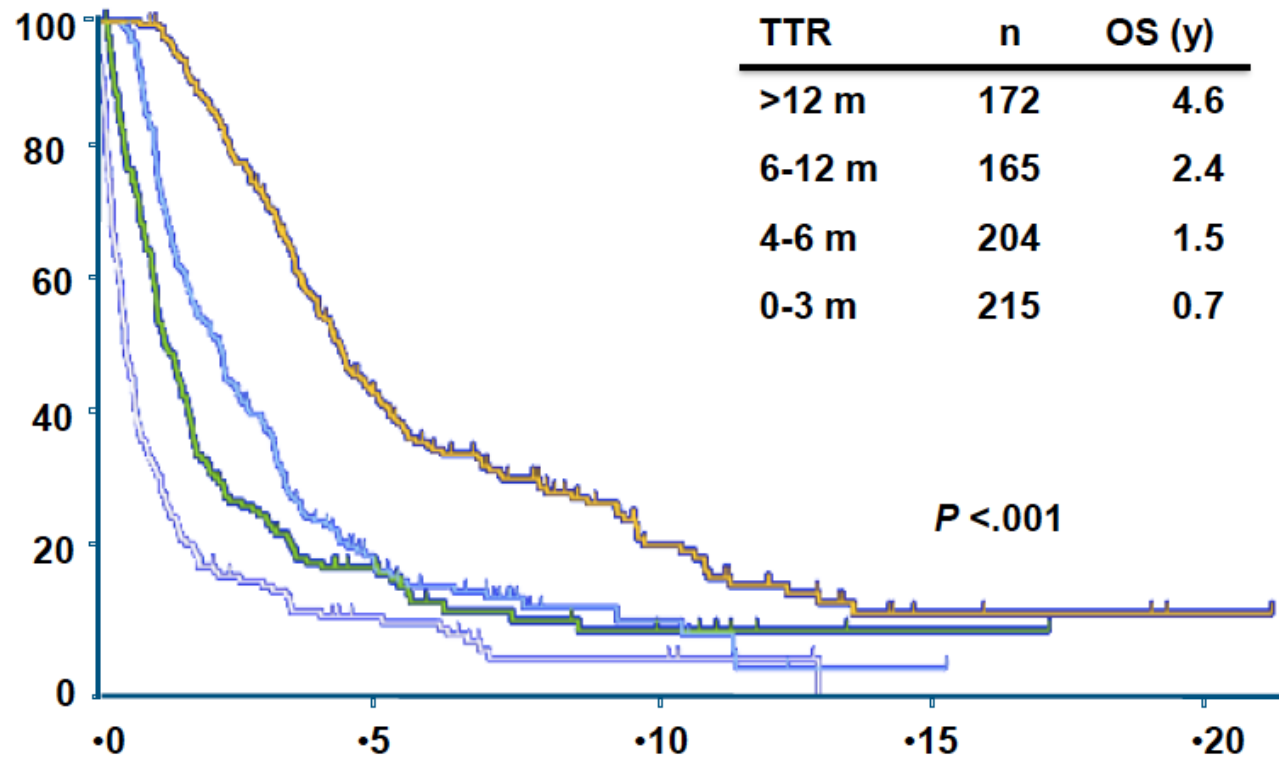


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# Risultati a 10 anni del TMO autologo in era pre-BV e/o CPI



Viviani S et al: Leukemia Lymphoma 2010; 51: 1251-1259



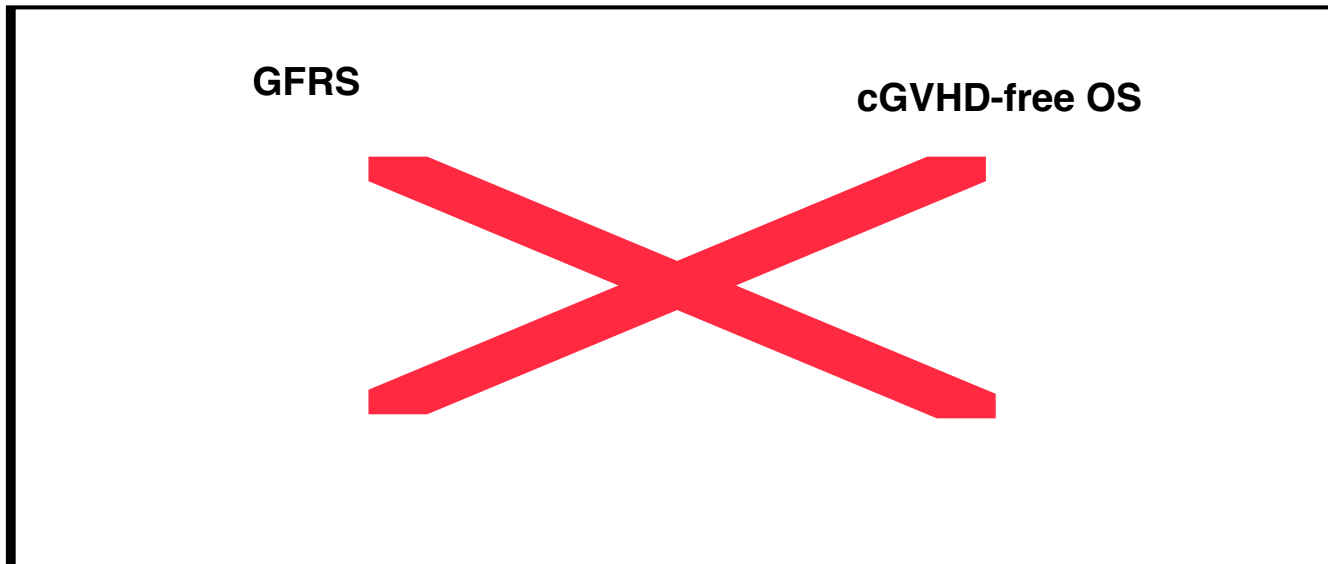
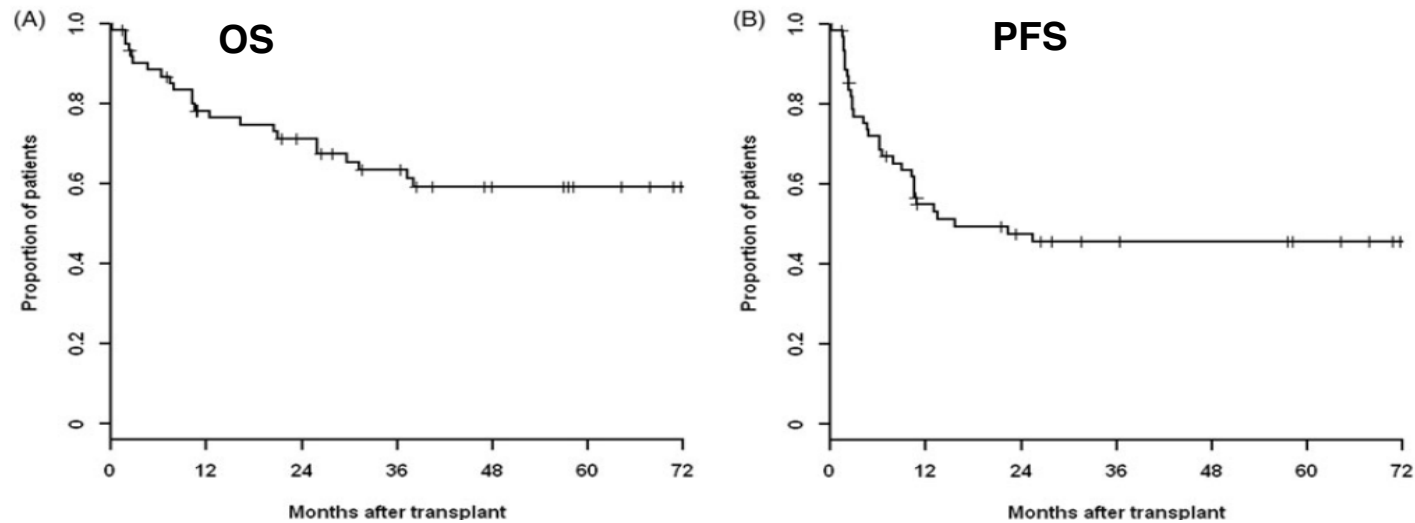
TTR, time to relapse; OS, overall survival

Arai S, et al. Leukemia Lymphoma 2013; 54:2531-3



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# Sopravvivenza a 5 anni dopo TMO allogenico



- Identificare precocemente i pz chemiorefrattari o a rischio di ricaduta per intensificare il trattamento e migliorare la sopravvivenza sia globale che libera da malattia
- Identificare i pz a buona prognosi per ridurre l'intensità dei trattamenti e quindi preservare dalla tossicità iatrogena acuta e soprattutto a lungo termine (malattia cardiovascolari, secondi tumori, sterilità, astenia)



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# Fattori prognostici

- Fattori prognostici clinici alla diagnosi: stadio, IPS
- FDG-PET, iPET, MTV
- Marcatori bioumorali: citochine, chemochine, rapporto linfociti/monociti
- Marcatori tissutali: microambiente immunosoppressivo
- Marcatori molecolari tissutali o circolanti



# Stadi Iniziali: Fattori prognostici sfavorevoli alla diagnosi

GHSG	EORTC	NCCN
Large mediastinal mass (ratio $\geq 1/3$ )*	Large mediastinal mass (ratio $\geq 0.35$ )	Large mediastinal mass (ratio $> 1/3$ ) Bulk $> 10$ cm
	<b>Age <math>\geq 50</math> yrs</b>	
<b><math>\geq 1</math> extranodal lesion*</b>		
ESR $\geq 50$ (A) or $\geq 30$ (B)	ESR $\geq 50$ (A) or $\geq 30$ (B)	ESR $\geq 50$ (A) B-symptoms
<b><math>&gt; 2</math> nodal areas</b> (out of 11 GHSG areas)	<b><math>&gt; 3</math> nodal areas</b> (out of 5 supra-diaphragmatic EORTC areas)	<b><math>&gt; 3</math> nodal regions</b> (out of 17 Ann Arbor regions)

Sopravvivenza libera da Progressione a 5 anni			
	GHSG	EORTC	NCCN
Favorevole	95.8 %	94.2%	95.3 %
Sfavorevole	86.4 %	87.6 %	86.7 %

# Stadi avanzati: Fattori prognostici sfavorevoli alla diagnosi

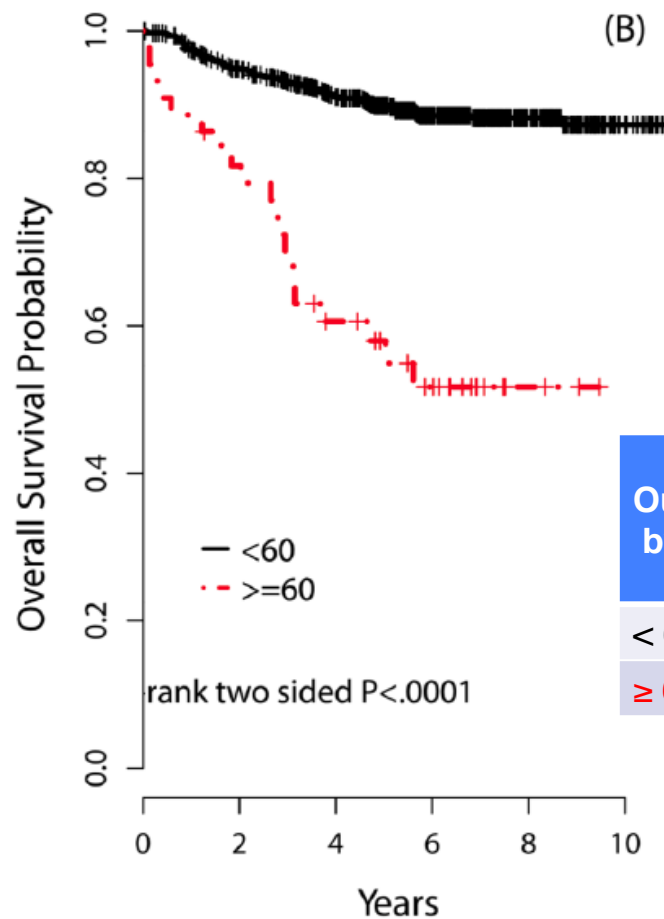
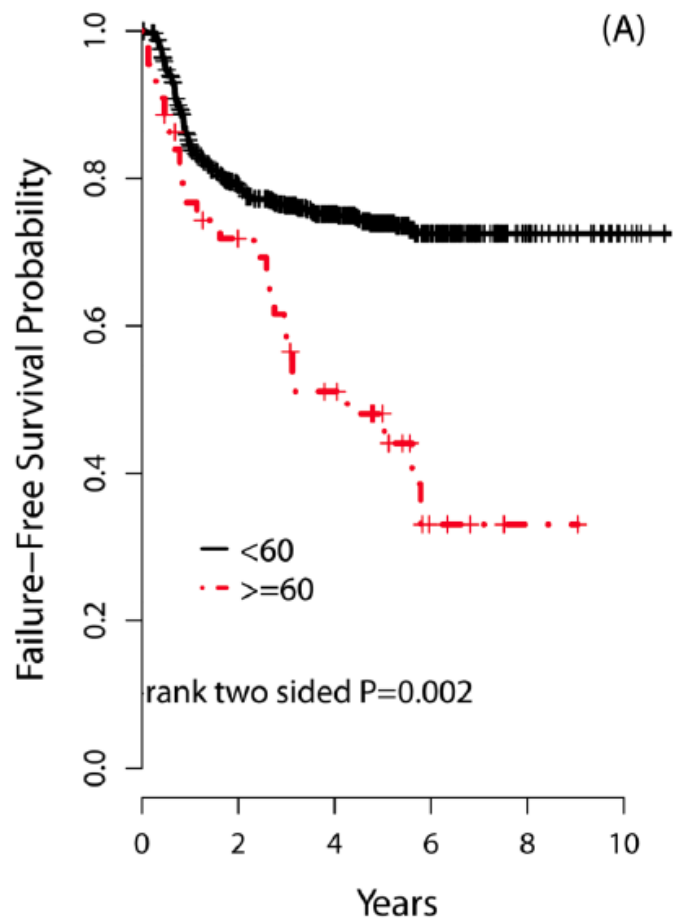
- Albumina < 4 g/dL
- **Hb < 10.5 g/dL**
- Sesso maschile
- **Stadio IV**
- **Età ≥ 45 anni**
- Leucociti ≥ 15 x 10<sup>9</sup>/L
- Linfociti < 0.6 x 10<sup>9</sup>/L o < 8%

IPS	n (%)	% FFP a 5 anni	% OS a 5 anni
0	57 (8)	88 ± 5	98 ± 2
1	195 (26)	84 ± 3	97 ± 1
2	195 (26)	80 ± 3	91 ± 2
<b>3</b>	<b>155 (21)</b>	<b>74 ± 3</b>	<b>88 ± 3</b>
<b>4</b>	<b>88 (12)</b>	<b>67 ± 5</b>	<b>85 ± 4</b>
<b>≥ 5</b>	<b>50 (7)</b>	<b>62 ± 7</b>	<b>67 ± 7</b>



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# Età come fattore prognostico negli stadi avanzati



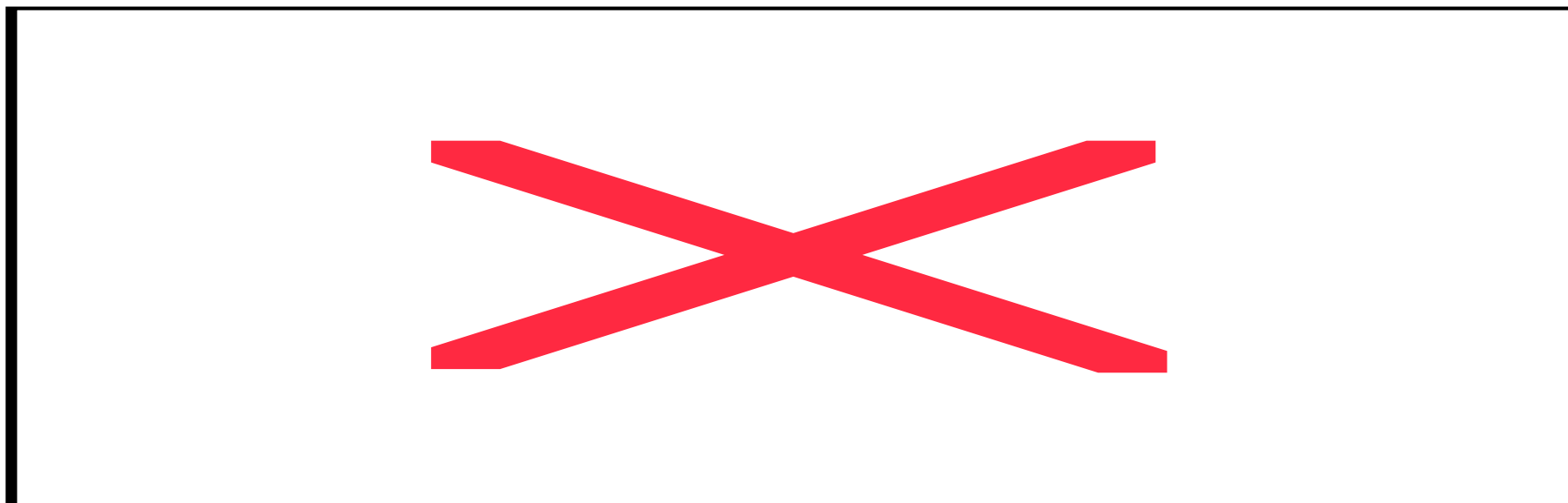
Outcome by Age	% FFS	% OS
	5 Yr	5 Yr
< 60 yrs	74	90
≥ 60 yrs	48	58

Evens AM, et al. Br J Haematol. 2013;161:76-86.



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# Sopravvivenza globale e libera da malattia negli stadi iniziali in rapporto all'età

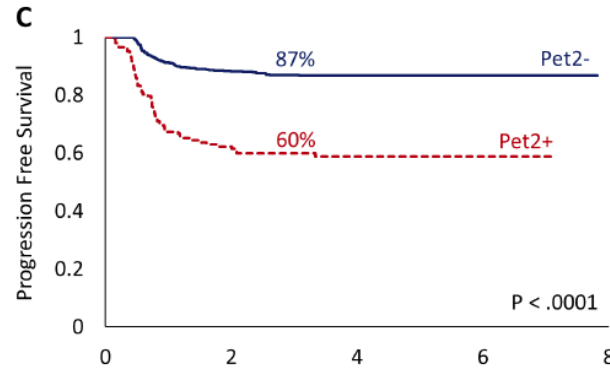
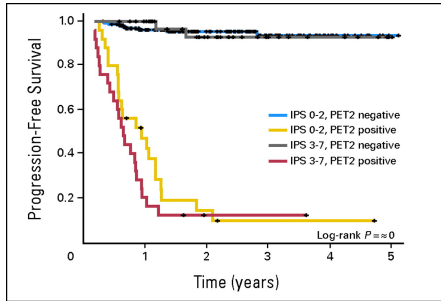


Boll B, et al. J Clin Oncol 2013; 31(12):1522-9



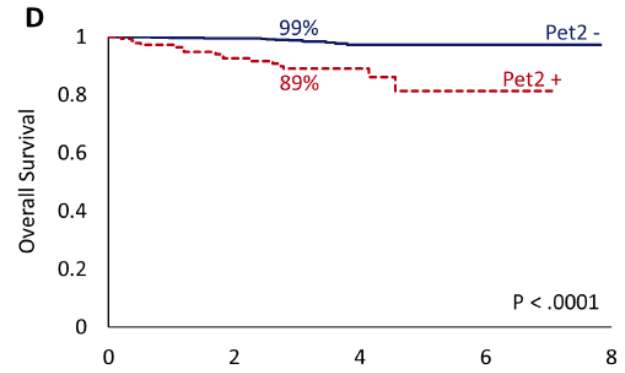
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# Interim PET post 2 cicli ABVD negli stadi avanzati



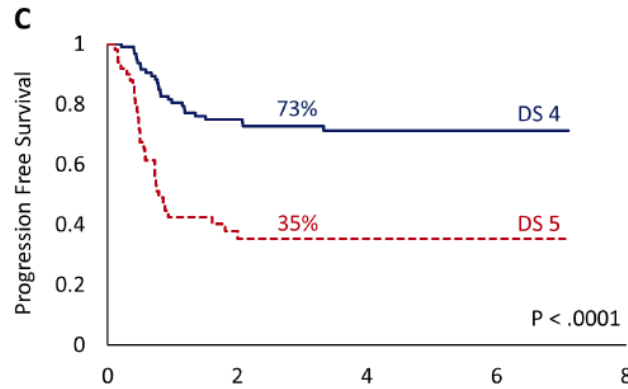
**N at risk (events)**

	0	2	4	6	8
Pet2 -	630 (73)	528 (8)	147 (0)	40 (0)	0
Pet2 +	150 (53)	83 (4)	26 (0)	4 (0)	0



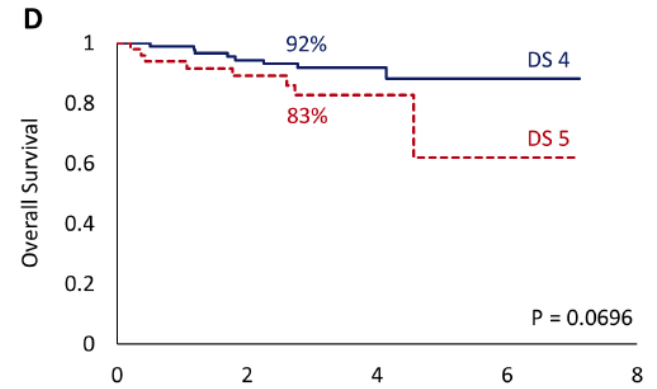
**N at risk (events)**

	0	2	4	6	8
Pet2 -	630 (3)	583 (9)	169 (0)	42 (0)	0
Pet2 +	150 (10)	116 (4)	37 (2)	4 (0)	0



**N at risk (events)**

	0	2	4	6	8
DS 4	101 (23)	68 (3)	23 (0)	3 (0)	0
DS 5	49 (30)	15 (1)	3 (0)	1 (0)	0



**N at risk (events)**

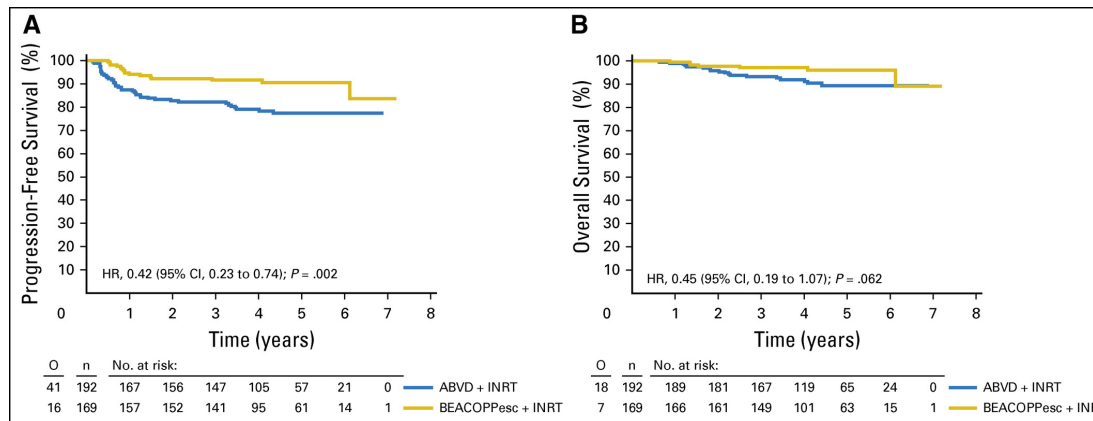
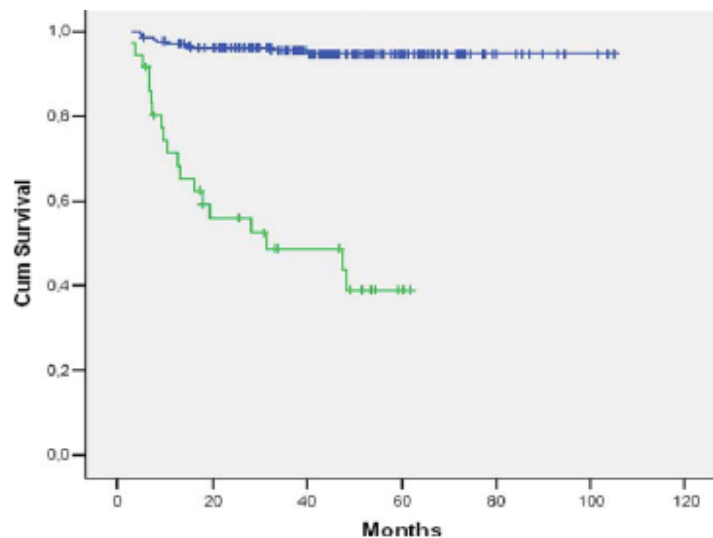
	0	2	4	6	8
DS 4	101 (5)	82 (2)	29 (1)	3 (0)	0
DS 5	49 (5)	34 (2)	8 (1)	1 (0)	0



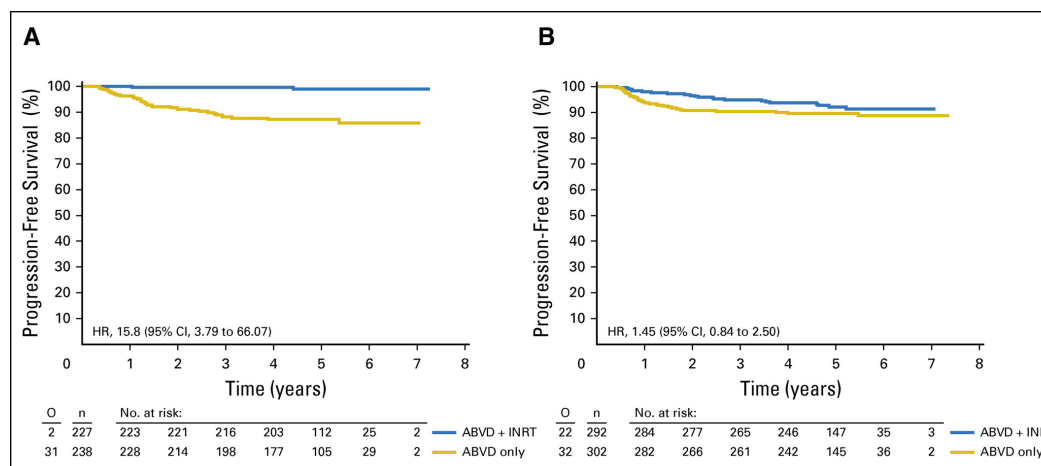
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# Interim PET, post-2 ABVD negli stadi iniziali

**PFS e OS nei PET-2 positivi: ABVDx 4 + INRT vs ABVD x 2 e BEACOPP x 2 + INRT**

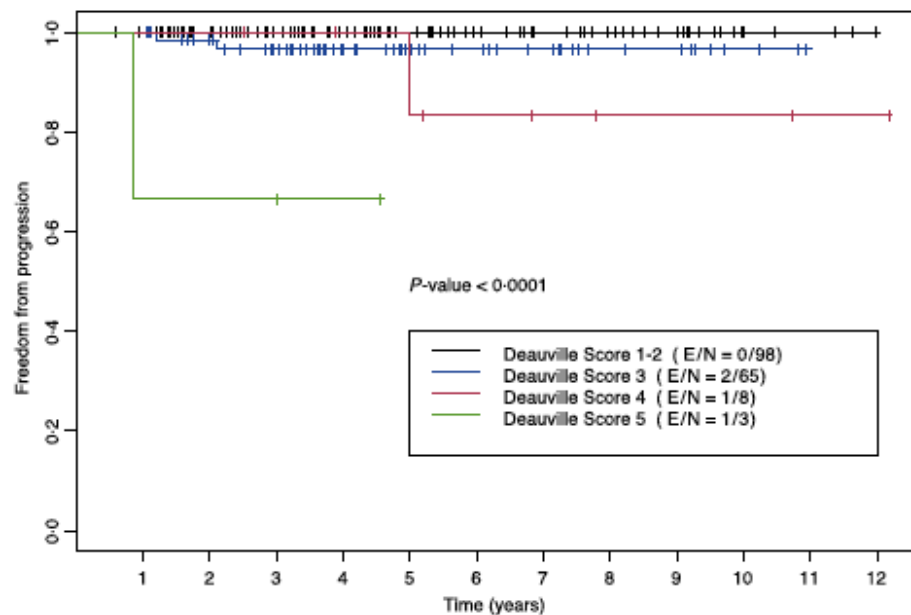


**PFS e OS nei PET-2 negativi: ABVD + INRT vs ABVD**



André MP, et al. JCO 2017; 35: 1786-94.

# PET-EOT negli stadi iniziali



Deauville 5-point score	n (% cohort)	Events	5-year FFP (95% CI)	Log-rank P
1-2	98 (56%)	0	100%	$P < 0.001$
3	65 (37%)	2	97% (92-100%)	
4	8 (5%)	1	83% (53-100%)	
5	3 (2%)	1	67% (13-100%)	

Milgrom SA et al. Br J Hematol 2017; 179:488-96

# PET basale: fattore prognostico nel HL?

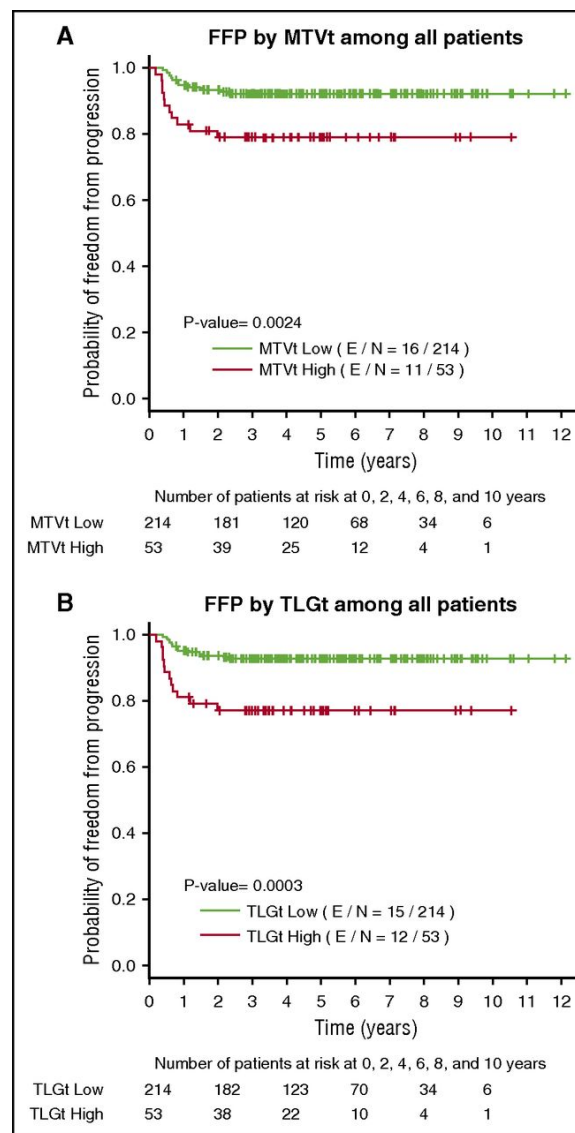
Volume metabolico tumorale totale

$$TMTV = \sum MTV_L$$

Volume glicolitico totale:

$$TLG = \sum (MTV_L \times SUVmean_L)$$

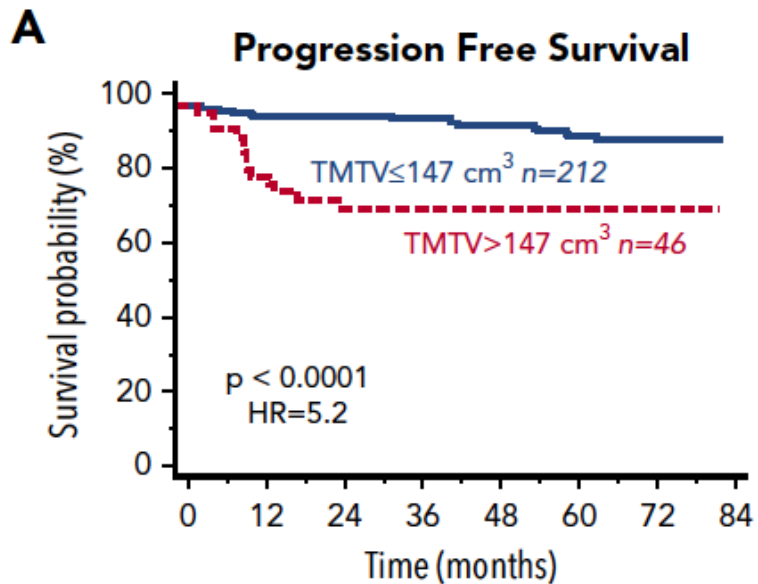
Akhtari M et al. Blood 2018;131:84-94



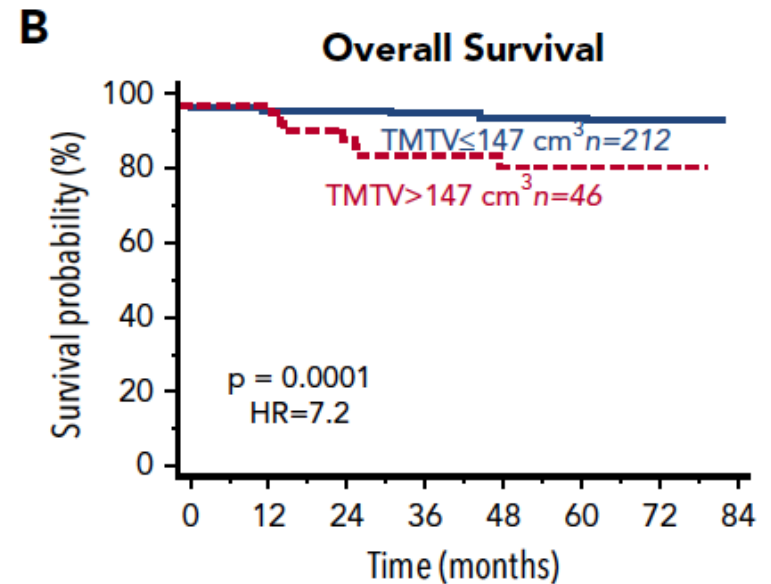




# Valore prognostico di TMTV basale negli stadi iniziali



5 y-PFS : 92% vs 71%



5 y-OS: 98% vs 83%

“TMTV and iPET2 independently prognostic. Combined identify 4 risk groups:

- low (TMTV  $\leq 147$  + DS 1-3; 5-year PFS, 95%)
- low- intermediate (TMTV  $> 147$ + DS 1-3; 5-year PFS, 81.6%)
- high-intermediate (TMTV  $\leq 147$ + DS4-5; 5-year PFS, 50%)
- high (TMTV  $> 147$ + DS4-5; 5-year PFS, 25%).”

Cottreau AS et al. Blood 2018;131:1456-63

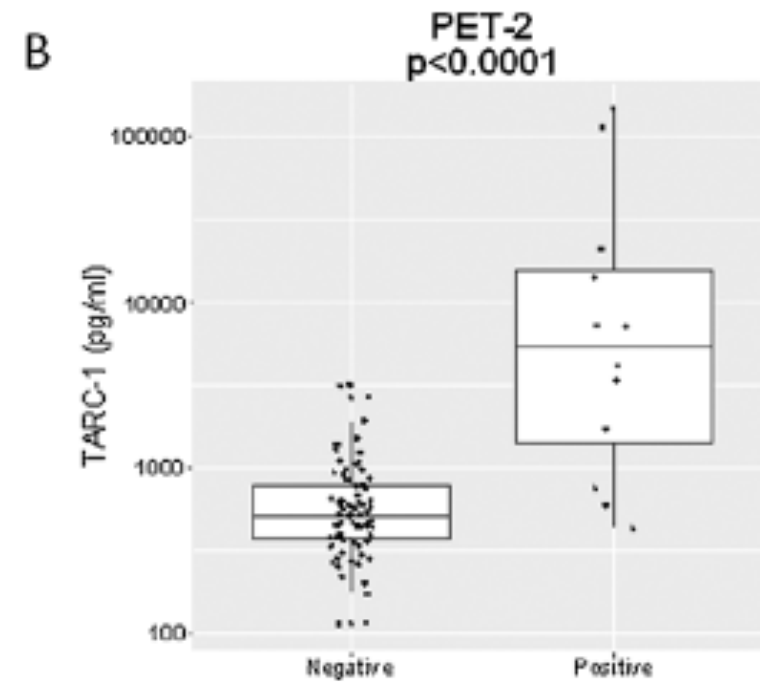
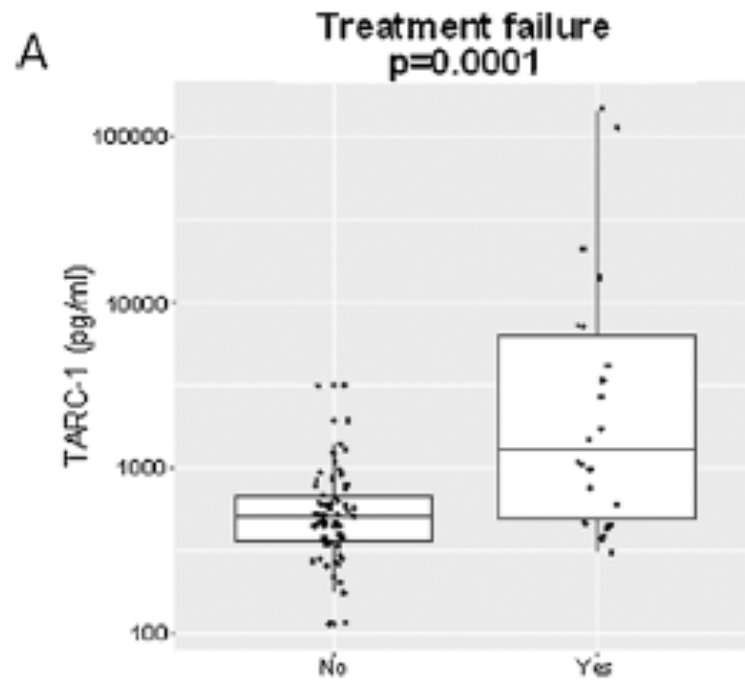
# Citochine/Chemochine sieriche: quale ruolo come fattori prognostici?

Autore	N Pz	Citochine	Alto rischio	PFS	FU (anni)
Visco	321	sCD30	≥ 200 U/mL	39%	5
Visco	69	IL-10	> 10 pg/mL	50%	5
Casanovas	519	IL-6	>668 pg/mL	22%	5
		IL-1RA	>30 pg/mL		
		sCD30	>80 U/mL		
Marri	140	IL-10		40%	5
		IL-1RA			
		IL-6	> 95 <sup>th</sup> pc		
		sIL-2R	> 95 <sup>th</sup> pc		
		sCD30			
		TARC			



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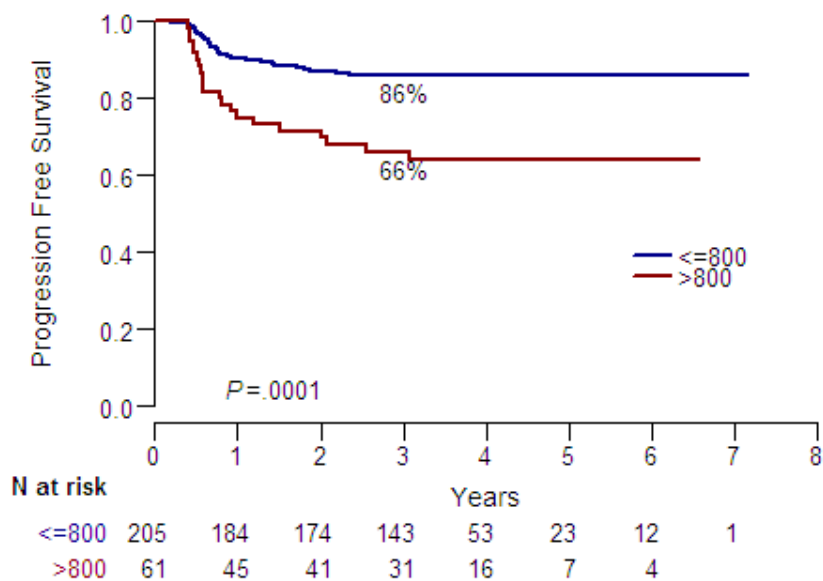
# Chemochina sierica TARC e prognosi



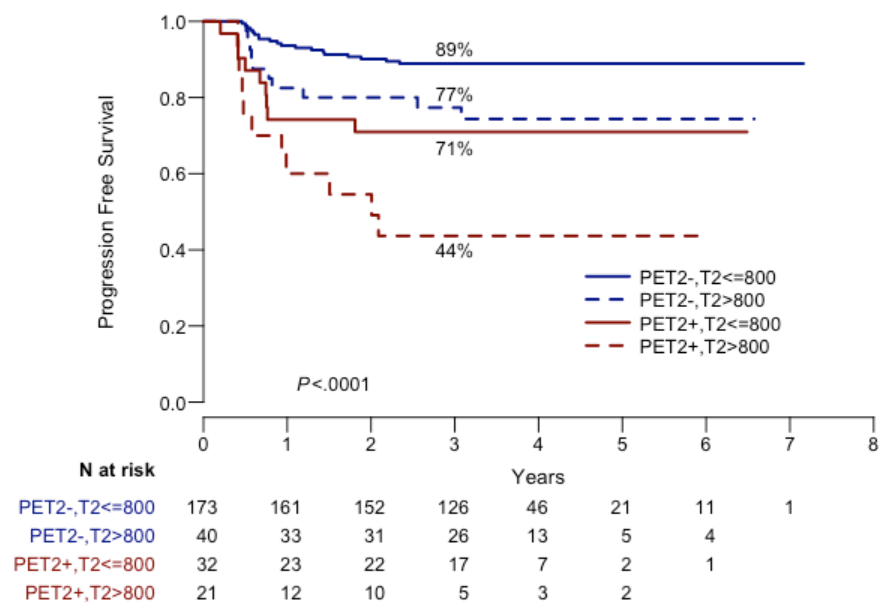
Guidetti A et al. Leukemia Res 2017; 62: 91-97

# Valore prognostico di TARC negli stadi avanzati trattati con strategia PET-adapted

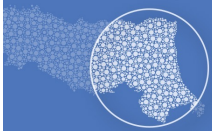
## TARC-2 $\leq$ 800 vs $>$ 800 pg/mL



## TARC-2 + PET-2



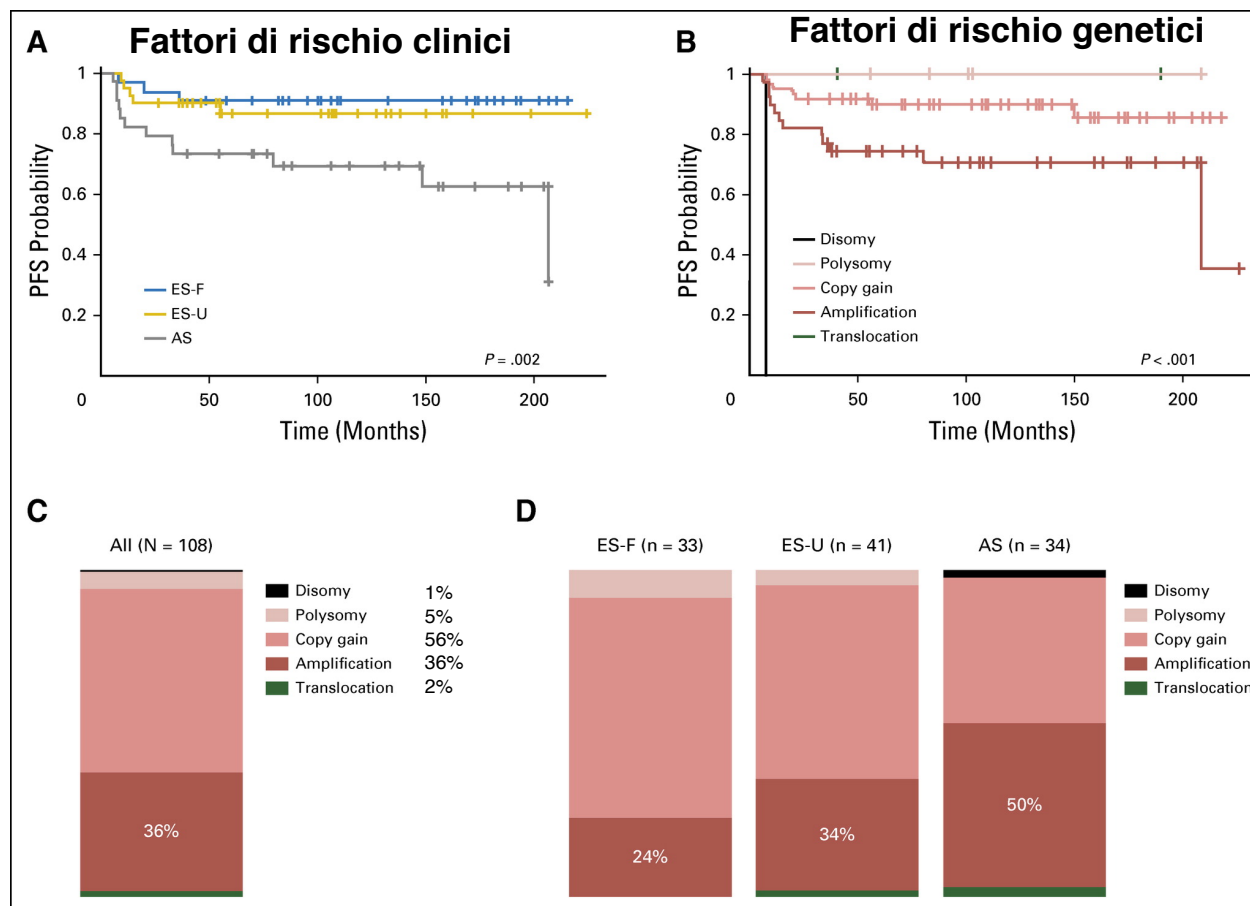
Viviani S et al. Blood 2017; 130: 1511



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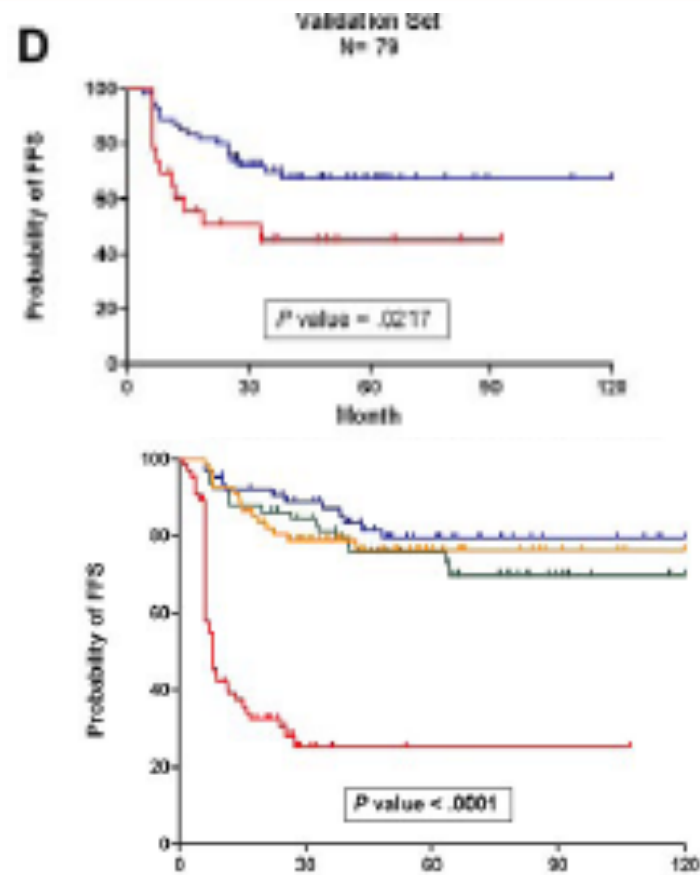
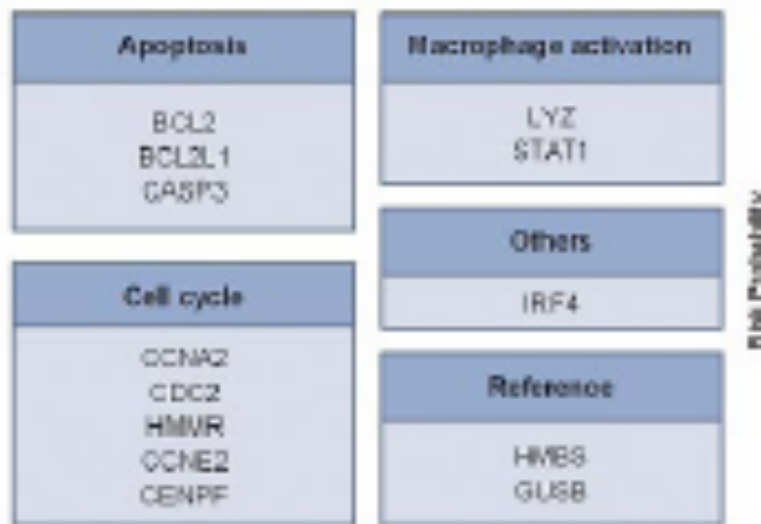
# Prospettive future: Marcatori Genetici per definire il rischio di ricaduta/progressione

Le alterazioni del locus 9p24 sono tipiche delle cell HRS e condizionano la prognosi



Roemer MG, et al. J Clin Oncol. 2016;34:2690-97

# Marcatori molecolari e prognosi



Signature di 11 geni + stadio IV identificano 25% di HL stadio avanzato con FFS a 5 anni del 24%

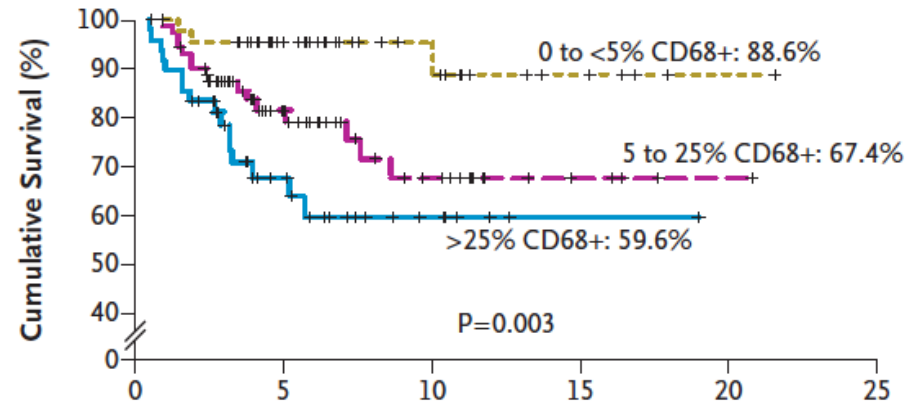
Sanchez-Espirdion B, et al. Blood 2010; 116: 12-7.



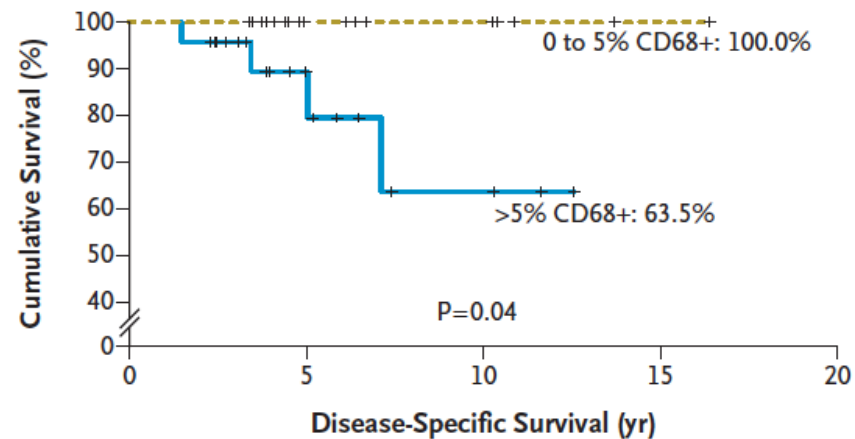
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# Ruolo prognostico dei macrofagi del microambiente

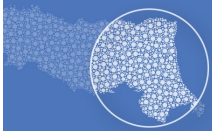
10-Yr Disease-Specific Survival in All Patients



10-Yr Disease-Specific Survival in Patients with Limited Disease

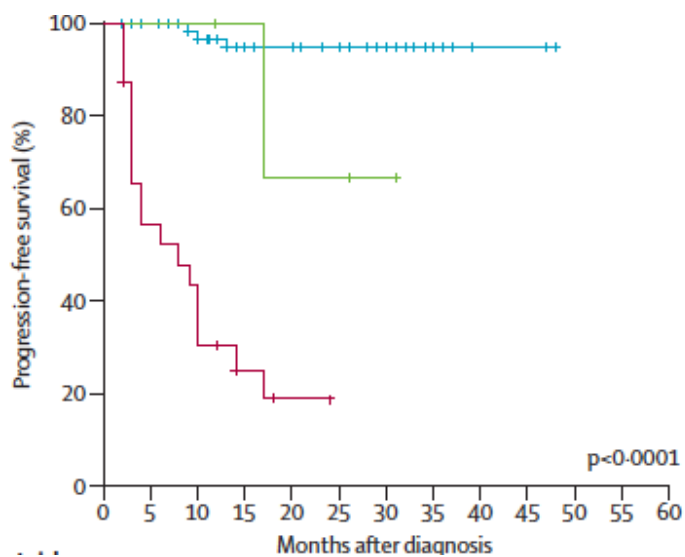
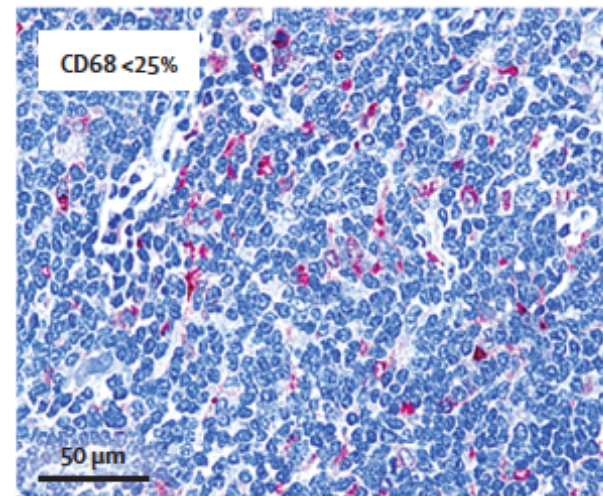
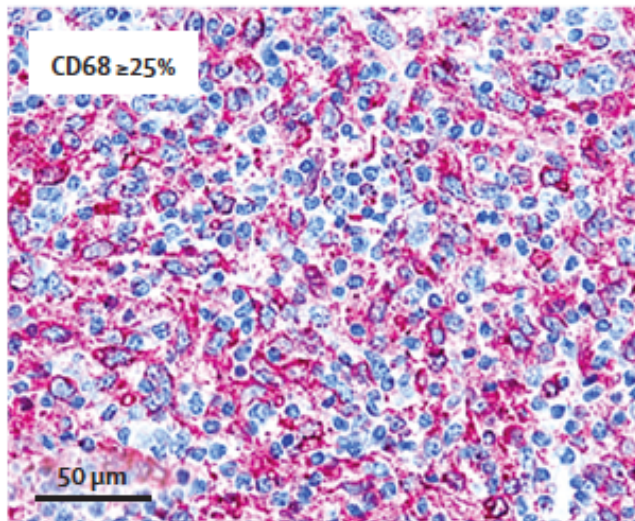


Steidl C, et al. N. Engl J Med 2010; 362:875-85



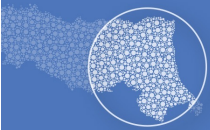
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# Ruolo prognostico di biomarcatori tissutali + iPET



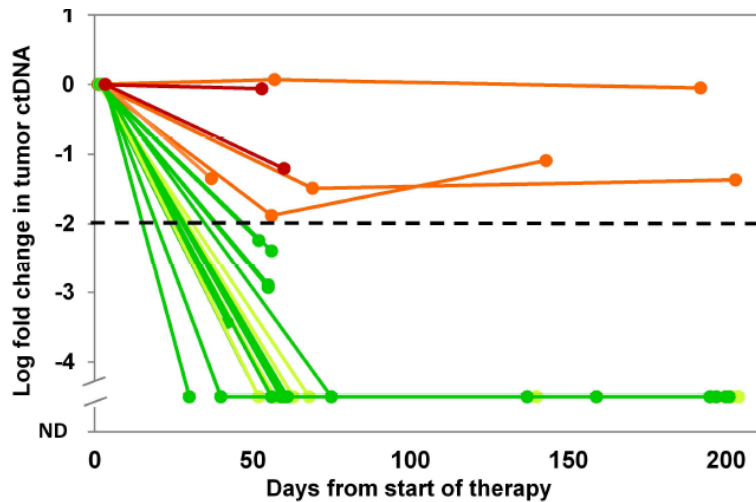
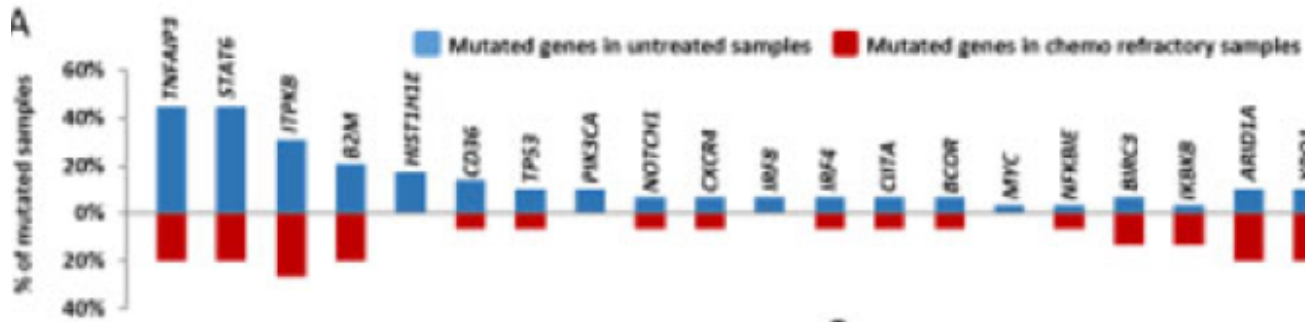
Agostinelli C, et al. Lancet Hematol 2016; 3: e467-79



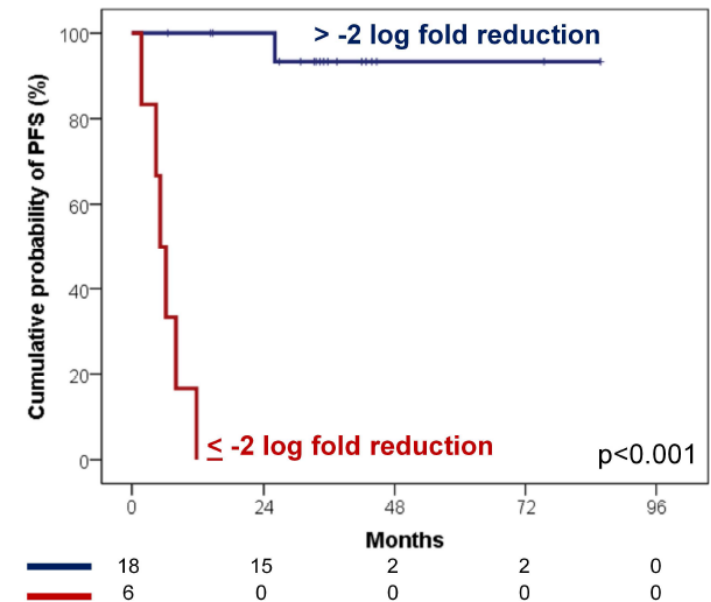


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# Prospettive future: Genotipizzazione del DNA plasmatico circolante



■ iPET positive – Progressive disease    ■ iPET negative – Progressive disease  
■ iPET positive – Cured    ■ iPET negative – Cured



Spina V, et al. Blood 2018; doi: 10.1182/blood-2017-11-812073



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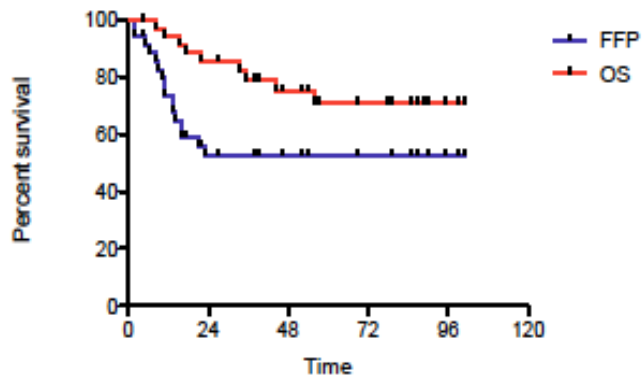
# Terapia di salvataggio nei ricaduti/refrattari

Terapia d'induzione	N	% ORR	% CR (mCR)
BV + ICE (sequenziale)	37	86	65
BV + augICE (sequenziale)	45	82	76
BV + ICE (concomitante)	16	94	69
BV + Bendamustine	55	93	74
BV + ESHAP (BRESHAP)	66	94	70
BV + DHAP	12	100	92
BV + Nivolumab	61	82	61
BeGEV	59	83	73

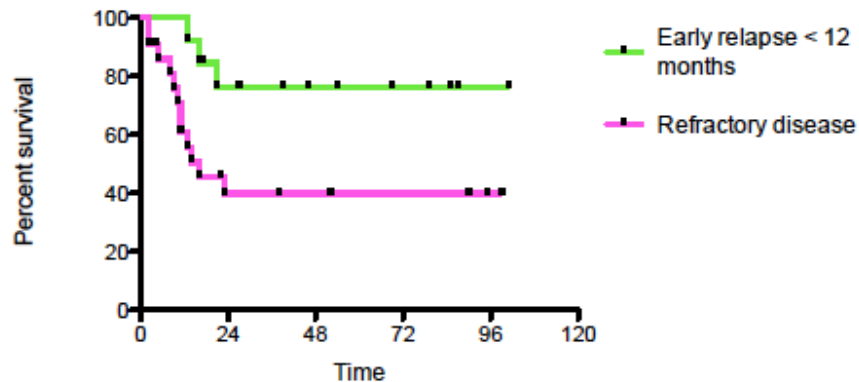
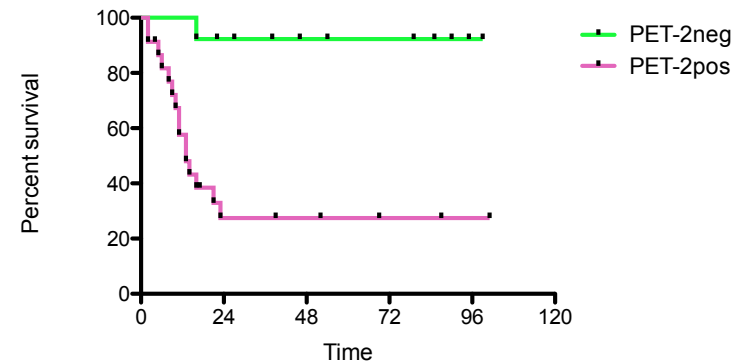


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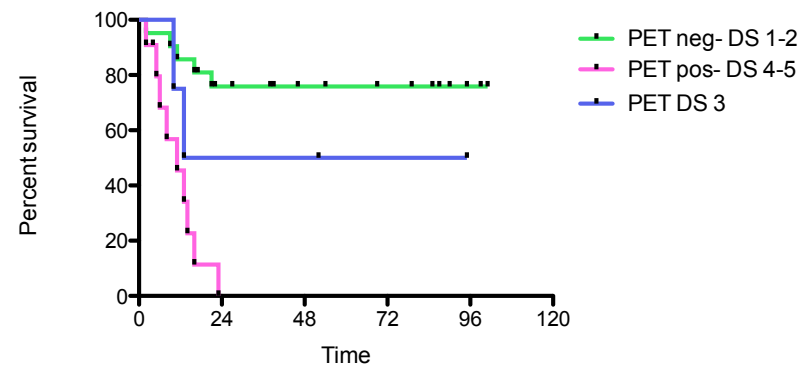
# Sopravvivenza dopo TMO autologo: Ricaduti precoci vs Refrattari e PET neg vs pos



3-yr FFS according to PET after the first 2 salvage CT cycles



3-Year FFS according to PET pre-ASCT



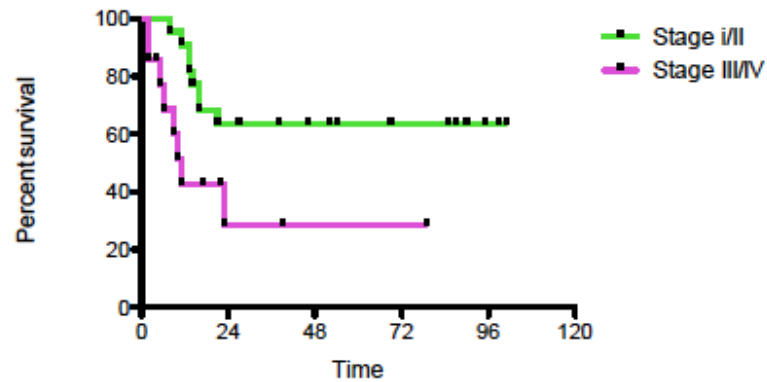
Viviani S, et al. Blood 2016,128: 3009



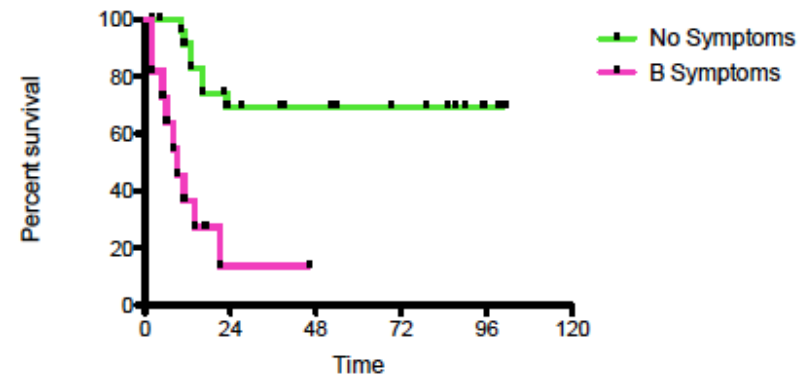
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# Sopravvivenza dopo TMO autologo: Ricaduti precoci vs Refrattari

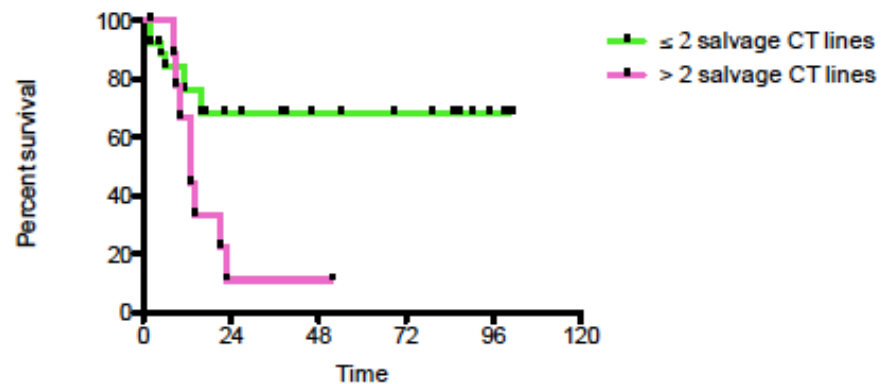
3-Year FFS according to Stage III/IV versus I/II



3-Year FFS according to B symptoms at relapse/progression



3-yr FFS according number of salvage CT lines : > 2 vs ≤ 2



Viviani S, et al. Blood 2016,128: 3009

# Risposta a BeGEV nei ricaduti vs refrattari

Farmaco	Dose	Giorno
Bendamustina	90 mg/sqm	2,3
Gemcitabina	800 mg/sqm	1,4
Vinorelbina	20 mg/sqm	1

ogni 21 giorni x 4 cicli

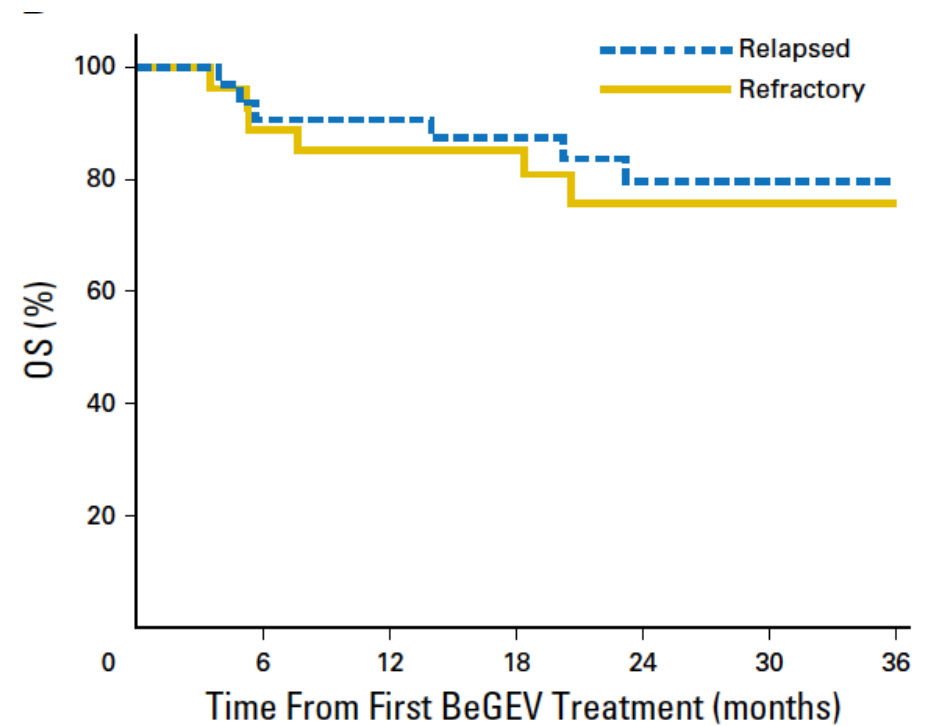
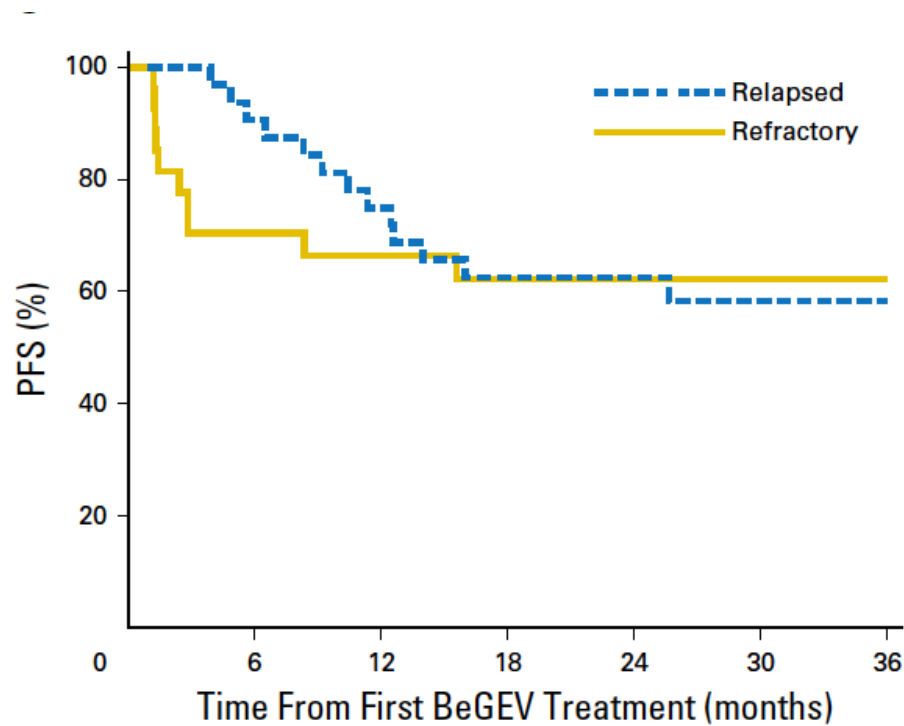
Parameter	No. of Patients
Response by ITT	59
Disease status at study entry	
Relapsed	32
Refractory	27

CR		PR	
No.	%	No.	%
43	73	6	10
27	84*	3	9
16	59*	3	11

Santoro A, et al. J Clin Oncol 2016; 34: 3293-9

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# Sopravvivenza dopo BeGEV + ASCT nei ricaduti vs refrattari

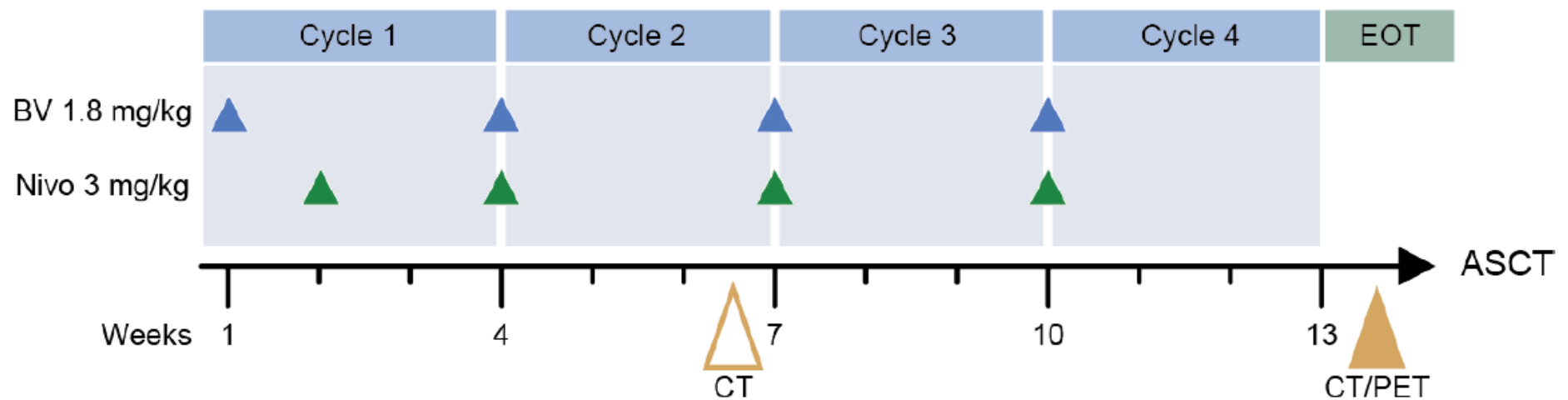


Santoro A, et al. J Clin Oncol 2016; 34: 3293-9



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# Risposta a Brentuximab Vedotin + Nivolumab nei ricaduti vs refrattari



ORR 82%, CR 61% in 61 pazienti trattati (ITT)

Herrer AF, et al. Blood 2018; 131: 1183-94



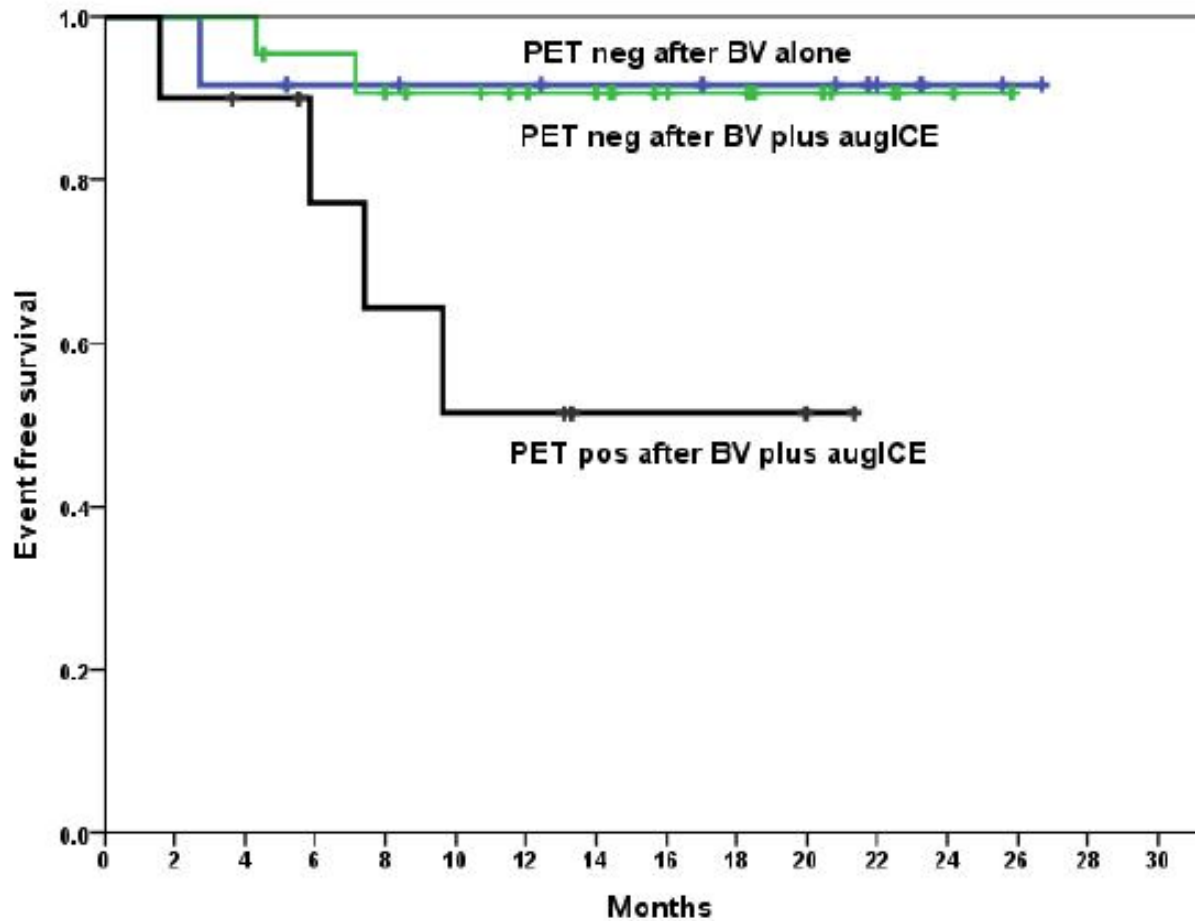
2018

# Risposta a Brentuximab Vedotin + Nivolumab nei ricaduti vs refrattari

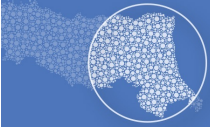
Risposta		N	% ORR	% CR
<b>Refrattari</b>	Totale	27	67	<b>48</b>
	PR o SD	10	80	70
	PD	17	59	35
<b>Ricaduti</b>	Totale	34	94	<b>71</b>
	>12 mesi	15	87	73
	≤12 mesi	19	100	68
<b>Età</b>	< 65 anni	57	81	63
	≥ 65 anni	4	100	<b>25</b>

Herrer AF, et al. Blood 2018; 131: 1183-94





Moskowitz A, et al. Lancet Oncol. 2015; 16: 284-92



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## Malattia recidivata o refrattaria: fattori di rischio

- Il 50% dei pazienti ricade o progredisce dopo TMO autologo
- La maggior parte delle ricadute si verifica entro 1 anno dal TMO

### **Fattori di rischio**

Mancato ottenimento CR con terapia di prima linea o ricaduta < 12 mesi

Malattia extranodale alla ricaduta/progressione

Sintomi B alla ricaduta/progressione

Necessità di ricevere > 2 linee di chemioterapia di salvataggio

PET positiva pre-TMO

# CONCLUSIONI

- ❖ I fattori prognostici clinici restano uno strumento valido per distinguere i gruppi a rischio e determinare le strategie terapeutiche
- ❖ La PET precoce permette di personalizzare il trattamento, soprattutto negli stadi avanzati
- ❖ La PET EOT è utile per decidere l' utilizzo della RT di consolidamento in prima linea
- ❖ La PET pre-ASCT identifica i pazienti che necessitano di ulteriori terapie prima di essere sottoposti alla fase mieloablativa
- ❖ I marcatori biologici sembrano promettenti soprattutto se combinati con la iPET, ma non trovano ancora applicazione nella pratica clinica