



SINTOMA²⁶

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society of hematologic oncology

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GERENCIAMENTO
E PRODUÇÃO

RV+
EVENTOS

Relapsed Follicular Lymphoma: POD24, Therapeutic Sequencing, and Novel Treatment Strategies

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BROWN
Legorreta Cancer Center

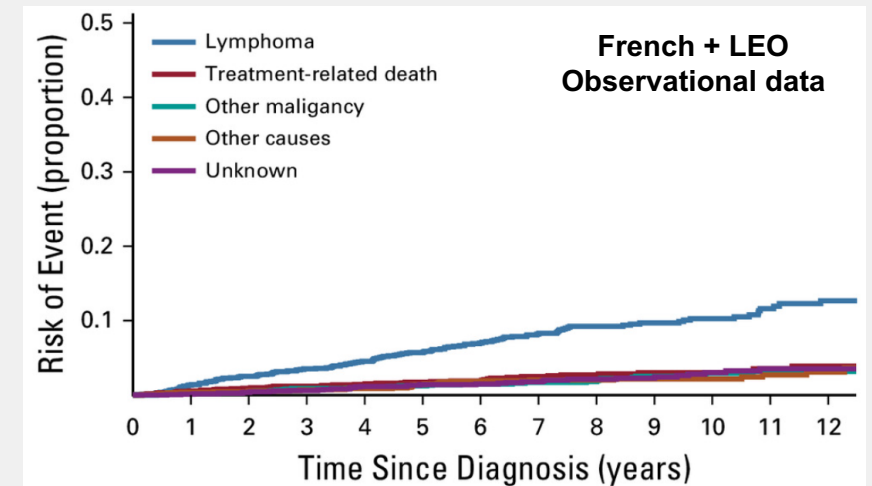
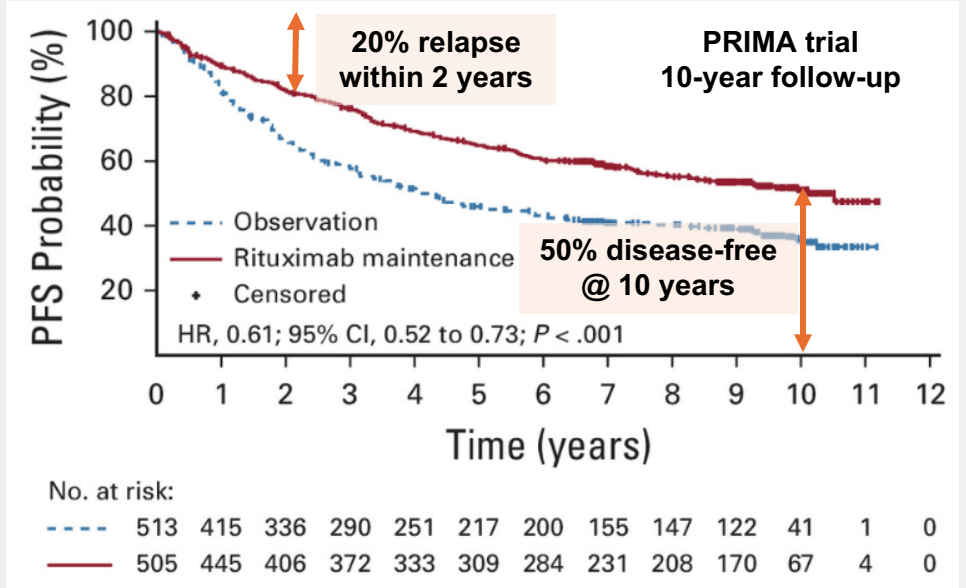
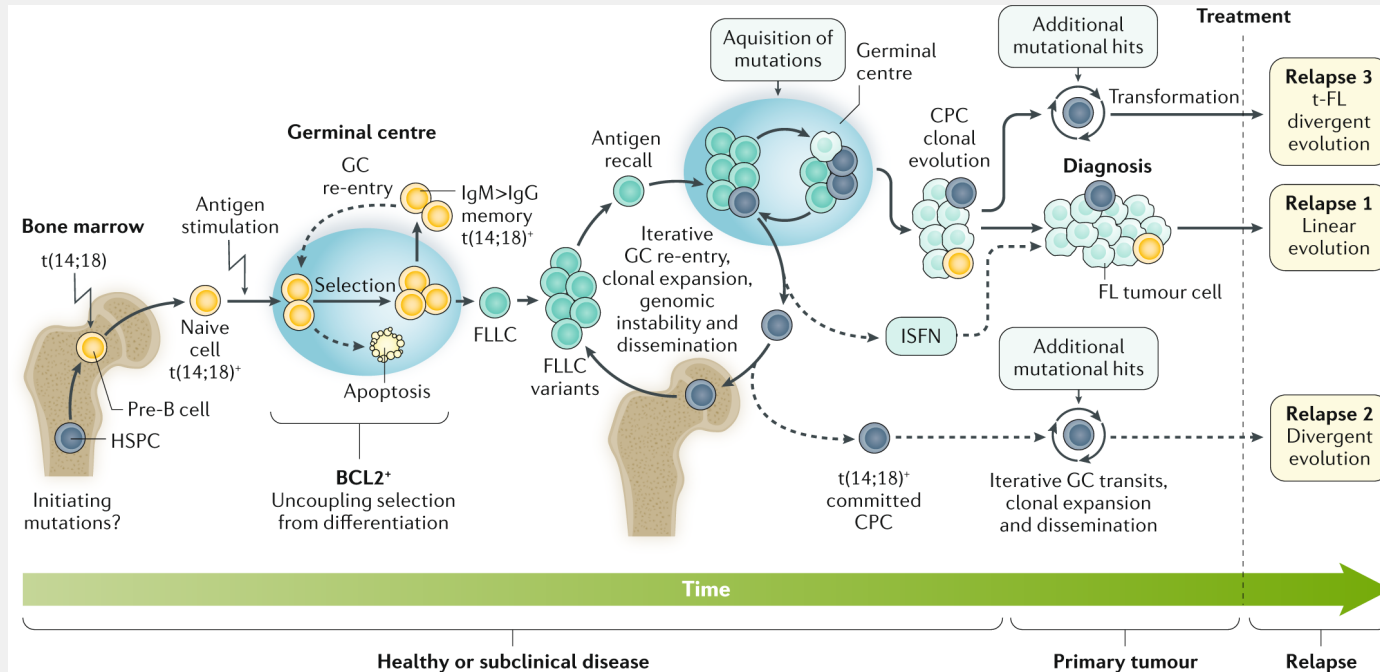
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- Consultancy: Roche, Genentech, Genmab, Schrodinger, ADC Therapeutics, BeOne, Bristol-Myers Squibb, Incyte.
- Research funding: Genmab, Schrodinger, Genentech, Inc., Precision Biosciences, Artiva, Pfizer, Kymera Therapeutics, Incyte, Bristol-Myers Squibb, Immugene.

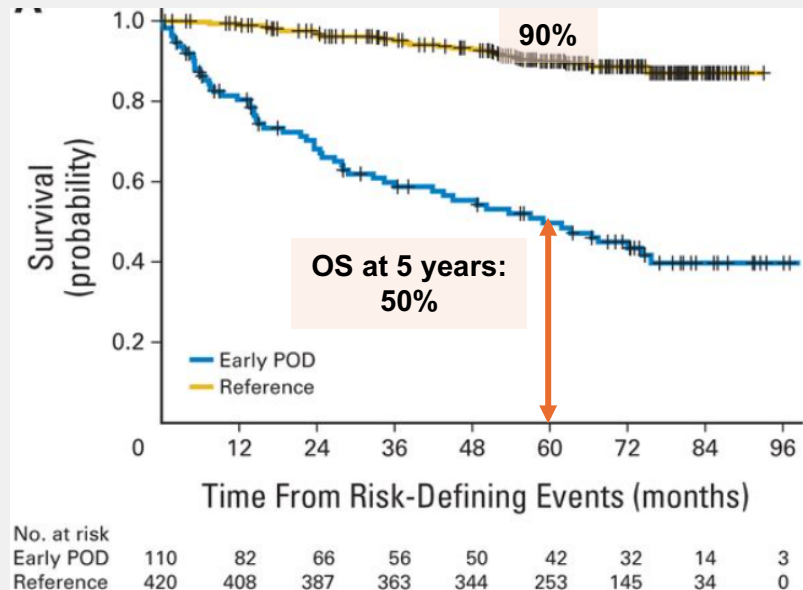
Current first line therapy outcomes
(immunochemotherapy + maintenance R)

- “Generally incurable” → relapses continue over decades
- Median PFS ~7-10 years
- ~20% have a relapse within 2 years of starting therapy



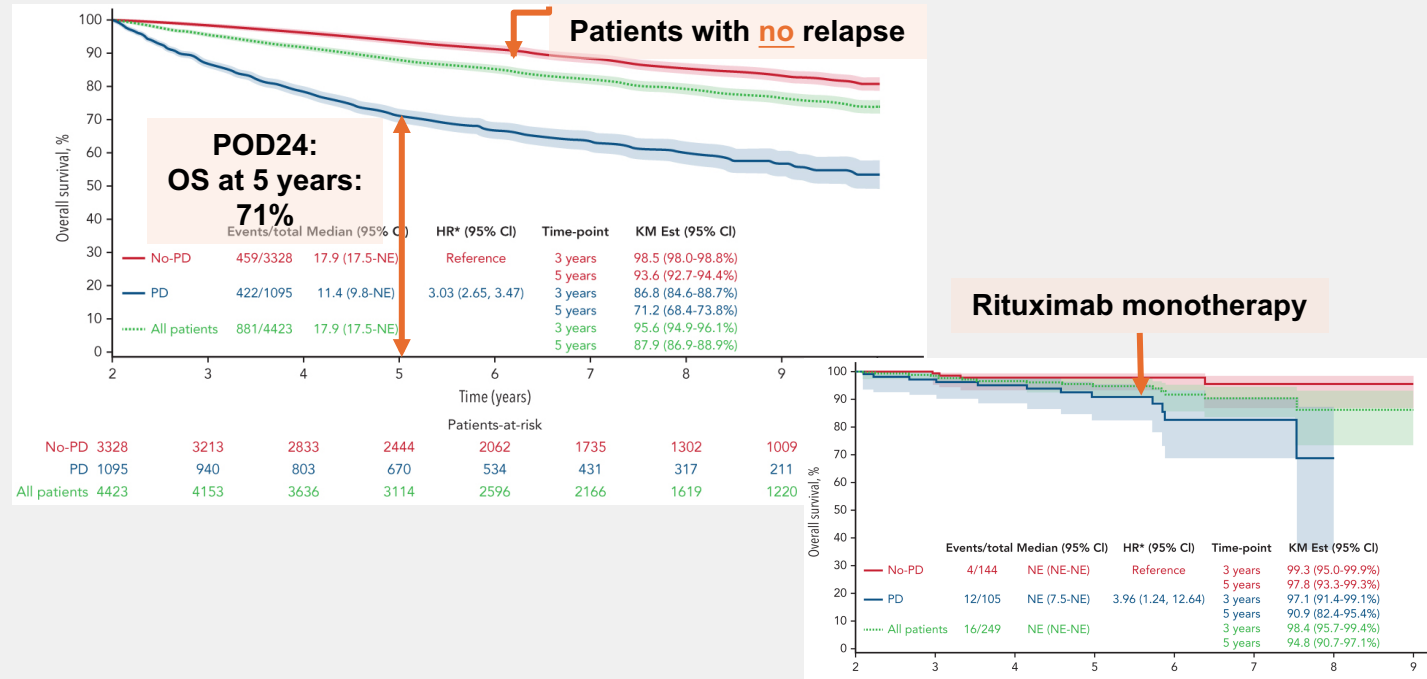
National LymphoCare study:

- POD24 (“*from diagnosis*”) occurred in **19%**
- POD24 **after R-CHOP** have markedly worse OS
- **5-year OS 50%** vs 90% for later relapses
- Clinical factors associated with POD24:
 - High FLIPI scores
 - Poor ECOG Performance Status (PS),
 - B symptoms,
 - Elevated LDH,
 - Stage 3 or 4 disease

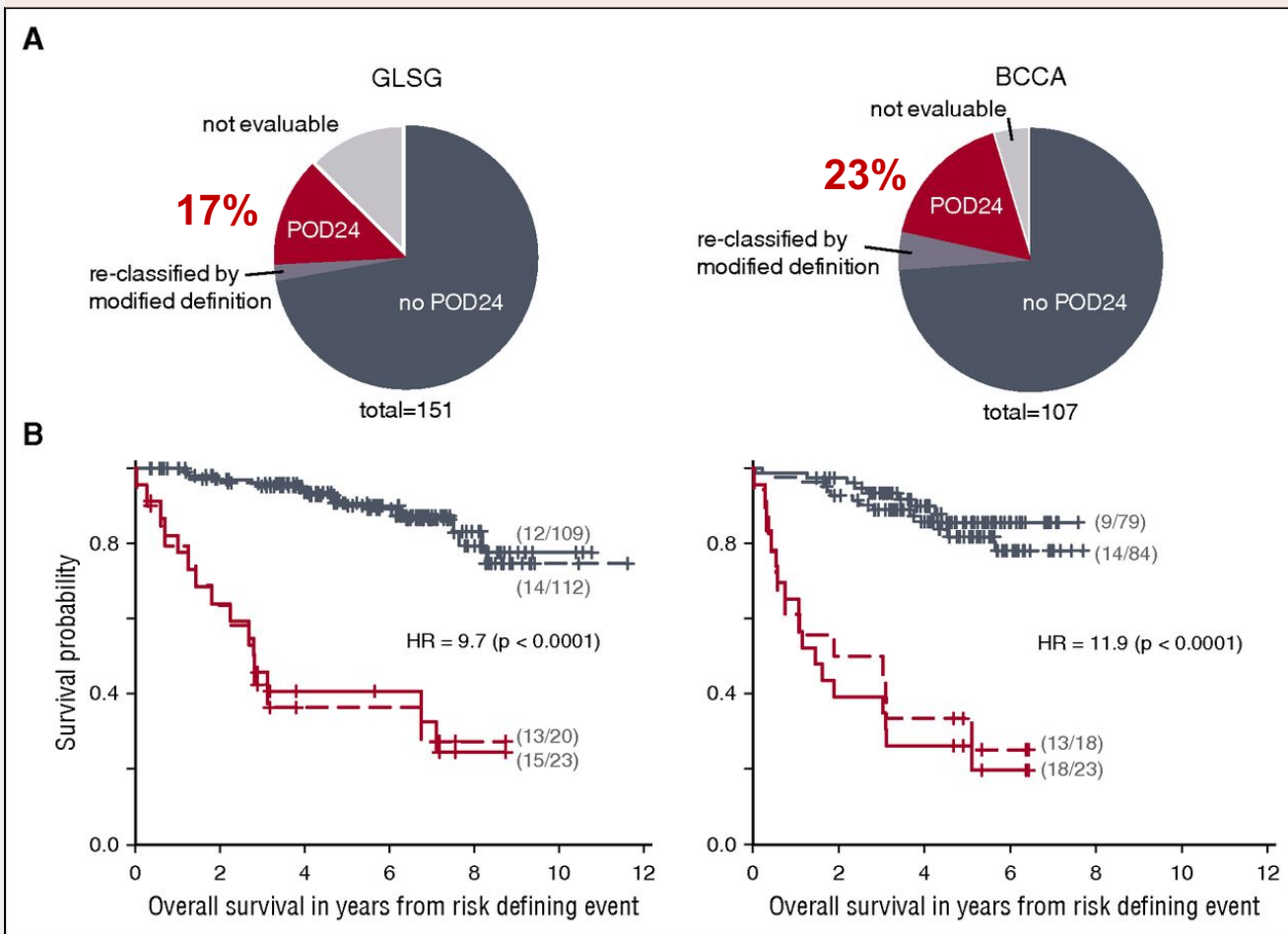


Validation in 13 randomized clinical trials

- 46% received R + chemotherapy
- 49% chemotherapy without R
- 5% R alone
- **5-year OS 71%** worse for POD24 compared with all other patients, including those who did not relapse

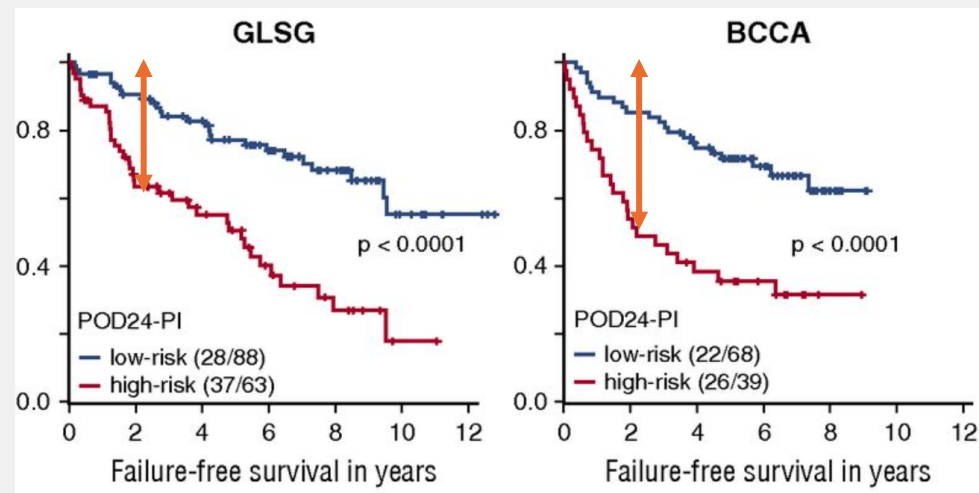
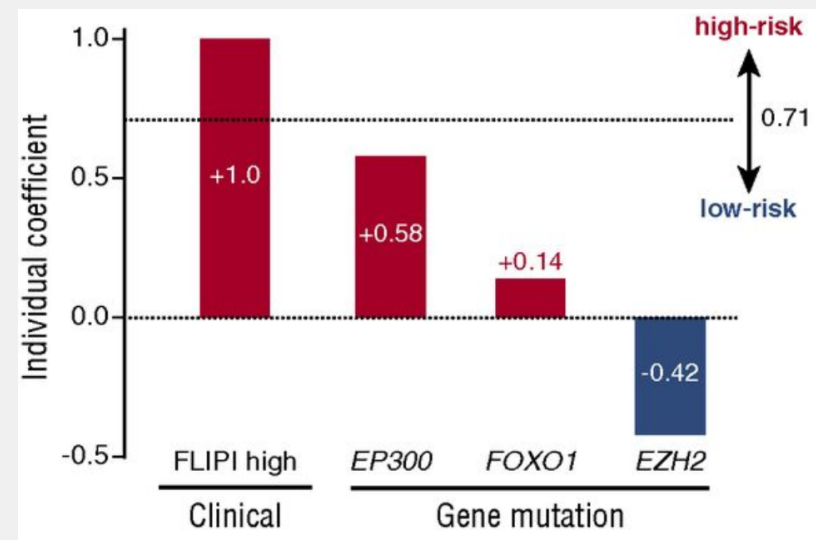


Consistent prognostic value of POD24 in two datasets



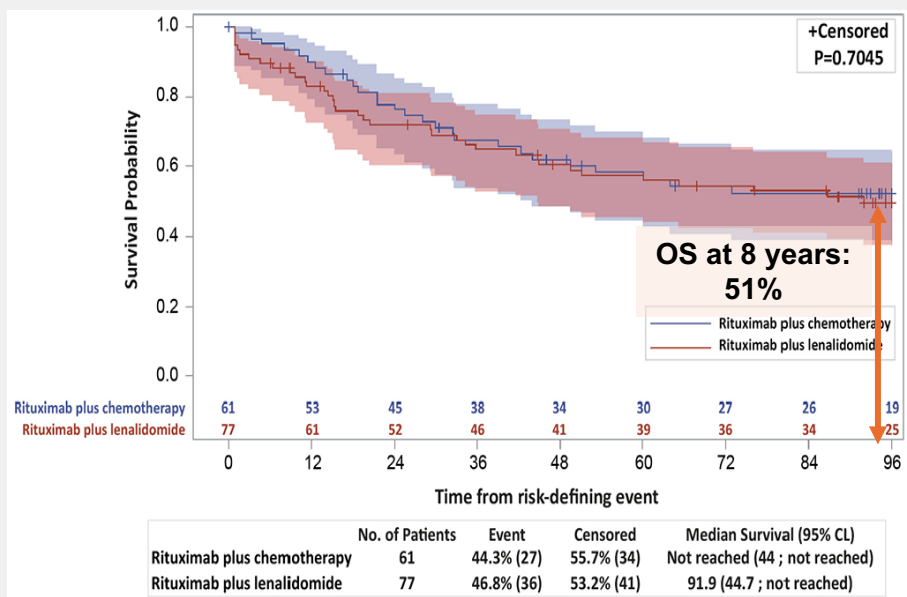
Jurinovic et al., Blood 2016

- POD24-PI predicted POD24 better than FLIPI



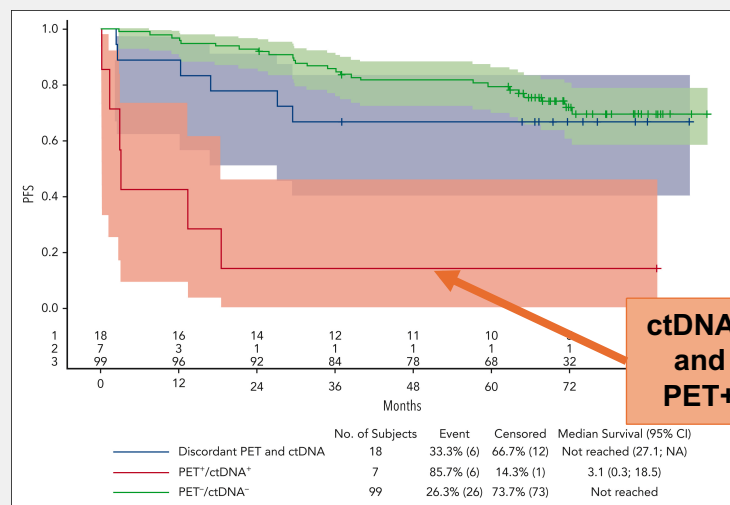
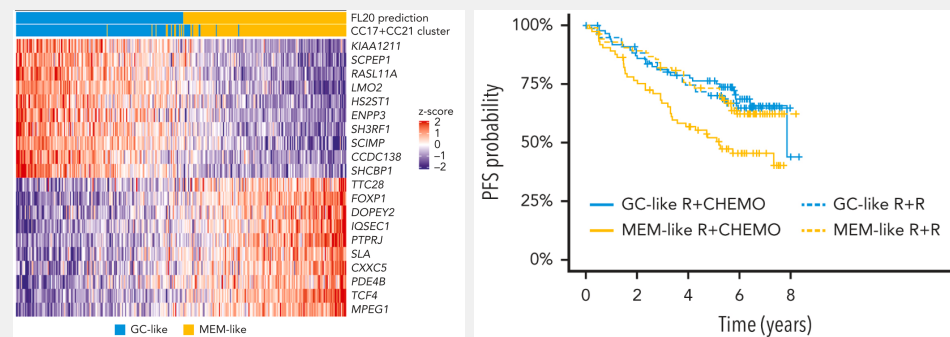
RELEVANCE

- >1000 patients randomized to R2 vs R-chemo
- **POD24: 17%**
- 8-year OS 51% after POD24
- Prognosis similar in both arms



Molecular analysis

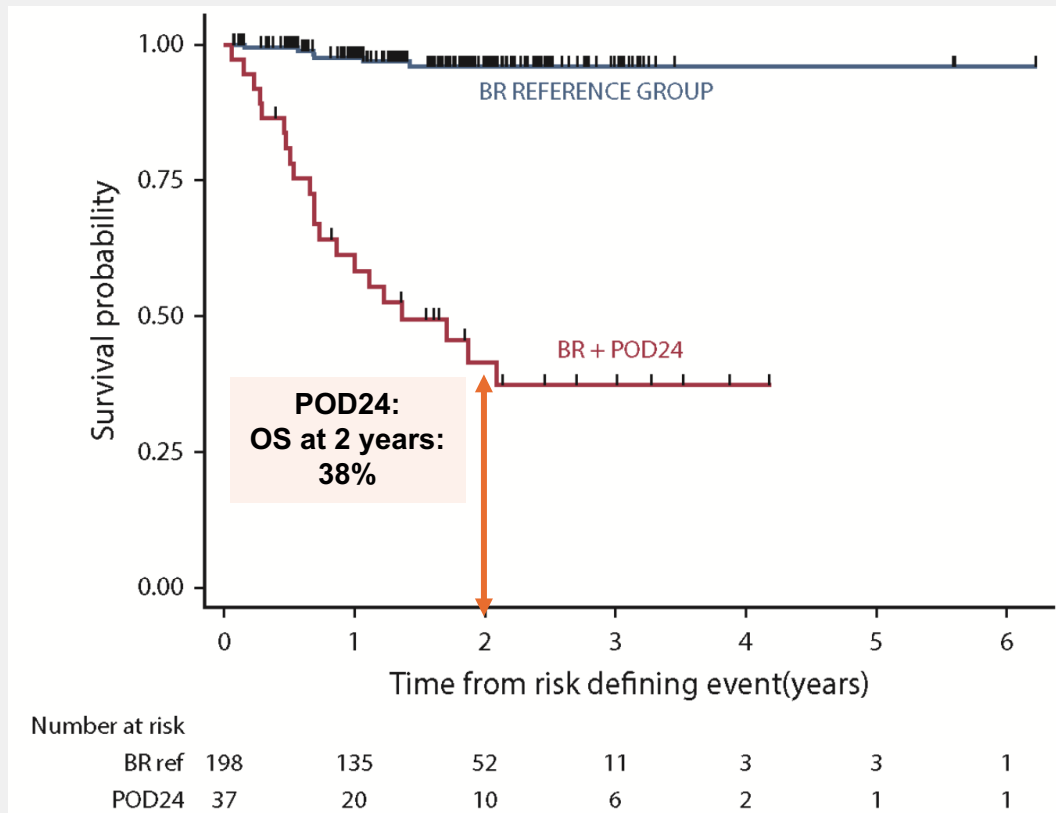
- Gene expression profiling: Memory-like B cell cluster:
- Increased rate of POD24 with chemotherapy (not R2)



ctDNA and PET predict POD24

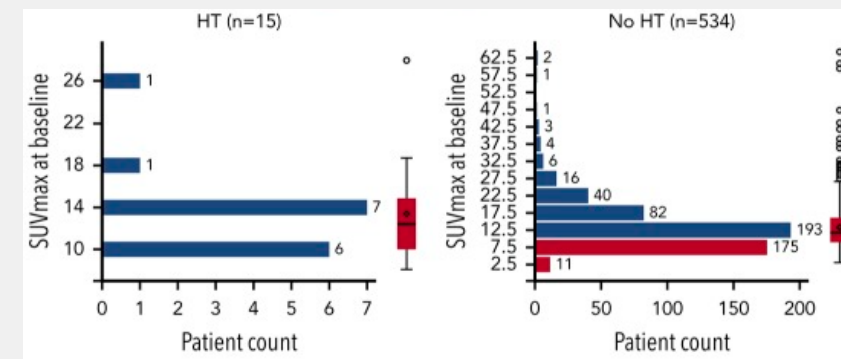
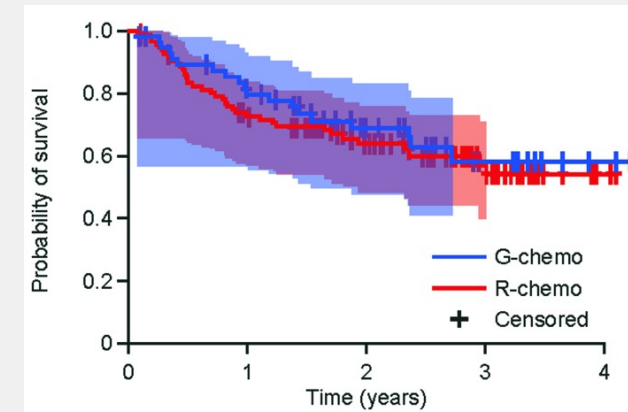
- ctDNA(-) at end of treatment: 92% NPV for lack of POD24
- ctDNA(+): PPV only 58%
- PET(-): NPV of 93%
- PET(+): PPV of 45%
- **ctDNA & PET+: PPV of 86%**

- **BCCA:** 296 patients treated in 2013-2018 with BR
- **POD24 in 13%** (historically with RCVP: 23%)
- **76%** with histologic transformation at POD24 events



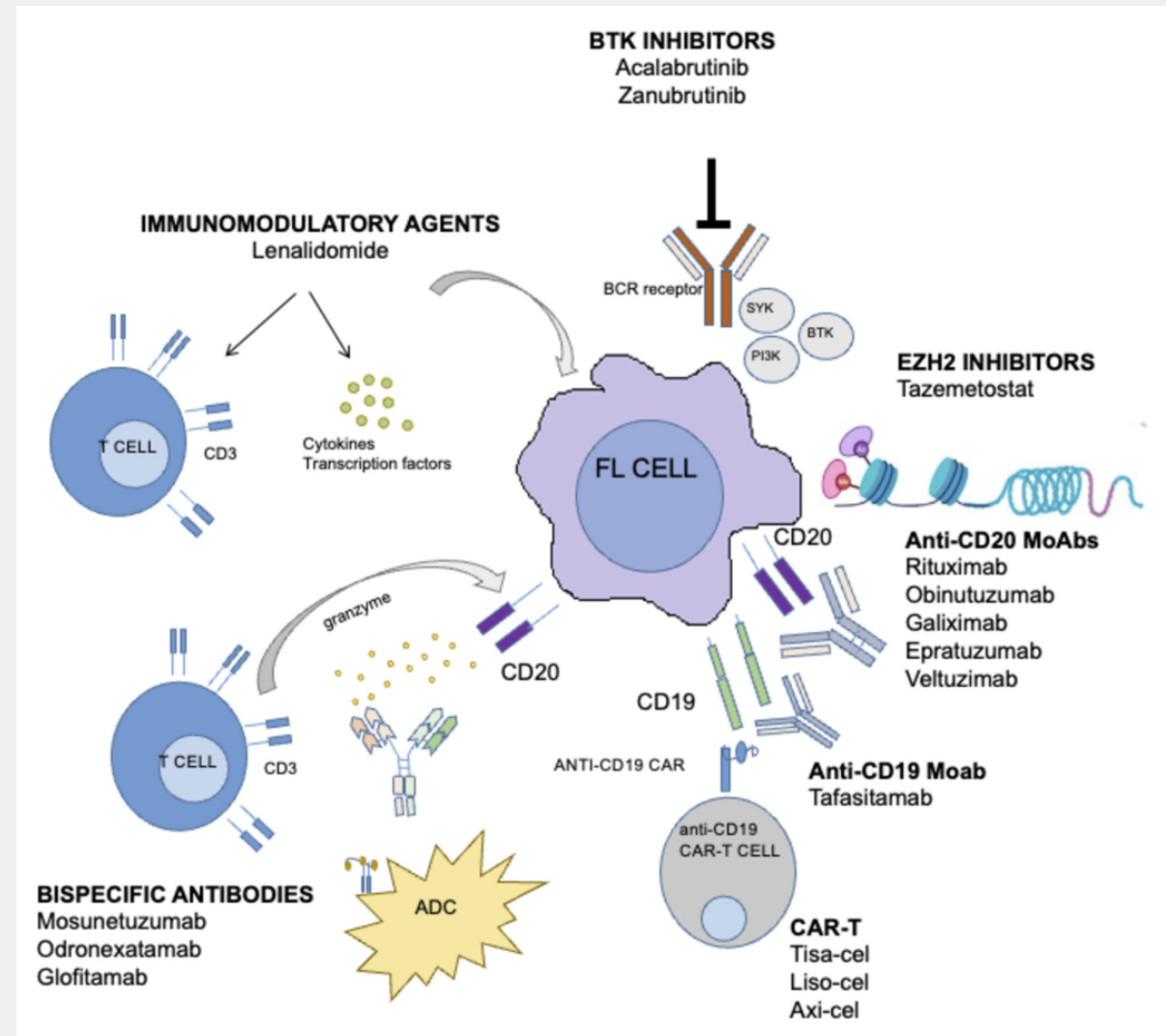
Freeman et al., Blood 2019;

- **GALLIUM:** N=1202 patients R/G + chemotherapy
- **POD24 10%** with obinutuzumab, 17% with R
- **19%** with histologic transformation at POD24 events
- **Baseline PET/SUV did not predict transformation** (median baseline SUVmax 12.4 vs 11.8)



Seymour et al, Haematologica 2019; Mir et al., Blood 2020

Relapsed/refractory FL	
Symptomatic / needs therapy	
<ul style="list-style-type: none"> • Remission >2 years OR • Unfit for other options 	Rituximab or <i>obinutuzumab</i> ⚠️ monotherapy
<ul style="list-style-type: none"> • Remission <2 years , CrCl>30 • Higher burden of disease 	Rituximab or <i>obinutuzumab</i> ⚠️ + lenalidomide
<ul style="list-style-type: none"> • <25% BM involvement • Platelets >100 x 10⁹/L 	⁹⁰ Y ibritumomab tiuxetan
<ul style="list-style-type: none"> • Weekly dosing preferred 	Copixisib
<ul style="list-style-type: none"> • Oral therapy preferred 	Umbralisib
<ul style="list-style-type: none"> • <i>EZH2</i> mutation 	Tazemetostat
<ul style="list-style-type: none"> • Fit for low-intensity chemotherapy 	Rituximab + chlorambucil or bendamustine



IMiD/CeMod/BTKi (2019)

- Rituximab/Obinutuzumab + lenalidomide
- BTKi: Rituximab + zanubrutinib

CAR T-cell therapy (2020)

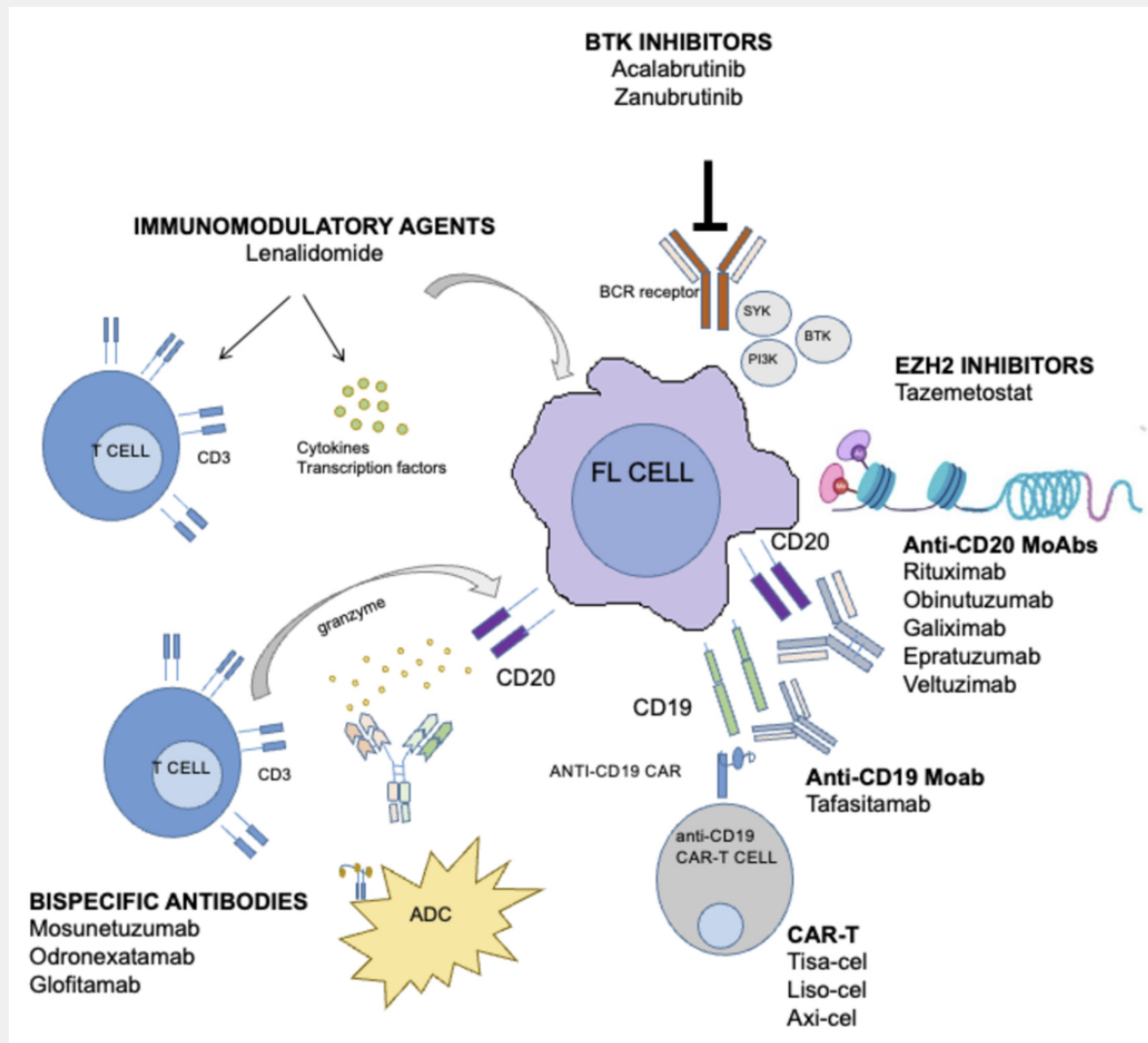
- Axi-cel
- Liso-cel
- Tisagenlecleucel

Bispecific antibodies (2023)

- Mosunetuzumab
- Epcoritamab
- Odronextamab

Immunotherapy combinations (2025)

- Tafasitamab-R2
- Epcoritamab-R2
- ADC's: loncastuximab tesirine



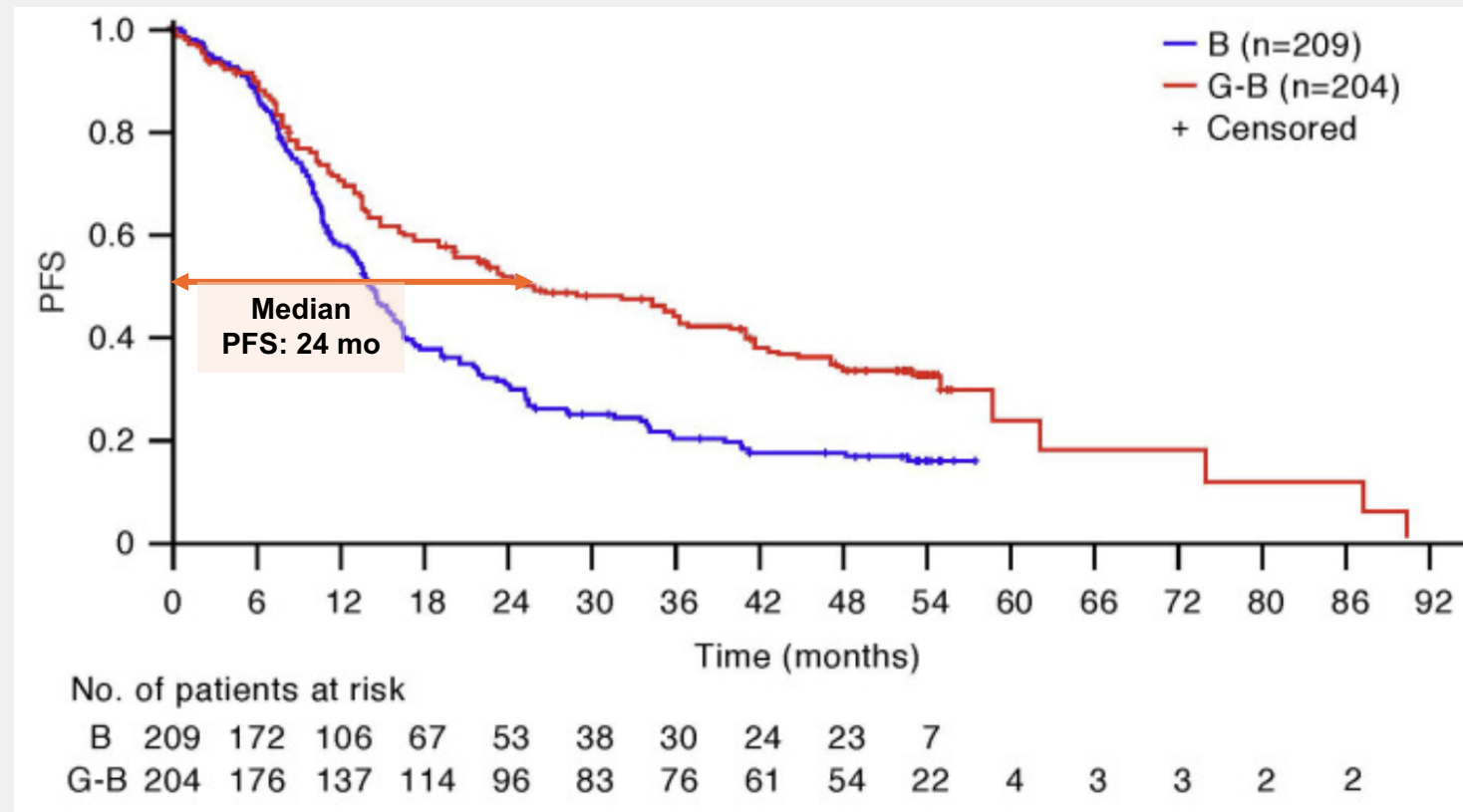
Patients:

- “documented rituximab-refractory iNHL”

Treatment:

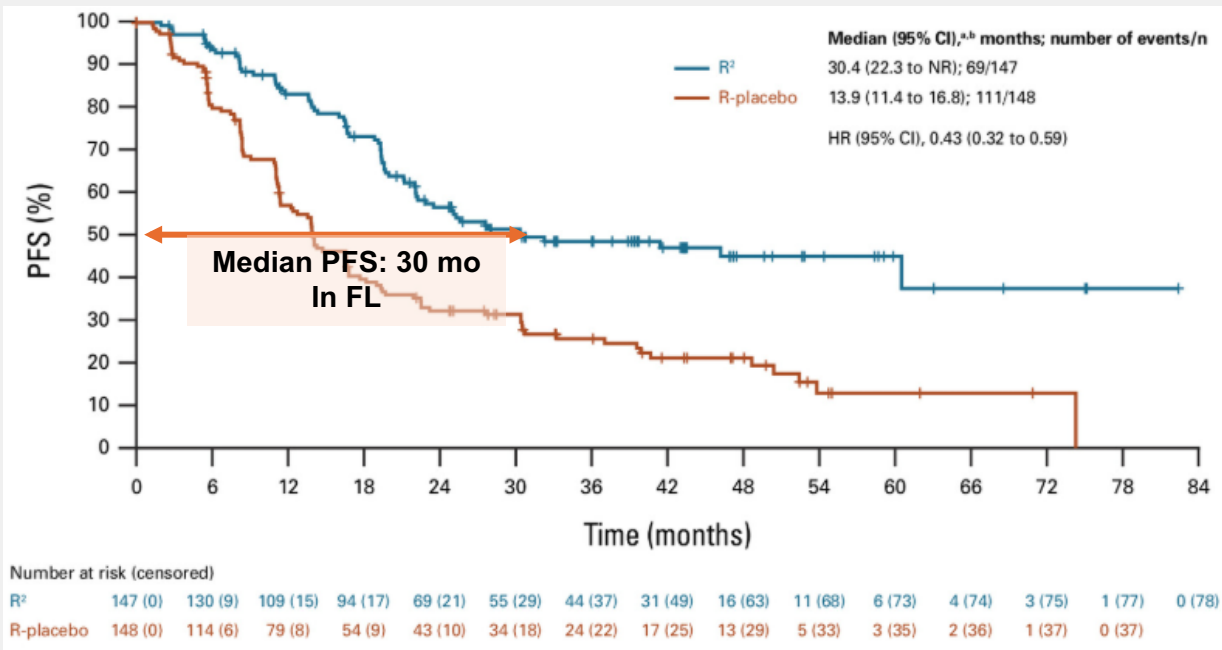
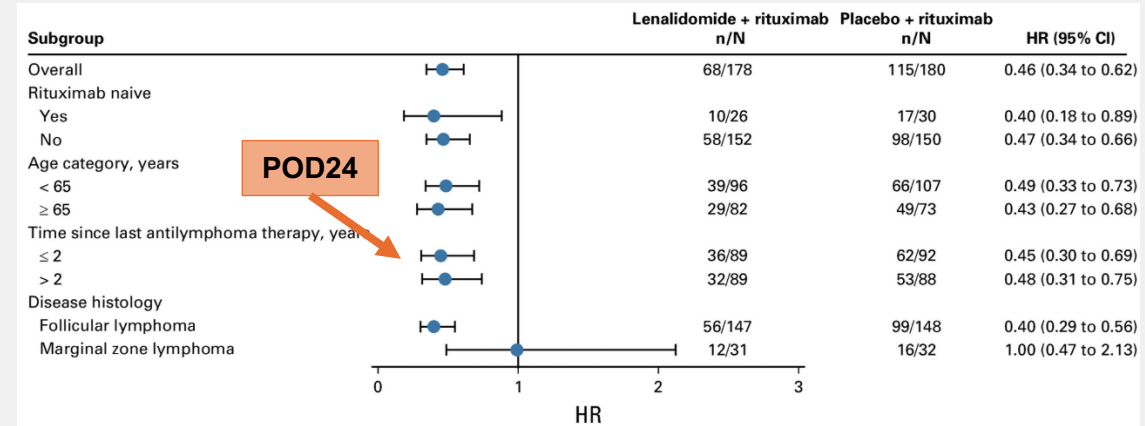
- Bendamustine 90 mg/m² + Obinutuzumab
- Includes 2 years of maintenance q2mo

	Obinutuzumab plus bendamustine (n=194)	Bendamustine monotherapy (n=202)
(Continued from previous column)		
Rituximab-refractory type		
Rituximab plus chemotherapy		
No response or progressive disease during or within 6 months after last rituximab induction dose	76/156	86/157 (55%)
Progressive disease during or within 6 months after last rituximab maintenance dose	76/156	70/157 (45%)
Other†	4/156 (3%)	1/157 (1%)
Rituximab monotherapy	38 (20%)	45 (22%)



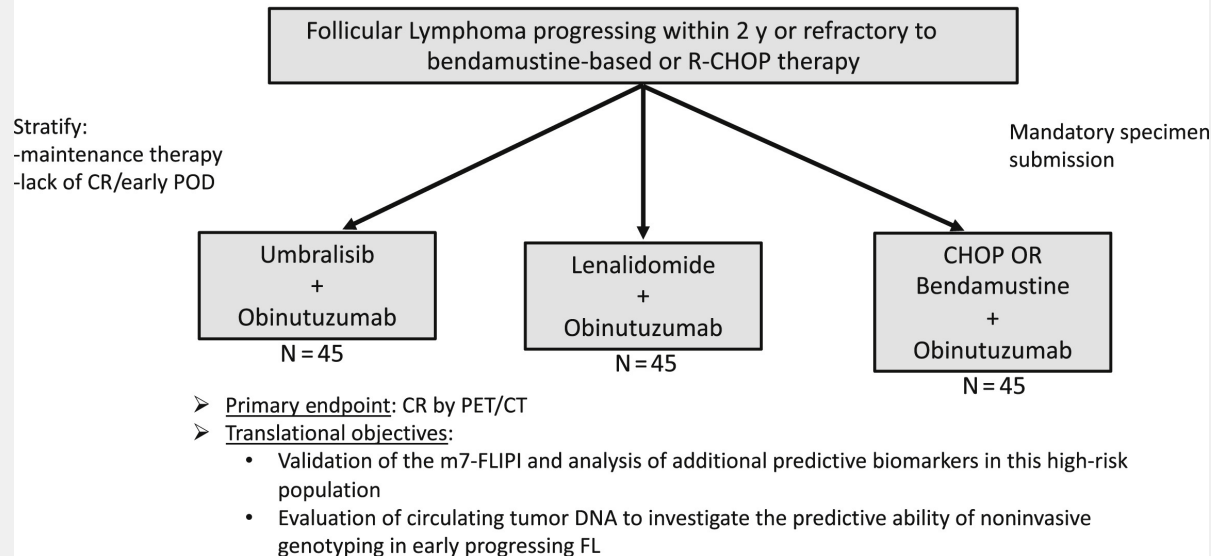
Rituximab + lenalidomide: AUGMENT trial

- N= 358 patients with FL (82%) or MZL (18%)
- Median age = 64 years (16—88)
- FLIPI score: 0/1 = 31%, 2 = 31%, 3/5 =37%
- Number of **prior therapies: Median = 1 (range, 1-12)**
- **POD24: 33%**
- Refractory to prior regimen: 16%

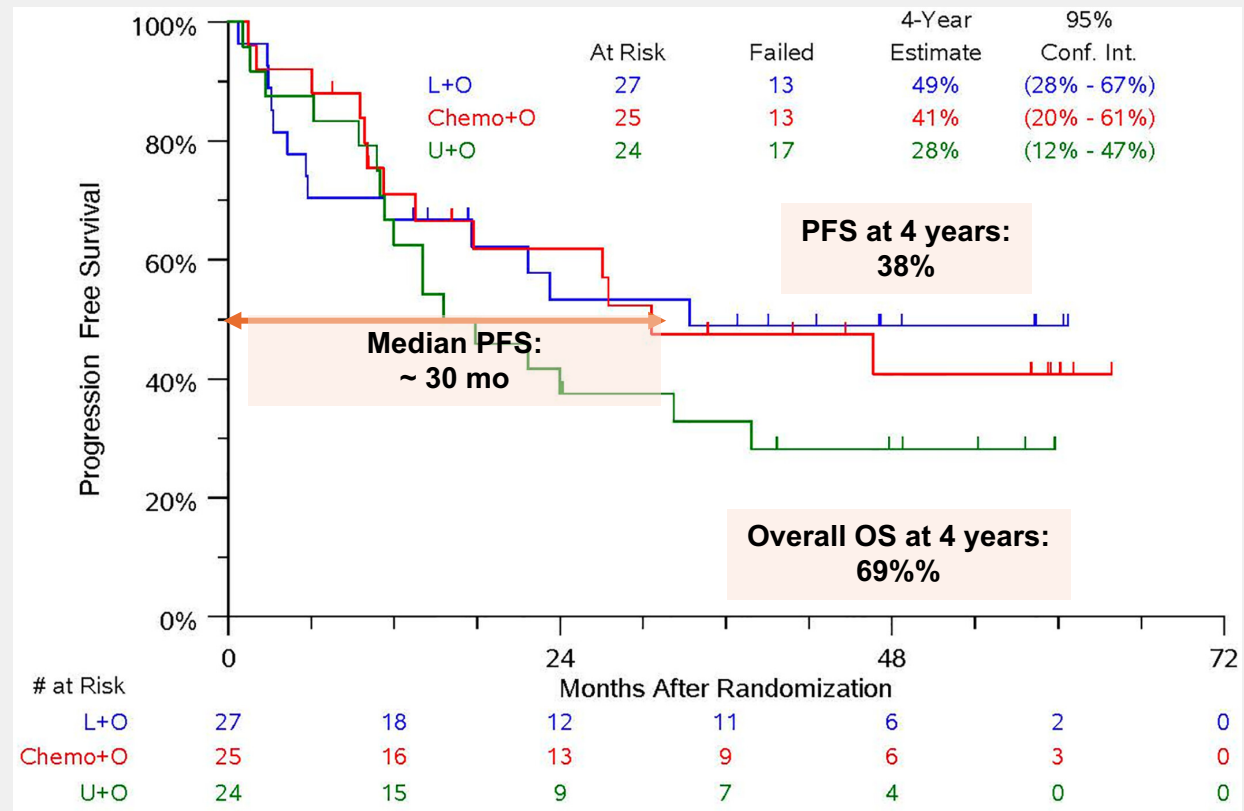


	All FL patients N=147	POD24 N=56	No POD24 N=89
Median PFS Mo	39.4	30.4	39.4
ORR %	80	80	80
CR, %	35	30	37

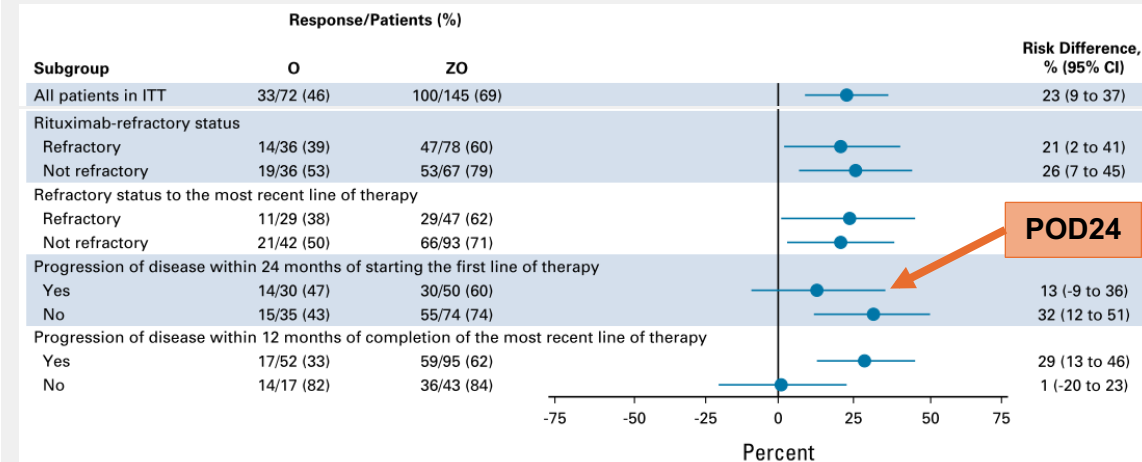
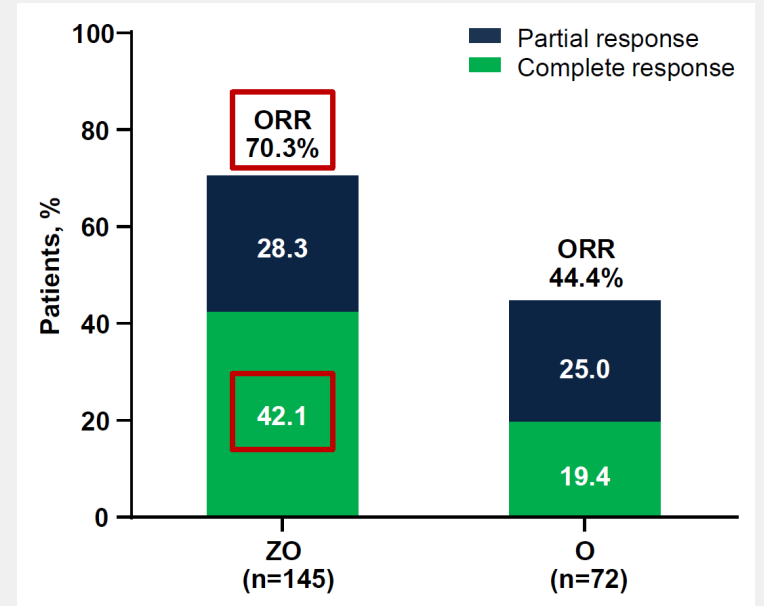
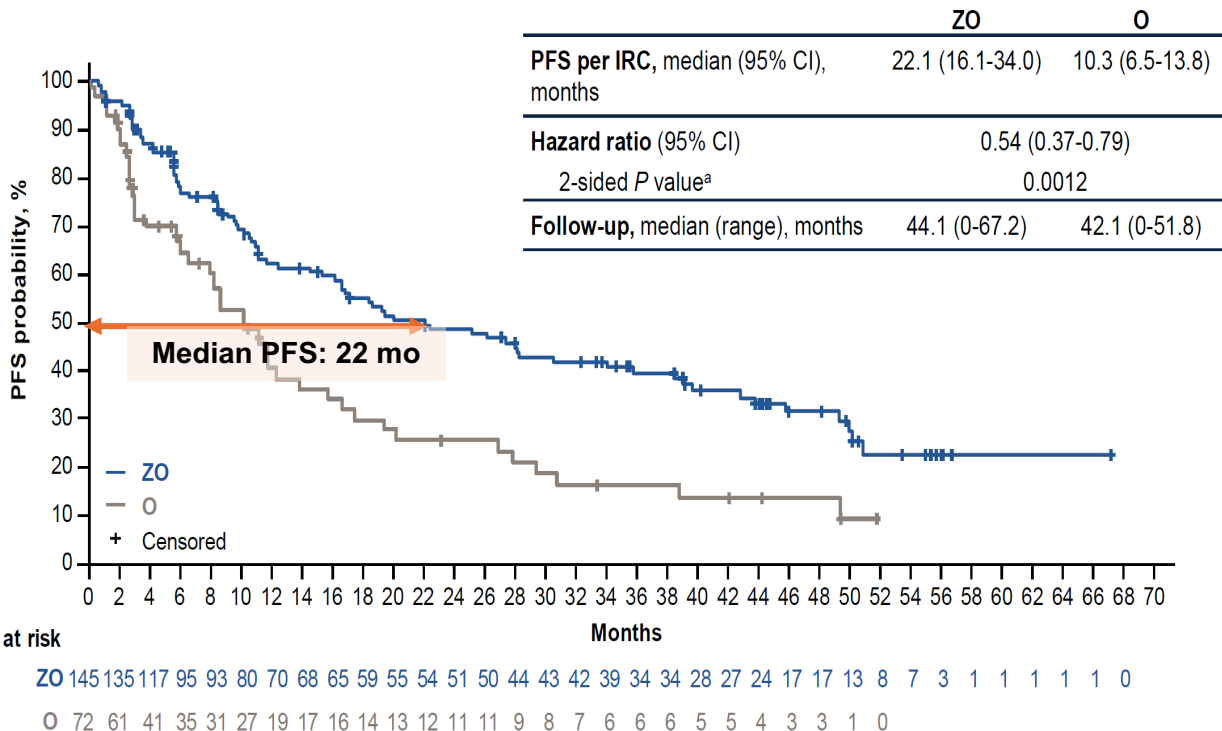
S1608: Randomized Phase II Trial in Early Progressing or Refractory Follicular Lymphoma



- First line treatment: RCHOP 53%, BR 47%
- CR rate: 52-64%
- 6 of 76 enrolled patients had ASCT in CR (with no relapses)

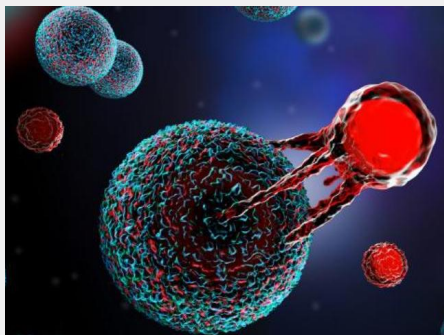


- N= 217 patients with FL
- Median age = 64 years (31—88)
- High FLIPI score: 53%
- Number of **prior therapies: Median = 3 (range, 2-11)**
- **POD24: 37%**
- Refractory to prior regimen: 35%



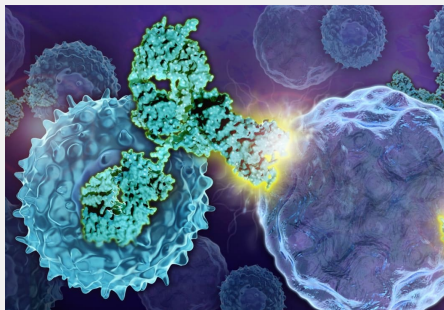


3rd-line option: **Immunotherapy**



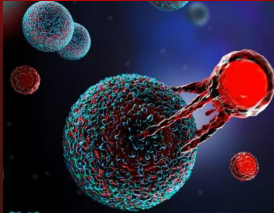
CAR T-cells (CD19)

- Axicabtagene autoleucel
- Lisocabtagene maraleucel
- Tisagenlecleucel



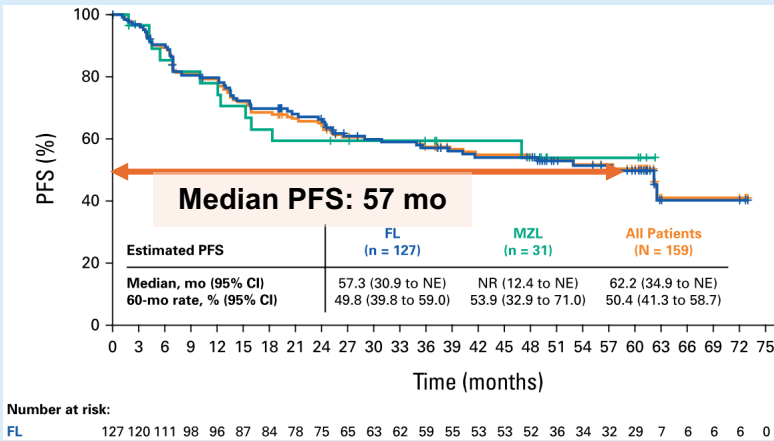
Bispecific antibodies (CD20×CD3)

- Mosunetuzumab
- Epcoritamab
- Odronextamab
- BsAbs + Len



Axi-cel (ZUMA-5)

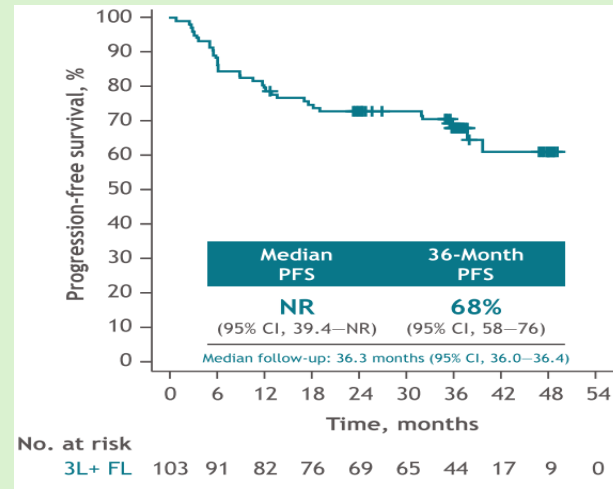
- 127 patients with FL (+ 31 MZL)
- Median 3 prior lines of therapy
- **POD24: 56%; ORR=94%, CR=79%**



- **CRS: 82%** (G3+: 7%)
- **ICANS: 60%** (G3+: 19%)
- **SAE: 50%**
- **G3+ infection: 18%**, IVIG = 31%
- Better responses with more naïve T cells in the product
- This correlates with benda exposure

Liso-cel (TRANSCEND FL)

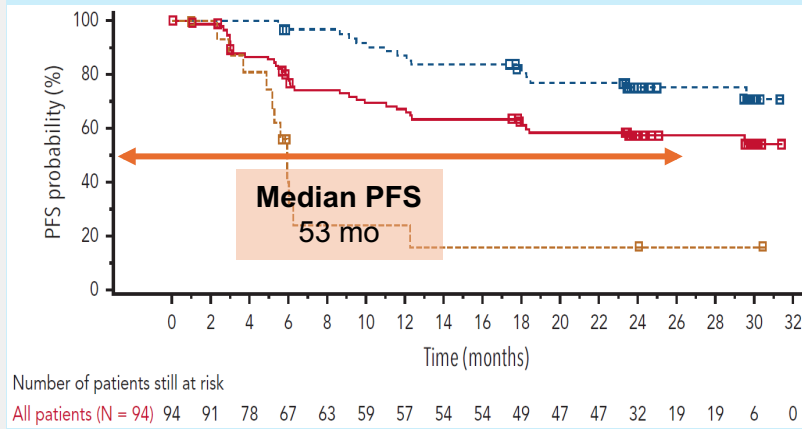
- 130 patients with FL (2L+)
- Median 3 prior lines of therapy
- **POD24: 56%; ORR=97%, CR=94%**



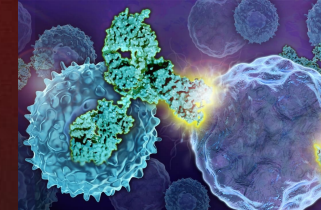
- **CRS: 59%** (G3+: 1%)
- **ICANS: 16%** (G3+: 2%)
- **SAE: 47%**
- **G3+ infection: 12%**

Tisagenlecleucel (ELARA)

- 98 patients with FL (+ 31 MZL)
- Median 3 prior lines of therapy
- **POD24: 63%; ORR=86%, CR=69%**

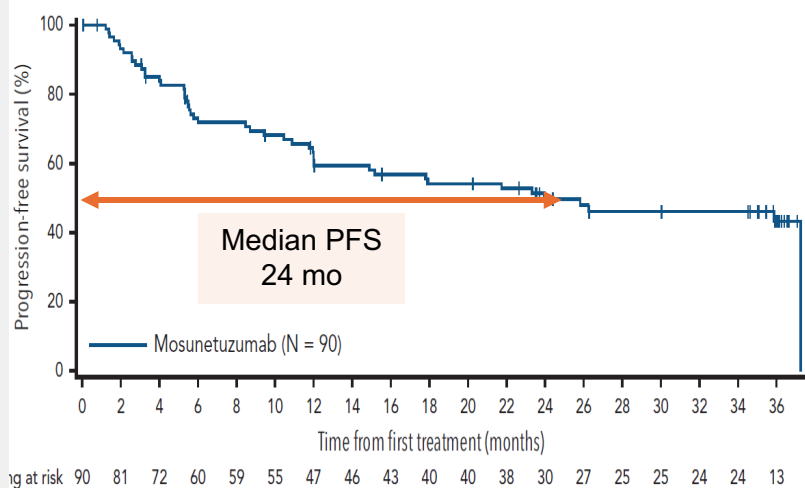


- **CRS: 49%** (G3+: 0%)
- **ICANS: 37%** (G3+ = 3%)
- **SAE: 28%**
- **G3+ infection: 5%**



Mosunetuzumab

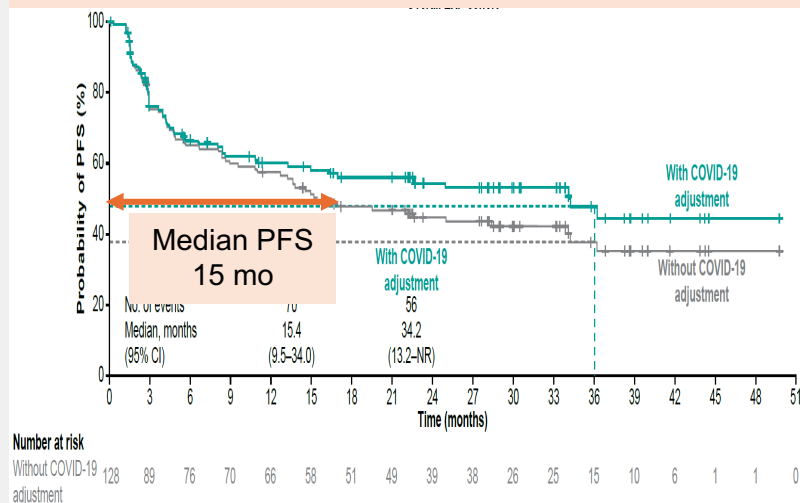
- 90 patients
- Fixed-duration, 6 months of therapy
- Median **3 prior lines** of therapy
- **POD24: 53%**



- **CRS: 44%** (G3+: 2%)
- SAE: 47%
- SAE infection: 20%

Epcoritamab

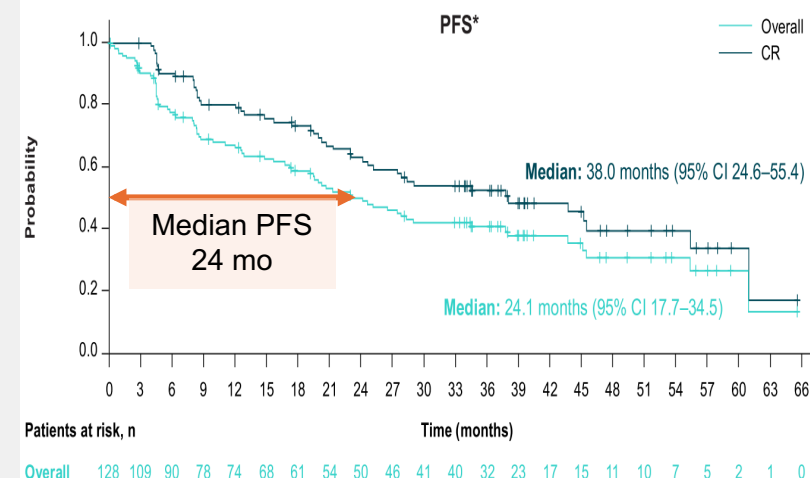
- 128 patients
- **Treatment until progression**
- Median **3 prior lines** of therapy
- **POD24: 42%**



- **CRS: 67%** (G3+: 2%)
- SAE: 69%
- G3+ infection: 35% (COVID-19: 7%)

Odronektamab

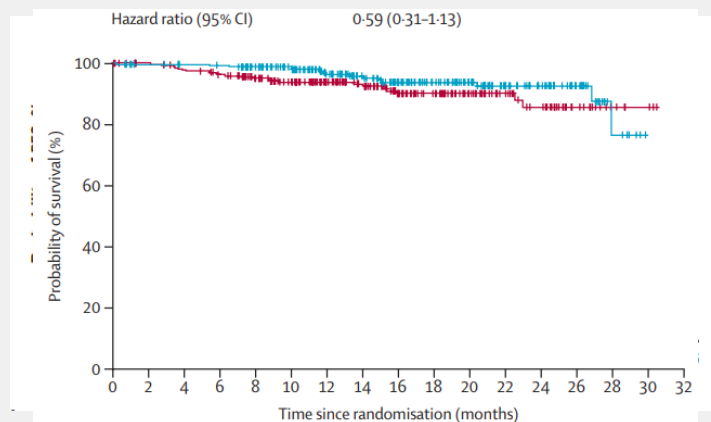
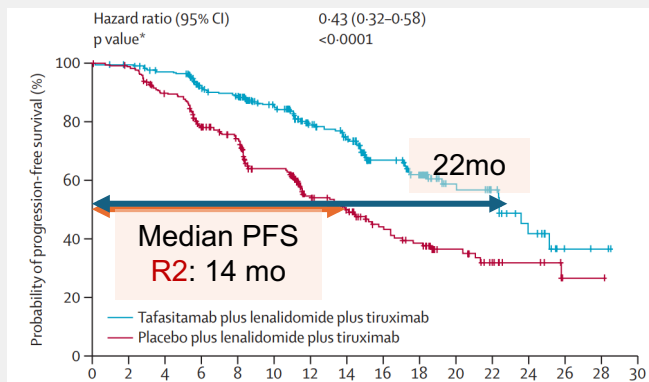
- 128 patients
- **Treatment until progression**
- Median **3 prior lines** of therapy
- **POD24: 49%**



- **CRS: 57%** (G3+: 1%)
- SAE: 68%
- G3+ infection: 31%

Tafasitamab + R2 vs R2

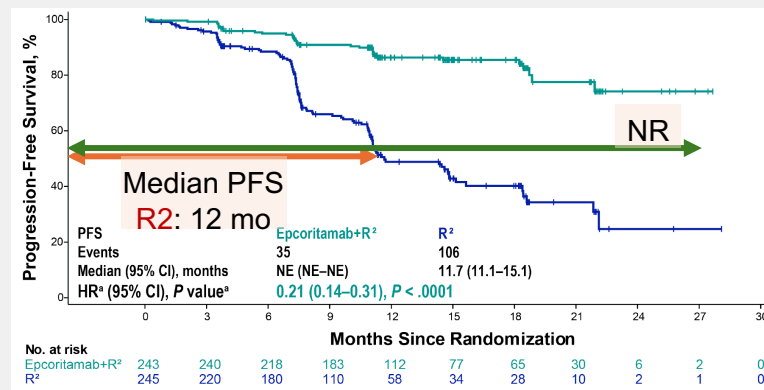
- 548 patients randomized to R2 vs Tafa-R2
- Tafa: weekly x3mo, **q2wks x9mo**
- **POD24: 32%** - no difference in PFS
- **SAE: 34%**



Sehn et al., Lancet 2026

Epcoritamab + R2 vs R2

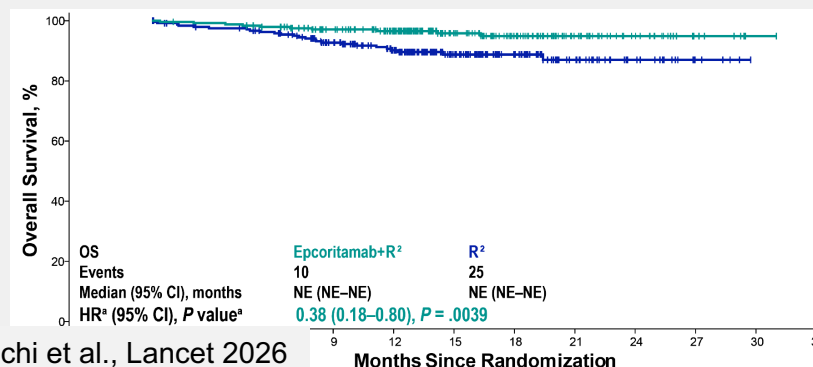
- 488 patients randomized to R2 vs Epcor-R2
- Epcor: weekly x3mo, **q4wks x 9mo**
- **POD24: 41%** - no difference in PFS
- **SAE: 56%**; infections: 77%, G3+: 33%



Sano et al., ASH 2025

Odronektamab + lenalidomide vs R2

- (OLYMPIA 5)
- Pending results

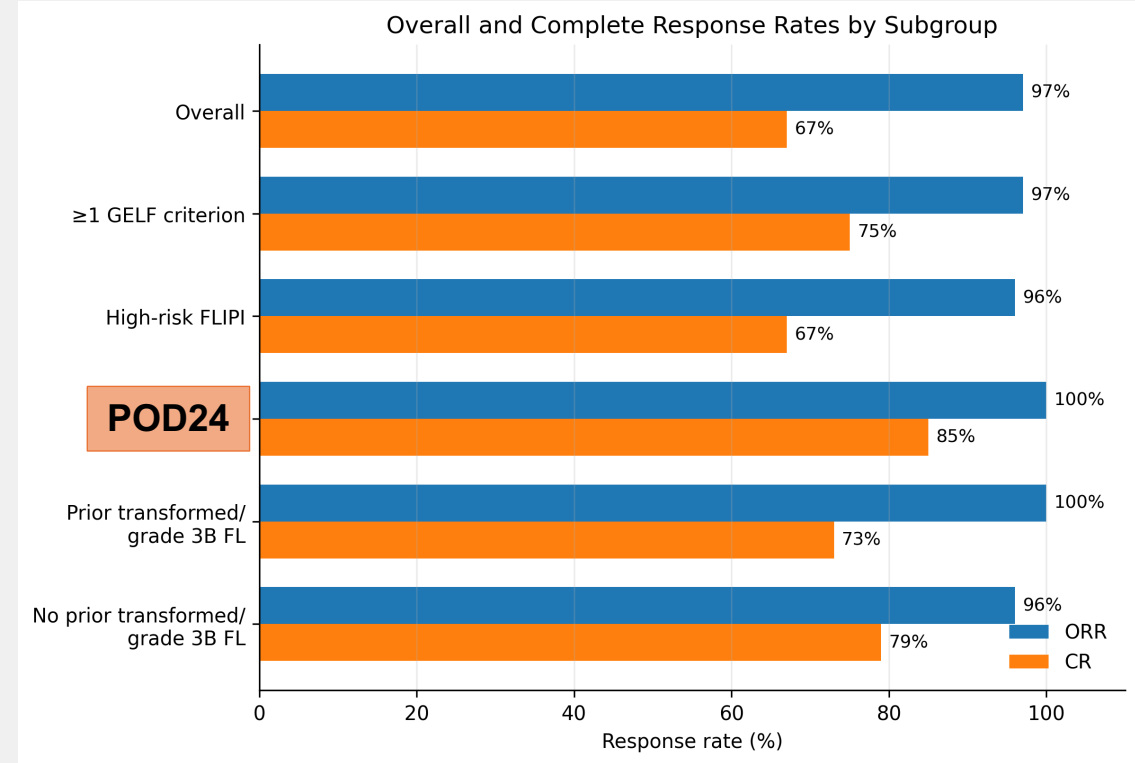
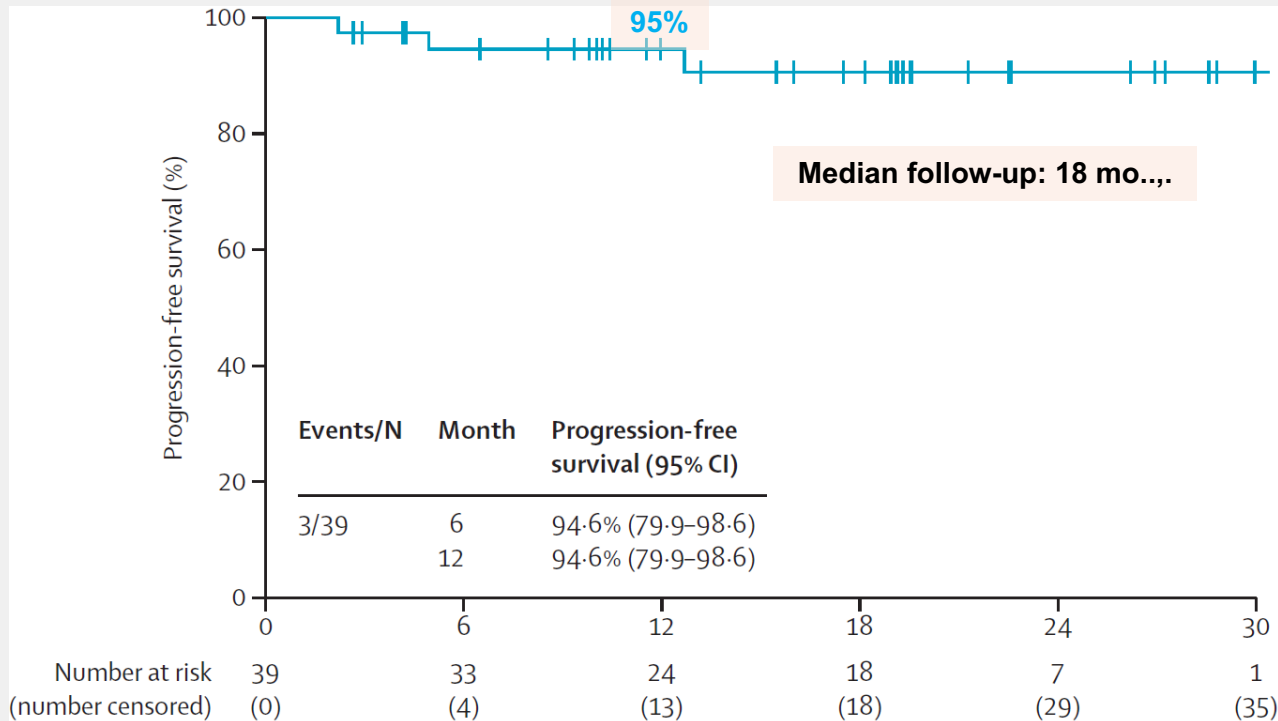


Vitolo et al., ASH 2025

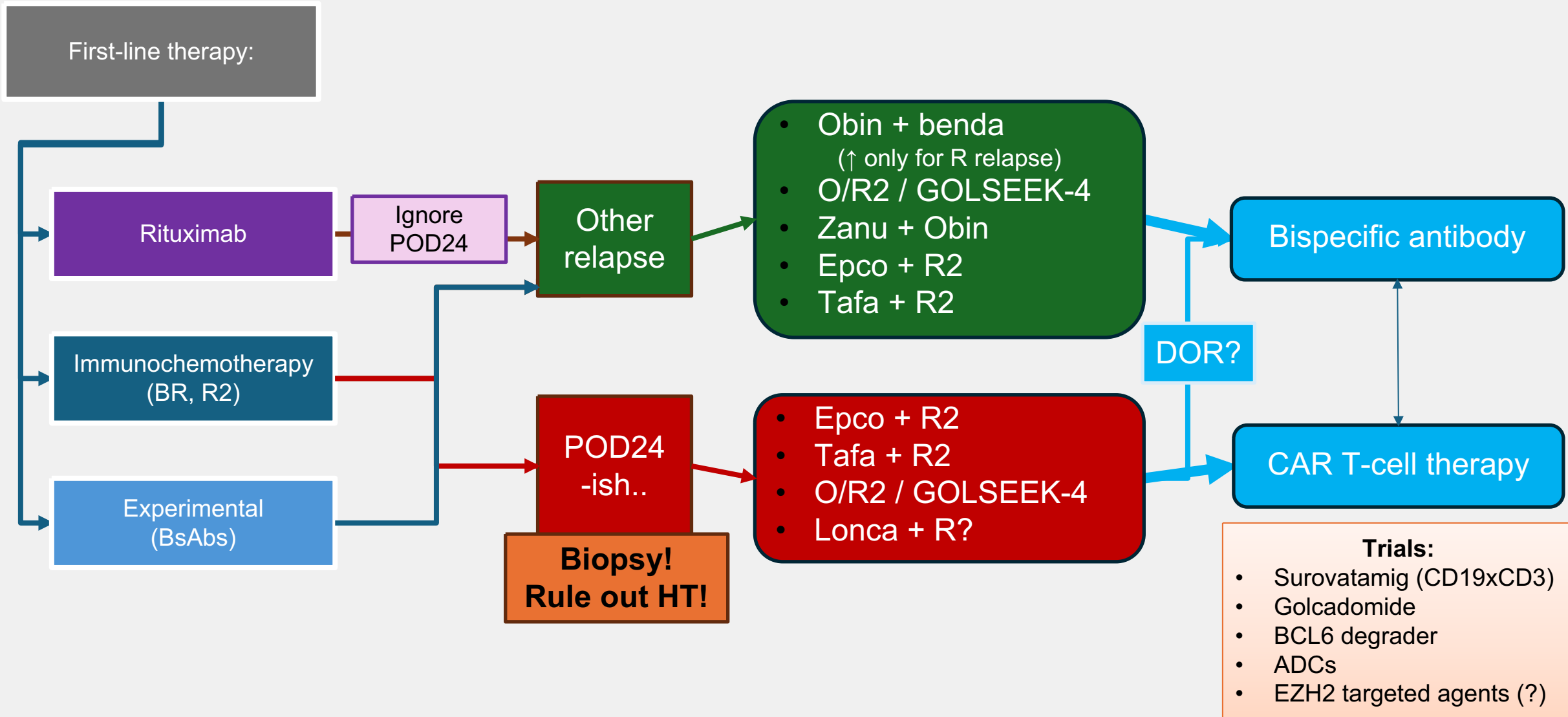
Falchi et al., Lancet 2026

CD19-directed ADC: loncastuximab tesirine + rituximab

- N= 39 patients with FL
- Median age = 68 years (58—77)
- High FLIPI score: 61%
- Number of **prior therapies: Median = 1 (range, 1-6)**
- **POD24: 51%**
- Refractory to prior regimen: 51%



	CAR T cells (liso-cel)	Bispecific antibodies (mosunetuzumab)	Bispecific combos (epco-R2)
ORR	97%	78%	95%
CR	94%	60%	83%
Median PFS	~55 months	24 months	?
PFS at 3y	68%	43%	?
CRS (all / G3+)	59% / 1%	44% / 2%	35% / 0%
Other toxicity issues	G3+ infections 12% Prolonged cytopenias IVIg dependence	SAE infections 20%	G3 infections 33%



Thank you!

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