POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

Linfomi aggressivi di derivazione B linfocitaria

Alessandra Tucci
ASST Spedali Civili - Brescia

Disclosures of Alessandra Tucci

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kiowa Kyrin						x	
Takeda					x		
Lilly					x		
Incyte					x		
Janssen					x		
Gentili					x		
Sanofi					x		

Chemo-free/chemo-reduced approach
- Immunotherapy (CAR-T and bispecific antibodies/ADC)
- Target drugs

Personalized treatment approach
- MRD driven strategies
- Prognostic scores

85 Oral abstracts

212 Poster abstracts

Smart Stop: Lenalidomide, Tafasitamab, Rituximab, and Acalabrutinib Alone and with Combination Chemotherapy for the Treatment of Newly Diagnosed DLBCL

J. Westin (MD Anderson) et al.

Lenalidomide
Tafasitamab
Rituximab
Acalabrutinib

Doses of "Smart Start" portion of the clinical trial, cycle = 21 days				
Drug Name	Dose	Route	Dosing per cycle	Day of therapy
Lenalidomide (L)	25mg	PO	Daily	1-10
Tafasitamab (T)	12mg/kg	IV	Weekly	1, 8, 15
Rituximab (R)	375mg/m2	IV	Once	1
Acalabrutinib (A)	100mg	PO	BID	1-21

Hypotheses:

1. LTRA for 4 cycles will improve upon Smart Start CR of 36%
2. CR after LTRA will allow for less or no chemotherapy, and p
   prove durable

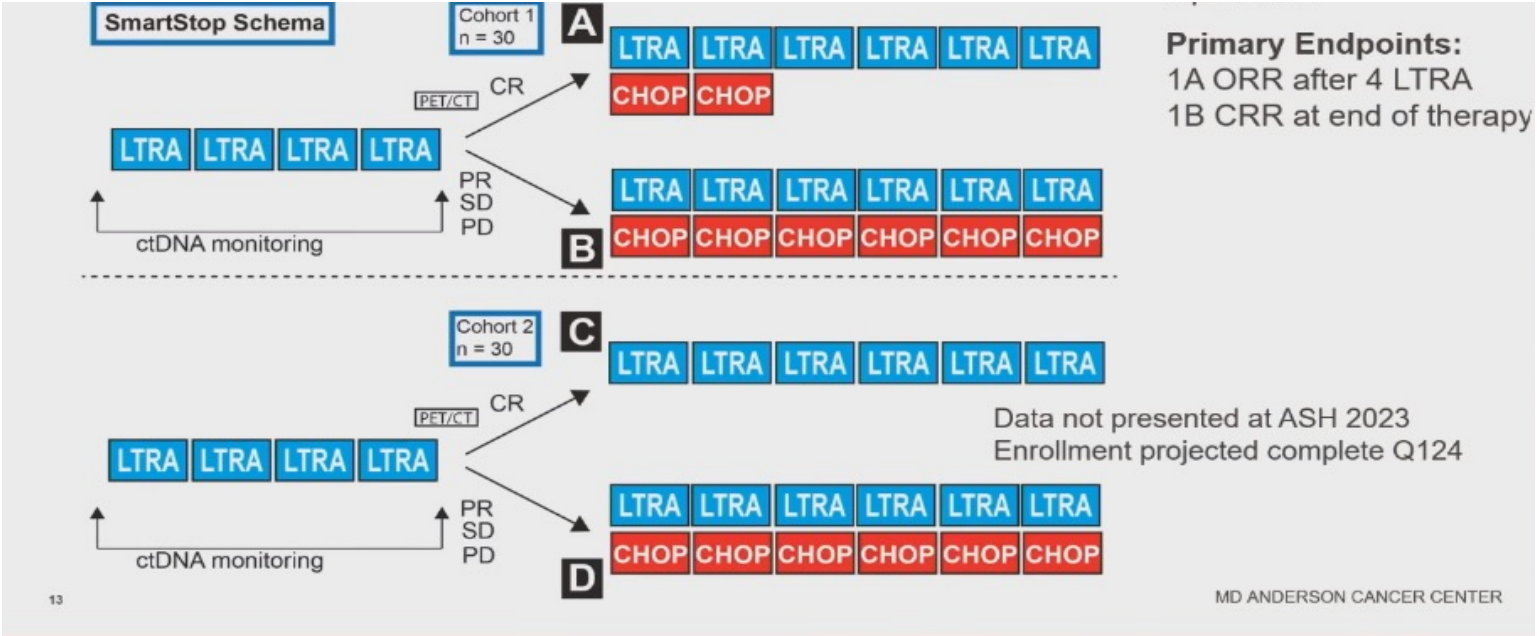
Inclusion criteria

- Histopathologically confirmed diagnosis of LBCL without prior treatment with measurable disease
  - Initially was restricted to Hans IHC-defined non-GCB but this criterion was removed
  - Prior indolent lymphoma allowed if no CHOP-based therapy
  - Any LBCL subtype could be eligible
- Age >= 18 years at the time of signing the informed consent
- Performance status of =< 3 (3 only allowed if decline in status is deemed related to lymphoma and felt potentially reversible by the treating physician)
- Adequate organ and bone marrow function
- No CNS involvement with lymphoma

Study design

Cohort 1

Cohort 2



J. Westin (MD Anderson) et al.

Patient demographics

N = 30 from cohort A	
Age, years, median (range)	61 (32-84)
>70, No (%)	9 (30%)
>80, No (%)	2 (7%)
Gender, No (%)	
Female	15 (50%)
Male	15 (50%)
Ethnicity	
Hispanic	3 (10%)
Race	
Asian	5 (17%)
African American	1 (3%)
Caucasian	24 (80%)

ECOG, No (%)	
0	9 (30%)
1	20 (67%)
2	1 (3%)
Elevated LDH, No (%)	25 (83%)
EN sites ≥2, No (%)	21 (70%)
Stage 3 or 4, No (%)	24 (80%)
Bulky tumor ≥7.5cm, No (%)	13 (43%)
IPI Score	
1	4 (13%)
2	6 (20%)
3-5	20 (67%)

COO via Hans on IHC, No (%)	
Non-GCG	25 (83%)
GCB	5 (17%)
PMBL	1 (3%)
Testicular	2 (6%)

Toxicities

40% of patients required a dose reduction of lenalidomide

AE	Any Grade (N=30)	Grade 3 or Higher (N=30)	Any Grade C1-C4 (LTRA ONLY)	Any Grade C5-C10 (LTRA + CHOP)
Anemia	26 (87%)	5 (17%)	19 (63%)	16 (53%)
Neutropenia	26 (87%)	18 (60%)	12 (40%)	24 (80%)
Fatigue	22 (73%)	0	14 (47%)	10 (33%)
Platelet count decreased	22 (73%)	3 (10%)	10 (33%)	18 (60%)
Creatinine increased	13 (43%)	0	8 (27%)	9 (30%)
Rash maculo-papular	13 (43%)	4 (13%)	13 (43%)	3 (10%)
Headache	11 (37%)	0	8 (27%)	5 (17%)
Nausea	11 (37%)	0	6 (20%)	8 (27%)
Transaminitis	10 (33%)	0	7 (23%)	3 (10%)
Edema limbs	10 (33%)	0	6 (20%)	4 (13%)
Infections	9 (30%)	2 (7%)	4 (13%)	5 (17%)
Infusion related reaction	9 (30%)	0	7 (23%)	2 (7%)
Peripheral sensory neuropathy	9 (30%)	3 (10%)	2 (7%)	8 (27%)
Constipation	8 (27%)	0	7 (23%)	1 (3%)
Cough	8 (27%)	0	6 (20%)	4 (13%)
Diarrhea	7 (23%)	0	2 (7%)	5 (17%)
Dizziness	6 (20%)	0	4 (13%)	3 (10%)
Mucositis oral	5 (17%)	0	2 (7%)	3 (10%)
Vomiting	5 (17%)	3 (10%)	2 (7%)	4 (13%)
Febrile neutropenia	4 (13%)	3 (10%)	1 (3%)	3 (10%)
Non-cardiac chest pain	4 (13%)	0	2 (7%)	2 (7%)

AE >10% of any patient, electrolyte or overlapping AEs not shown

J. Westin (MD Anderson) et al.

	All (N=30)
CR	28 (93.3%)
PR	2 (6.7%)
SD	0
PD	0
ORR	100%

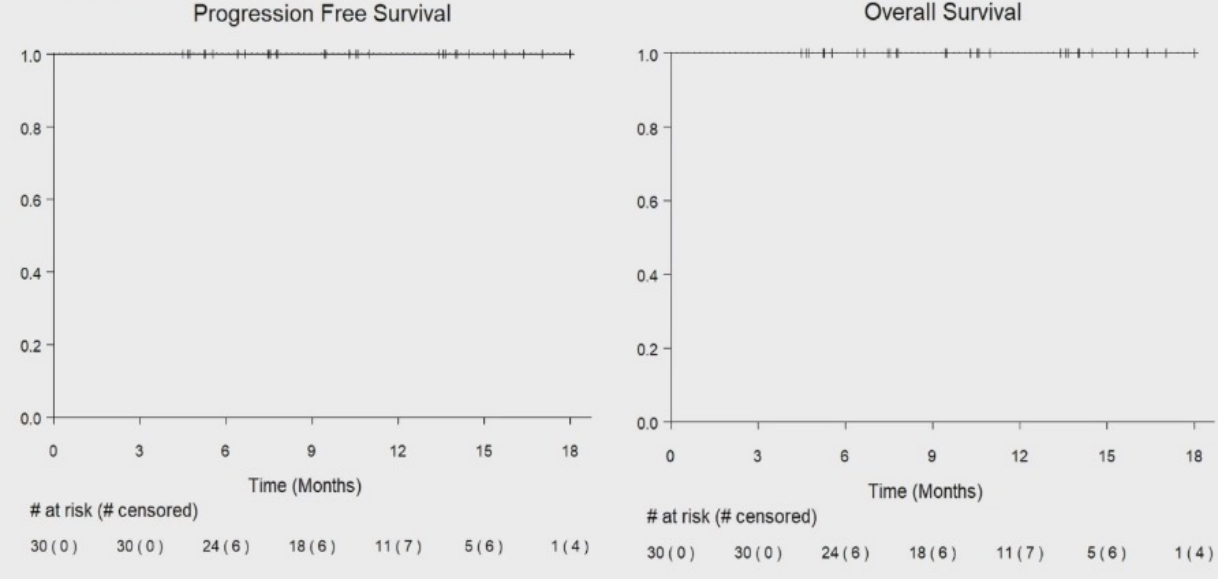
	All (N=30)	GCB (N=5)
CR	19 (63.3%) (95% CI: 50.0 ~ 75.2%)	4 (80%)
PR	11 (36.7%)	1 (20%)
SD	0	0
PD	0	0
ORR	30 (100%) (95% CI: 92.6 ~ 100%)	

N = 22		Group A (2 CHOP, N=19)	Group B (6 CHOP, N=11)
CR	22 (100%)* (95% CI: 90.1 ~ 100%)	19 (100%)	11 (100%)*
PR	0*	0	0*
SD	0	0	0
PD	0	0	0
Pending (On treatment)	8	5	3

*FDG avid lesion biopsied with benign inflammatory response without lymphoma cells

J. Westin (MD Anderson) et al.

Progression-free and Overall Survival



Median follow up 11 mesi

MRD after 4 LRTA

2023 ASH Abstract: 856, Smart Stop, Jason Westin, MD

Depth of response: ctDNA with PhasED-Seq

PET Response	N=15
CR	12 (80%)
PR	3 (20%)

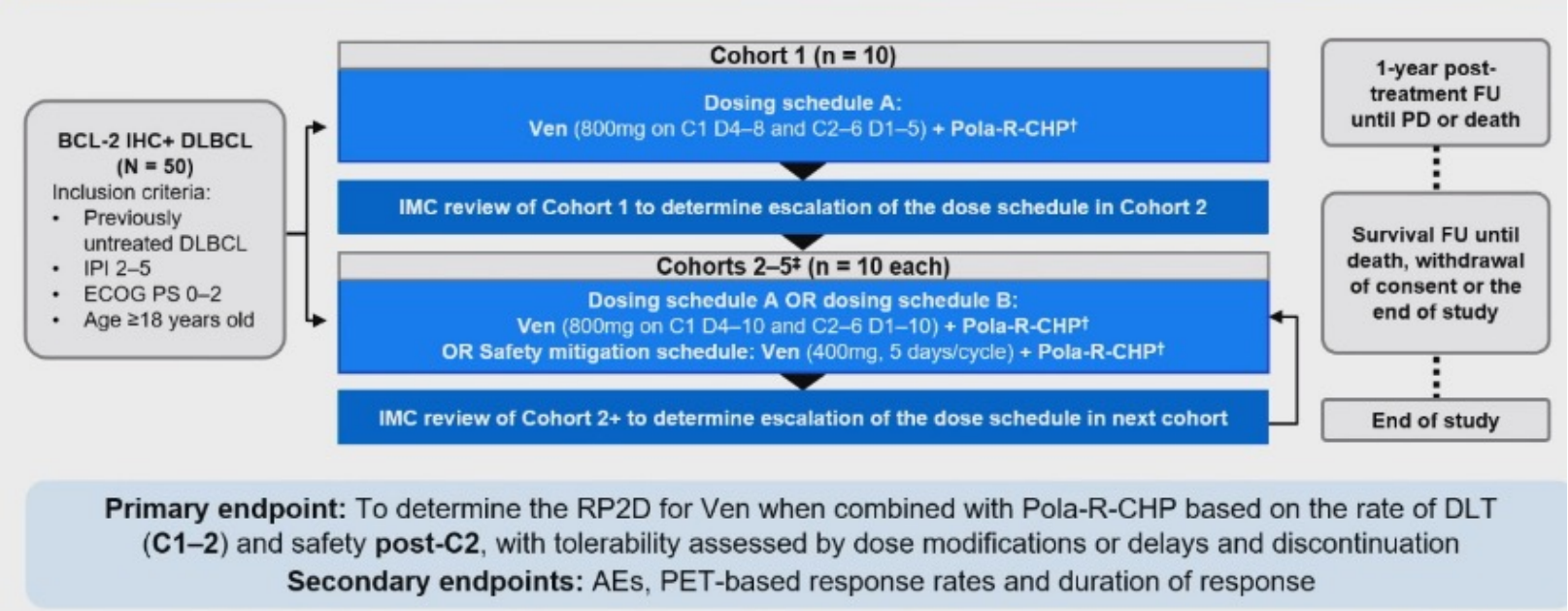
PhasED Seq Response	N=15
Undetectable	**5 (33%)**
>3 log-fold reduction	9 (60%)
>2 log-fold reduction	13 (87%)

In conclusion, targeted therapy with reduced chemotherapy appears feasible

J. Westin (MD Anderson) et al.

Early Results Indicate Acceptable Safety and Promising Efficacy of Venetoclax in Combination with Pola-R-CHP for Untreated High-Risk BCL-2-Positive B-Cell Lymphoma Including Double/Triple Hit Lymphoma

A. D. Zelenetz (MSKCC) et al.



Baseline characteristics

- The current analysis has been performed on the first 4 cohorts (n = 40) who completed the expected duration of treatment.

	Total (n = 40)
Age, median (range)	64.0 (29.0–80.0)
Sex, n (%)	
Male	26 (65.0)
Female	14 (35.0)
ECOG PS at baseline, n (%)	
0–1	35 (87.5)
2	5 (12.5)
Ann Arbor staging at study entry, n (%)	
Stage II	4 (10.0)
Stage III	9 (22.5)
Stage IV	27 (67.5)

	Total (n = 40)
IPI score, n (%)*	
2	7 (17.5)
3	19 (47.5)
4–5	11 (29.7)
DLBCL chromosomal category, n (%)	
MYC BCL-2 DHL / MYC BCL-2 BCL-6 THL	5 (12.5) / 1 (2.5)
COO (RNAseq), n (%)	
ABC	20 (50.0)
GCB	18 (45.0)
Unevaluable	2 (5.0)†

Cut-off date: September 1, 2023. *Excluding three patients who had Grade 3b FL diagnosis at study entry. †COO status assessed by IHC: one patient as GCB, and one patient as non-GCB.
ABC, activated B-cell-like; BCL-6, B-cell lymphoma 6; COO, cell of origin; DHL, double-hit lymphoma; GCB, germinal center B-cell-like; RNAseq, RNA sequencing; THL, triple-hit lymphoma.

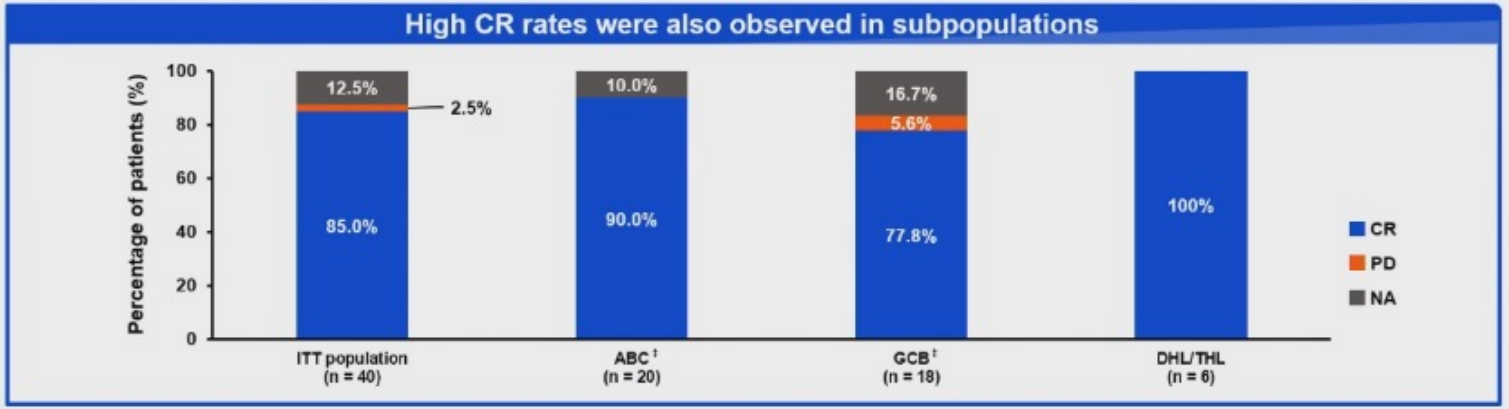
Safety analysis

Addition of Ven 800mg for 5 days to Pola-R-CHP in BCL-2+ DLBCL was acceptable with no unexpected safety signals

n (%)	R-CHOP (POLARIX)[1]	Pola R-CHP (POLARIX)[1]	Ven R-CHOP (CAVALLI)[2]*	Ven+Pola-R-CHP (BO42203)
BCL-2+ patients	**202**	**202**	**105**	**40**
Any AE	199 (98.0)	195 (97.5)	104 (99.0)	39 (97.5)
Total Grade ≥3 AEs	113 (55.7)	123 (61.5)	93 (88.6)	28 (70.0)
Total SAE	58 (28.6)	70 (35.0)	63 (60.0)	17 (42.5)
AE leading to treatment withdrawal	10 (5.0)	13 (6.5)	25 (23.8)	5 (12.5)
Grade ≥3 neutropenia	61 (30.0)	59 (29.5)	74 (70.5)	20 (50.0)†
Grade ≥3 febrile neutropenia	14 (6.9)	27 (13.5)	30 (28.6)	7 (17.5)

A. D. Zelenetz (MSKCC) et al.

Outcome



Conclusions

Ven 800mg/day for 5 days/cycle has been determined as the RP2D in combination with Pola-R-CHP.

Early results show acceptable safety for untreated BCL-2 IHC+ DLBCL: treatment did not produce any unexpected safety signals.

Preliminary efficacy results were promising: high CR rates were observed across all cohorts at EOT, including patients with DHL/THL.

A. D. Zelenetz (MSKCC) et al.

Mosunetuzumab and Polatuzumab Vedotin Demonstrates Preliminary Efficacy in Elderly Unfit/Frail Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

Olszewski AJ et al. Brown University, Providence, RI

Table: Baseline and disease characteristics

Characteristics, n (%)	M-Pola Cohort (N=108)
Median age (range), years	81.0 (66–94)
Age ≥80	66 (61.1)
sGA*	
Fit	1 (0.9)
Unfit	64 (59.3)
<80 years	41 (38.0)
≥80 years	23 (21.3)
Frail	43 (39.8)
Gender	
Female	56 (51.9)
Ann Arbor stage	
III–IV	71 (65.7)
aa-IPI	
0	21 (19.4)
1	32 (29.6)
2	41 (38.0)
3	14 (13.0)
Extranodal involvement	77 (71.3)
Elevated LDH	59 (54.6)
Bulky disease (≥7.5cm)	30 (27.8)
HGBCL†‡	
Double hit	8 (7.4)
Triple hit	2 (1.9)
Cell of origin‡	
GCB	49 (45.4)
Non-GCB	56 (51.9)
Unknown	3 (2.8)

* Merli et al. JCO

Pola 1.8mg/kg iv on D1 of C1-6

Mosun step-up 5/15/45mg (D1/8/15) C1

Mosun 45mg sc on D1 of C2-8 → 17

ORR	55% (45% CR)
PD	9%
Without assessment	36% (40% AE)

2 pts CRS Gr 3
8 COVID-19/COVID-19 pneumonia

End-of-Treatment Response Assessment after Frontline Therapy for Aggressive B-Cell Lymphoma: Landmark Comparison of a Singular PET/CT Scan Versus Ultrasensitive Circulating Tumor DNA

M. Roschewski (Bethesda) et al.

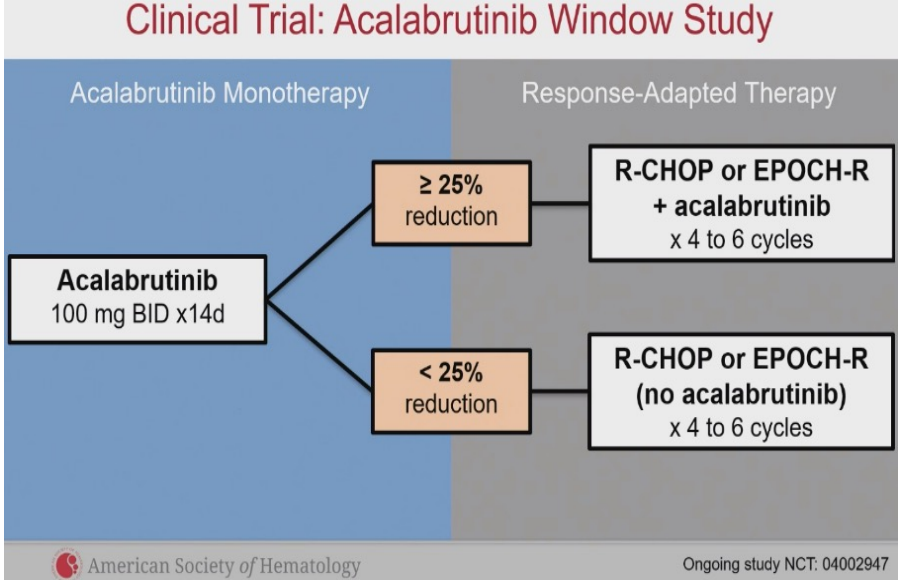
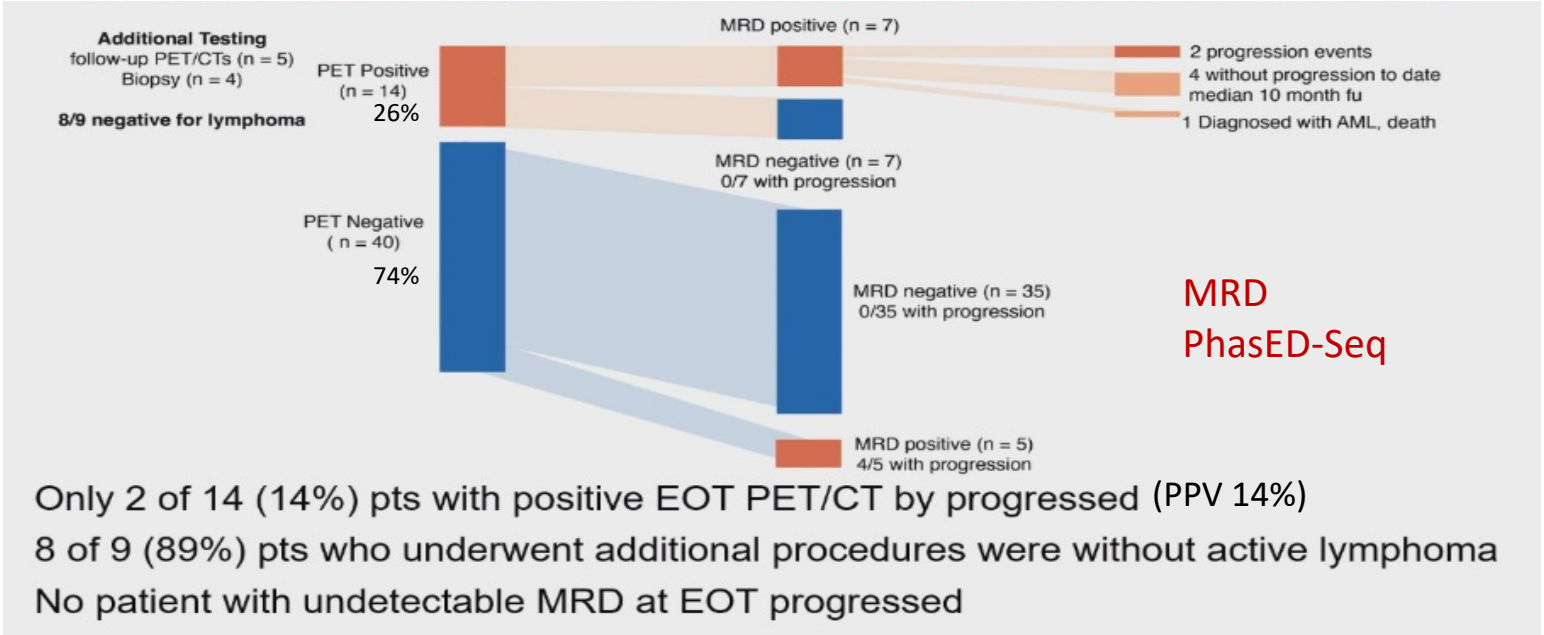


Table 1. Characteristics of the Patients

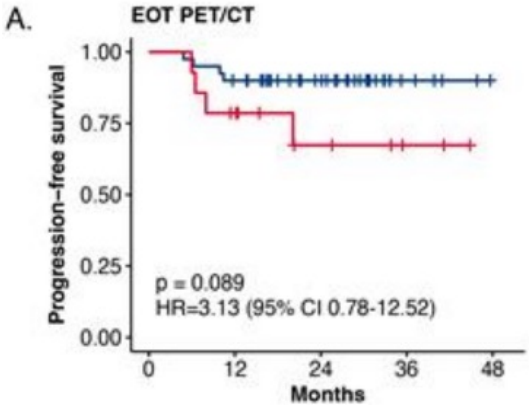
Characteristic	N (%)
Number of patients	54
Female sex	22 (41%)
Age	
Median (range) - yr	62 (26-85)
< 60 years	22 (41%)
60-69 years	22 (41%)
≥ 70 years	10 (18%)
International Prognostic Index	
0-1 (low-risk)	13 (24%)
2 (low-intermediate risk)	15 (28%)
3 (high-intermediate risk)	18 (33%)
4-5 (high risk)	8 (15%)
DLBCL:NOS subtype (Hans)	46 (85%)
Non-GCB	21 (39%)
GCB	24 (44%)
T-cell/histocyte rich	1 (2%)
HGBL with MYC and/or BCL2 or BCL6	8 (15%)

Procedures at EOT to Determine Remission

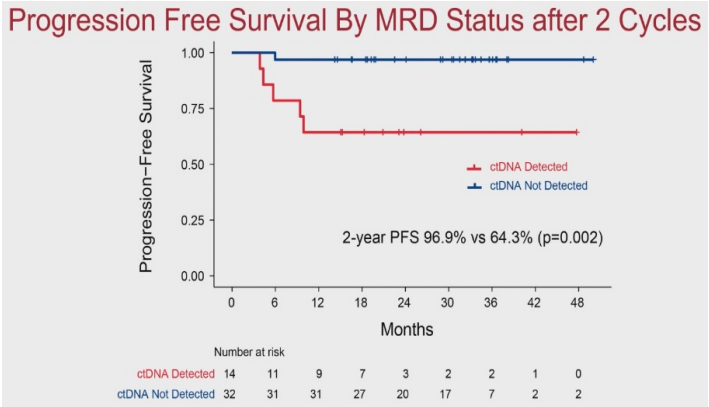


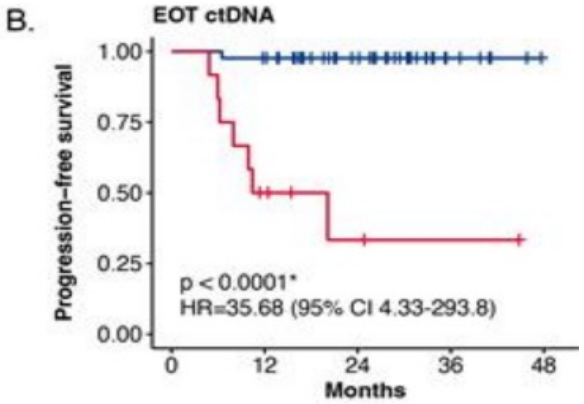
M. Roschewski (Bethesda) et al.

Procedures at EOT to Determine Remission



PET CR
PET no CR





ctDNA Undetected
ctDNA Detected

Conclusions

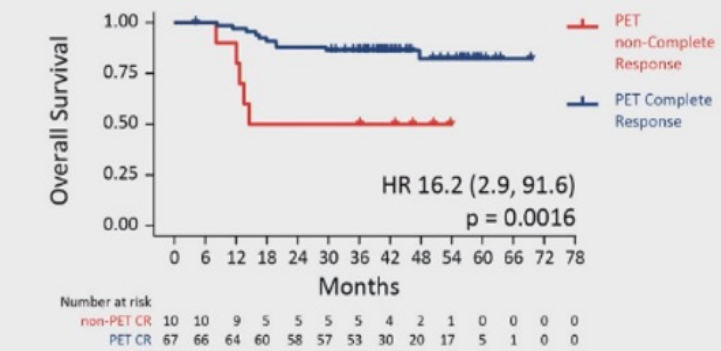
- ctDNA by PhasED-Seq is prognostic both after 2 cycles and at EOT
- Undetectable ctDNA by PhasED-Seq at EOT predicts a very low likelihood of progression with greater predictive value than PET/CT
- Additional procedures (biopsy, repeat PET/CT scans) are often required to adjudicate EOT PET/CT scans; most do not have active lymphoma
- Salvage therapy should not be delivered based on a singular EOT PET/CT

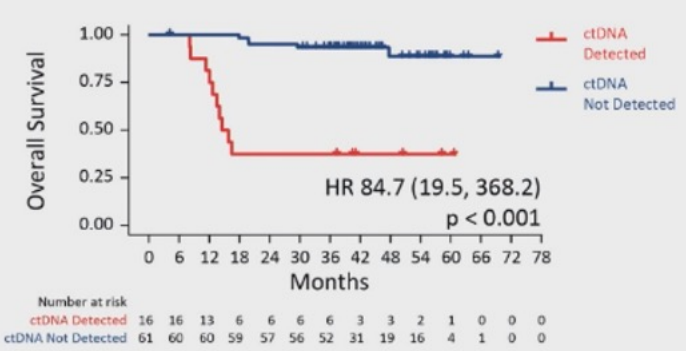
M. Roschewski (Bethesda) et al.

Prognostic Utility of Minimal Residual Disease (MRD) after Curative Intent Induction Therapy for DLBCL: A Prospective Real-World Ctdna Study

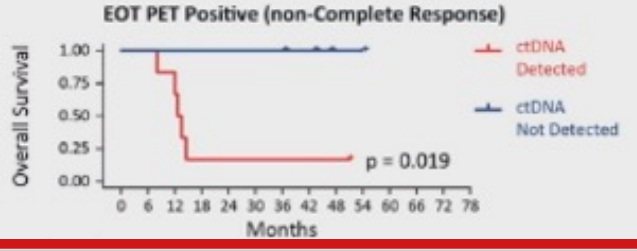
Sworder BJ et al. University of California

ctDNA by PhasED-Seq outperforms PET/CT scan for response assessment





Use of ctDNA-MRD for confirmatory testing in PET-CT positive patients at EOT could eliminate the need for confirmatory biopsy to inform treatment decisions following the completion of first-line therapy.



Glofitamab (Glofit) Plus R-CHOP Has a Favorable Safety Profile and Induces High Response Rates in Patients with Previously Untreated (1L) Large B-Cell Lymphoma (LBCL) Defined As High Risk By Circulating Tumor DNA (ctDNA) Dynamics: Preliminary Safety and Efficacy Results

Lorenzo Falchi et al MSKCC

121 pts R-CHOP21

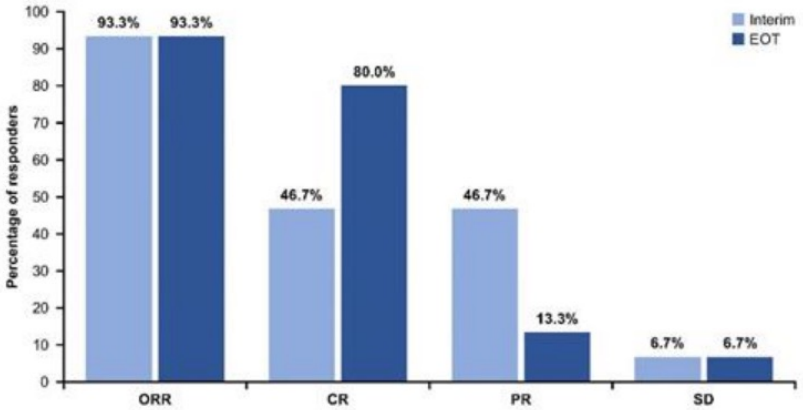
↓

24 pts high risk (<2-log reduction in plasma ctDNA after 1 R-CHOP)

↓

+ glofitamab step-up in C3 (2.5-10mg)
30mg on D8 of C4-6, and on D1 of C7-10

15 pts reached the **EOT** assessment



CRS 21% gr 1-2

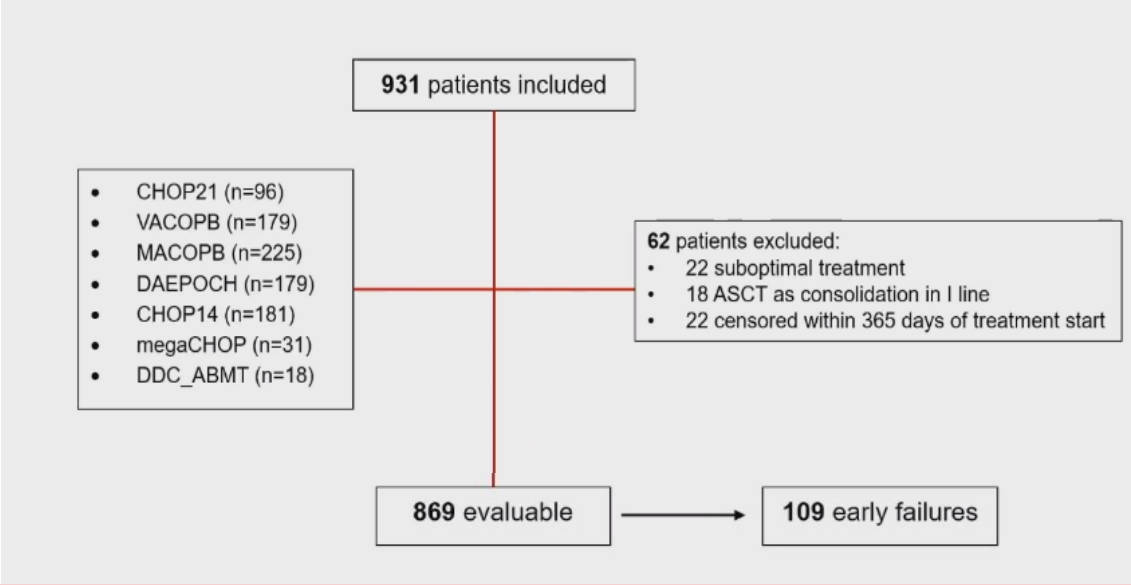
Description of a Clinical Score to Identify PMBL Patients at High Risk of Early-Failure after Rituximab Doxorubicin Back-Bone Chemoimmunotherapy. a FIL Real-World Study

E. Iannitto, M. Balzarotti et al.

Retrospective cohort study of an unselected population PMBCL patients > 18 years old, treated in 37 FIL centers from 2007 to 2019

Objective of the study

The development of a clinical score aimed at estimating the risk of early failure of PMBL



PATIENT CHARACTERISTICS

	FIL population [1-2]	Cook meta-analysis DI-CIT[3]	Cook meta-analysis S-CIT
N^ pts	891	1860	1307
Median age (range)	35 (28-44)	32.8 (9-82)	33.8 (11-88)
Female gender	61.6%	60.5%	56.3%
Stage I-II	78.1%	67.7%	70.7%
Stage III-IV	21.6%	32.3%	29.3%
B-symptoms	38.3%	41.2%	34.6 %
Bulky Disease	71.5%	72.7%	62.7%
Extranodal disease	29.1%	35.6%	35.3%
Pleural effusion	42.5%	35.0%	33.0%
Pericardial effusion	37%	27.2%	22.9%

All patients received treatment with:
R-CHOP21 (n=98), R-CHOP14 (n=181), R-megaCHOP (n=31), R-MACOPB (225), R-VACOPB (n=179), R-DAEPOCH (n=179)

Candidate clinical predictors:
- Age
- ECOG PS
- LDH >ULN
- Ann Arbor Stage
- B symptoms
- Bulky mediastinum > 10 cm
- N° extra-nodal sites
- Pericardial or pleural effusion

→ Multivariable logistic model with Backward Selection (level to stay p<0.1)

↓ Categorical variables demonstrating similar effects were collapsed

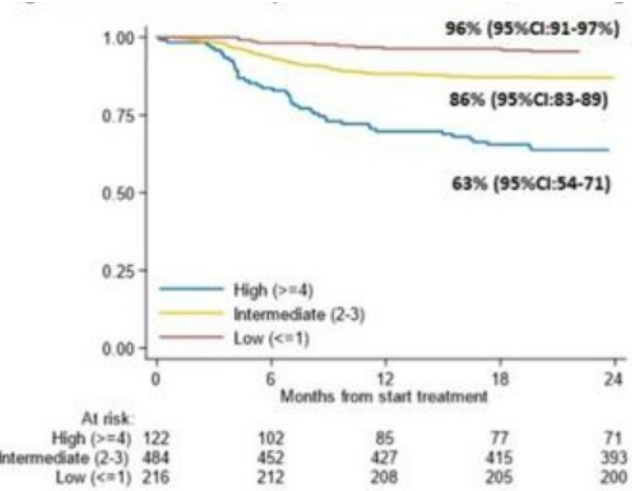
↓ Optimism-corrected AUROC were estimated based on the results of the bootstrap process (internal validation)

↓ A weight proportional to the smallest coefficient (B-symptoms) has been assigned to each factor

	Coefficient	Odds ratio	P	Score weight
Systemic B symptoms	0.566	1.76	0.007	1
Bulky mediastinum >10cm	0.75	2.12	0.017	1
Stage II	0.79	2.2	0.018	1
Stage III-IV	1.005	2.73	0.017	2
Number of extra-nodal sites >=2	1.059	2.88	<0.001	2

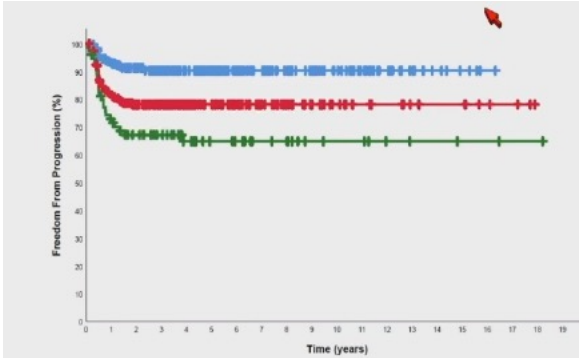
E. Iannitto, M. Balzarotti et al.

FFS



	Coefficient	Odds ratio	P	Score weight
Systemic B symptoms	0.566	1.76	0.007	1
Bulky mediastinum >10cm	0.75	2.12	0.017	1
Stage II	0.79	2.2	0.018	1
Stage III-IV	1.005	2.73	0.017	2
Number of extra-nodal sites >=2	1.059	2.88	<0.001	2

Validation cohort



Validation of FIL score on an external cohort from a retrospective international series (31 centers) of an ***eastern mediterranean and Saudi Arabia Grou***p (T Vassilakopulos, ICML 17) .

In conclusion a simple and practical **prognostic score** was built that subdivide patients into **three clear-cut groups** with different likelihoods of experiencing **early failure**

E. Iannitto, M. Balzarotti et al.

TAKE home messages

New perspectives from San Diego

- A chemo-free/chemo-reduced strategy could become a new therapeutic proposal even in aggressive lymphoma in a near future

- ctDNA MRD assessment could rapidly become a new tool to better select refractory patients for intensification treatment or to avoid overtreatment

Novità dal Meeting della Società Americana di Ematologia

Verona, 15-16-17 Febbraio 2024

Grazie
per
l'attenzione