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Overcoming barriers to improve outcomes in lymphoma: some thoughts from my journey as a clinical translational physician

Andrew D. Zelenetz, M.D., Ph.D.

Attending Physician, Lymphoma Service

Professor of Medicine, Weill-Cornell Medical College

Chair, NCCN B-Cell Lymphoma Guideline Panel

Disclosures for Andrew D. Zelenetz, MD, PhD

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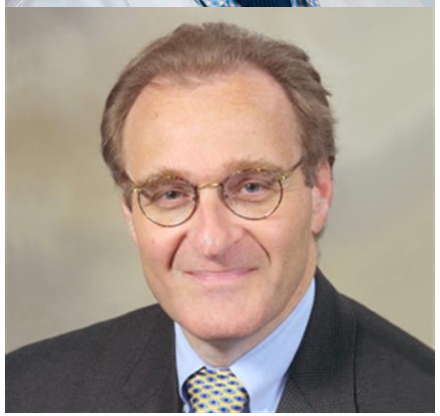

How can we improve outcome in lymphoma?

- Clinical trial design
- Role of MRD in trial design
- Are response kinetics better than end of treatment (EOT) undetectable minimal residual disease (uMRD)?
- Education, guidelines

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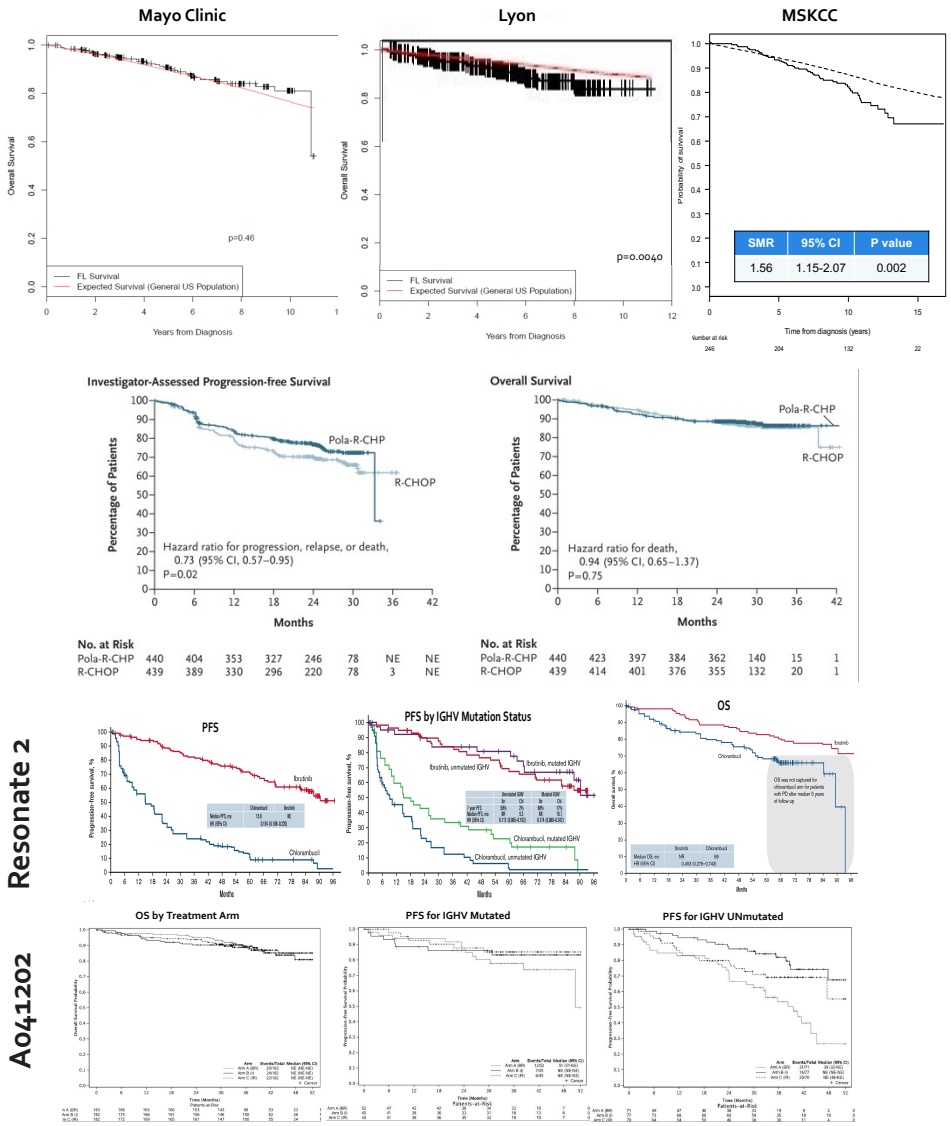
Improving Clinic Trial Design

Lymphoma clinical trial challenges

- We are victims of our own success
  - We may have achieved functional cure in FL
    - Chemoimmunotherapy results in PFS 5-10 year depending on antibody and use of maintenance with anti-CD20
    - Poses challenges to improve outcomes with less toxicity
  - Outcome with R-CHOP in DLBCL has been difficult to improve using R-CHOP + x; however, the excellent results inhibit development of novel regimens
- FDA requirements for a validated control can lead to trials that are not clinically relevant
  - Resonate 2 failed to demonstrate the efficacy of chemoimmunotherapy for IGHV mutated cases
  - Overstated the OS benefit compared to a trial with a relevant control (A041202)

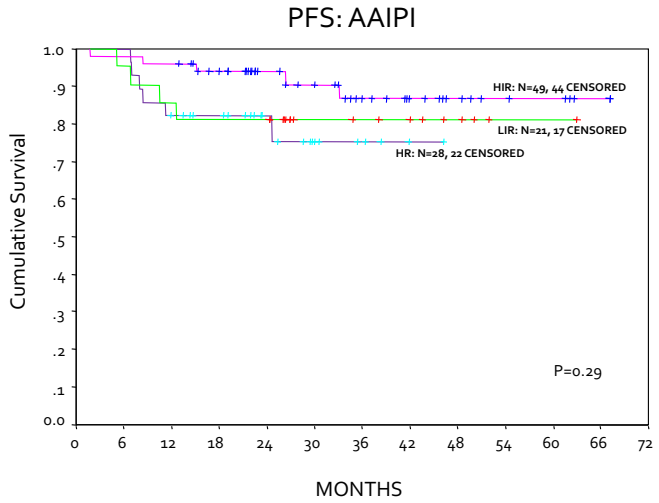


Mauer M et al, ASH 2014; Soumerai J et al. ASH 2016; Tilly et al. NEJM 2022 386:351-363; Barr et al. Blood Adv (2022) 6:3440–3450; Woyach et al. N Engl J Med (2018) 379:2517-2528

Lymphoma clinical trial challenges

- We lack robust measurable biomarkers to guide clinical trials
  - For example: ZUMA 23
    - **Hypothesis:** Early intervention with CAR T-cell therapy will be particularly beneficial for patient with high-risk aggressive lymphoma (DLBCL, HGBL, transformed FL or MZL [no prior anthracycline])
    - **Design:** Randomization to SOC versus axicabtagene ciloleucel after one cycle of R-CHOP
    - **High Risk Definition:** International Prognostic Index (IPI) score of 4 or 5 at initial diagnosis.
    - **Problem:** Conventional chemotherapy may overcome IPI

Sequential R-CHOP > ICE
AAIPI did not impact PFS



Westin et al. J Clin Oncol (2023) 41 (16_spuppl), abstract; Moskowitz et al. J Clin Oncol (2010) 28(11): 1896-1903

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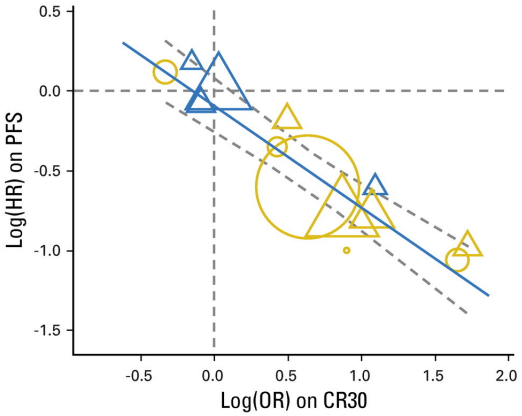
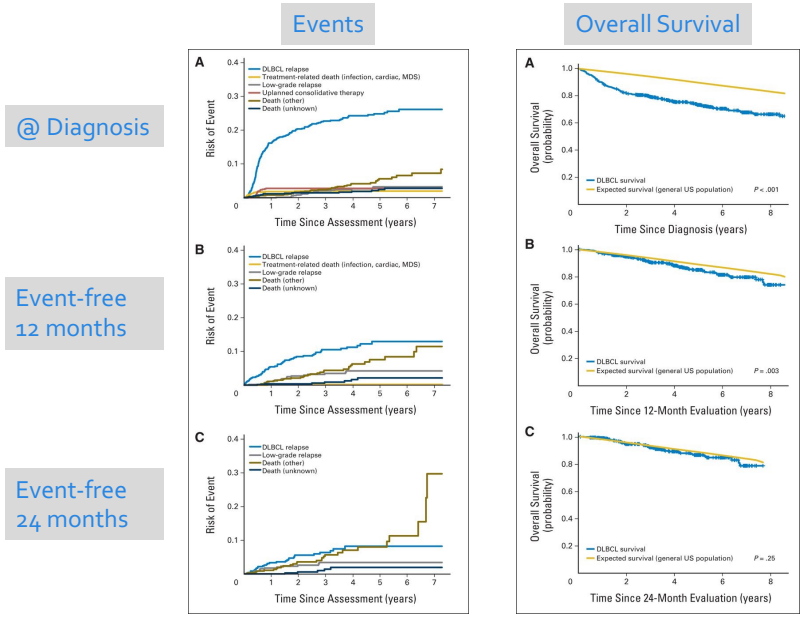
Lymphoma clinical trial challenges

- Clinical trials take too long, existing surrogates still require at least 2 years of follow-up
  - In FL, CR30 has been shown to be a robust surrogate for progression free survival



  - In DLBCL, EFS at 24 months is an excellent predictor of OS



Qian et al. J Clin Oncol (2016) 35(5): 552 - 560m; Maurer M J et al. J Clin Oncol 2014;32:1066-1073

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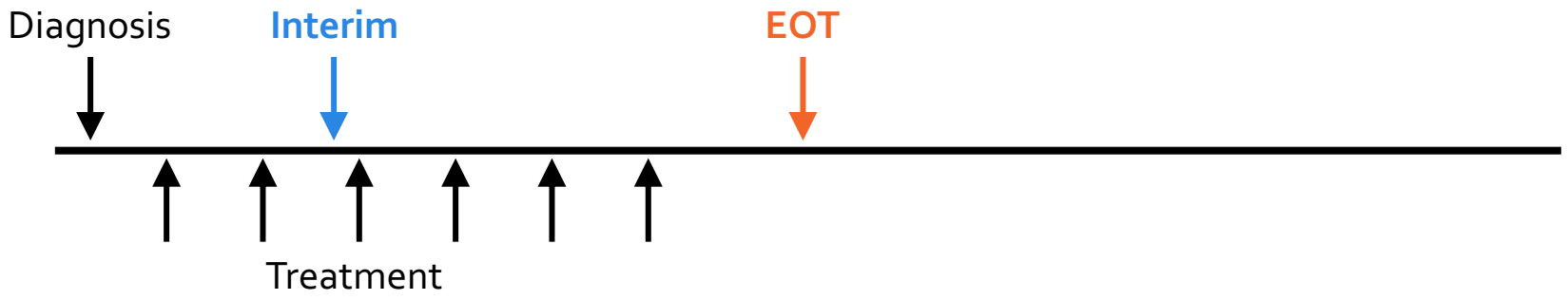
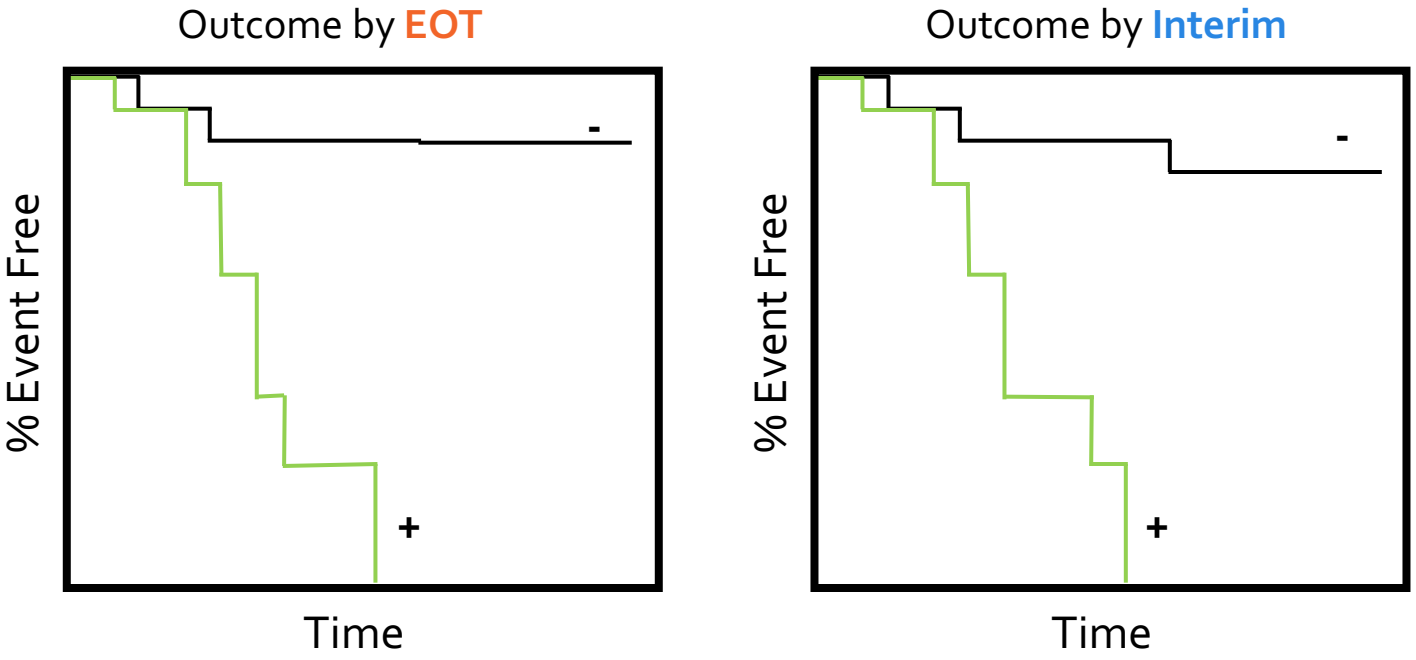
What is an optimal surrogate?

High PPV and NPV are key for a robust surrogate endpoint





- Reasonable conclusions:
  - **EOT** result provides strong prediction EFS (surrogacy)
  - **Interim** result has similar potential for surrogacy
  - Provides no information about impact of changing therapy after **Interim** versus **EOT**

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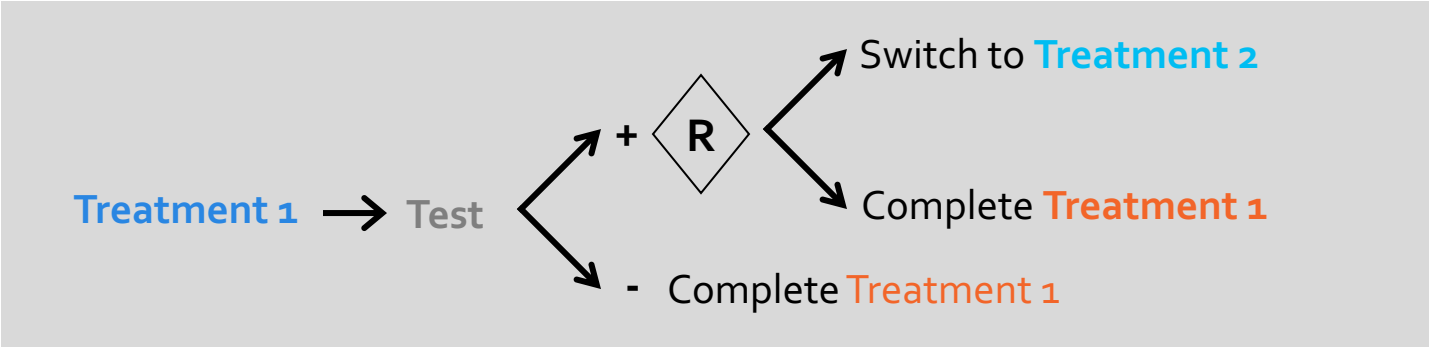
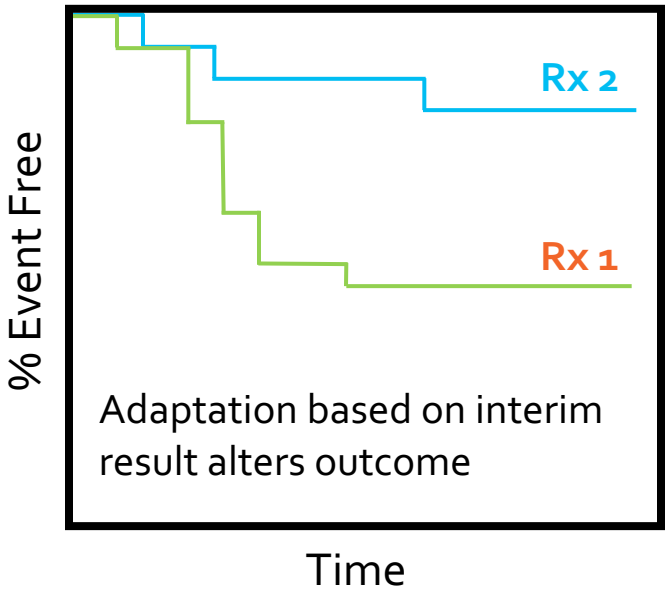
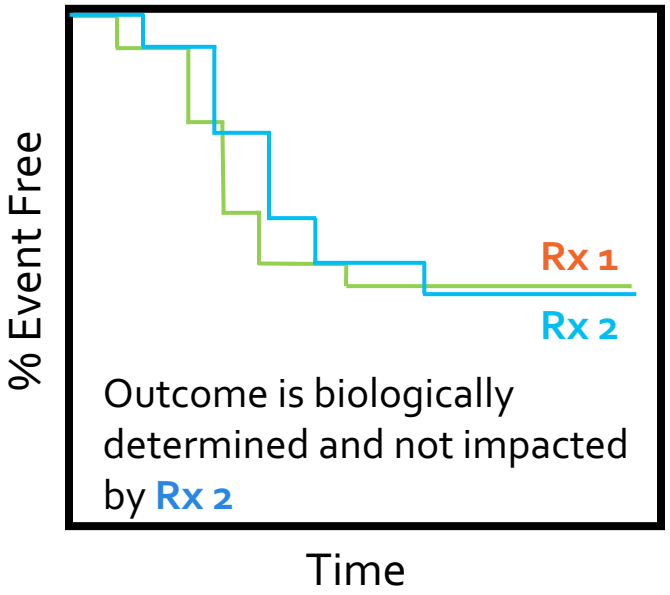
Value of interim testing: Proving an outcome benefit

Patients may/should be pre-selected based on known biomarkers; e.g. gene mutation or a molecular classifier to maximize treatment effect (and reduce sample size)



Outcome Following Randomization





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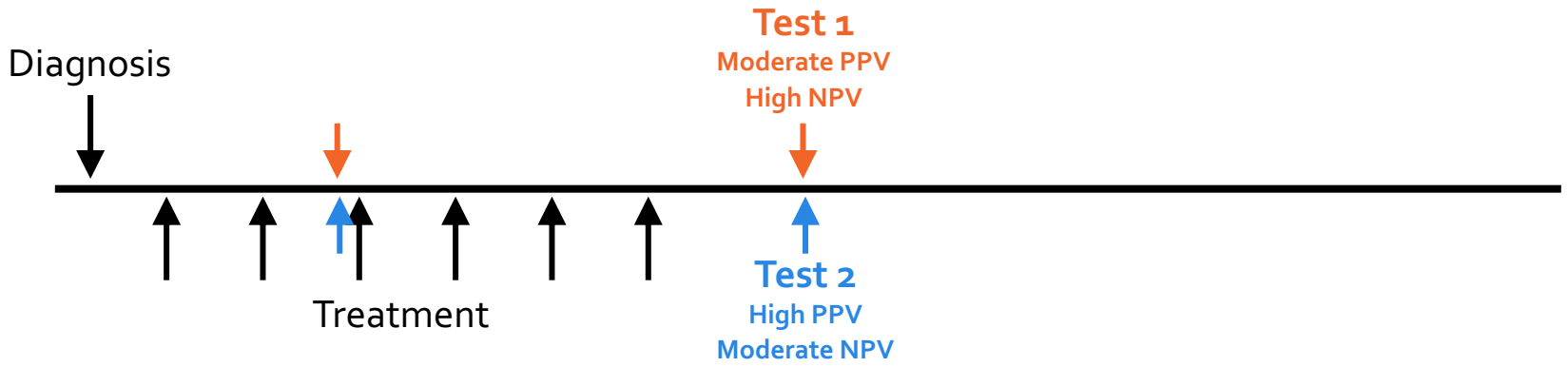
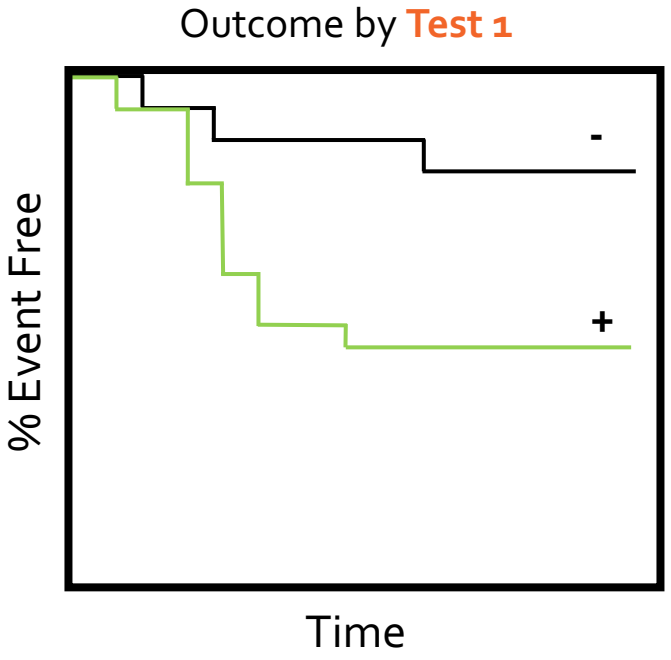
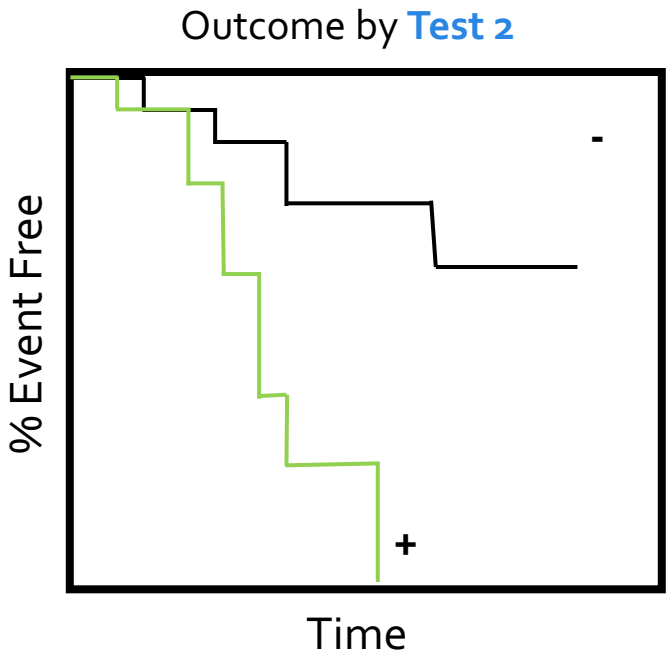
Testing characteristics can impact value of biomarkers







- Reasonable conclusions:
  - Prognostic value of Test 1 limited by false positive results
  - An alternative will treat a number of patients who are destined to do well
  - Prognostic value of Test 2 limited by false negative results
  - Cannot identify patients for an alternative treatment is

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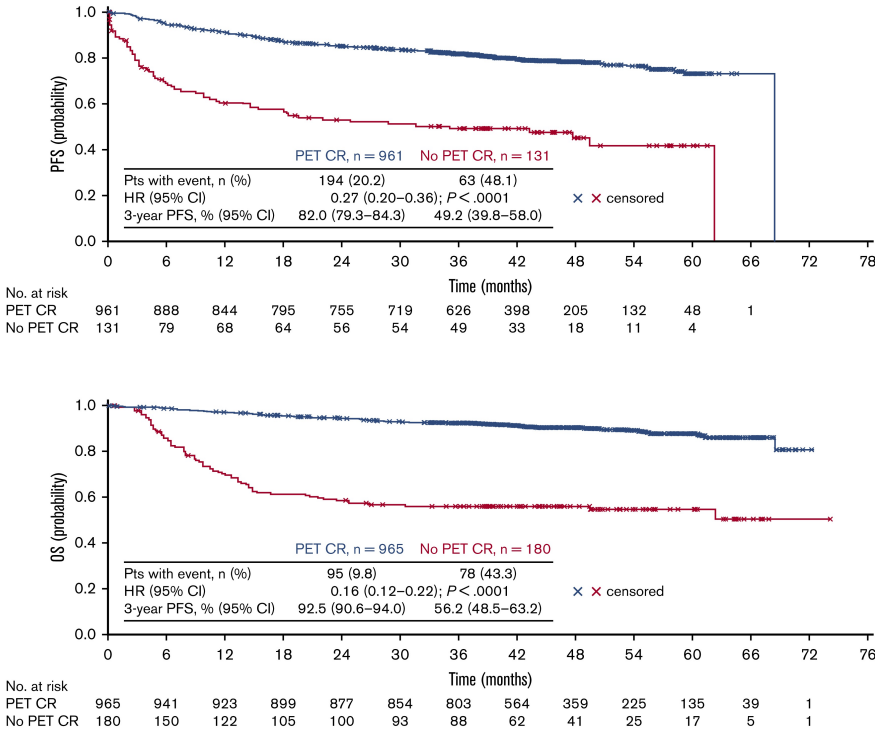
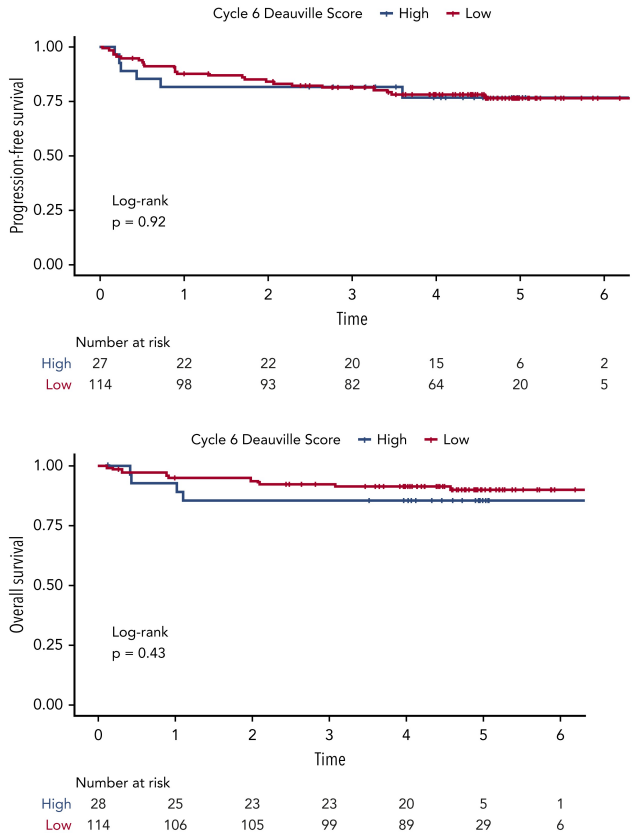
PET has been the standard for EOT evaluation despite variable results

GOYA EOT PET by 5-Point Score (1-3 negative)



Notably: More PFS and OS events among patients with EOT PET 5-PS 1-3

ALLIANCE 50303 EOT PET by 5-Point Score (1-3 negative)



Proposals to improve PET

- Incorporate metabolic tumor volume (MTV)
  - Potential pre-treatment variable
- Use of interim PET
  - ΔSUV
- Radiomics
  - Textural
  - Whole Body Geometry
- Alternative tracers
  - ^{18}Fl-Thymidine
  - ^{11}C-Methionine
  - ^{18}Fl-Fludarabine

Kostakoglu L et al. Blood Advances (2021) 5(5):1283-1290; Schöder H et al. Blood (2020) 135(25): 2224-2234; Tabaa et al. Cancers (Basel) (2021) 13(20): 522

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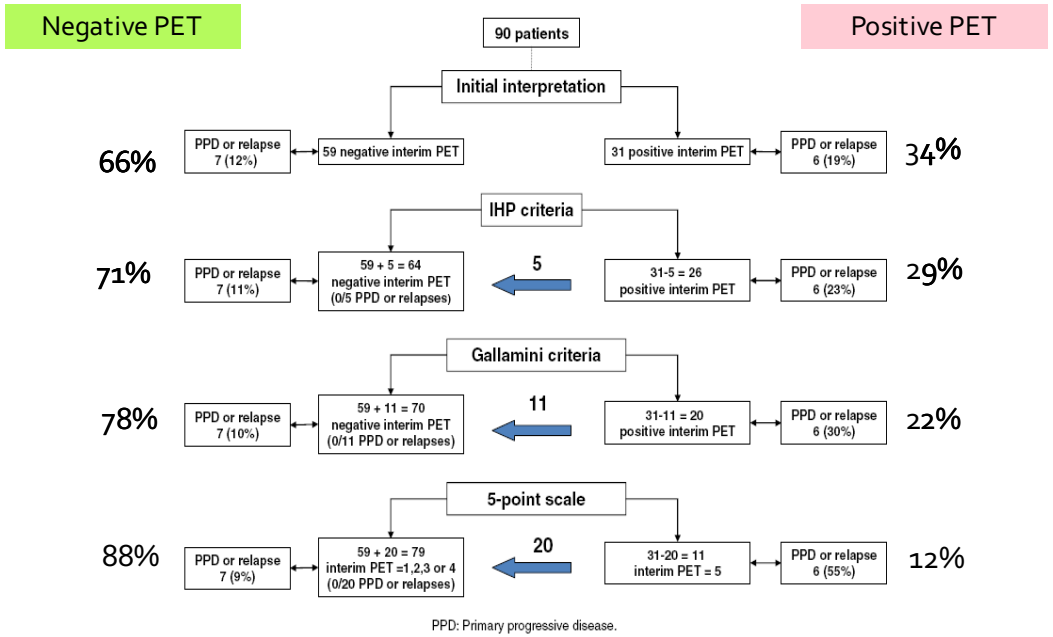
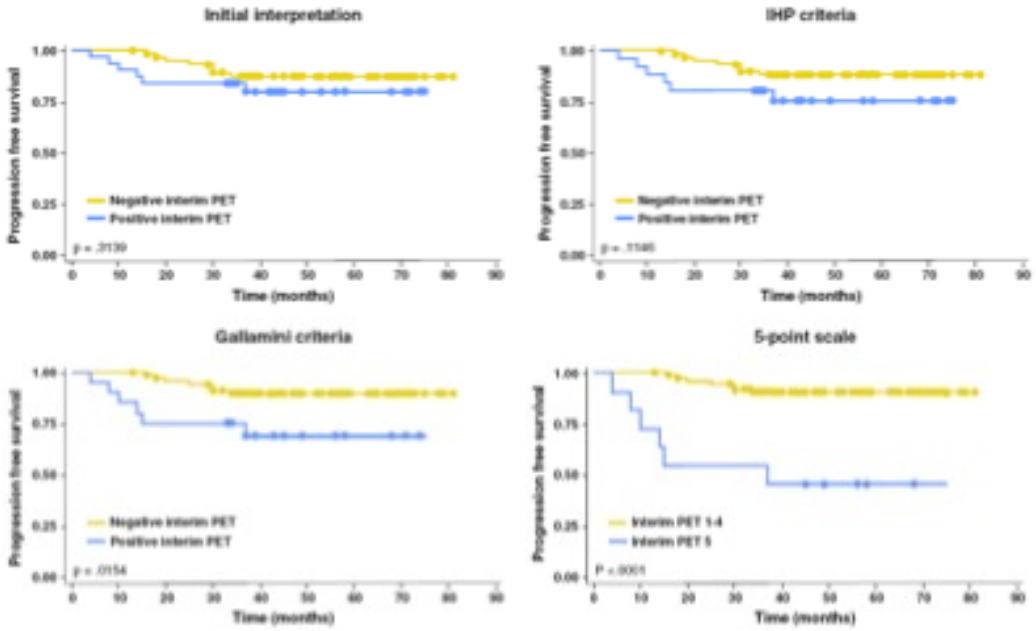
Predictive value of interim PET/CT varies according to the criteria used





- **Deauville Criteria**
  - Score 1 no uptake
  - Score 2 uptake ≤ mediastinum
  - Score 3 uptake > mediastinum but ≤ liver
  - Score 4 uptake > liver at any site
  - Score 5 uptake >> liver ± new sites of disease
  - Score X: new areas of uptake unlikely to be related to lymphoma

Le Roux PY Eur J Nucl Med Mol Imaging 2011; Meignan M et al. Leuk Lymphoma 2009;50:1753-6

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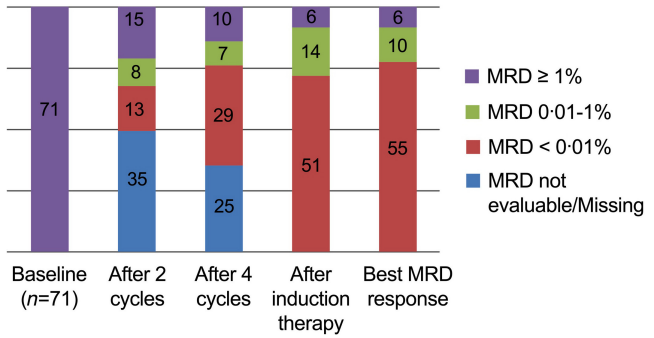
Can minimal residual disease testing be an outcome surrogate?

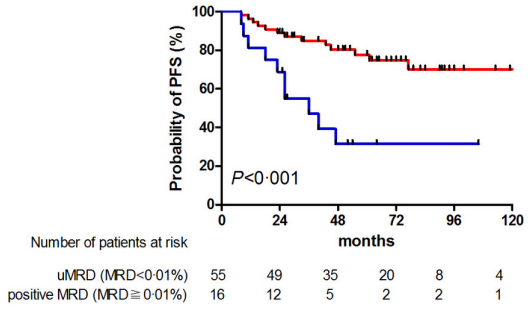
Method: Multiparameter Bone Marrow Flow; Sensitivity 10^{-4}

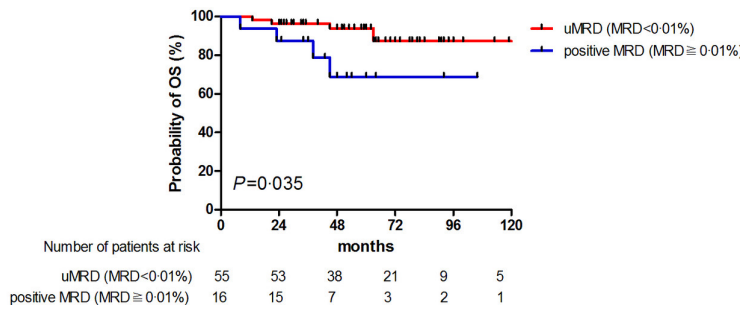
Investigator Treatment of Choice (n=71)

Rituximab monotherapy (n=6)	+MRD 33%
R-CHOP (n=55)	+ MRD21.8%
FCR (n=10)	+ MRD 20%
→Maintenance R (2-year) (n=31)	

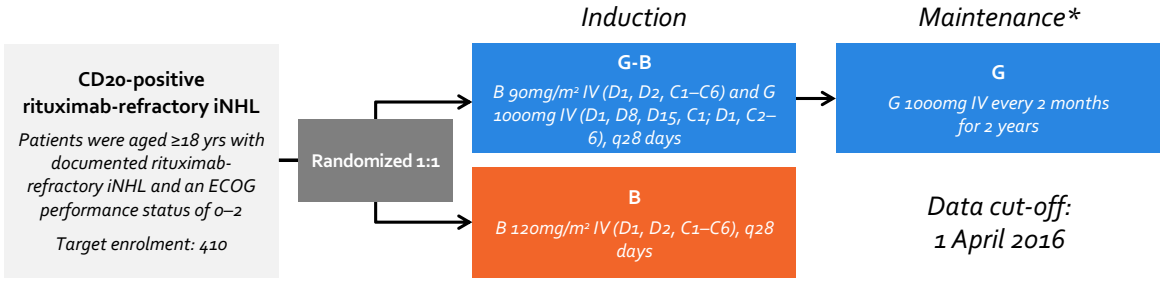
Bone marrow multiparameter flow every 6 months

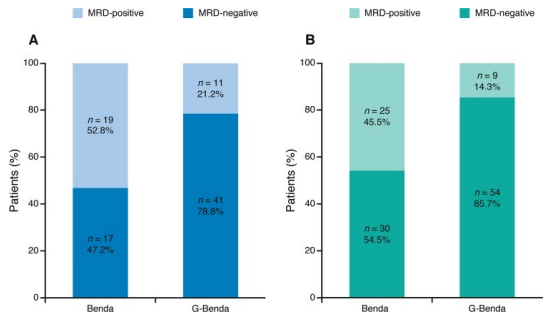


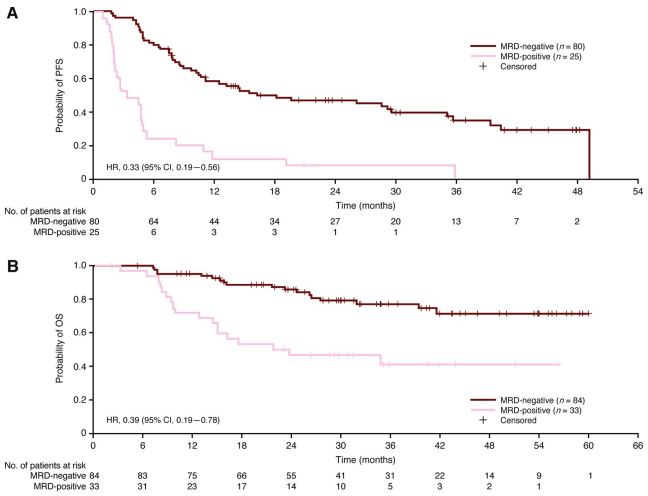




Method: Real-time quantitative PCR for IGHV and/or IGH/BCL2; Sensitivity 10^{-4}







Lyu et al. Brit J Haematol (2021) https://doi.org/10.1111/bjh.17703; Pott et al. Leuk (2020) 34:522-532

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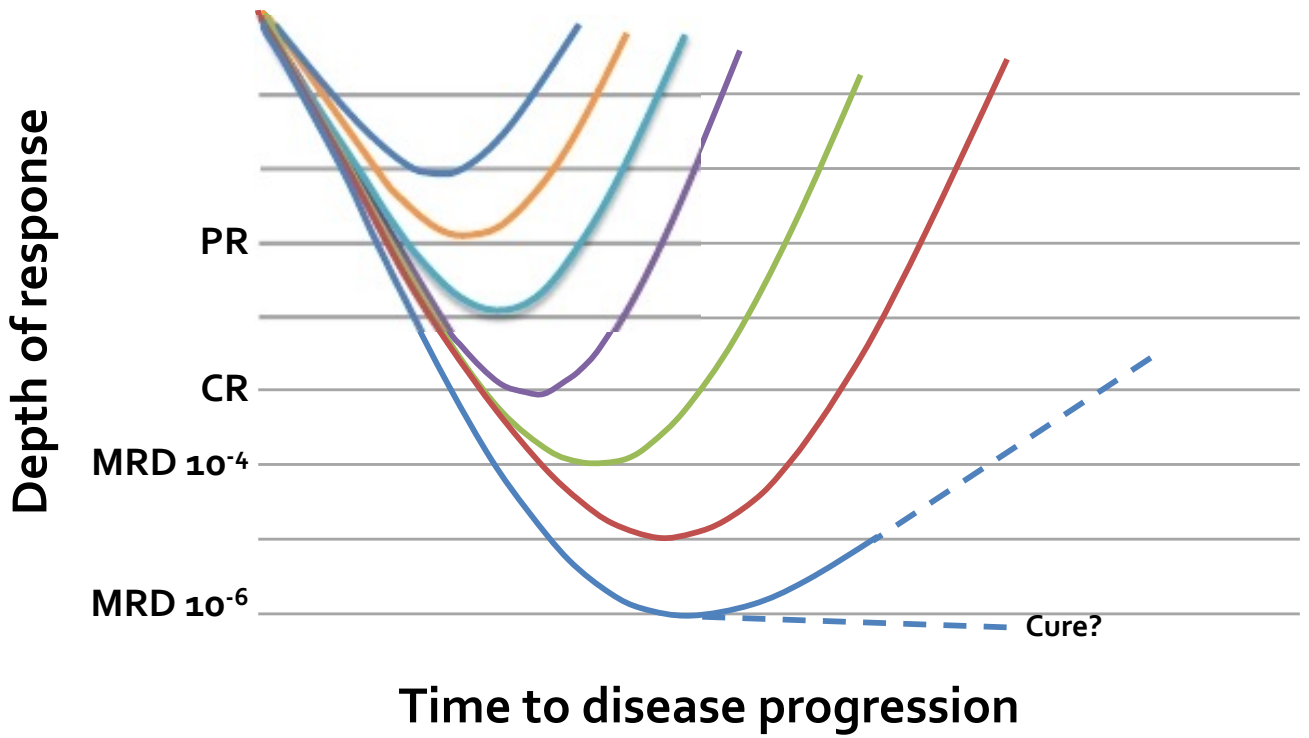
A guide to minimal residual disease

What is Minimal Residual Disease (MRD)?

- Persistence (or re-emergence) of detectable tumor cells
- Definition of MRD is a moving target
  - Efficacy of therapy is a major determinant of residual tumor burden
  - Sensitivity of MRD testing is limited depending on the method
  - Response kinetics may improve the dynamic range of MRD testing



Why measure MRD?

- Measurement of treatment efficacy (**clinical utility** and **research**)
  - Potentially superior to conventional measurements of efficacy such as imaging
  - Enable comparison of regimen (when control for other variables)

- Predicts outcome (**clinical utility**)
  - Surrogate for time to event outcomes

- Ideally a tool for clinical decision making (**clinical utility** and **research**)
  - Response adapted therapy

- Definition of good/risk versus poor risk patients (**research**)
  - Identify biomarkers for response
  - Identify new targets for therapy

Methods for determining MRD

- **Crude (~10^{-1})**
  - PE
- **Insensitive (~10^{-2}-10^{-3})**
  - CT imaging
  - MRI imaging
  - PET imaging
- **Sensitive (potentially has clinical application) (~10^{-4})**
  - Multi-parameter flow cytometry (PB or BM)
  - CAPP-Seq
- **Highly sensitive (~10^{-5}-10^{-6})**
  - PCR digital droplet (10^{-5})
  - Linked Somatic Variant (LSV) (10^{-5})
  - PhasED-seq (10^{-6})
  - Immunosequencing (10^{-6})

Undetectable Minimal Residual Disease (uMRD)

- The threshold of MRD is based on the test being used.
  - For example, in CLL
    - Multiparameter flow has a sensitivity of 1 cell in 10,000
    - Immunosequencing can detected 1 cell in 1,000,000 (with adequate input DNA)
  - A sample with 50 cells per 1,000,000 would be "negative" on flow and positive by immunosequencing

- Best to call a "negative" result ***undetectable***

- **Proposal for MRD nomenclature**
  - Use undetectable (u) and detectable (d) when reporting result
  - Include the limit of detection
    - Flow, with a LOD of ~1 in 10,000, if undetected would be uMRD4
    - PhasED-seq, with a LOD of ~1 in 1,000,000, if undetected would be uMRD6

DNA-based methods for detection of MRD

Method	Sensitivity	Target	Pros	Cons
PCR, qualitative	10^{-5}	IGH, IGH/BCL2, IGH/CCND1, TCR	Sensitive Standardized	Not quantitative, targeting translocation may limit application
PCR, quantitative	10^{-4}-10^{-5}	IGH, IGH/BCL2, IGH/CCND1, TCR	Quantitative Sensitive Standardized	Requires standard reference
PCR, digital droplet	10^{-5}	IGH, IGH/BCL2, IGH/CCND1, TCR, MYD88 L265P, BRAF	Quantitative Sensitive Applicable to mutations	Not standardized
Immunosequencing	10^{-6}	IGL, IGK, IGH, TCRB, TCRG	Standardized Highly sensitive	Stereotyped variable gene usage may limit assay
CAPP-Seq*	10^{-4}-10^{-5}	Panel of mutations	Monitor clonal evolution	Limited sensitivity for MRD
PV-Seq**/LSV***	10^{-5}-10^{-6}	Mutations clustered within ~1400 bp	High sensitivity	Need to identify clustered mutations, limits loci that will be informative

*CAncer Personalized Profiling by deep Sequencing; **Phase Variant Sequencing; ***Linked somatic variants

Modified from Galimberti et al. Front Oncol https://doi.org/10.3389/fonc.2019.00528; Kurtz et al. Blood (2019) 134:552

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Tumor Reservoirs

Cellular

Site	Diseases	Comment
Peripheral Blood	SLL/CLL; SMZL; MCL; HCL	Easily accessible, collection in CPT tubes
Bone Marrow	SLL/CLL; SMZL; MCL; HCL; FL	Invasive
Residual tumor site	All nodal NHL	Invasive, subject to sampling error

Cell Free

Site	Disease	Comment
Circulating tumor DNA (ctDNA)	Potentially all NHL	Possible differential sensitivity based on the disease; sample collection needs to be optimized*

*Literature supports use of Streck BCT, PAXgene cfDNA, RochecfDNA, CellSave, or Blood Exo DNAProTeck tube
Cell free DNA analysis highly dependent on pre-analytical and analytical workflows

Greytak et al Clin Canc Res DOI: 10.1158/1078-0432.CCR-19-3015

Discordance between detection of MCL in cellular versus cell-free fraction

- KEY ELIGIBILITY CRITERIA
  - Histologically confirmed MCL
  - Clinical stage 2 with abdominal involvement or stage 3 - 4
  - Ages 18-70, KPS ≥ 70%
  - Transplant eligible with adequate organ function

R-CHOP-14 x 4 cycles

PET/CT

CR/PR

SD/PD

Off study

R-HIDAC x 2 cycles

PET/CT*

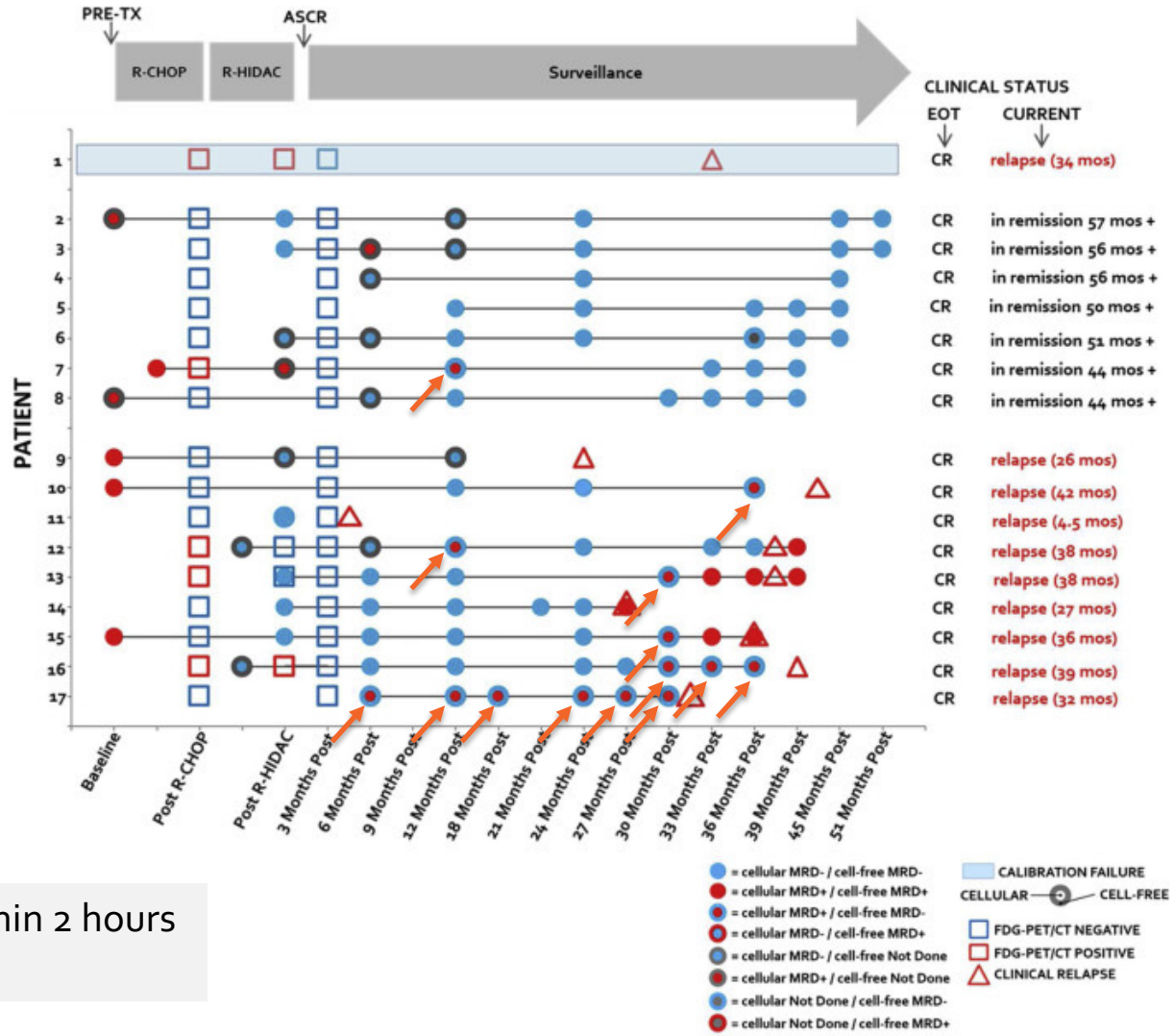
CR/PR

SD/PD

Off study

Iodine ^{131}I – Tositumomab/BEAM/ASCR

*Only if FDG-PET/CT positive after R-CHOP



cfDNA was collect in EDTA tubes and processed generally within 2 hours
MRD was analyzed by immunosequencing (Adaptive Biotech)

Kumar et al. Clin Lymph Myeloma & Leuk (2021) 21:230-237

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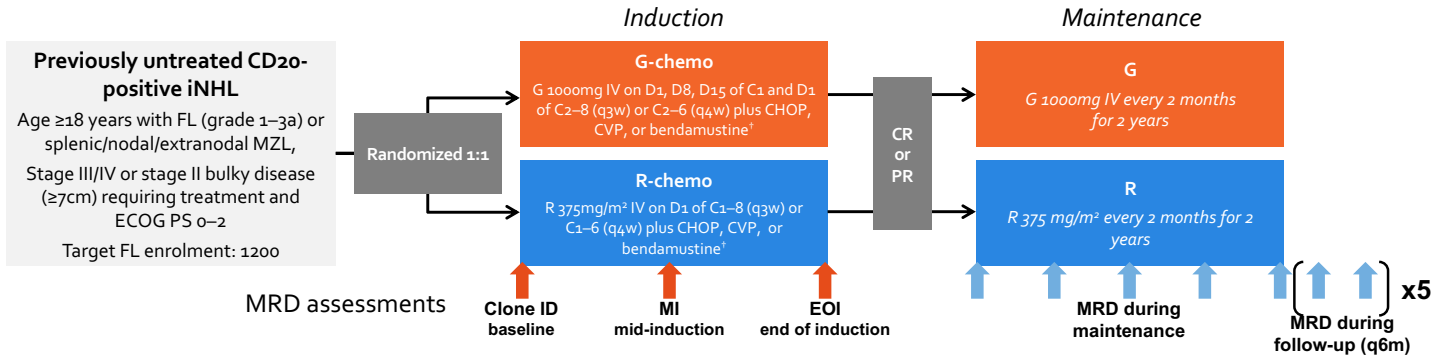
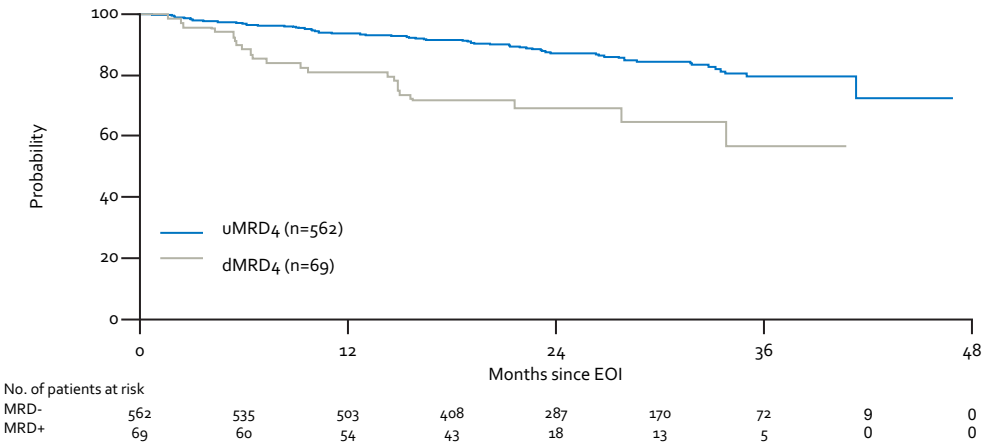
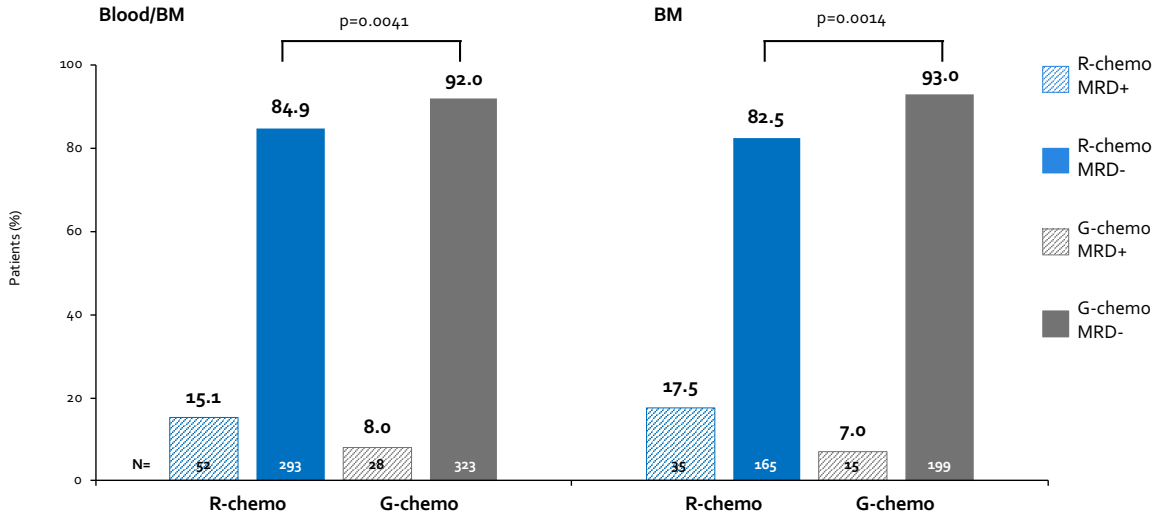
Clinical application of MRD testing

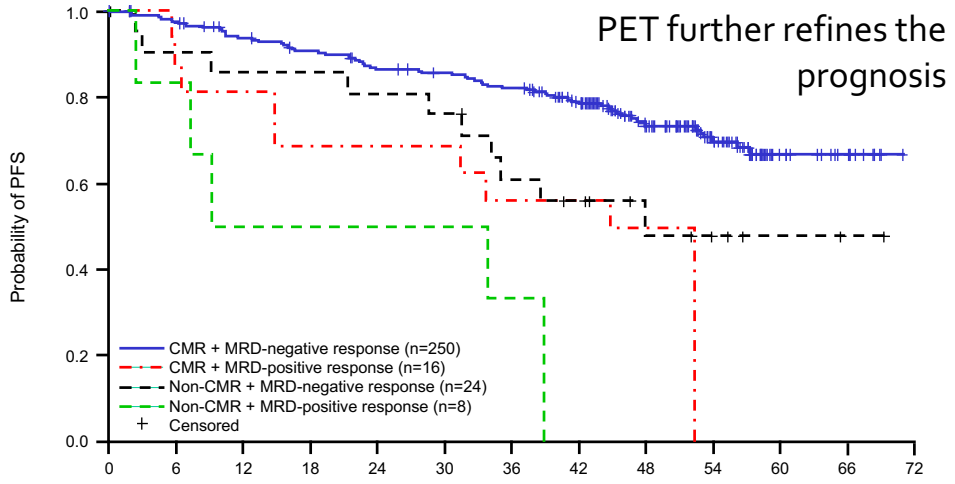
MRD in the GALLIUM study

Method: Real-time quantitative PCR for IGHV and/or IGH/BCL2; Sensitivity 10^{-4}



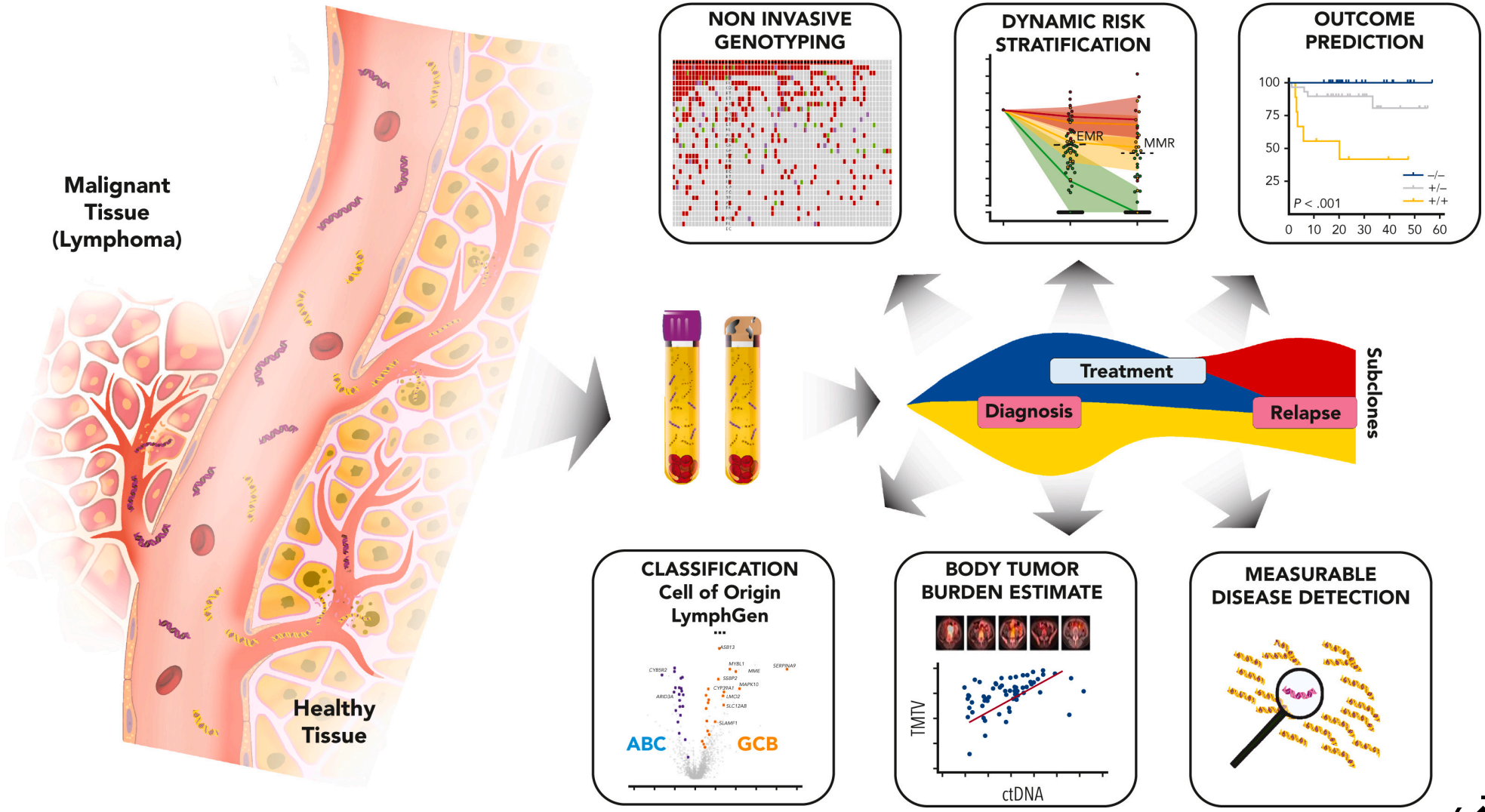






Pott et al. Blood (2016) 128:613; Trotman et al. ASCO 2018

Applications of circulating tumor DNA (ctDNA) in lymphoma



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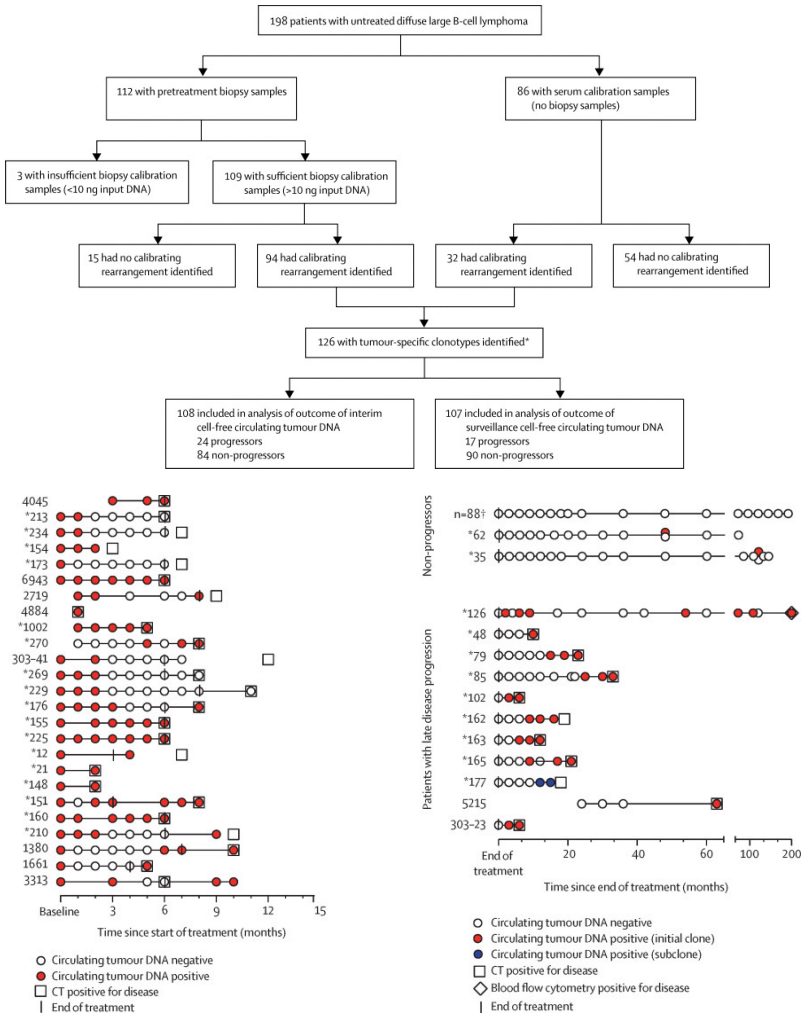
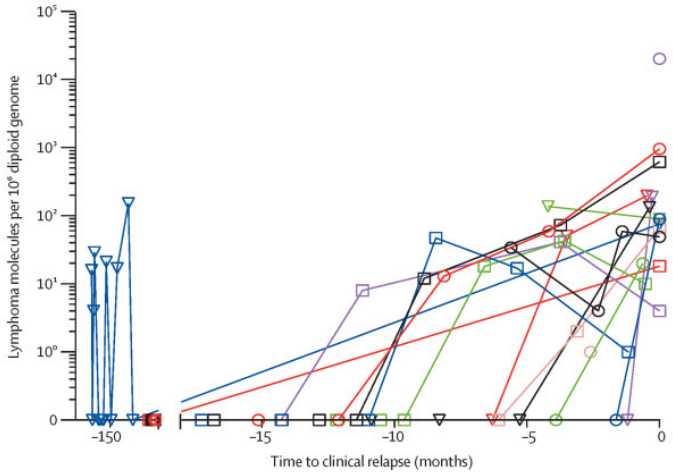
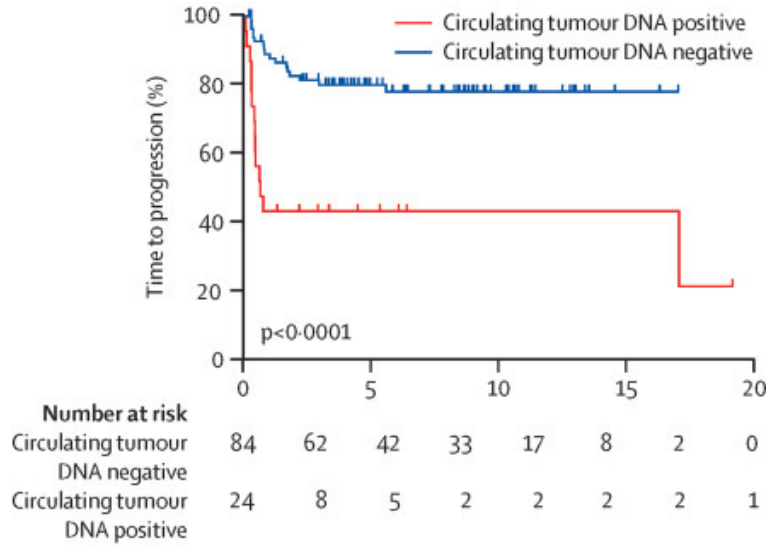
DLBCL: Retrospective analysis of ctDNA

Method: Immunosequencing (Adaptive Biotech); Sensitivity 10^{-6}







Roschewski, et al. Lancet Oncol (2015) 15: 541-549

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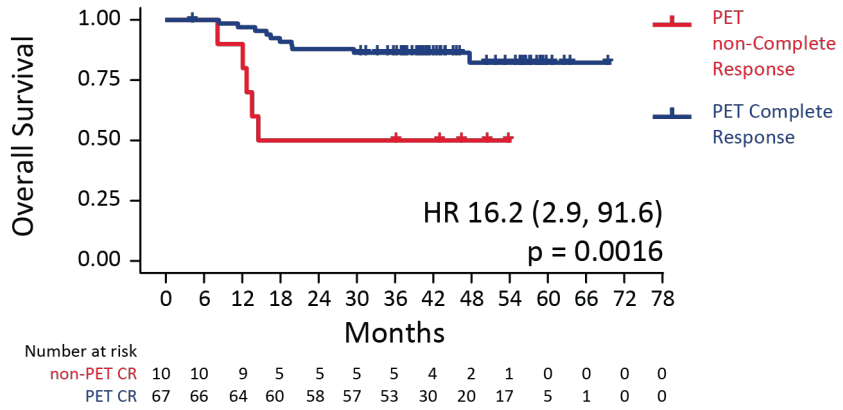
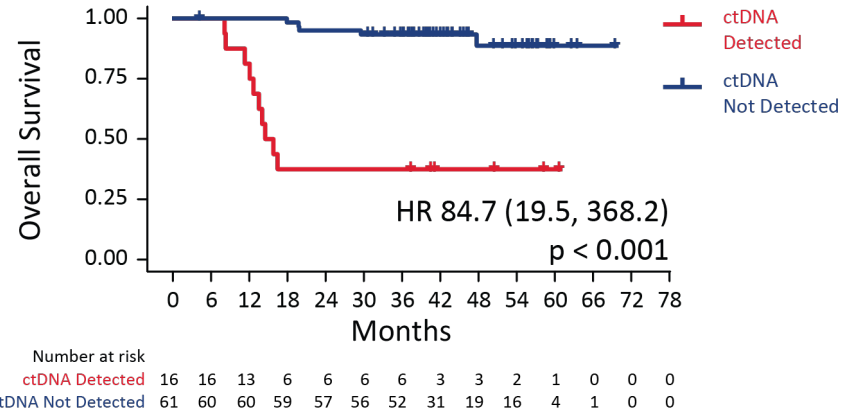
Prospective evaluation of ctDNA with PhasED-seq versus PET

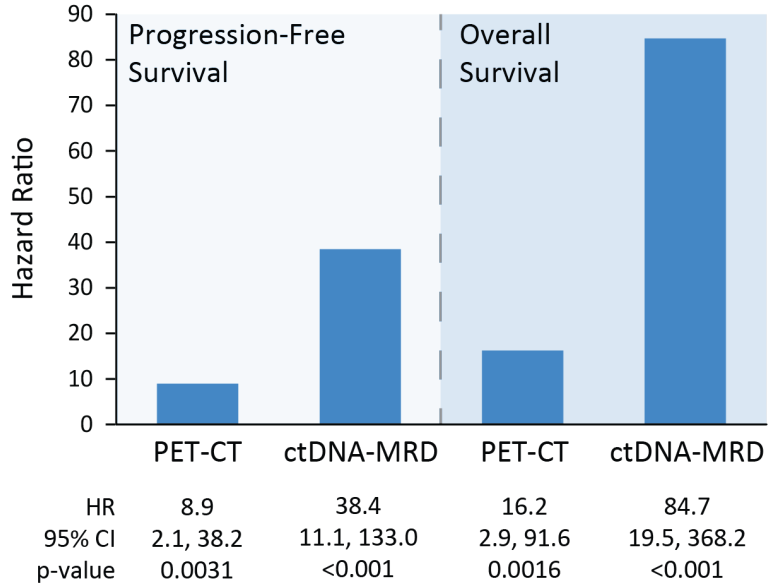
OS Stratified by 1L EOT PET or ctDNA





ctDNA better stratified both PFS and OS versus PET

	PET-CT		ctDNA-MRD	
	Positive non-CR	**Negative** CR	**Positive** ctDNA detected	**Negative** ctDNA not detected
PFS at 24 mos	40%	74%	25%	82%
OS at 24 mos	50%	86%	38%	93%



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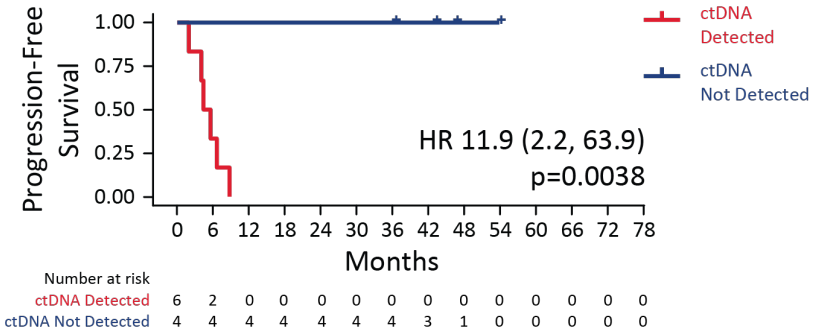
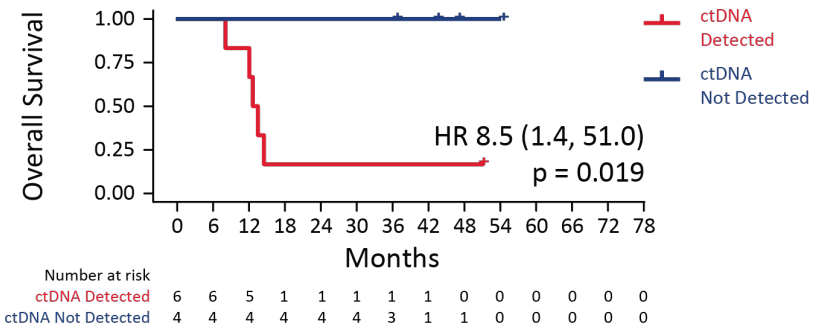
Sworder et al, ASH 2023, Abstract 192

Prospective evaluation of ctDNA versus PET

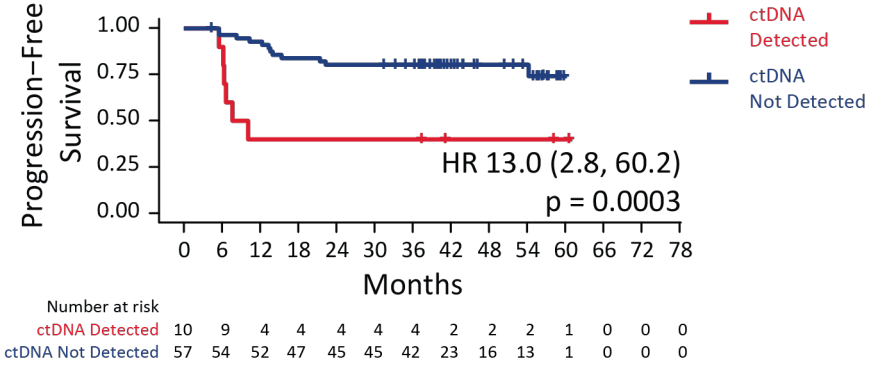
ctDNA Stratifies PET Positive Patients

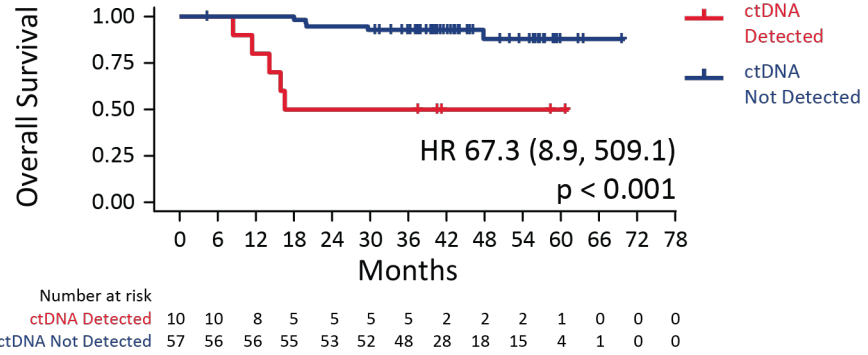




	MRD Positive ctDNA detected	MRD Negative ctDNA not detected
PFS at 24 mos	0%	100%
OS at 24 mos	17%	100%

ctDNA Stratifies PET Negative Patients





	MRD Positive ctDNA detected	MRD Negative ctDNA not detected
PFS at 24 mos	**40%**	80%
OS at 24 mos	50%	93%

Sworder et al, ASH 2023, Abstract 192

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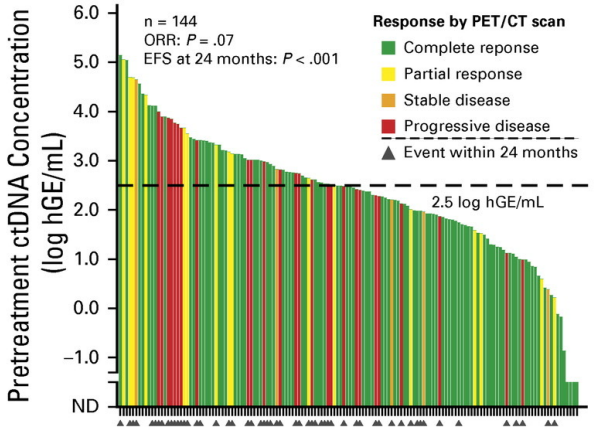
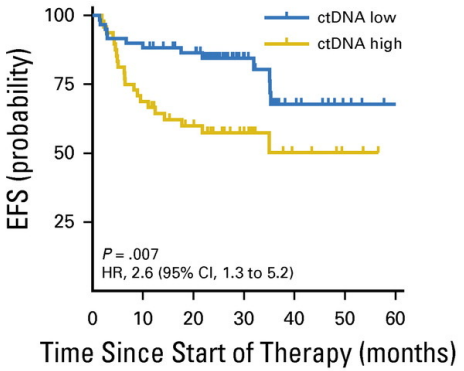
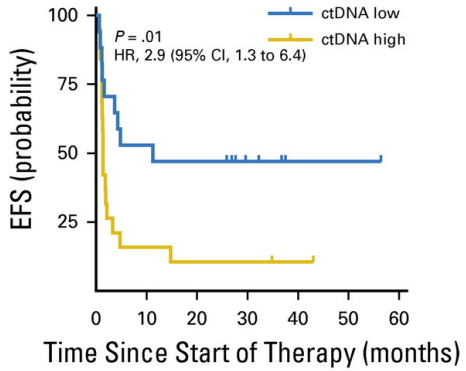
Response kinetics may extend dynamic range of MRD testing

DLBCL: Pre-treatment ctDNA and molecular response (MR) by CAP-Seq Predicts outcome

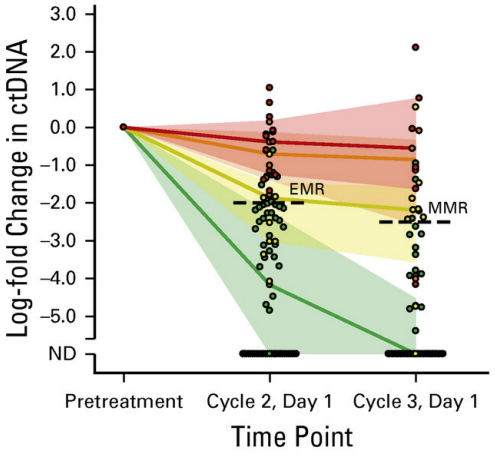
Method: CAncer Personalized Profiling by deep Sequencing (CAPP-Seq); Sensitivity 10^{-4}





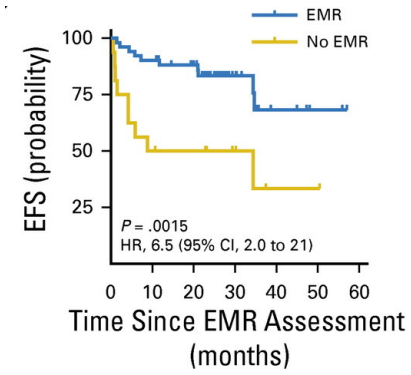


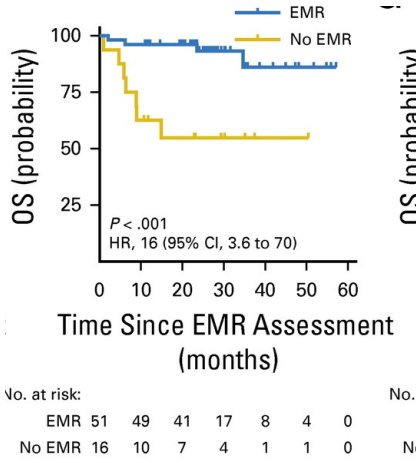
Correspondence of PET response to Early Molecular Response (EMR) and Major Molecular Response (MMR)



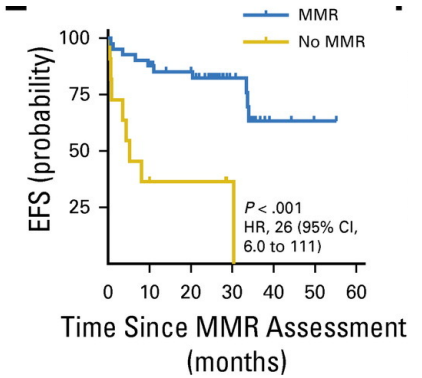
Early Molecular Response (EMR): -2 log at C2D1
Major Molecular Response (MMR): -2.5 log at C3D1

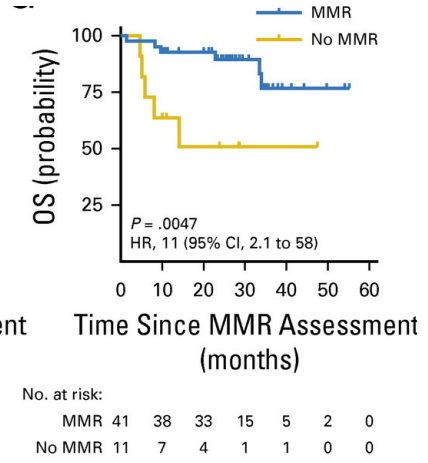
Outcome by EMR





Outcome by MMR





Newman et al. Nat Med (2014) 20: 548–554; Newman et al. Nat Biotechnol (2016) 34: 547–555; Kurtz, Scherer et al. J Clin Oncol (2019) 36:2845-2853.

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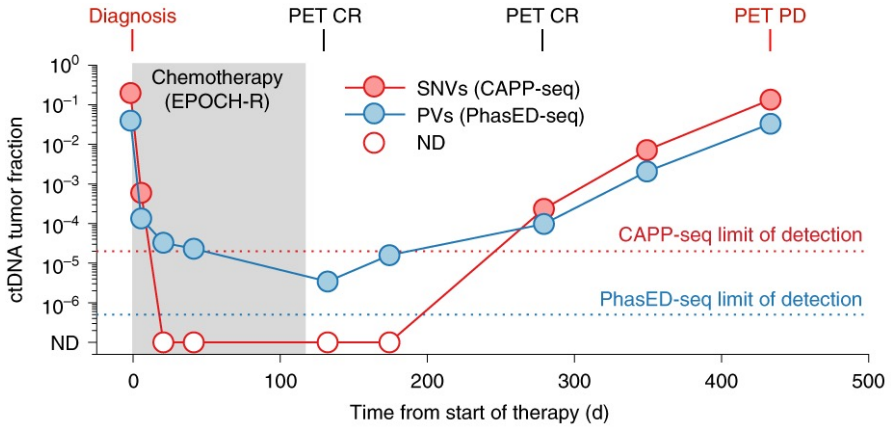
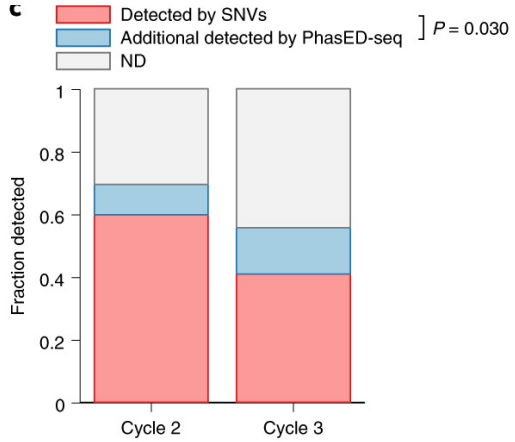
PhasED-seq v CAPP-seq

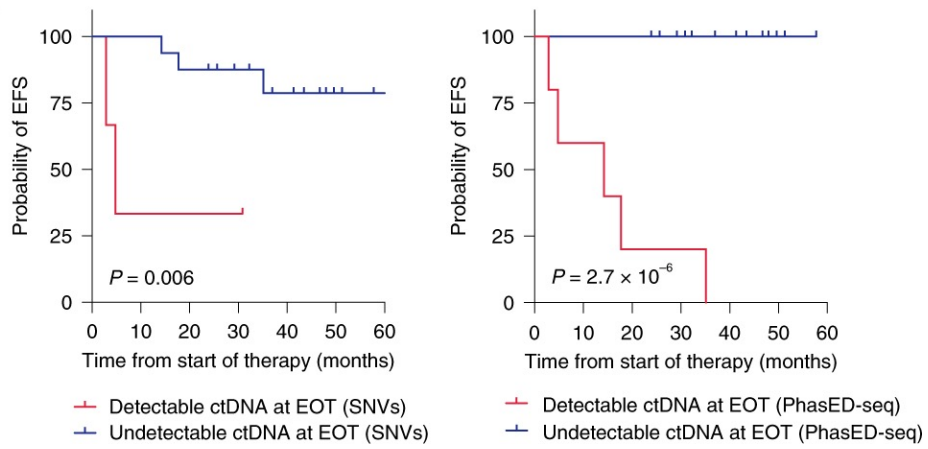
Example of Differential Detection of ctDNA

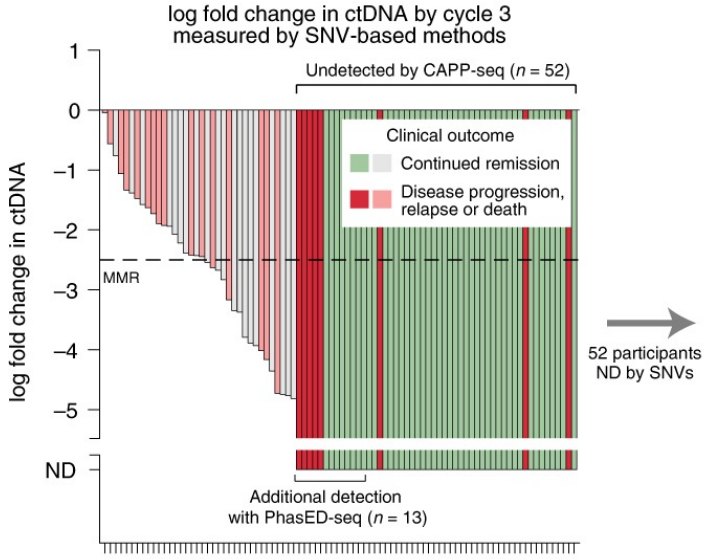


Kinetics of Response



K-M Outcome by EOT

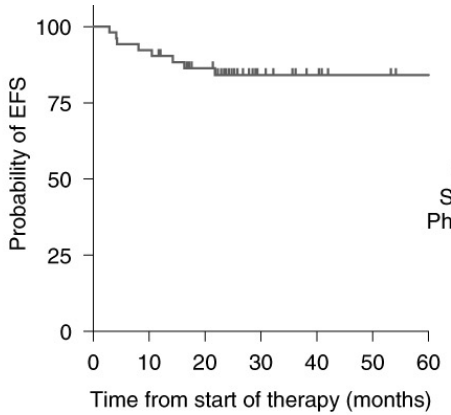




52 participants ND by SNVs

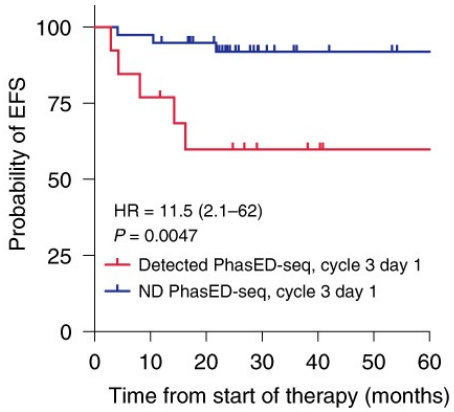
K-M Outcome by Cycle 3 Day 1 Kinetics

CAPP-seq

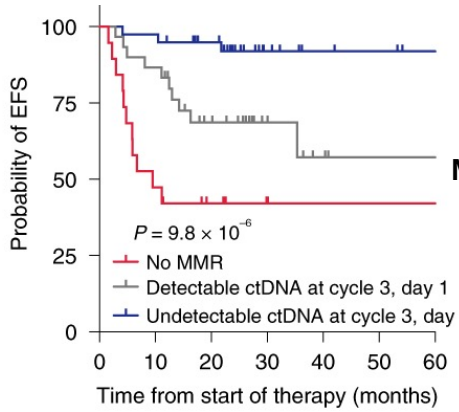


Stratify by PhasED-seq

PhasED-seq



PhasED-seq by MMR
(>2.5 log reduction)



MMR >2.5 log reduction

Kurtz et al. Nat Biotechnol (2021) 39(12):1537-1547

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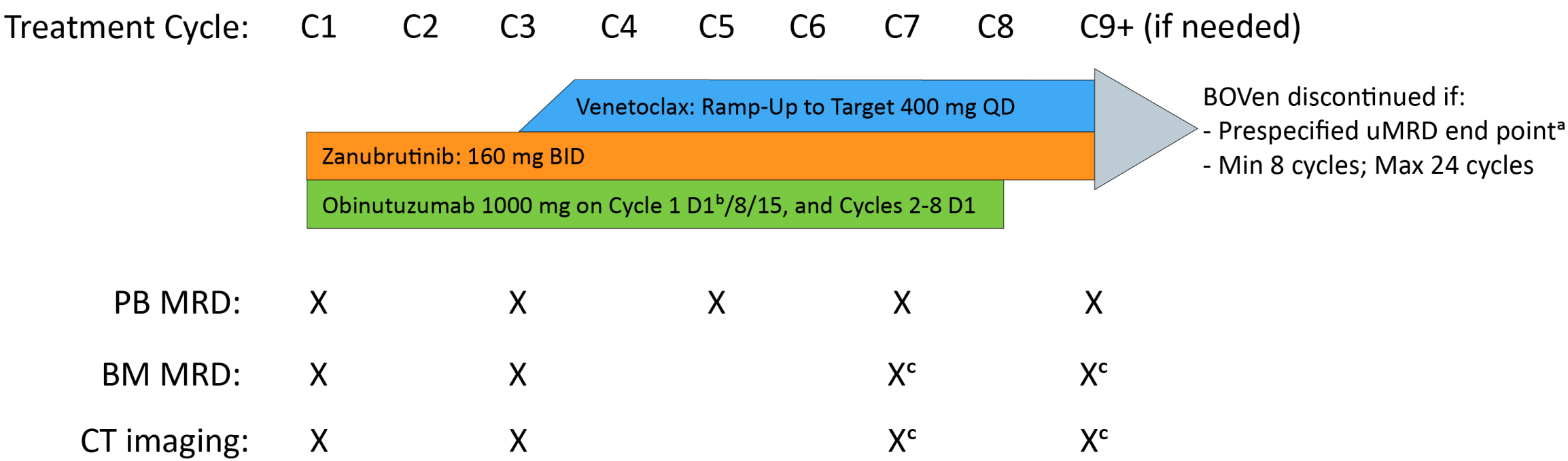
BOVen Treatment Schema



a- Once peripheral blood (PB) uMRD is determined and confirmed in bone marrow (BM), patients complete 2 additional cycles followed by confirmatory MRD peripheral blood testing; if PB uMRD x 2 and BM uMRD x 1, therapy is discontinued.

b- Obinutuzumab split over days 1-2 of cycle 1 if ALC >25,000.

c- BM biopsy obtained at Screening and C3D1; thereafter BM is only obtained if PB-uMRD.
CT imaging obtained at Screening, C3D1, C7D1, EOT, then every 6 months during post-treatment surveillance.

Soumerai, Lancet Haematology DOI:https://doi.org/10.1016/S2352-3026(21)00307-0

MGH 1811

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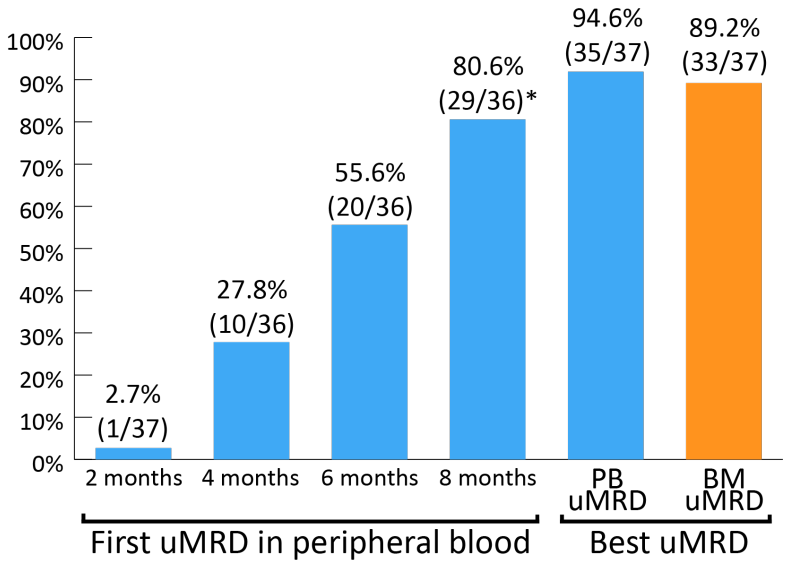
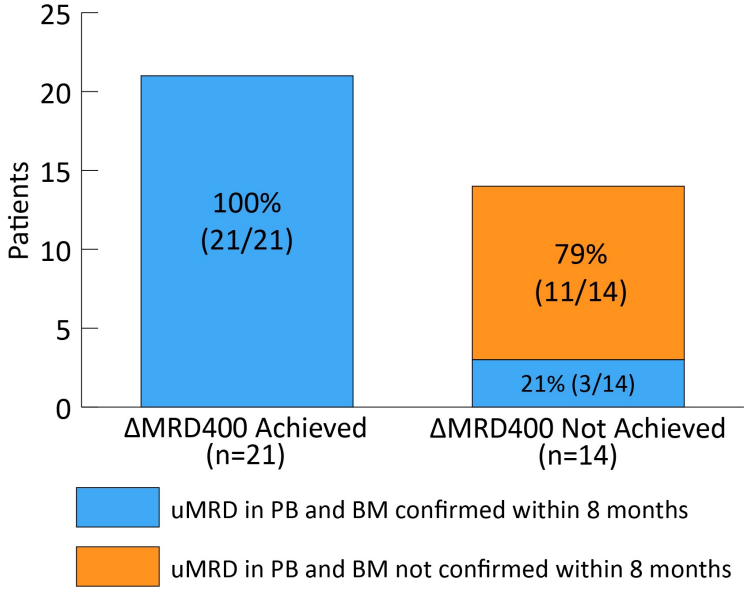
BOVen: ΔMRD400 predicts for BM uMRD and sustained post-treatment MRD at $<10^{-5}$

Definition: ΔMRD400 is a 400-fold decrease in tumor burden by C5D1

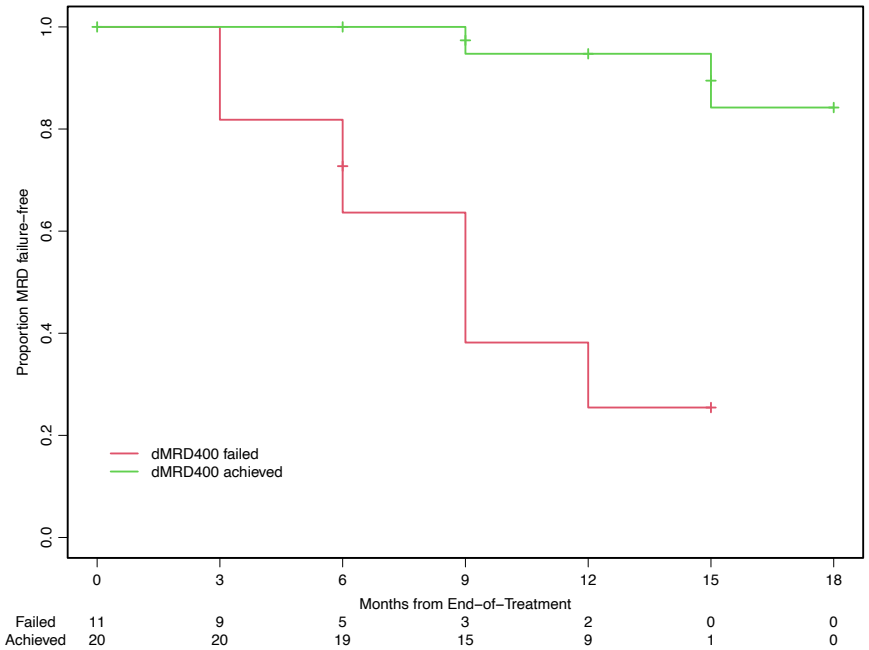
MRD response by flow cytometry



ΔMRD400 as a surrogate endpoint for early undetectable MRD in bone marrow



ΔMRD400 as a Predictive marker for Post-treatment MRD kinetics (MRD by NGS)



We hypothesize that patients with ΔMRD400 can have sustained remission with limited treatment duration

Soumerai, Lancet Haematology DOI:https://doi.org/10.1016/S2352-3026(21)00307-0

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MRD in NHL

- Achievement of undetectable MRD has generally (though not universally) been associated with improvements in time to event endpoints including OS

- The compartment to be analyzed (cellular v cell-free) may vary by disease
  - Diseases with leukemic phase (SLL/CLL, MCL, MZL, HCL) *may* have better sensitivity with the cellular fraction, needs further study

- Current clinical utility is largely based on the *prognostic* information provided

- Ongoing work is evaluating the role of MRD to risk-adapt therapy

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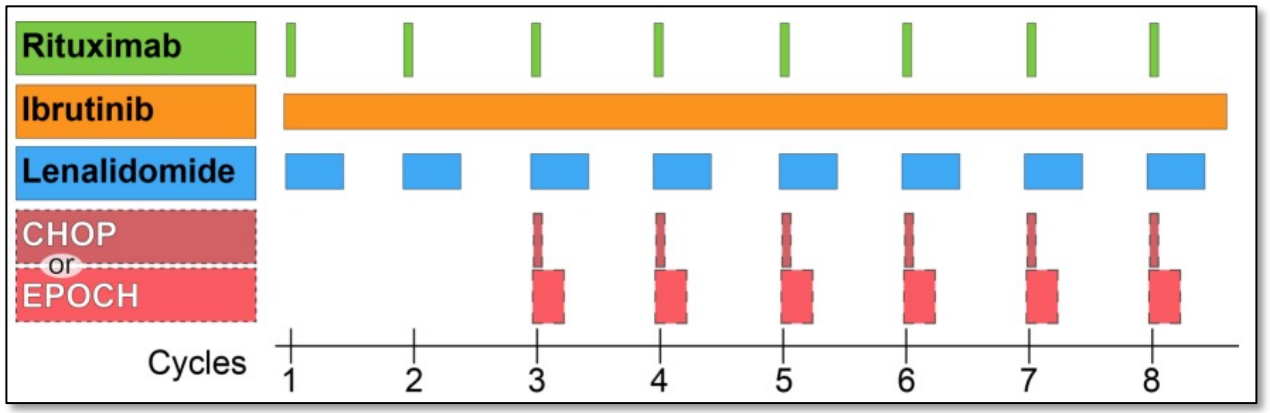
Break the mold to improve outcomes

Improving on R-CHOP-21: R-CHOP + X

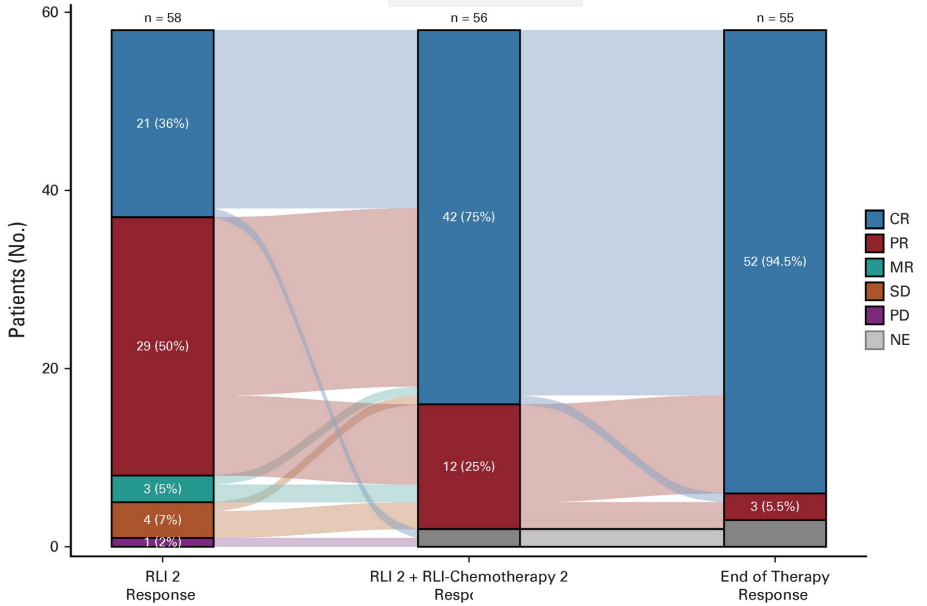
Investigational Arm (X)	PFS HR (p-value)	OS HR (p-value)	Comments	Ref
Bortezomib	0.81 (0.085)	0.86 (0.32)	Randomization after cycle 1 R-CHOP	**Davies et al. Lancet Oncol 2019 doi.org/10.1016/S1470-2045(18)30935-5**
	0.65 (0.041)	0.58 (0.032)	ABC Subset	**Davies et al. J Clin Oncol (2023) doi.org/10.1200/JCO.23.00033**
Iburtinib	0.934 (0.5906)	0.991 (0.9593)	OS benefit for patients <60	**Younes et al. J Clin Oncol 2019 DOI: 10.1200/JCO.18.02403**
Lenalidomide	NS	NR		**Nowakowski et al. J Clin Oncol (2021) 39(12) 1317-1328**
	0.66 (0.03 one-sided)	0.69 (0.08 one-sided)	ECOG 1412 Ph 2	**ICML 2019**
Polatuzumab	0.73 (0.02)	0.94 (0.75 one-sided)	POLARIX ~6% improvement in PFS @ 2y	**Tilly et al. NEJM 2022 386:351-363**
Venetoclax	0.61 (v matched GOYA)	0.72 (v matched GOYA)	Phase I/II Only	**Zelenetz et al. Blood 2019 Morschauser et al. Blood 2021**

Window Study: Rituximab, lenalidomide, ibrutinib for 1L DLBCL (Smart Start)

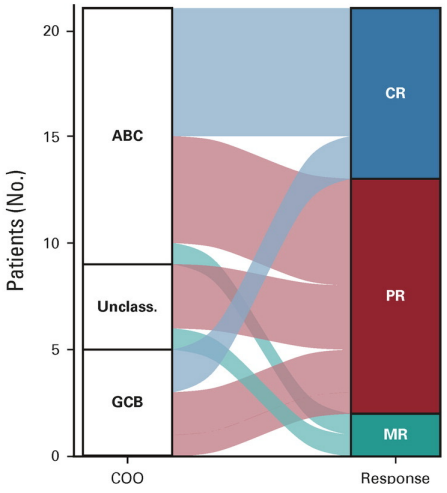
Schema

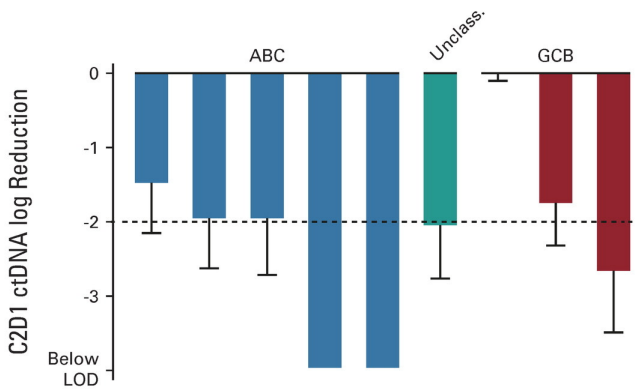


Response

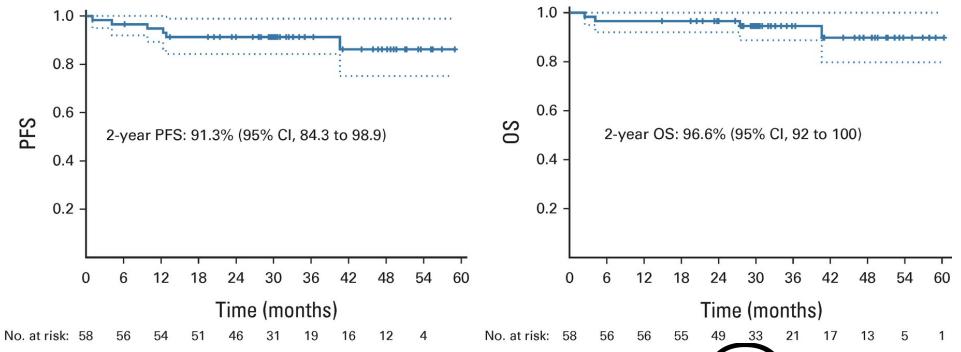


ctDNA Response by Cell of Origin





PFS and OS



Westin et al, J Clin Oncol (2023) 41(4): 745-755

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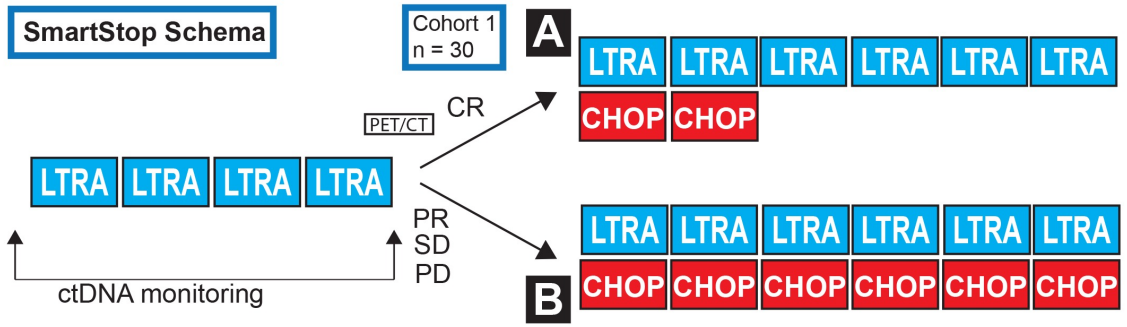
Smart Stop: Is Len-Tafa-Ritux-Acal (LTRA) enough therapy?



Drug Name	Dose	Route	Dosing/cycle	Days
Lenalidomide (L)	25 mg	PO	Daily	1-10
Tafasitamab (T)	12 mg/kg	IV	Weekly	1, 8, 15
Rituximab (R)	375 mg/m^2	IV	Once	1
Acalabrutinib (A)	100 mg	PO	BID	1-21

Response to LTRA x 4 Lead In

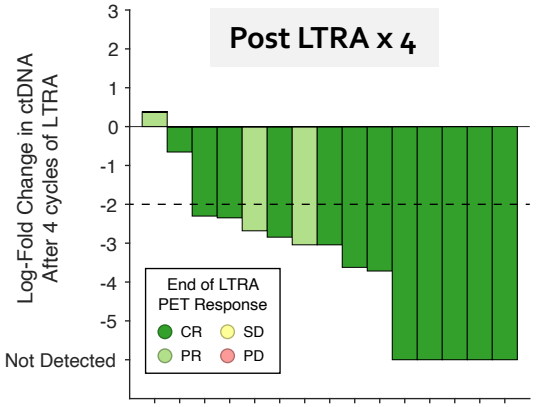
	All (N=30)	GCB (N=5)
CR	**19 (63.3%)** (95% CI: 50.0 ~ 75.2%)	**4 (80%)**
PR	11 (36.7%)	1 (20%)
SD	0	0
PD	0	0
ORR	30 (100%) (95% CI: 92.6 ~ 100%).	

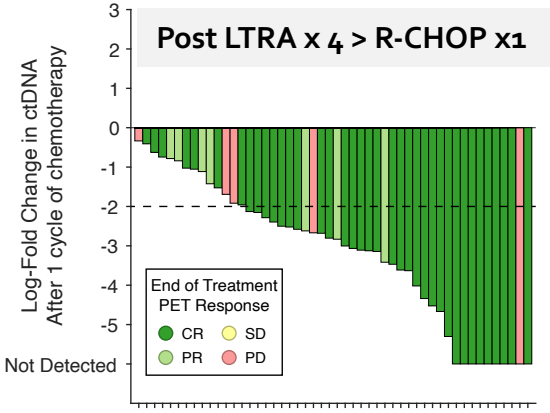
EOT Response

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
On Treatment	8	5	3

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

MRD by PhasED-seq





In the next two cohorts, patient in CR after LTRA x 4 will continue with additional LTRA x6 and those with PD, SD, PR will get CHOP + LTRA x 6

Westin et al. ASH 2023, Abstract 856

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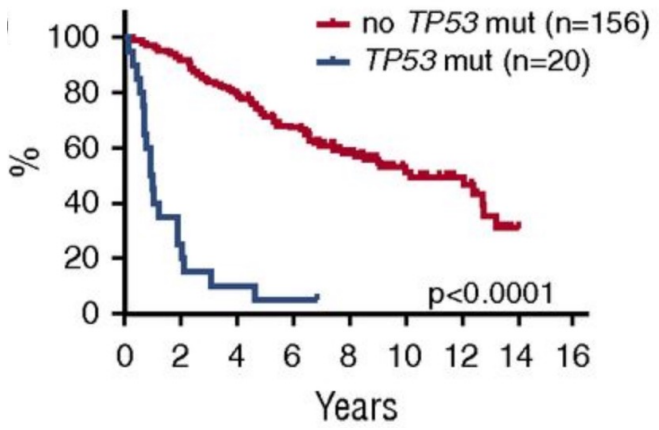
BOVen for TP53 Mutant MCL: Background

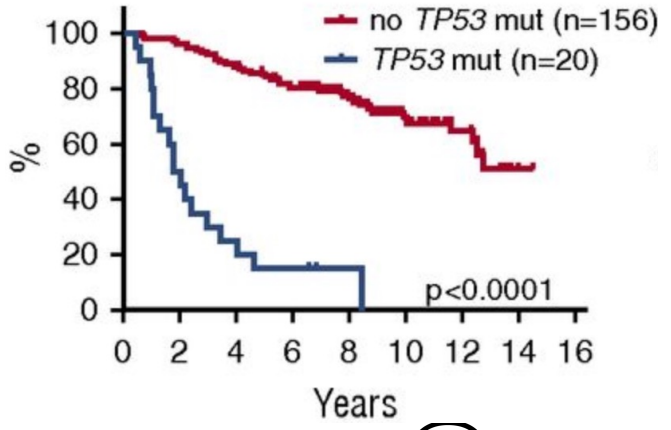
- *TP53*-mutant mantle cell lymphoma (MCL) is associated with poor survival outcomes in patients treated with chemoimmunotherapy
- No standard frontline treatment exists
- Dual Bruton's Tyrosine Kinase (BTK) and BCL2 inhibition was synergistic and active in relapsed, refractory MCL (AIM and SYMPATICO)
- The triplet (ibrutinib, obinutuzumab, and venetoclax) was efficacious in relapsed and untreated MCL, including *TP53*-mutant MCL (OAsIs)
- **Study Hypothesis:** The BOVen triplet (zanubrutinib, obinutuzumab, and venetoclax) will be well tolerated and efficacious in untreated *TP53*-mutant MCL

NORDIC MCL-2 and MCL-3

Progression Free Survival



Overall Survival



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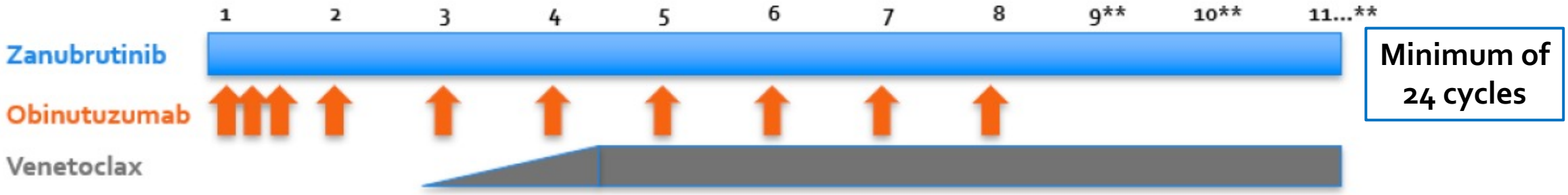
Eskelund Blood 2017; Tam NEJM 2018; Wang ASH 2023; Le Gouill Blood 2021

Study Design for BOVen



Dosing:

Zanubrutinib 160 mg oral twice daily
Until EOT or intolerance**

Obinutuzumab 1000 mg IVPB
Cycle 1: day 1, 8, 15
Cycle 2-8: day 1

Venetoclax 400mg oral daily
5-week ramp-up: 1 week each of 20mg; 50mg; 100mg; 200mg; 400 mg oral daily

After 24 cycles, MRD-driven approach to limit treatment duration in selected patients:

CR and uMRD	→	Stop treatment
<CR and/or dMRD	→	Continue ZANU and VEN

Key Eligibility Criteria:

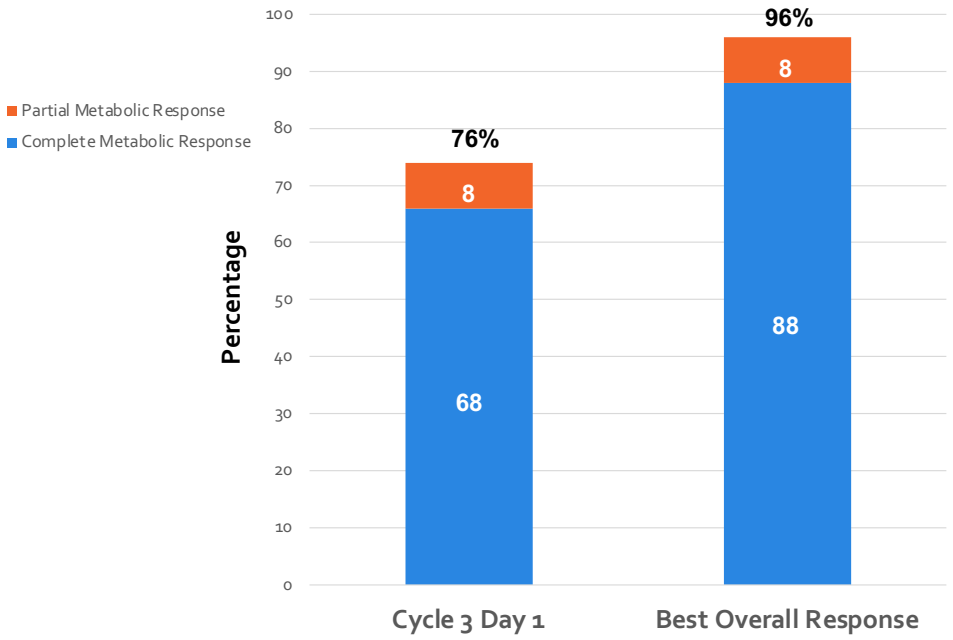
- Previously untreated MCL (except localized RT prior)
- *TP53* mutation (of any variant allele frequency)
- ECOG ≤2, adequate organ and hematologic function (ANC >1, PLT >75, HGB ≥9 (unless due to MCL))

Primary Endpoint:

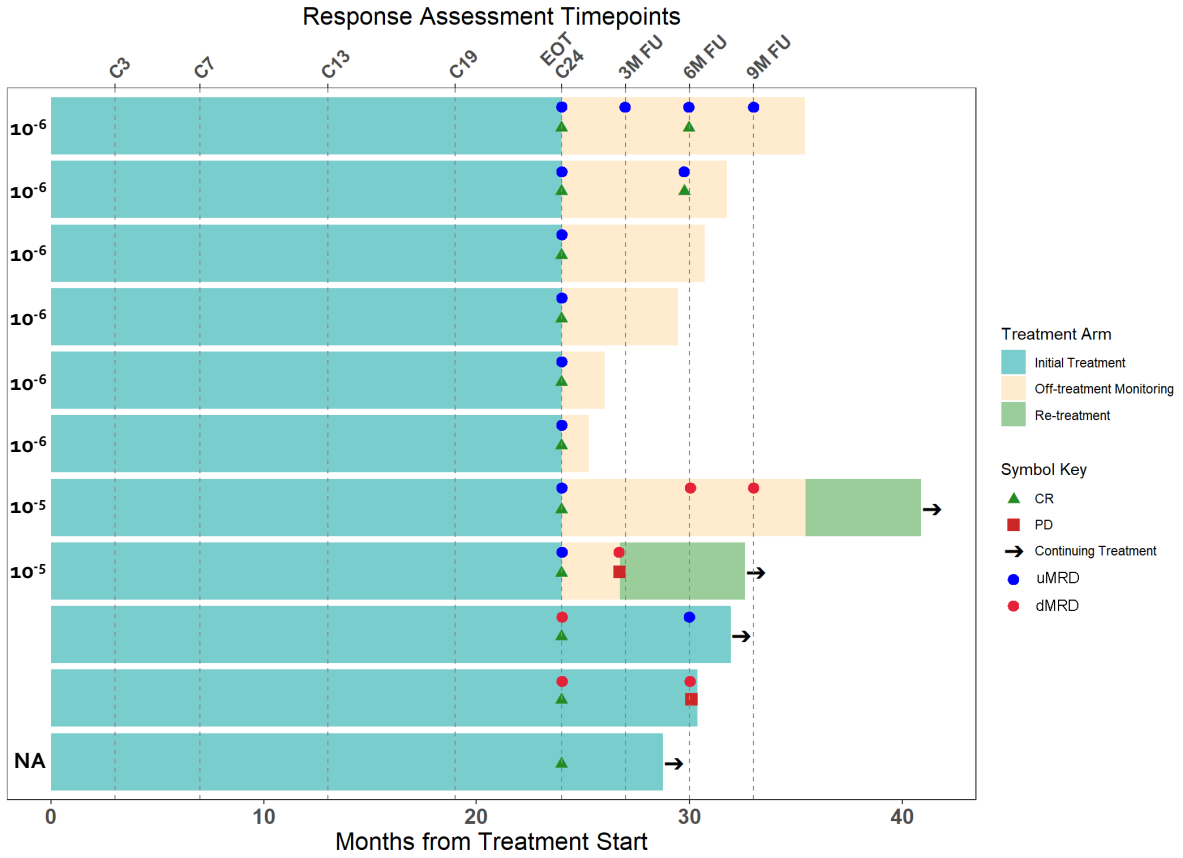
- 2-year progression-free survival.
- A promising 2-yr PFS rate ≥55% and an unacceptable rate ≤30%
- If ≥11 patients were progression-free at 2 years, the treatment regimen would be declared effective

Kumar et al. ASH 2023, Abstract 738

Response Rates By Timepoint



- High Metabolic Response Rates after 2 cycles of Zanu+Obin
- High Overall Metabolic Response Rate with Zanu+Obin+Ven



- 11 patients completed have 24 cycles of therapy
- MRD
  - 1 patient without MRD result
  - uMRD5 2 patients
  - uMRD6 6 patients
  - dMRD5 2 → continued ZANU + VEN

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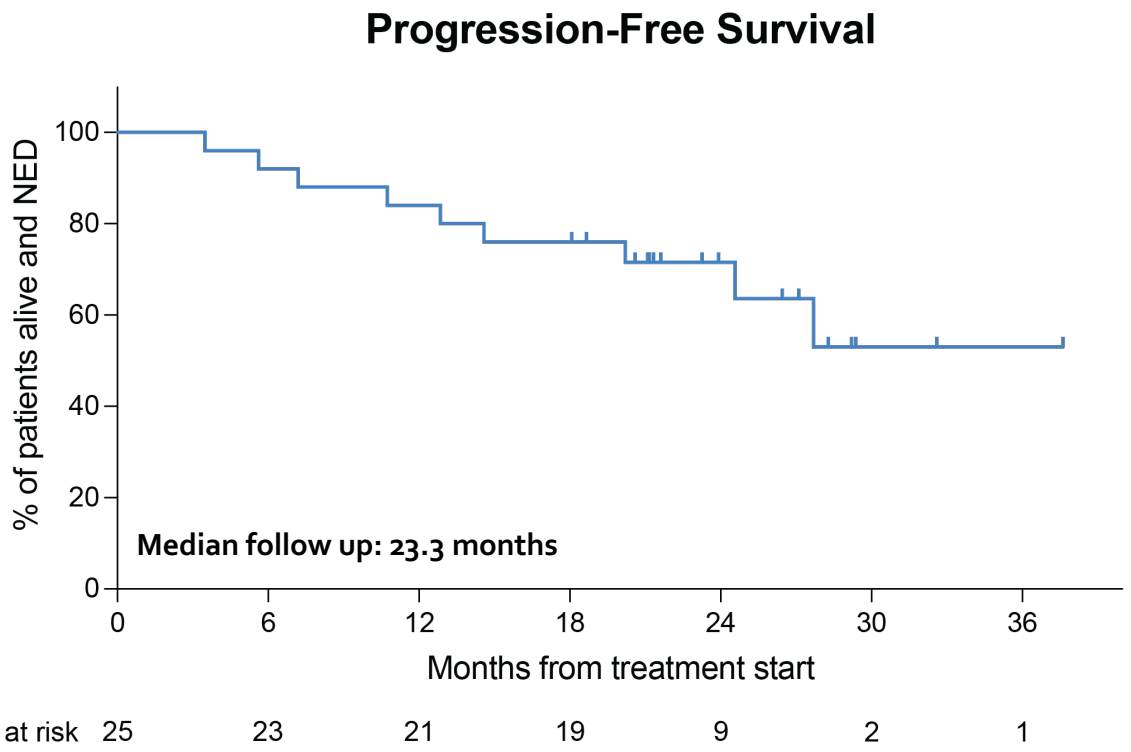
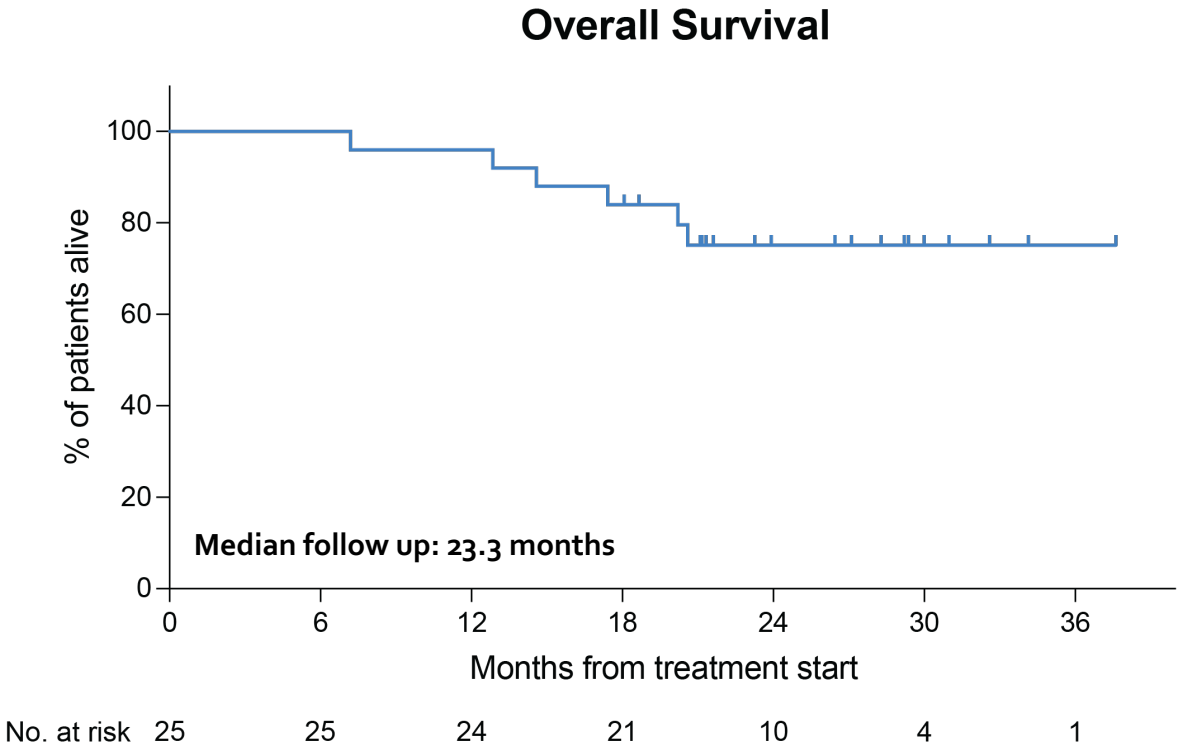
BOVen TP53 Mutant MCL: Progression-Free and Overall Survival Outcomes





2-year PFS: 72% [95% CI: 56, 92]
Median PFS: not reached

2-year OS: 75% [95% CI: 58, 93]
Median OS: not reached

Primary PFS Endpoint is Met:
11 patients are progression-free at 2 years

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Disseminating expert recommendations: Role of Guidelines

Institute of Medicine (IOM): Guidelines We Can Trust

- Be based on a **systematic review** of the existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patient preferences, as appropriate
- Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of recommendations
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

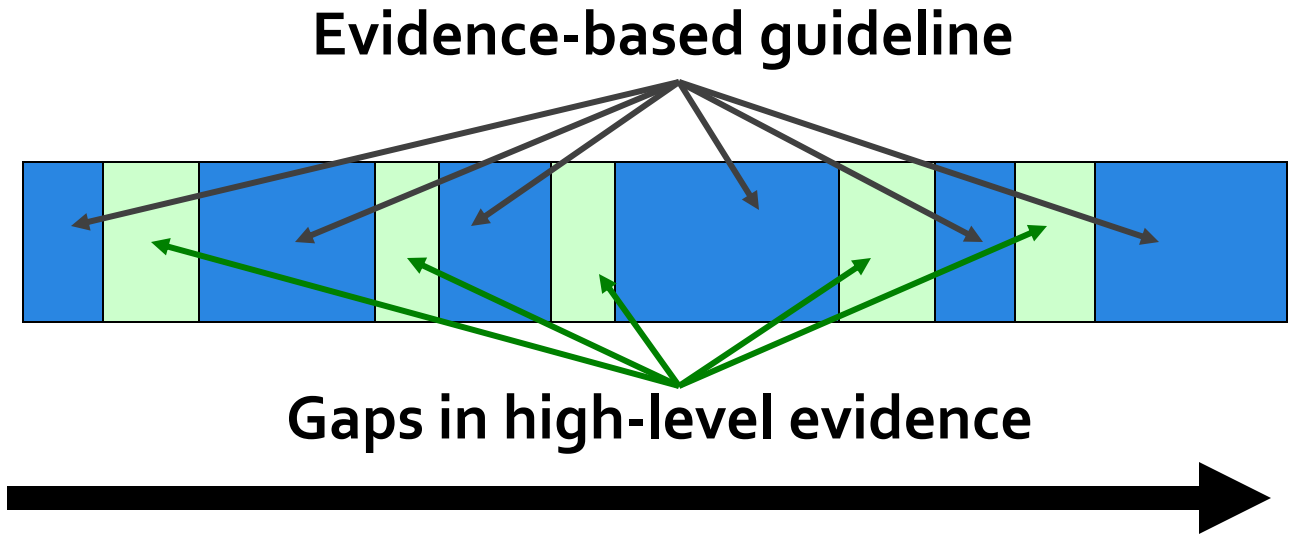
CAVEAT: "The committee's proposed standards have yet to be tested by clinical practice guideline developers and users to determine whether the standards produce unbiased, scientifically valid, and trustworthy clinical practice guidelines, and whether implementation of the clinical practice guidelines based on the committee's standards improve health outcomes."

Institute of Medicine: Clinical Practice Guidelines We Can Trust, National Academies Press (US); 2011.

NCCN Guidelines

- Comprehensive across all stages, modalities and **continuum of care**
  - Systematic review not possible at all points of care
  - Category of evidence and consensus designated for each recommendation
- Multidisciplinary expert panels to cover adult and pediatric cancer
- Takes advantage of the best practices of NCI-designated cancer centers
- Cancer screening, diagnosis, treatment, supportive care and survivorship
- **Updated at least annually and up to 4 times per year since first Guidelines developed in 1995**
- Transparent processes
- Readily accessible to support quality oncology care

Evidence-based Consensus Allows Comprehensive Guideline



High-level evidence exists

Gaps in evidence filled with expert consensus

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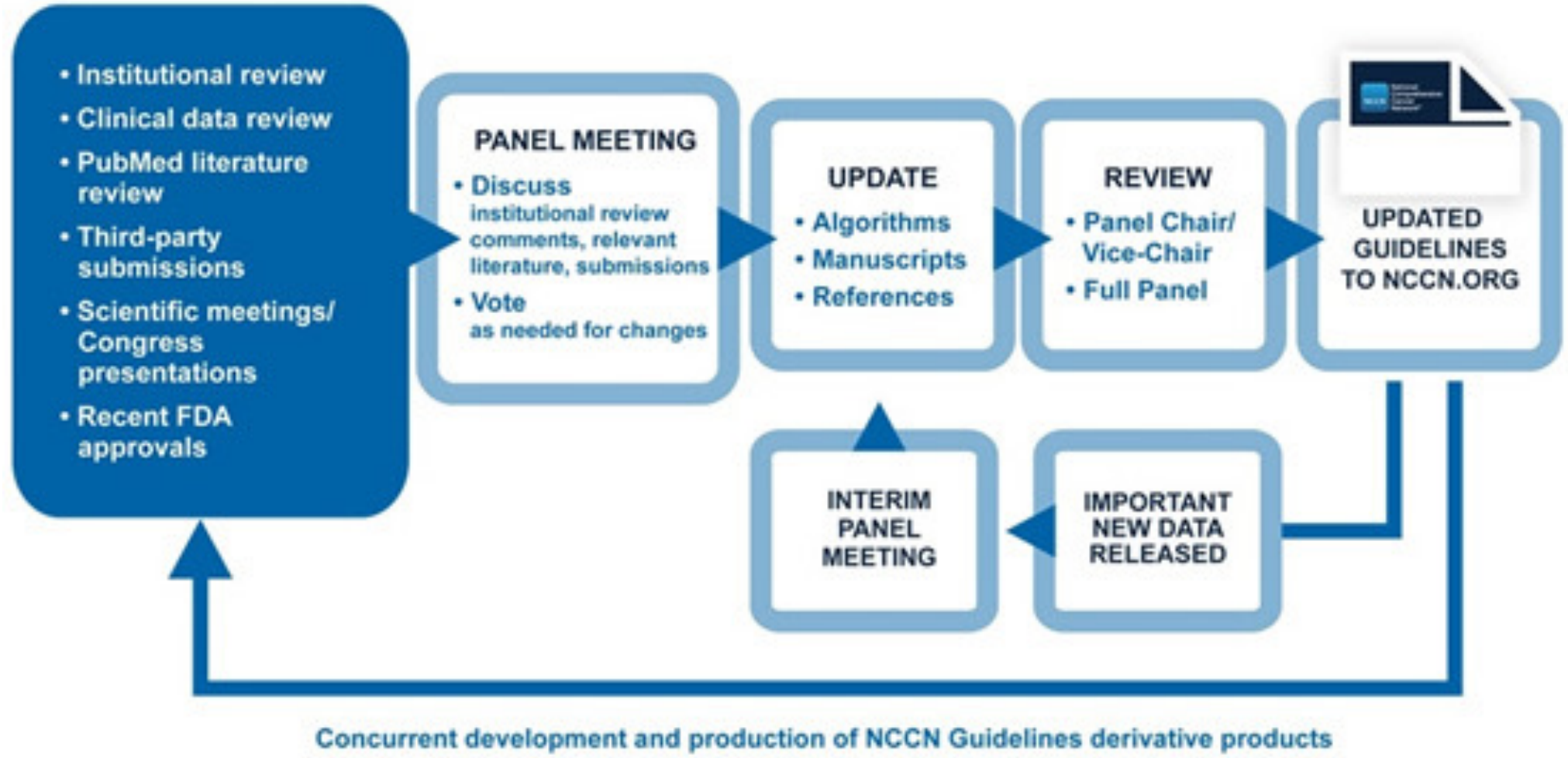
Guideline Development and Continual Updating Process



NCCN Guideline Update Process, https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines

NCCN Levels of Evidence

- **Category 1:** The recommendation is based on high level evidence* and there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** The recommendation is based on lower level evidence^ and there is uniform NCCN consensus that the intervention is appropriate. (2A is the default category unless otherwise indicated.
- **Category 2B:** The recommendation is based on lower level evidence^ and there is NCCN consensus that the intervention is appropriate.
- **Category 3:** The recommendation is based on any level of evidence; there is major NCCN disagreement that the intervention is appropriate.

* Randomized controlled trials or meta-analyses

^ Smaller randomized clinical trials, well-designed controlled trials without randomization, well-designed cohort/retrospective studies, or historical practice patterns

Who Makes Up the NCCN B-Lymphoma Panel?

- Representatives from each member institution
- Multi-disciplinary with representation from:
  - Pathology
  - Radiation oncology
  - Medical oncology
  - Patient representative
- Additional members maybe included if they have specialized expertise in less common forms of lymphoma

NCCN Management of Conflicts of Interest

- No industry funds are used to support panel meetings
- Panel members are not paid for their work on Guidelines
- Industry representatives are not allowed at meetings
- Because of their expertise, panel members often are involved with trials and may have industry relationships
  - Individual panel members disclose conflicts of interest at each panel meeting
  - Financial conflicts of interest at the individual level are published on NCCN Web site for each Guideline panel
  - Members are excused from deliberations when degree of conflict warrants

How Do Guidelines Fit into Decisions about Treatment?

- Guidelines are defined for each step in the clinical decision sequence
- One treatment or a range of appropriate treatment options for specific situations may be found in the Guidelines
  - Data may not support a single treatment at a given node
  - Appropriate treatments may be tailored to special populations, e.g. significant co-morbidities which impact on treatment
- The goal is to enhance quality of care by recommending the most appropriate treatment choices
- 100% concordance is usually not appropriate

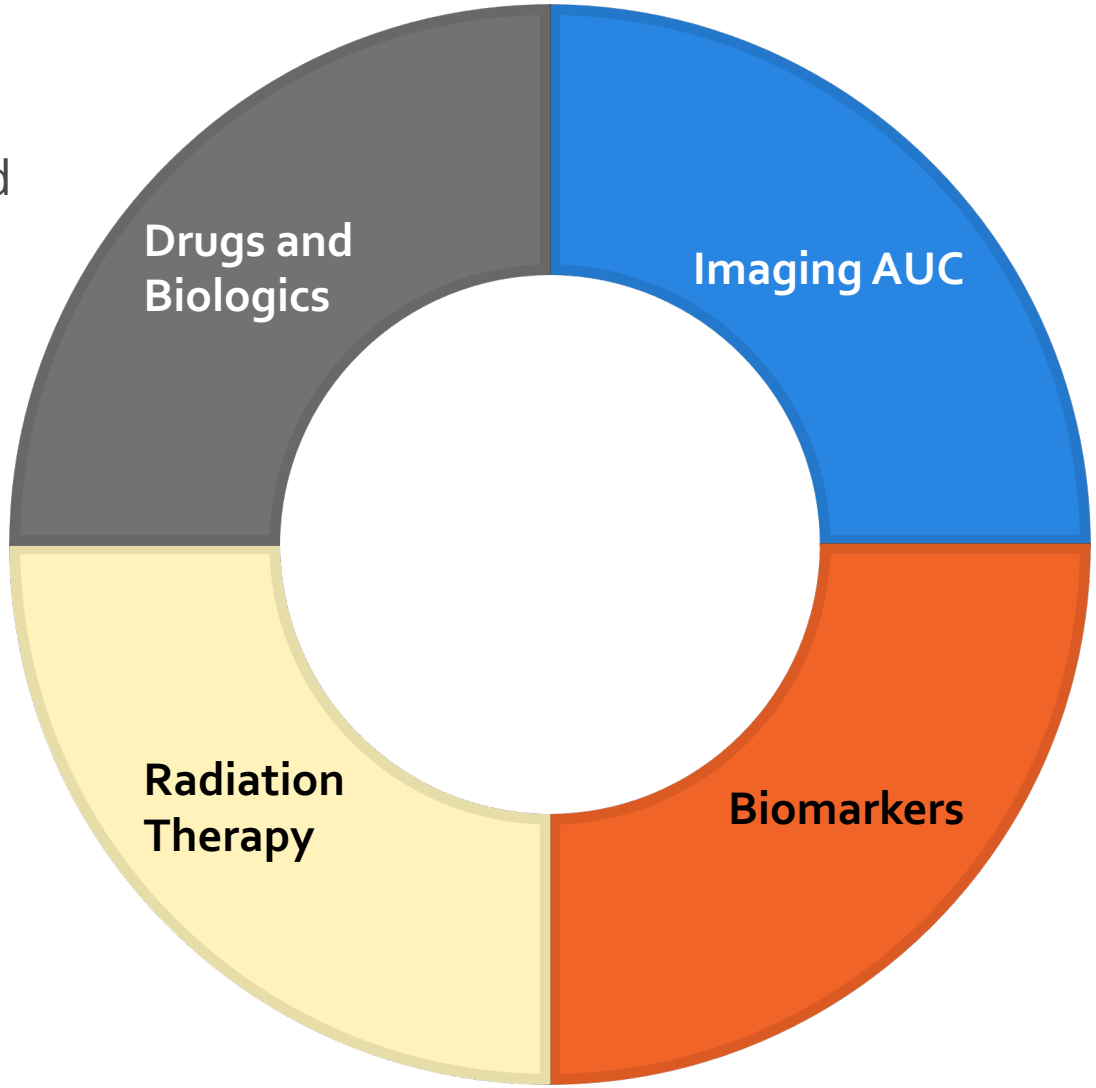
NCCN Compendia

Drugs and Biologics

- Recommendations for appropriate use of drugs and biologics base on relevant NCCN Guidelines
- Includes clinical context, route of administration, and NCCN category of evidence

Radiation Therapy

- For support clinical decision-making around the use of radiation therapy based directly on relevant NCCN Guidelines.



Imaging AUC

- Include recommendation based on relevant NCCN Guidelines for: Indications; Screening; Diagnosis; Purpose; Frequency; Staging; Response assessment; Follow-up and surveillance

Biomarkers

- Details tests (including genomics) which have been included in Guidelines to aid: Diagnosis; Screening; Monitoring; Surveillance; Prediction; Prognostication

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NCCN NHL Guidelines

- NHL guidelines represent a complex series of algorithms to help guide practicing clinicians in the care of lymphoma
  - Twenty therapeutic and diagnostic guidelines are included
  - One of the largest set of NCCN guidelines
  - Updated annually in a data-driven review process
  - Updated as necessary during the year based on emerging data

- NCCN process meets most of the IOM recommendations for "Clinical Practice Guidelines We Can Trust"
  - Inadequate data exists for many decision points in lymphoma
  - Rather then provide no guidance, the approach is to provide expert consensus

Mission Possible: Improving outcomes in patients with lymphoma

- Clinical trial design
  - Need to maximize the use of our most precious resource – **patients**
  - Selected patient population to maximize effect size with clinically relevant controls in randomized studies
  - Need to change paradigms by moving away from established regimens

- Role of MRD in trial design
  - Important role to guide clinic trials
  - Needs to determine if MRD is an appropriate surrogate
    - May not be a single universal surrogate for all histologies

- Is kinetics better than end of treatment (EOT) undetectable minimal residual disease (uMRD)?
  - Do early treatment kinetics extend the dynamic range of our MRD testing?

- Critical role for education and guidelines
  - Outcomes will not improve unless new treatments are used widely

It takes a village

- **MSK**
  Anita Kumar, MD
  Gilles Salles, MD PhD
  Ahmet Dogan, MD PhD
  Venkatraman Seshan, PhD
  Maria Arcila, MD
  Kimon Argyropoulos, MD
  Alexander Boardman, MD
  Philip Caron MD
  Aleaxnader Chan, MD
  Kojo Elenitoba-Johnson, MD, PhD
  Kevin David, MD
  Lorenzo Falchi, MD
  Paul Hamlin, MD
  Brandon Imber, MD
  Andrew Intlekofer, MD, PhD
  Steven Horwtiz
  William Johnson, MD
  Megan So-Young Lim, MD, PhD
  Oscar Lin, MD
  Jennifer Lue, MD
  Efrat Lutwak, MD

- **MSK**
  Anthony Mato, MD
  Alison Moskowitz, MD
  Ariela Noy, MD
  Lindsey Roeker, MD
  Colette Owens, MD
  Lia Palomba, MD
  Filiz Sen, MD
  Rafeal Steiner, MD
  Robert Stuver, MD
  Meghan Thompson, MD
  Palawi Torka, MD
  Mariko Yabe, MD
  Joachim Yahalom, MD, PhD
  Maria Chabowska BSc
  Clare Grieve, MPH
  Ashlee Joseph
  Alyssa Labarre
  Natalie Slupe
  Joanna Mi, NP

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- **Massachusetts General Hospital**
  Jacob Soumerai, MD
  Jeremy S. Abramson, MD
  Jeffrey A. Barnes, MD PhD

- **Northwester Medicine**
  Leo Gordon, MD, co-chair NCCN
  Shou Ma, MD
  Reem Karmali, MD

- **NCCN**
  Representatives from all the member institutions
  Mary Dwyer, MS
  Hema Sundar, PhD
  Kristina Gregory, RN