9th POSTGRADUATE
Lymphoma
Conference

Is it time to explore the concept of "replace R-CHOP”

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MD Anderson Cancer Center

Florence,
March 20-21, 2025

Hotel Brunelleschi

President:
P.L. Zinzani

Disclosures

Disclosures of Jason Westin

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie, Allogene, ADC Therapeutics, AstraZeneca, BMS, Genentech, GenMab, Janssen, Kite/Gilead, Morphosys/Incyte, Novartis, Nurix, Regeneron, SeaGen			x				
ADC Therapeutics, Allogene, AstraZeneca, BMS, Genentech, Janssen, Kite/Gilead, Morphosys/Incyte, Novartis, Nurix, Regeneron	x						

Is it time to explore the concept of "replace R-CHOP”

When will the sun set on RCHOP?

St Francis of Assisi
Pala Bardi
Santa Croce
The Healing of Bartholomew of Narni
"Any sufficiently advanced technology is indistinguishable from magic."
Arthur C. Clarke

Replace RCHOP?

Are you crazy? Sei pazzo?

- **RCHOP works**
  - It cures 2/3 of patients
  - With ~180K diagnoses globally each year, ~120K cured/year
  - Used for 25 years, ~3 million cured with RCHOP
- **RCHOP is easy**
  - Oncologists globally can give it locally, no special testing required
- **Replacing RCHOP has failed, many times**
  - RCHOP+X has killed many good drugs (ibrutinib, lenalidomide, etc)

Replace RCHOP!

Are you crazy? Sei pazzo?

- **RCHOP doesn’t work well enough**
  - It fails 1/3 of patients
  - With ~180K diagnoses globally each year, ~60K not cured/year
  - Used for 25 years, ~1.5 million not cured with RCHOP
- **RCHOP is not optimal**
  - Why accept 1970s chemotherapy for a potentially fatal illness in 2025? 2055?
- **Replacing RCHOP has failed due to trial design**
  - RCHOP+X presumes synergy or additivity in unselected patients, why?

CHOP has been standard of care for 49 years

HYDROXYLDAUNOMYCIN (ADRIAMYCIN) COMBINATION CHEMOTHERAPY IN MALIGNANT LYMPHOMA

Eugene M. McKelvey, MD, Jeffrey A. Gottlieb, MD, Henry E. Wilson, MD, Arthur Haut, MD, Robert W. Talley, MD, Ronald Stephens, MD, Montague Lane, MD, Jess F. Gamble, MD, Stephen E. Jones, MD, Petre N. Grozea, MD, Jordon Gutterman, MD, Charles Coltman, Jr., MD, and Thomas E. Moon, PhD

Table 1. CHOP–HOP Chemotherapy for Non-Hodgkin's Lymphoma

C	Cyclophosphamide	750 mg/m²		d1
H	Adriamycin	50 mg/m²		d1
O	Vincristine	1.4 mg/m²	(max 2 mg)	d1
P	Prednisone	100 mg daily × 5		d1–5

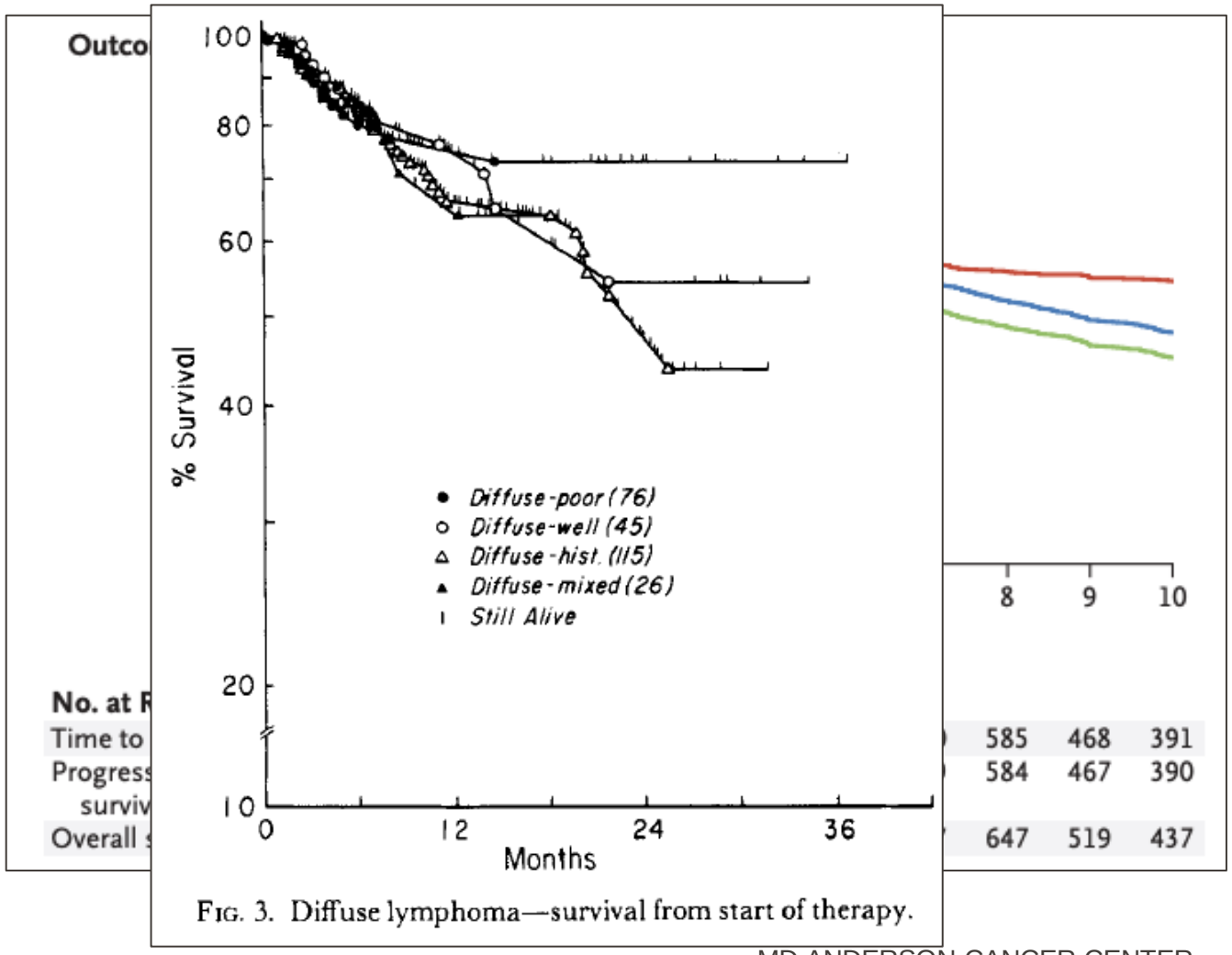


Fig. 3. Diffuse lymphoma—survival from start of therapy.

[7] *Cancer* 38:1484–1493, 1976.

Sehn and Salles, NEJM 2021

Is CHOP optimal?

Year	Drug Name
1949	Mechlorethamine
1949	Ethinyl Estradiol
1953	Triethylenemelamine
1953	Mercaptopurine
1953	Methotrexate
1954	Busulfan
1957	Chlorambucil
1959	Cyclophosphamide
1959	Thiotepa
1961	Vinblastine
1962	Uracil Mustard
1963	Vincristine
1964	Melphalan
1964	Actinomycin D
1966	Pipobroman
1966	Thioguanine
1967	Hydroxyurea
1969	Cytarabine
1969	Procarbazine
1974	Doxorubicin
1976	Lomustine

By 1976, there were ~21 drugs that were approved for the treatment of cancer

Of 21 drugs, how many possible 4 drug combinations can be created?

The probability of a specific **4-drug combination** being optimal from a **set of 21 drugs** is calculated using the **binomial coefficient** formula:

$$\text{Total combinations} = \binom{21}{4} = \frac{21!}{4!(21-4)!}$$

$$= \frac{21!}{4! \times 17!}$$

Breaking this down:

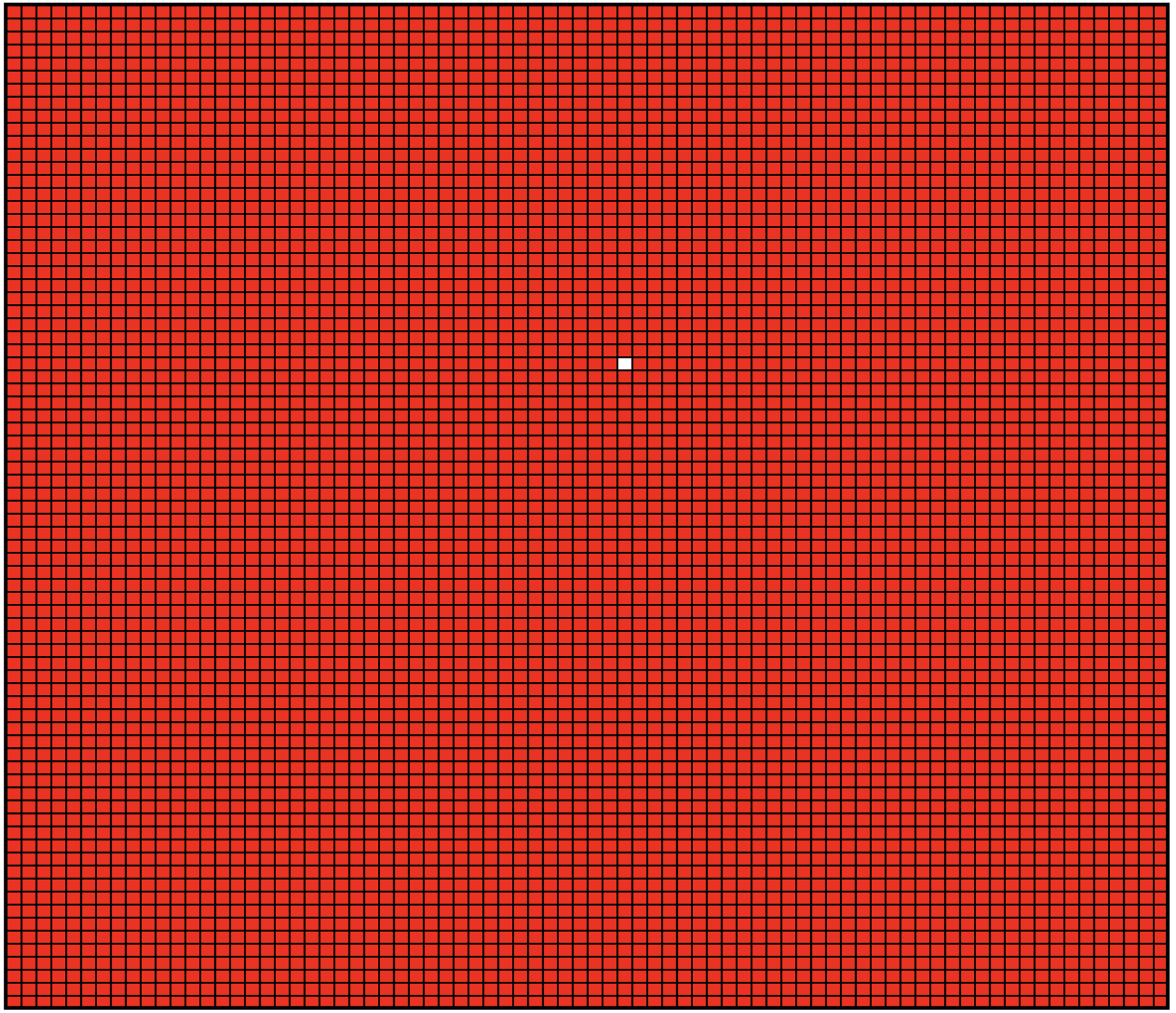
$$= \frac{21 \times 20 \times 19 \times 18}{4 \times 3 \times 2 \times 1}$$

$$= \frac{7980}{4 \times 3 \times 2 \times 1} = \frac{7980}{24} = 5985$$

Is CHOP optimal?

1 of 5985 is 0.0167%

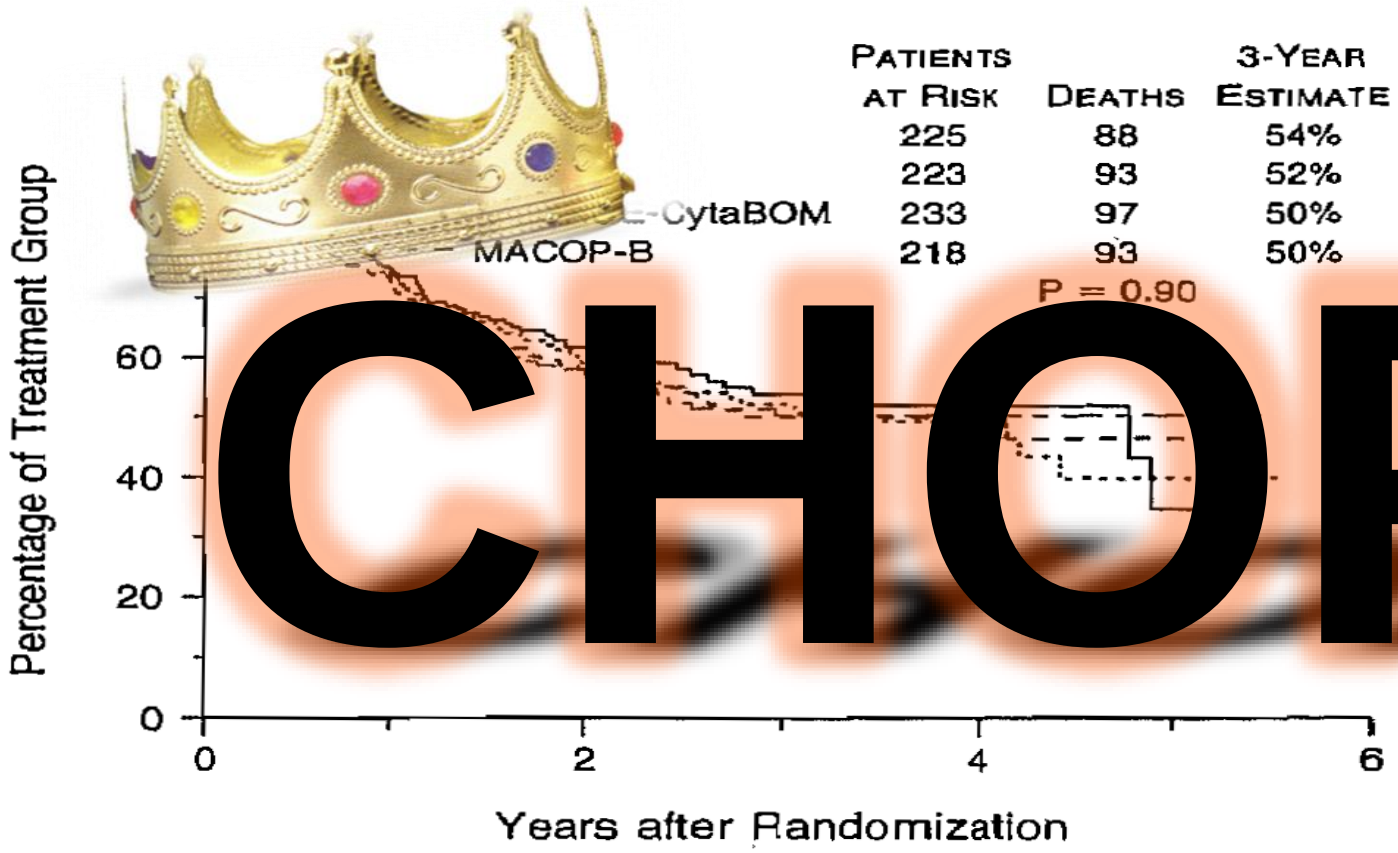
5984 of 5985 is 99.983%



Replace RCHOP - Westin 2025

COMPARISON OF A STANDARD REGIMEN (CHOP) WITH THREE INTENSIVE CHEMOTHERAPY REGIMENS FOR ADVANCED NON-HODGKIN'S LYMPHOMA

RICHARD I. FISHER, M.D., ELLEN R. GAYNOR, M.D., STEVE DAHLBERG, M.S., MARTIN M. OKEN, M.D., THOMAS M. GROGAN, M.D., EVONNE M. MIZE, JOHN H. GLICK, M.D., CHARLES A. COLTMAN, JR., M.D., AND THOMAS P. MILLER, M.D.



PATIENTS AT RISK	DEATHS	3-YEAR ESTIMATE
225	88	54%
223	93	52%
233	97	50%
218	93	50%

Figure 2. Overall Survival in the Treatment Groups. The three-year estimate is of overall survival.

CHOP

m-BACOD

- **MTX, Bleo, Dox, CTX, VCR, Dex**

MACOP-B

- **TX, Dox, CTX, VCR, Pred, Bleo**

Pr ACE-CytaBOM

- **CTX, Dox, Etop, Pred, AraC, Bleo, VCR, Bleo**

NEJM, 1993:328:1002-6

Who Are These Men?

- **Rulers and Nobles** – Kings, dukes, and other European leaders.
- **Military Commanders** – Famous generals and warlords.
- **Scholars and Writers** – Philosophers, poets, and scientists.
- **Artists and Musicians** – Renaissance and earlier figures from various disciplines.
- **Clergy and Religious Figures** – Popes, bishops, and religious scholars.

CHOP is very unlikely to be optimal

So what?

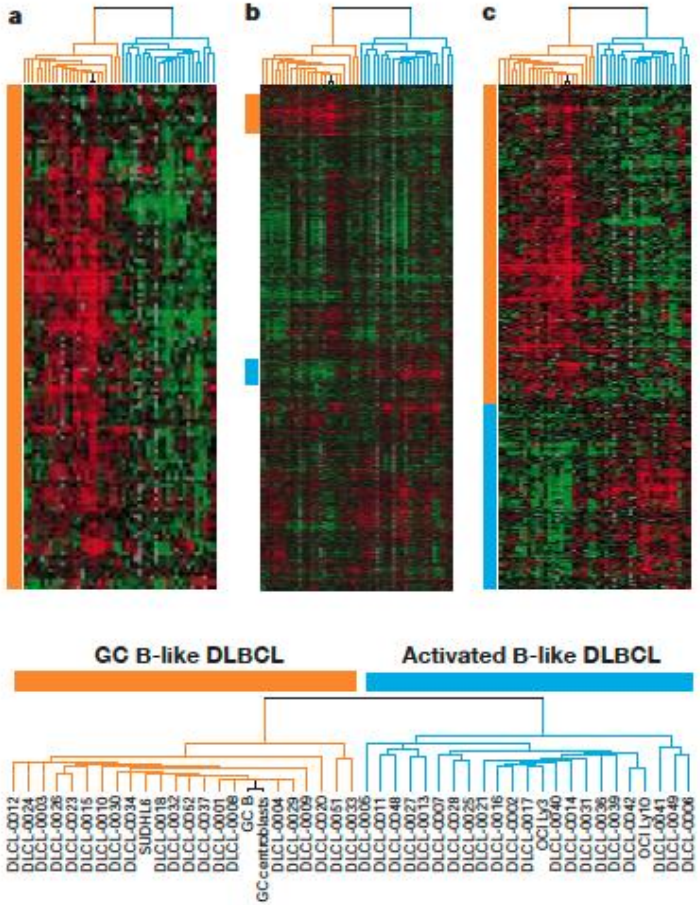
It is not 1976

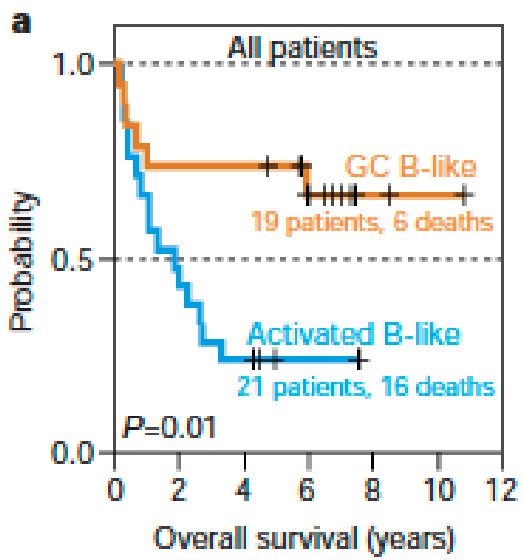
~600 approved drugs for oncology by 2025

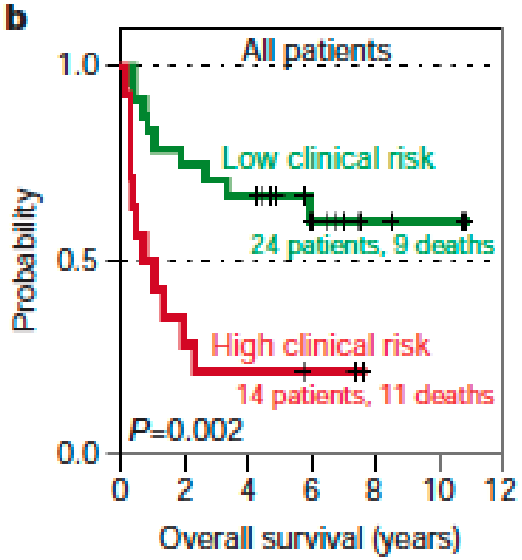
- 5,346,164,850 possible 4 drug combinations
- 0.0000000187% that one combination is optimal

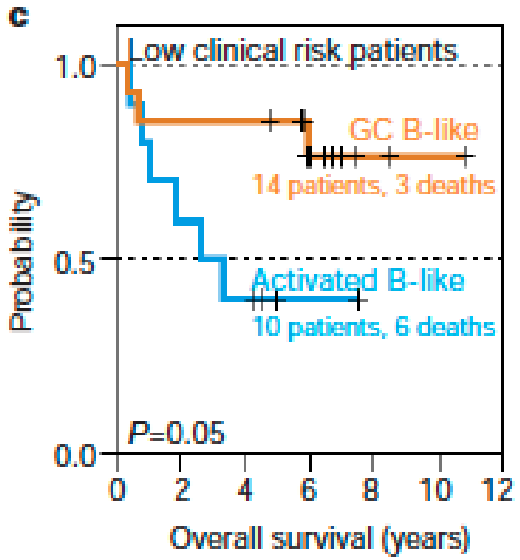
- 1 second to name each 4 drug combo = 169 years, 4 months, 28 days

Heterogeneity of DLBCL



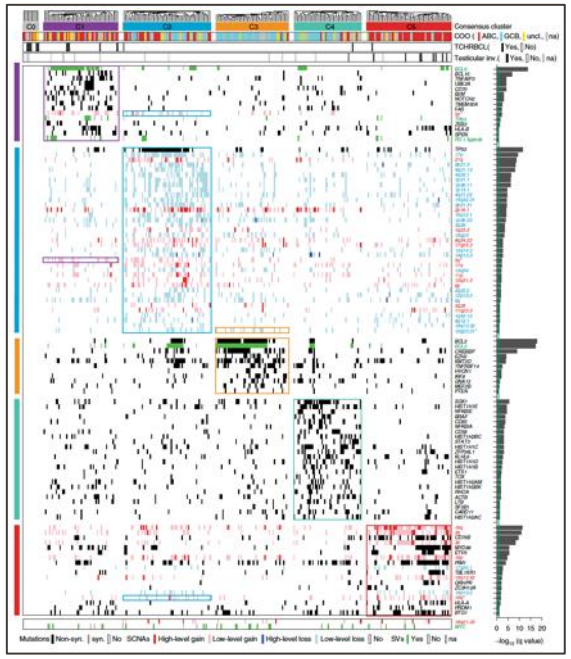


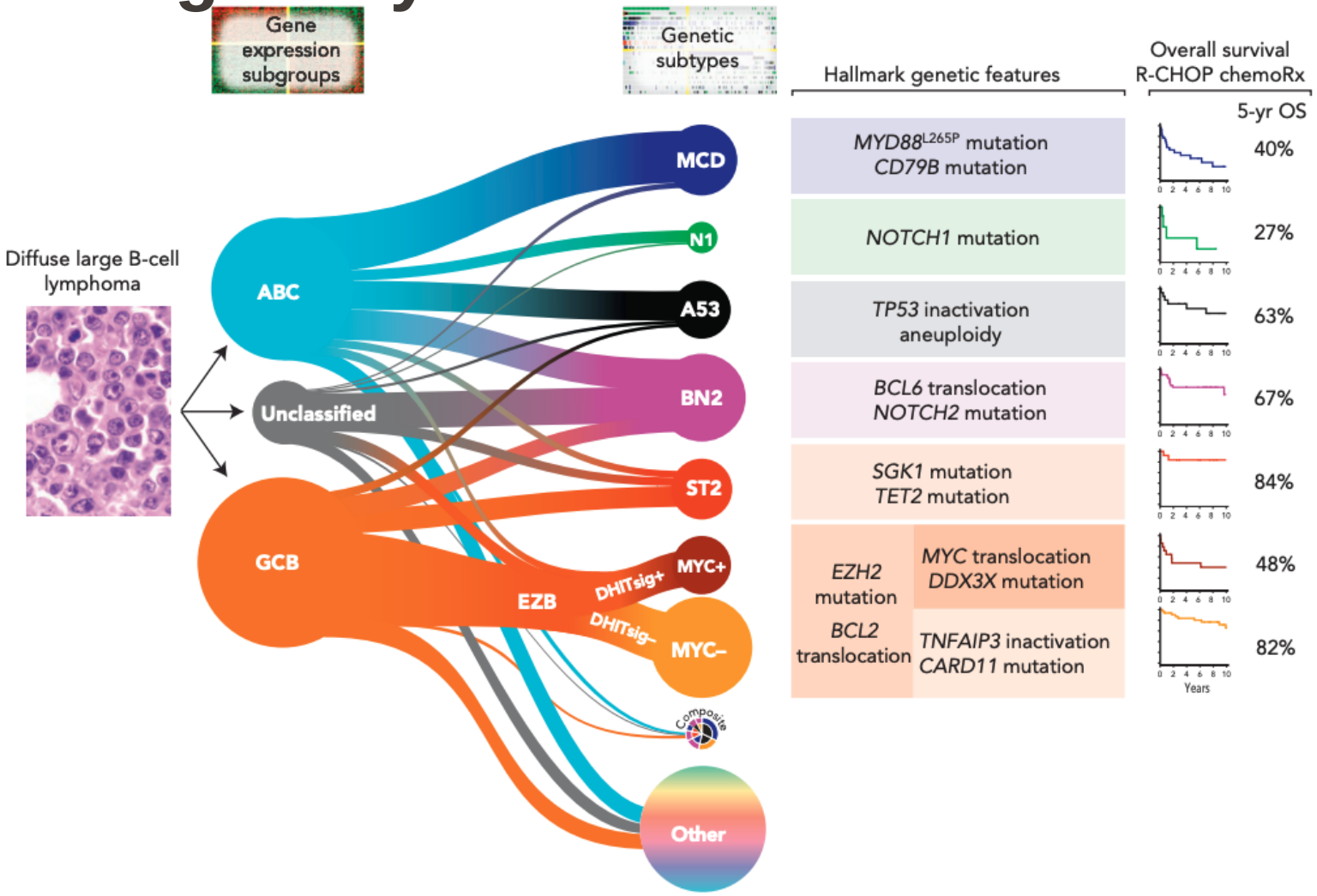




Alizadeh, Staudt et al Nature 2000

Even more heterogeneity of DLBCL





Chapuy/Shipp, Nature Medicine 2018
Wright, Staudt et al, Cancer Cell 2020,
de Leval, Scott et al Blood 2022

The use of molecular profiling for patient selection
DW Scott

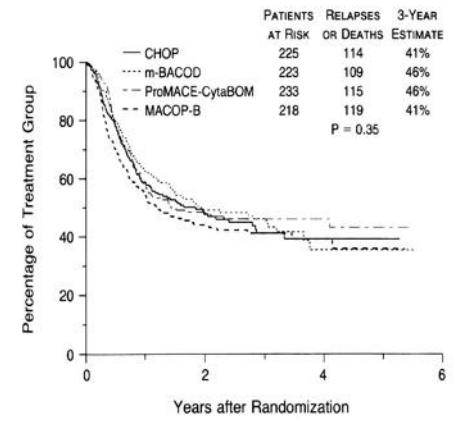
Current trials do not account for disease biology

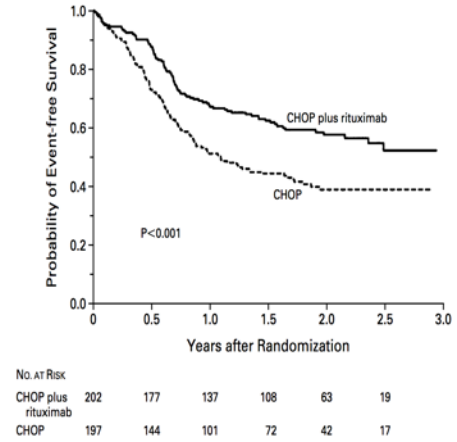
IPI is a crude surrogate

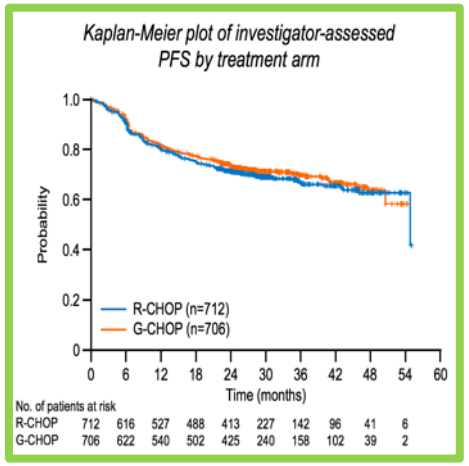
- Advanced age may correlate with more ABC subtype
- Advanced stage, EN sites, LDH may correlate with aggressive biology
- Poor PS could be related to disease or comorbidities

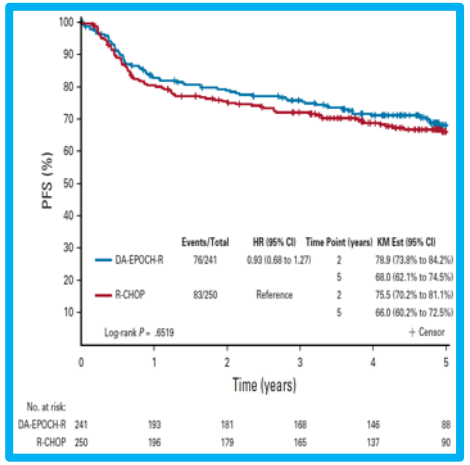
DLBCL trials

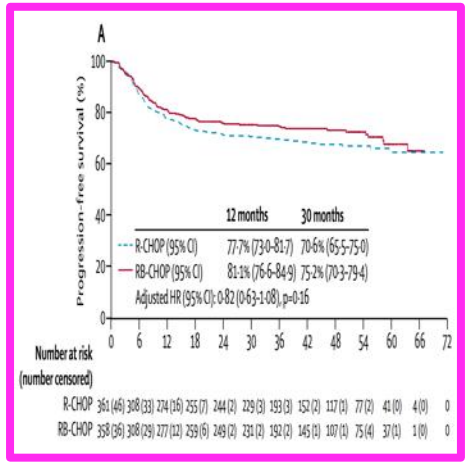
- CHOP[1,2]
- RCHOP[3]
- RCHOP vs GCHOP[4]
- RCHOP vs REPOCH[5]
- RCHOP +/- Bortezomib[6]
- RCHOP +/- Ibrutinib[7]
- RCHOP +/- Lenalidomide[8,9]
- RCHOP vs RCHP-Pola[10]

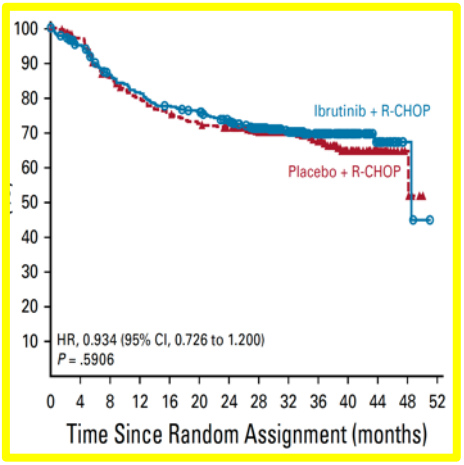


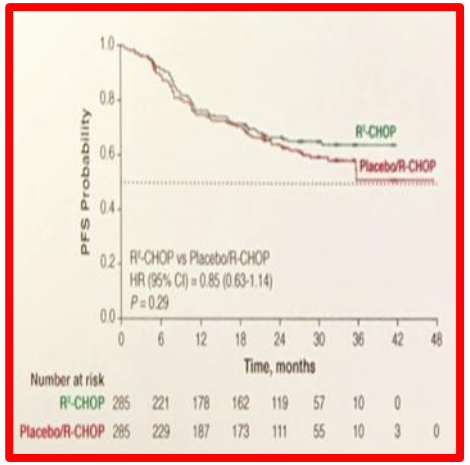


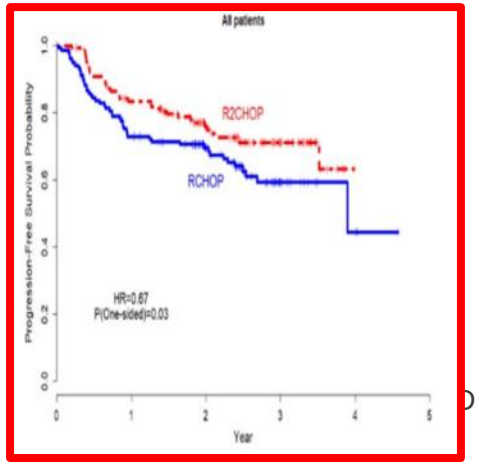


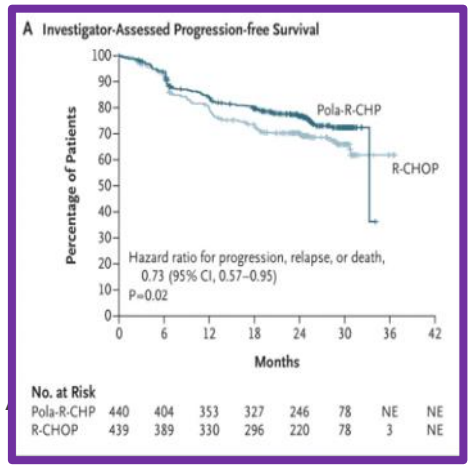












1. McKelvey et al, Cancer 1976, 2. Fisher et al, NEJM 1993, 3. Coiffier et al, NEJM 2002, 4. Vitolo et al, JCO 2018, 5. Bartlett et al, JCO 2019, 6. Davies et al, Lancet 2019, 7. Younes et al, JCO 2019, 8. Vitolo et al, ICML 2019, 9. Nowakowski et al, ICML 2019, 10. Tilly et al, NEJM 2022

Frontline treatments in DLBCL: the actual scenario and the ongoing trials speculations and potential future vision

GS Nowakowski

My opinion: DLBCL in 2030

3 or more 1L approved treatment options

0 biomarker informed

Clinical Chaos – how to choose?

Research Chaos:

- What is the control arm?
- What is the sequence if 1L bisp or 1L CAR?
- How to combine novel agents with 1L therapy?

Even if CHOP isn’t optimal and doesn’t synergize with targeted therapy, why replace it?

A “one size fits most” strategy would be like

- If shoe companies only produced size 10 shoes
- If all infections were treated with ciprofloxacin
- If all restaurants served the same one meal

Why are we still using CHOP + X?

Regulatory inertia

Misaligned incentives

Why are we still using CHOP + X?

Regulatory inertia

FDA's Preference for Known Mechanisms

- Regulators often favor trial design that follow well-established pathways (e.g., change 1 variable) over new combinations that require more data (contribution of components).

High Costs & Risk Aversion

- Conducting a large Phase 3 trial costs hundreds of millions of dollars. Companies hesitate to take big risks on novel treatments with uncertain approval pathways.
- Investors favor lower-risk, faster-to-approval strategies, leading to more me-too drugs (e.g., slightly different kinase inhibitors).

Regulatory Uncertainty & Approval Pathways

- Without precedent, companies fear the FDA will ask for additional trials, delaying approval and increasing costs.

Why are we still using CHOP + X?

Misaligned incentives

Large trials are largely funded by Pharma

- **Help patients**
- **Make profit**

If DLBCL has 5 different treatment relevant subtypes, would a for profit company view it more logical to:

- **Seek a 95% chance of approval for 1/5th of the market?**
- **Seek a 19.5% chance of approval for all of the market?**
  - If there is a >19% probability of success, it is more logical to choose the unselected approach

Do we have ”95% chance” approval approaches?

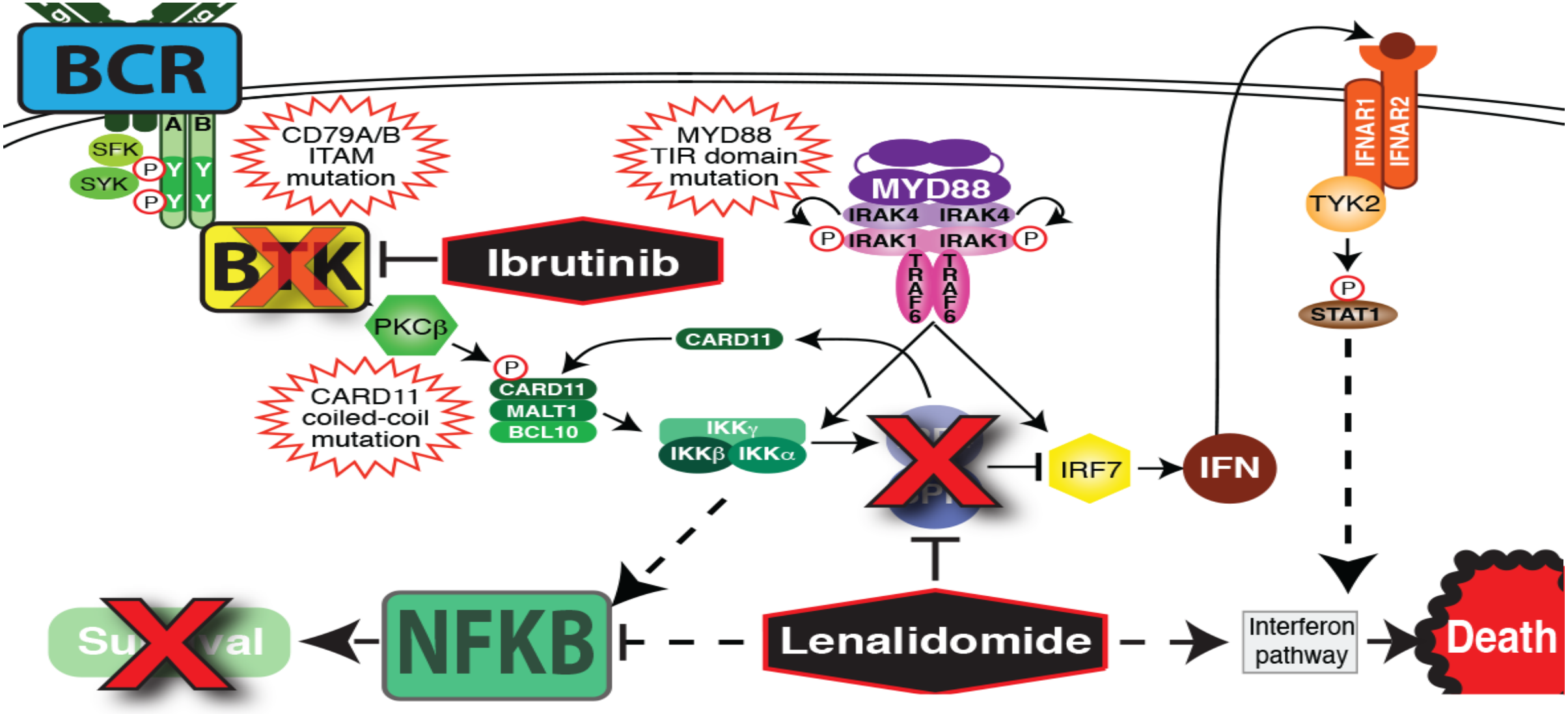
The biology informed classifier approach (COO, DHL, etc) has not move the needle

We need therapy informed disease classifiers

A way forward

Smart Start and **Smart Stop** may not be the answer, but they open the door

Synthetic Lethality of Lenalidomide and Ibrutinib

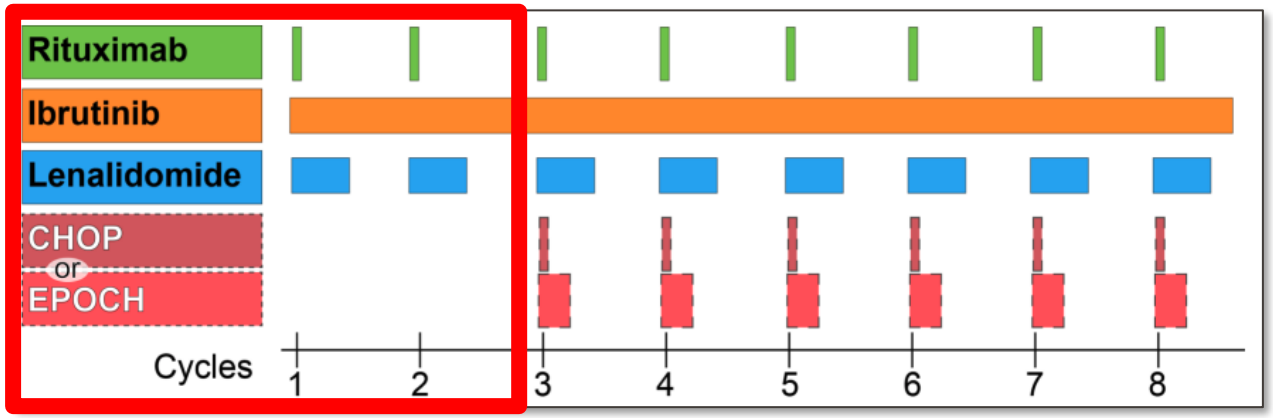


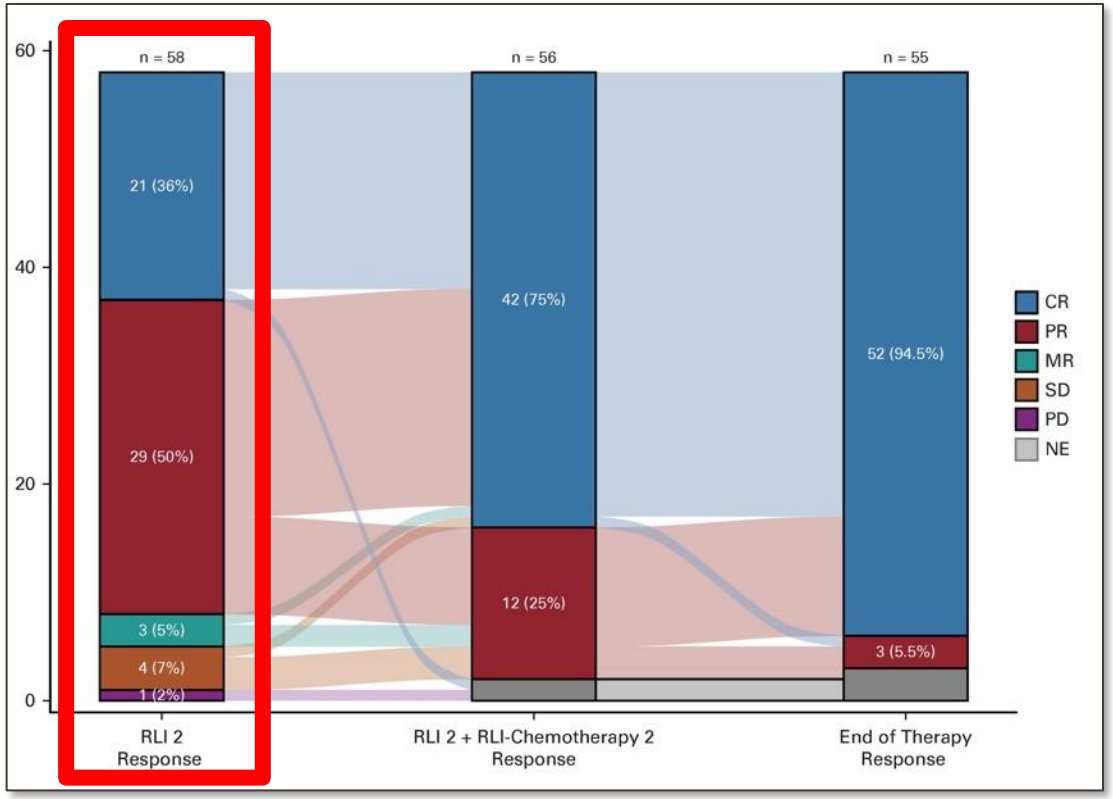
Len: Upregulate IL2 in T-cells
Ibr: ITK inhibition shift Th2 to Th1

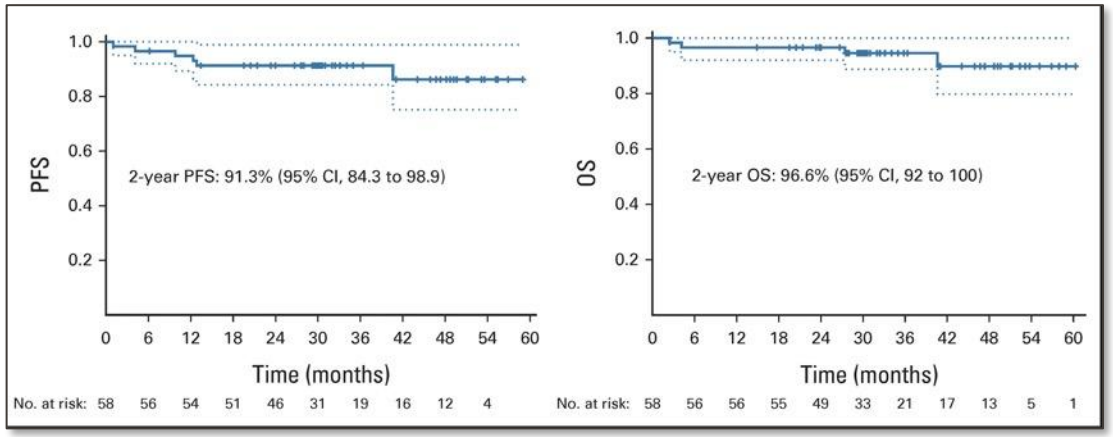
Yang, Staudt Cancer Cell 2012

Smart Start: Rituximab, Lenalidomide, and Ibrutinib in Patients With Newly Diagnosed Large B-Cell Lymphoma

Jason Westin, MD, MS[1]; R. Eric Davis, MD[1]; Lei Feng, MS[2]; Fredrick Hagemeister, MD[1]; Raphael Steiner, MD[1]; Hun Ju Lee, MD[1]; Luis Fayad, MD[1]; Loretta Nastoupil, MD[1]; Sairah Ahmed, MD[1]; Alma Rodriguez, MD[1]; Michelle Fanale, MD[1,3]; Felipe Samaniego, MD[1]; Swaminathan P. Iyer, MD[1]; Ranjit Nair, MD[1]; Yasuhiro Oki, MD[1]; Nathan Fowler, MD[1]; Michael Wang, MD[1]; Man Chun John Ma, PhD[1]; Francisco Vega, MD[4]; Timothy McDonnell, MD[4]; Chelsea Pinnix, MD, PhD[5]; Donna Griffith, RN[1]; Yang Lu, MD[6]; Sanjit Tewari, MD[6]; Ryan Sun, PhD[2]; David W. Scott, MBChB, PhD[7]; Christopher R. Flowers, MD[1]; Sattva Neelapu, MD[1]; and Michael R. Green, PhD[1,8]







Westin et al, JCO 2023

Smart Stop dosing

Lenalidomide

Tafasitamab

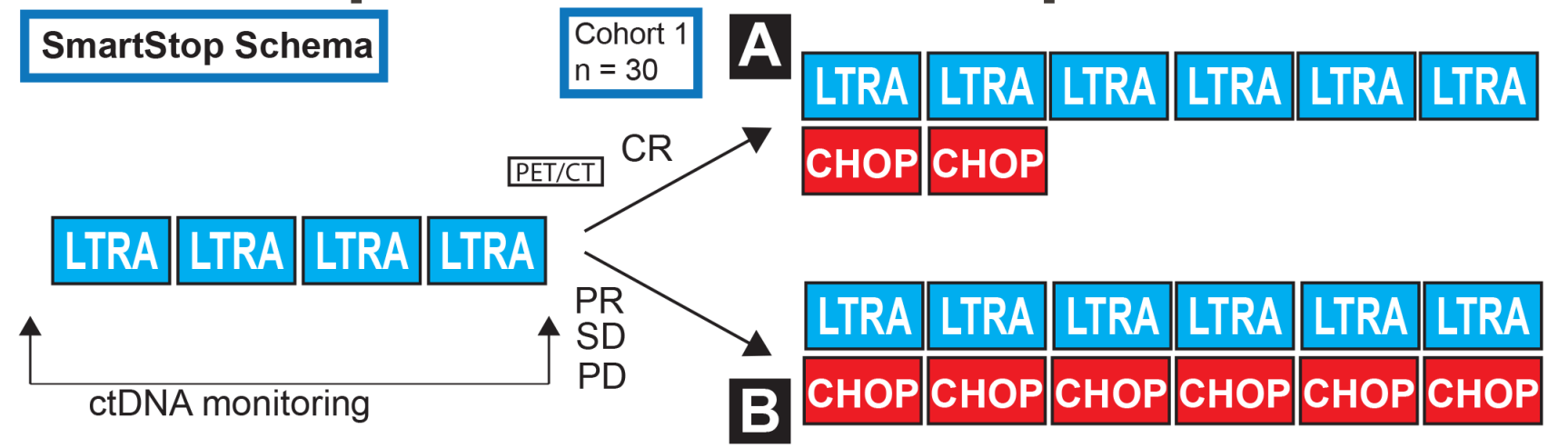
Rituximab

Acalabrutinib

LTRA

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

Smart Stop Schema and Endpoints



Phase II
Single center
Investigator Initiated
Open label

Primary Endpoints:
1A ORR after 4 LTRA
1B CRR at end of therapy

Data not presented at ASH 2023
Stay tuned for ASH 2025!

Smart Stop Eligibility

- 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

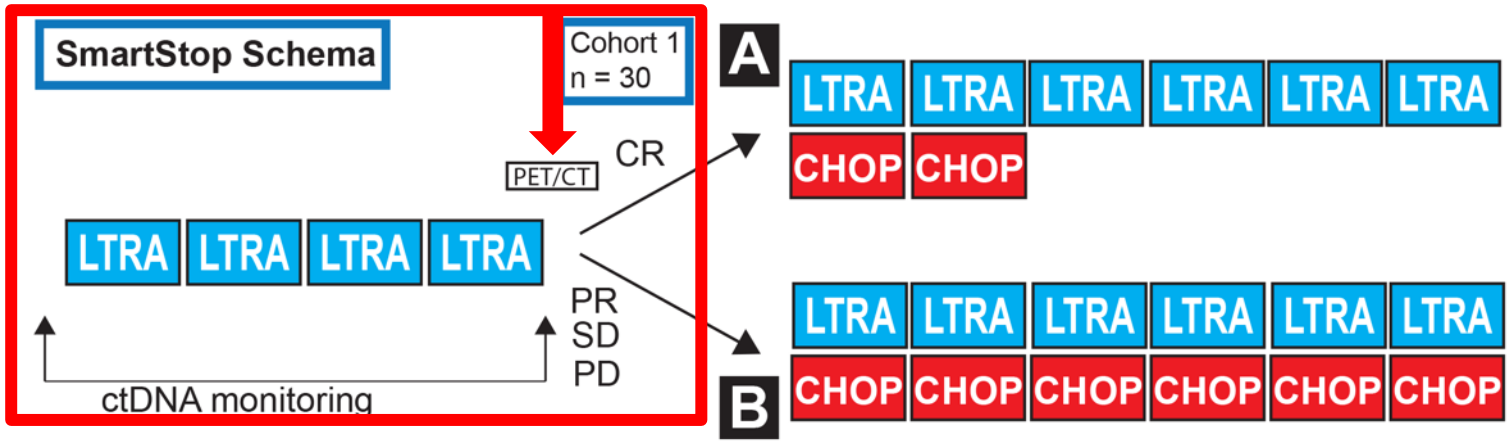
Patient demographics

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%)

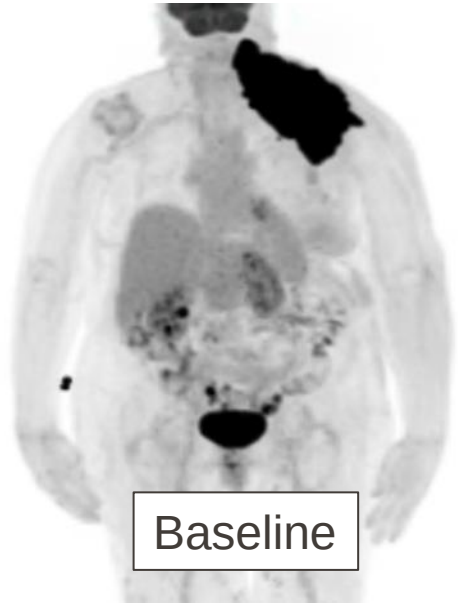
Results – after 4 cycles of LTRA



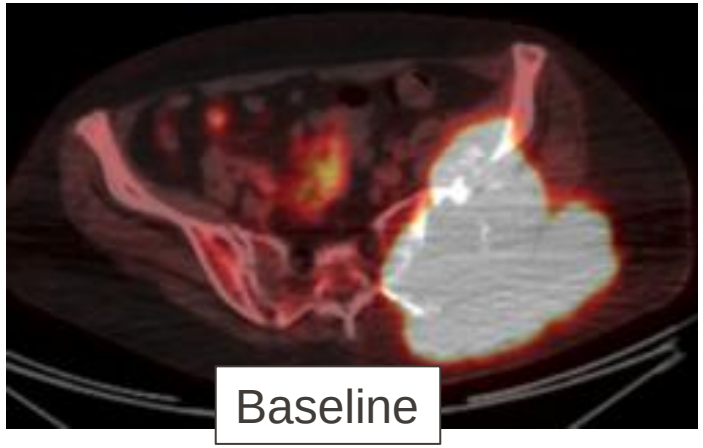
Primary Endpoint 1A: ORR after 4 LTRA is 100%

	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%).	

PR example 1

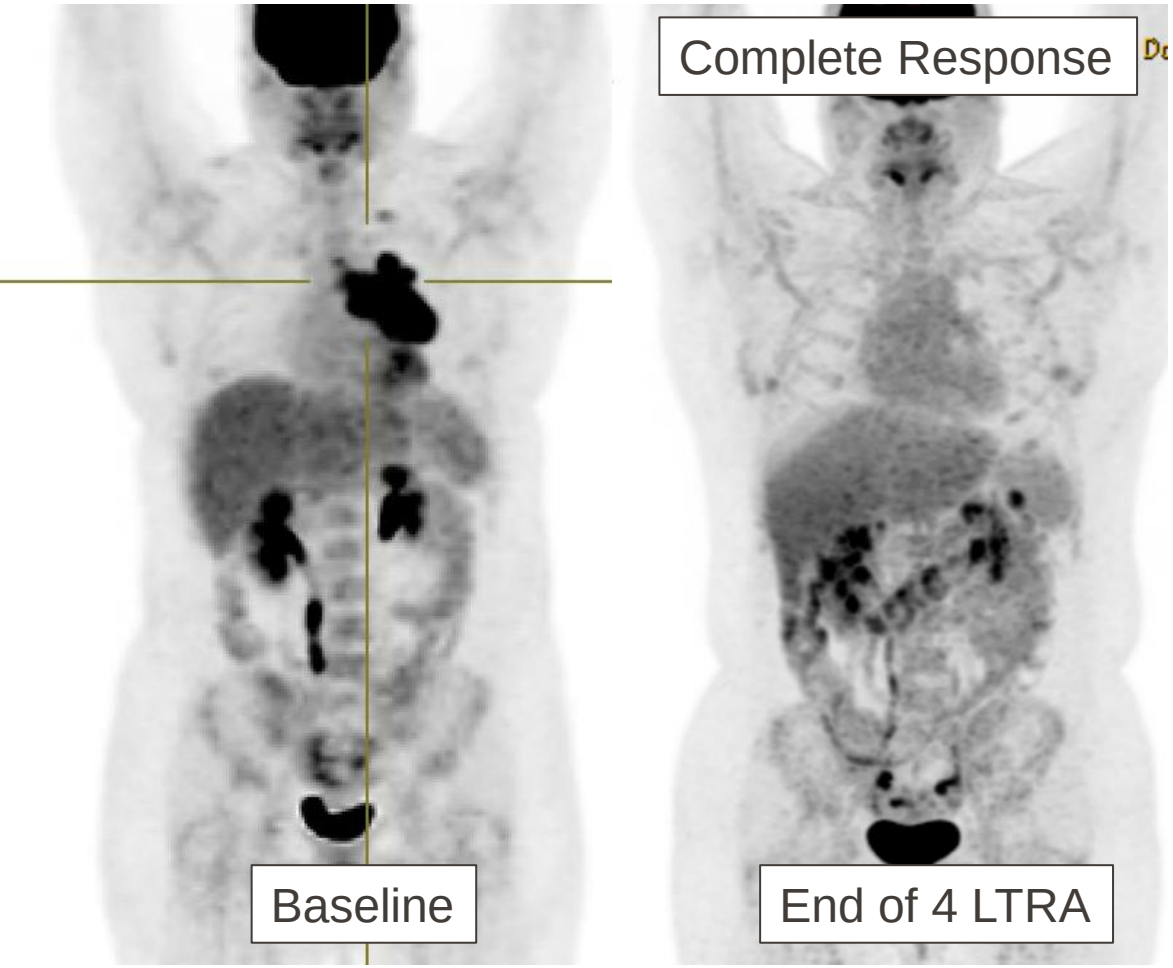


PR example 2

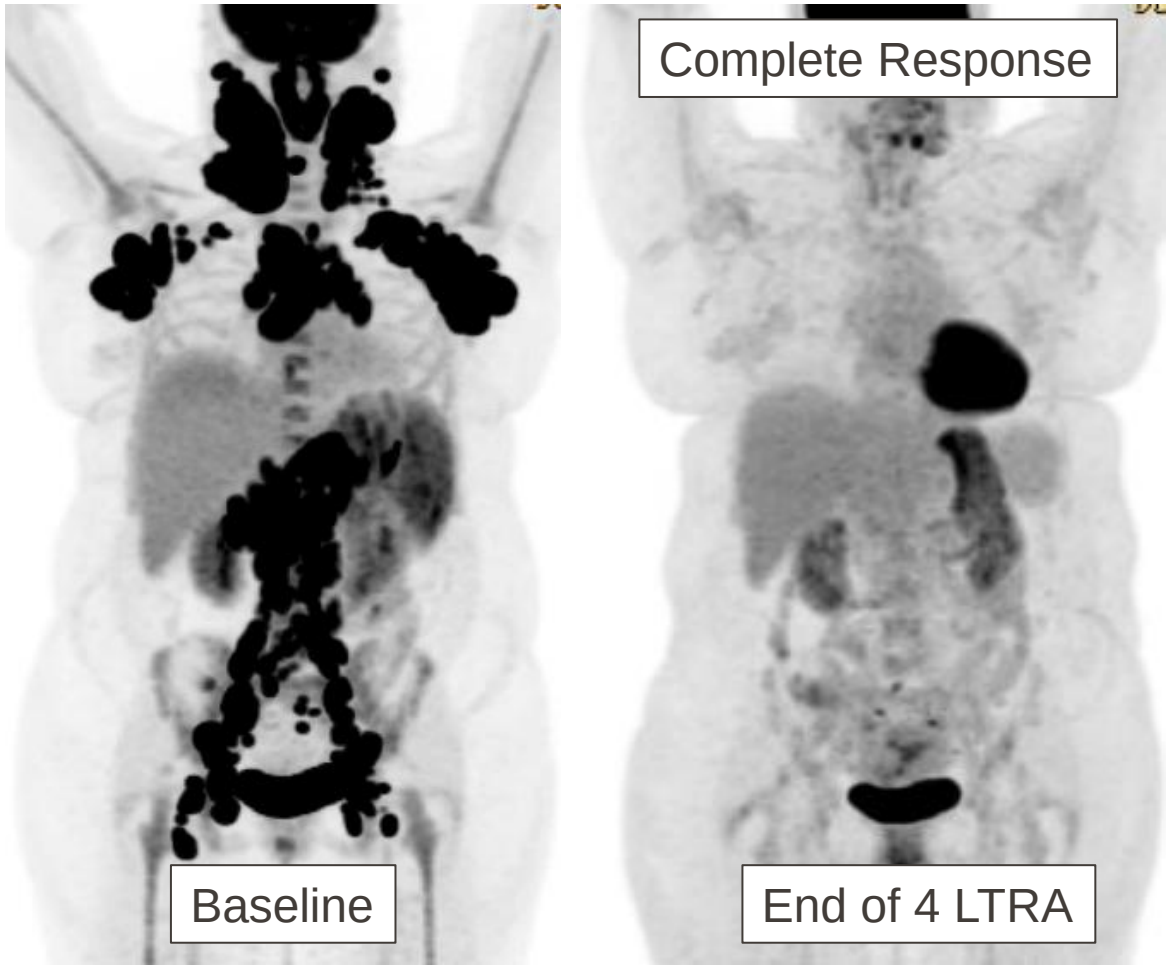


Results – after 4 cycles of LTRA: Complete Response

Example 1



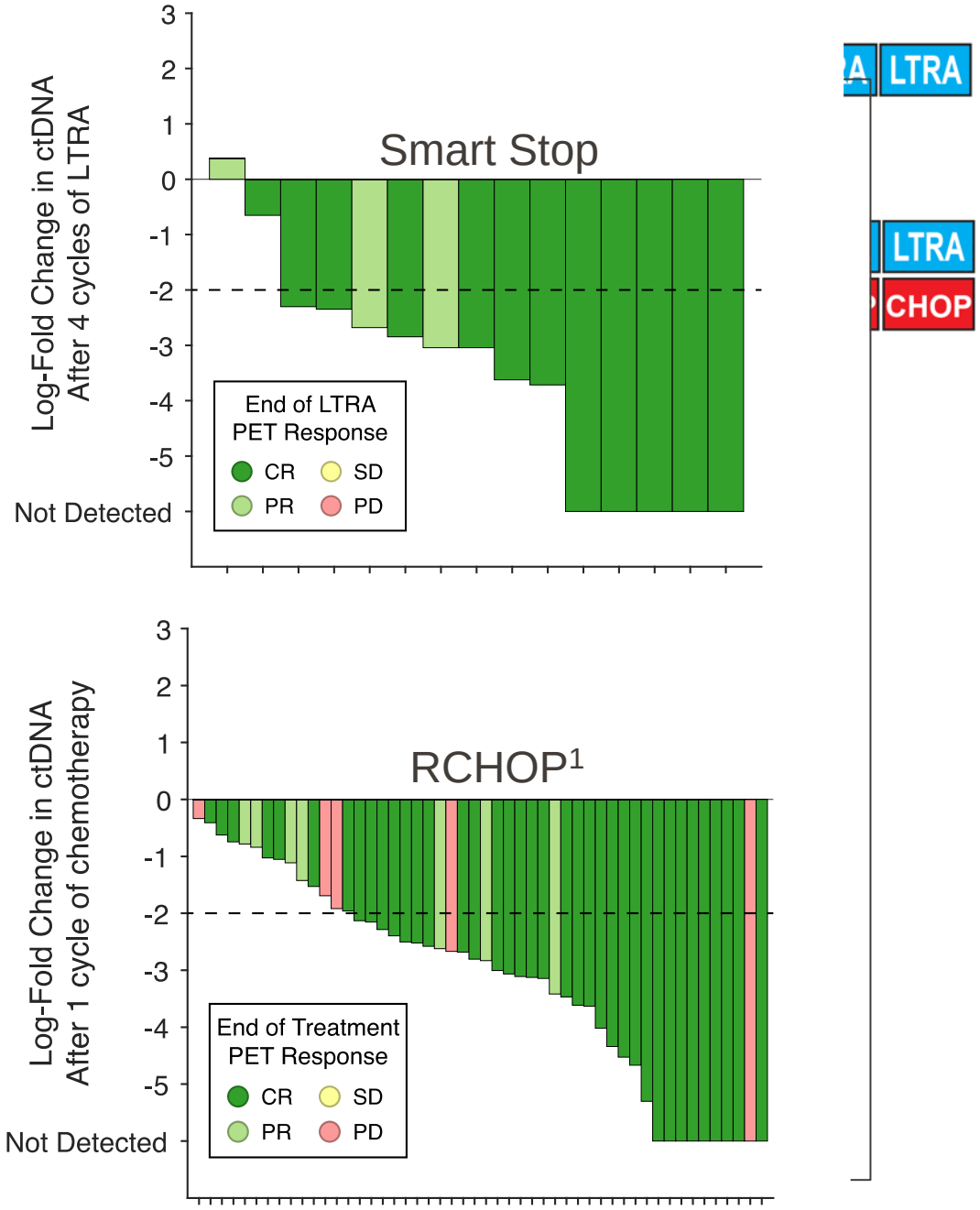
Example 2



Depth of response: ctDNA with PhasED-Seq

PhasED Seq Compare	LTRA (Westin ASH 2023)	CHOP (Roschewski ASH 2022)
Undetectable	33%	20%
Molecular Response	87%	72%

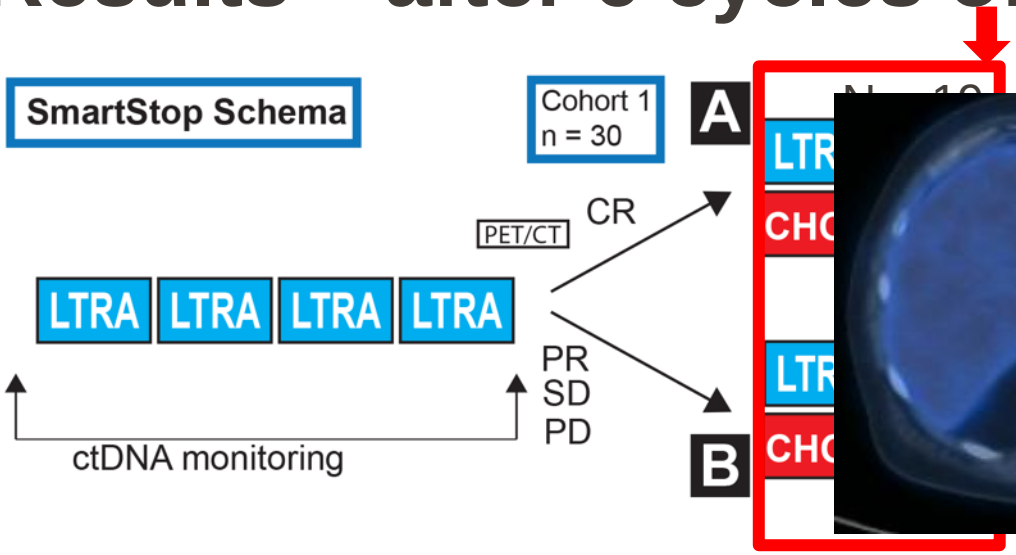
PhasED Seq Response	N=15
Undetectable	**5 (33%)**
>3 log-fold reduction	9 (60%)
>2 log-fold reduction	13 (87%)



1. Roschewski et al, ASH 2022

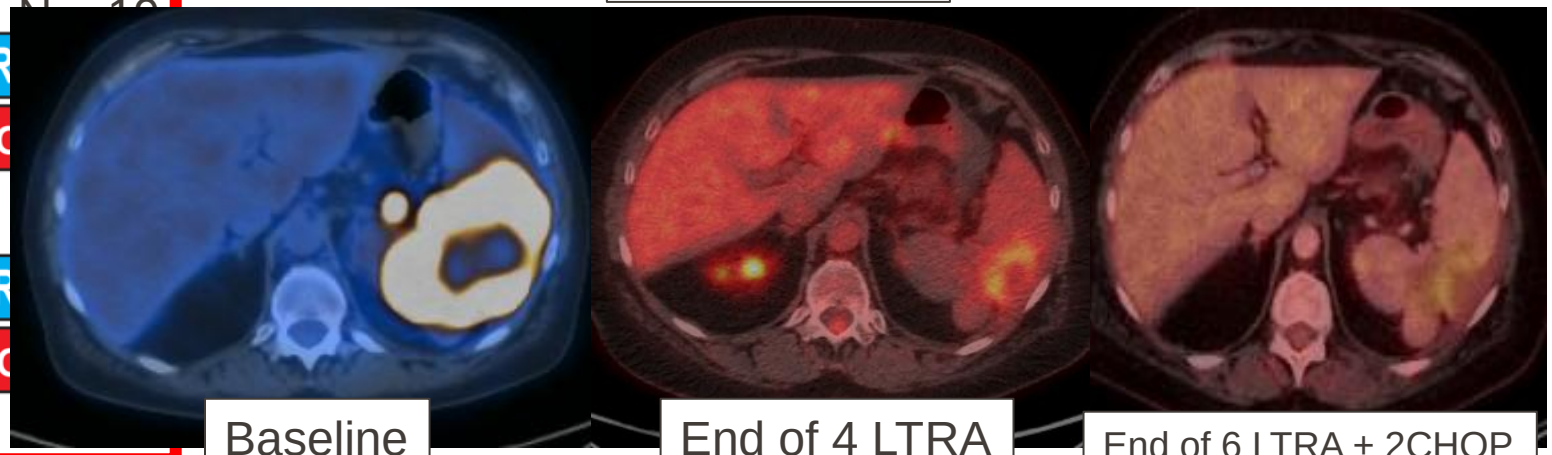
Analysis performed by Foresight Diagnostics, Aurora, CO

Results – after 6 cycles of LTRA and 2 cycles of CHOP



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

PR example 1



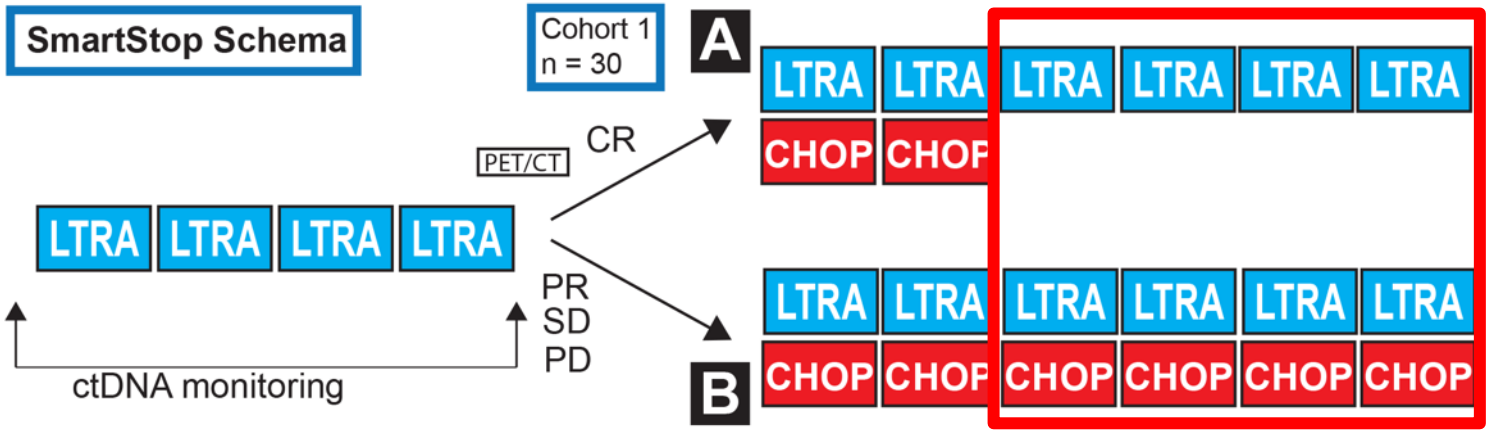
Baseline | End of 4 LTRA | End of 6 LTRA + 2CHOP

PR example 2

Baseline | End of 4 LTRA | End of 6 LTRA + 2CHOP

Results – end of treatment

Primary Endpoint 1B: CRR at EoT:



N = 30		Group A (2 CHOP, N=19)	Group B (6 CHOP, N=11)
CR	28 (93%)*	19 (100%)	9 (82%)*
PR	2*	0	2*
SD	0	0	0
PD	0	0	0

*FDG avid lesion biopsied with benign inflammatory response without lymphoma cells (n=1) and spleen lesion followed without progression for 1y+ (n+1)

To be updated at ASH 2025

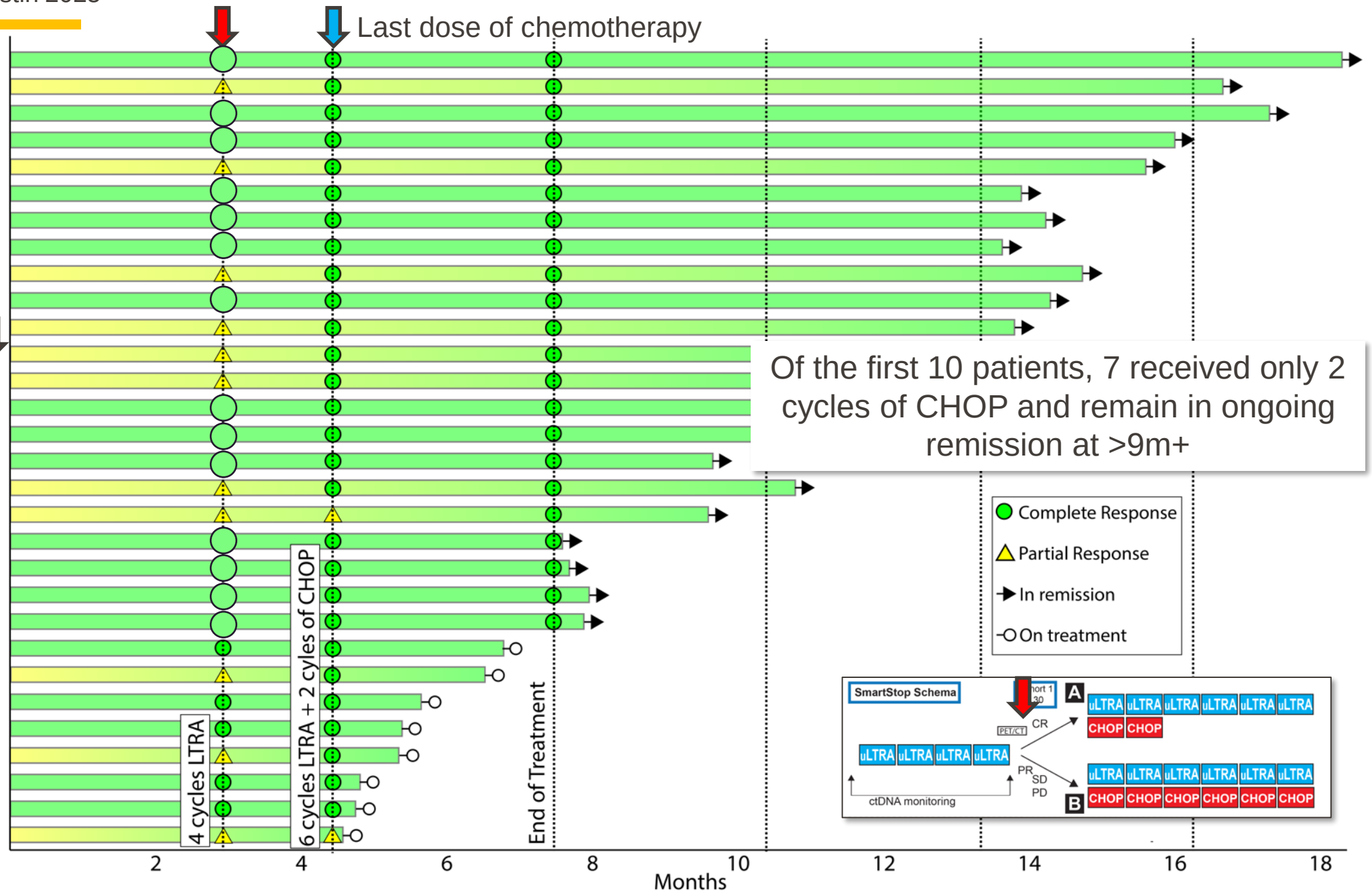
Results

After 4 LTRA cycles:

- 2 cycles of CHOP
- 6 cycles of CHOP

Last dose of chemotherapy

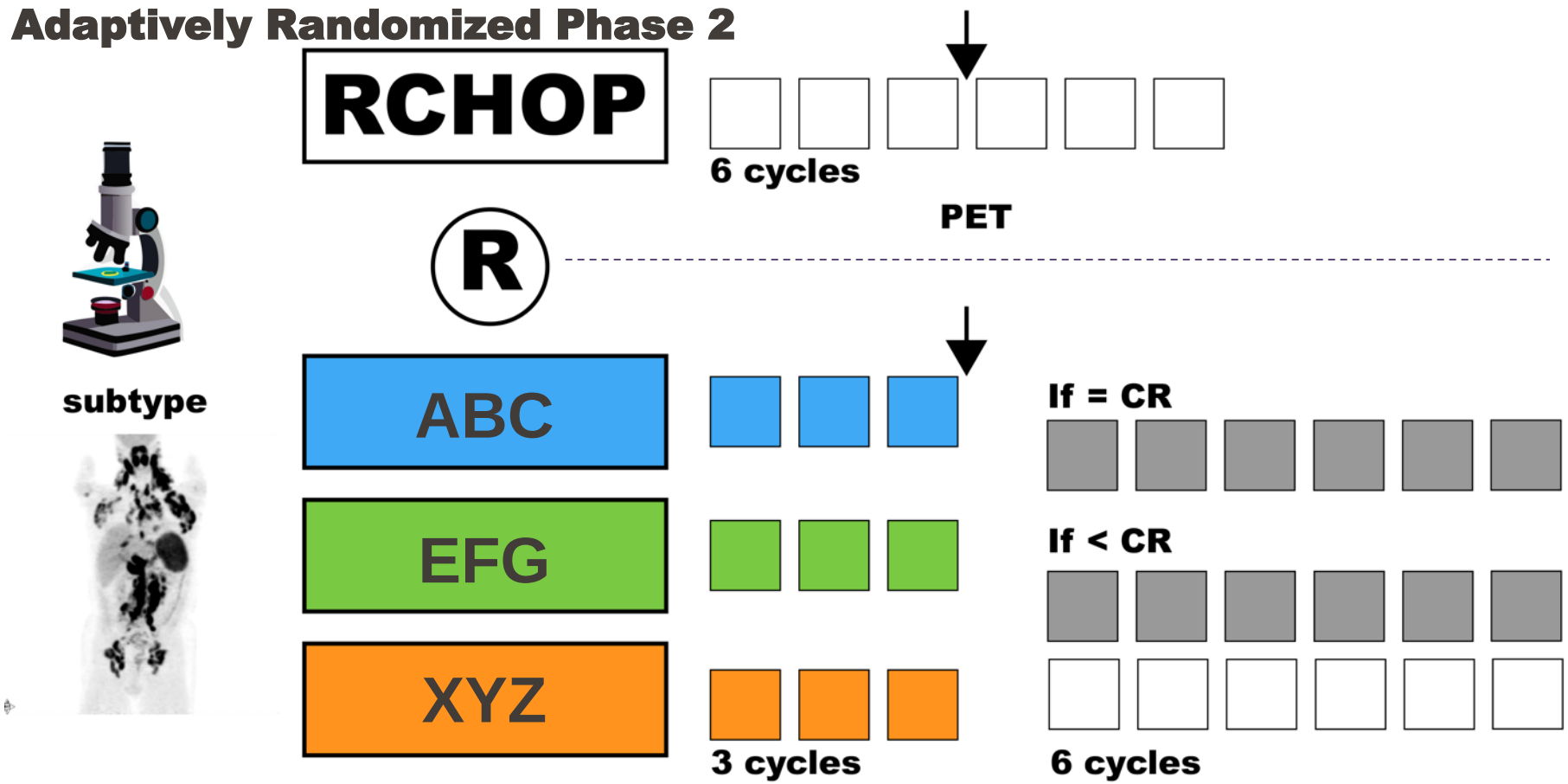
Of the first 10 patients, 7 received only 2 cycles of CHOP and remain in ongoing remission at >9m+



Conclusions

- CHOP is unlikely to be the optimal backbone
- Response adapted trials are feasible
- Novel combinations can allow for less or no chemotherapy
- Limited ctDNA data shows high molecular response, including undetectable in 1/3rd

- With therapy defined classifiers, we could run trials like:



Each subtype has an independent randomization weight started at 1:1:1:1 to each arm, or 25% per group
After 12 patients of a subtype enrolled, weights change based on CR at 3 cycles (e.g.,% of 15:25:25:35)
Continue to adapt until 60 patients/subtype enrolled (e.g., # treated of 7:15:15:23)

Winner for each subtype graduates to Phase 3 (if ethical)

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Thank you!