Novel Therapies for Follicular Lymphoma

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Dana-Farber Cancer Institute

Disclosures

- Advisory board: Genmab, Bristol Myers Squibb, Abbvie, Ipsen, KITE, Pfizer, AstraZeneca.
- Consulting: Abbvie, Third Bridge.
- Honararia: Genmab, Abbvie.
- Institutional research funding: Merck, Bristol Myers Squibb, Genmab, Genentech/Roche.

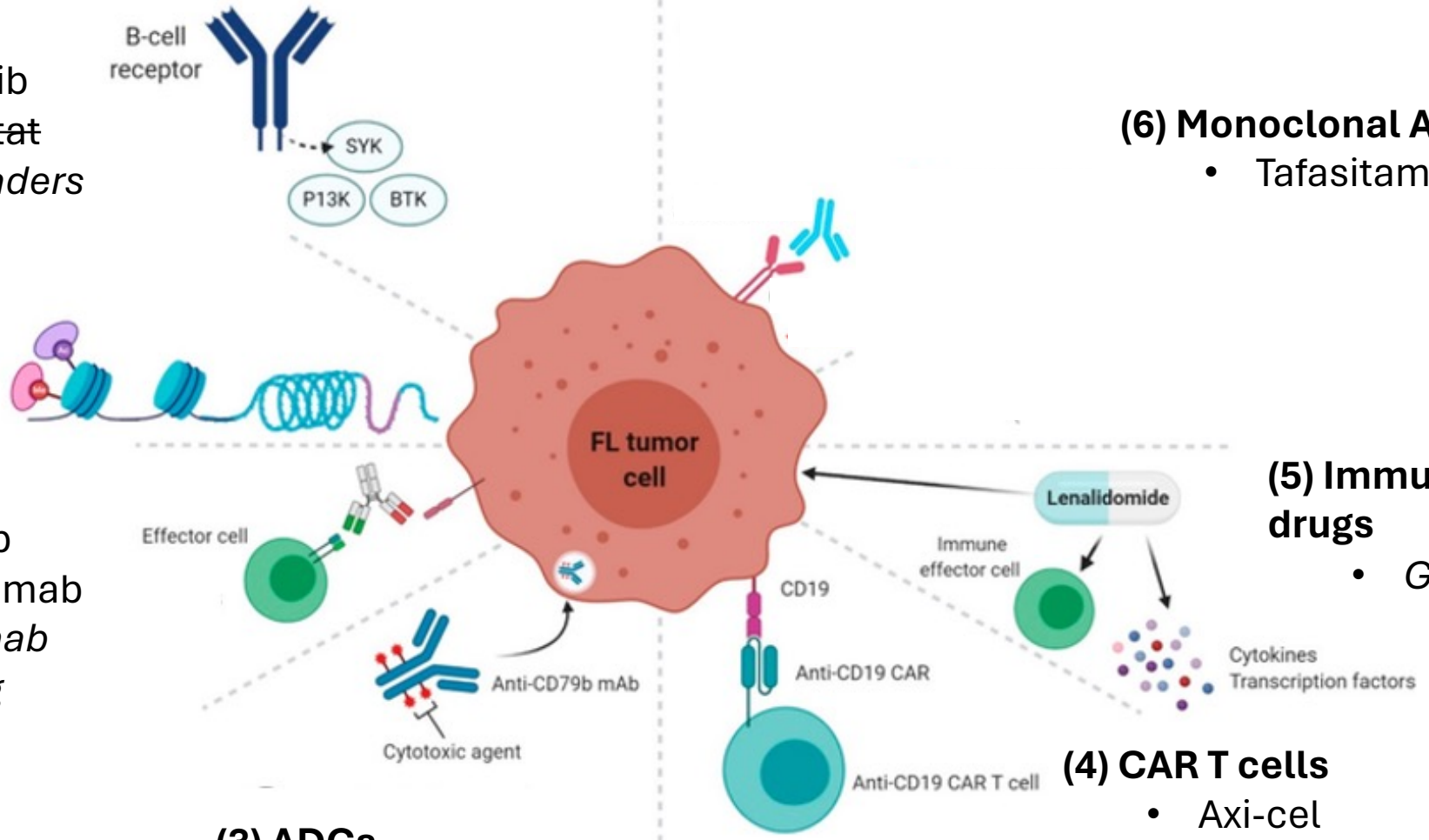
Novel Agents for Follicular Lymphoma

(1) Targeted drugs

- Zanubrutinib
- ~~Tazemetostat~~
- *BCL6 degraders*

(2) BsAbs

- Epcoritamab
- Mosunetuzumab
- *Odronextamab*
- *Surovatamig*



(3) ADCs

- Loncastuximab

(4) CAR T cells

- Axi-cel
- Tisa-cel
- Liso-cel

(5) Immunomodulatory drugs

- *Golcadomide*

(6) Monoclonal Abs

- Tafasitamab

Nath, JPM 2021

Agenda

- Novel agents are challenging traditional treatments across all lines
- Where are novel agents now?
  - BsAbs
  - Other (Zanubrutinib, Loncastuximab, Golcadomide)
  - CD19 CAR T cell therapy**
- Where will novel agents be in the (near) future
  - 2L treatment
  - 1L treatment

Current NCCN guidelines for FL treatment

First-line treatment

High tumor burden

- Chemoimmunotherapy (R or G + bendamustine, CHOP or CVP)*
- Lenalidomide + rituximab (R2)

Low tumor burden

- Rituximab*
- Watchful waiting

2L treatment

- Chemoimmunotherapy (R or G + bendamustine, CHOP or CVP)*
- R2
- **Tafasitamab** + R2
- **Epcoritamab** + R2

Older or Infirm

- Rituximab*
- ~~**Tazemetostat**~~

3L treatment

Preferred

- **CD19 CAR T cell therapy (axi-cel, liso-cel, tisacel)**
- **CD20 BsAb (epcoritamab, mosunetuzumab)**

Other Recommended

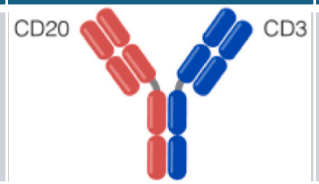
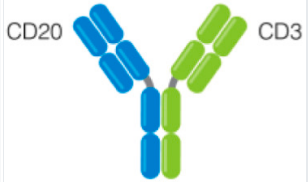
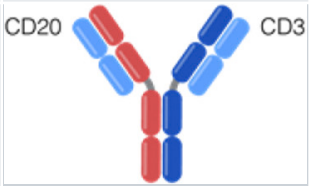
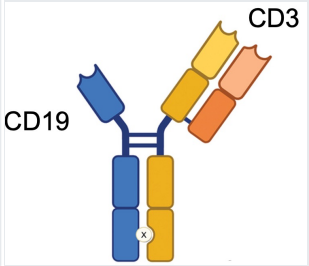
- ~~**Tazemetostat**~~
- **Zanubrutinib + obinutuzumab**
- **Loncastuximab tesirine**

*with optional CD20 mAb maintenance therapy

R – Rituximab
G – Obinutuzumab
CHOP – Cyclophosphamide, doxorubicin, vincristine, prednisone
CVP - Cyclophosphamide,, vincristine, prednisone

Recommended regimens based on NCCN guidelines

Bispecific Antibodies

	Schematic Depiction	Formulation	Pre-treatment	Step-up dosing	Duration of monotherapy tx for FL	FDA approvals
Epcoritamab (CD3/CD20)		SC	No	2→3 step-up doses	Indefinite	**FL (3L, 2L with R2)** DLBCL (3L)
Mosunetuzumab (CD3/CD20)		IV (SC)	No	2 step-up doses	~6 months for CR, 12 months for others	**FL (3L)**
Odronextamab (CD3/CD20)		IV	No	6 step up doses	Indefinite	NA
Surovatamig (CD3/CD19)		IV	No	2 step-up doses (Cycle 1 doses currently inpatient)	24 months	NA

Images from *Falchi, Blood 2023*

BsAbs - Efficacy

	N	Median prior lines	POD24	High-risk FLIPI	ORR	CMR	PFS	Citations
Mosunetuzumab	**90**	**3**	**52%**	**42%**	80%	60%	Median PFS - 24.0 m 3-year PFS – 43%	Sehn, Blood 2024
Epcoritamab	**128**	**3**	**53%**	**60%**	82%	63%	Median PFS – 15.4 m 3-year PFS – 38%	Linton, ICML 2025
Odronextamab	**157**	**3**	**49%**	**58%**	81%	74%	Median PFS 23.0m 3-year PFS - 38%	Jagadeesh, ASCO 2025

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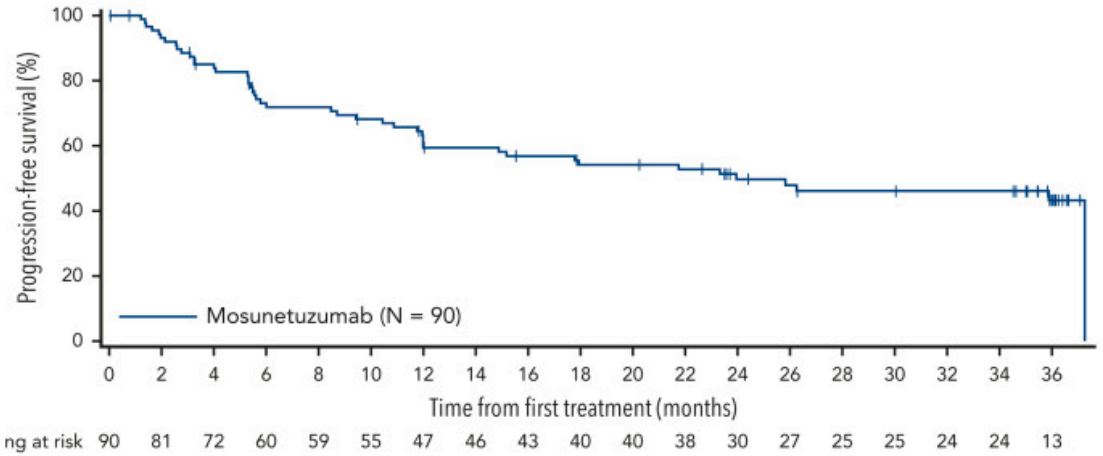
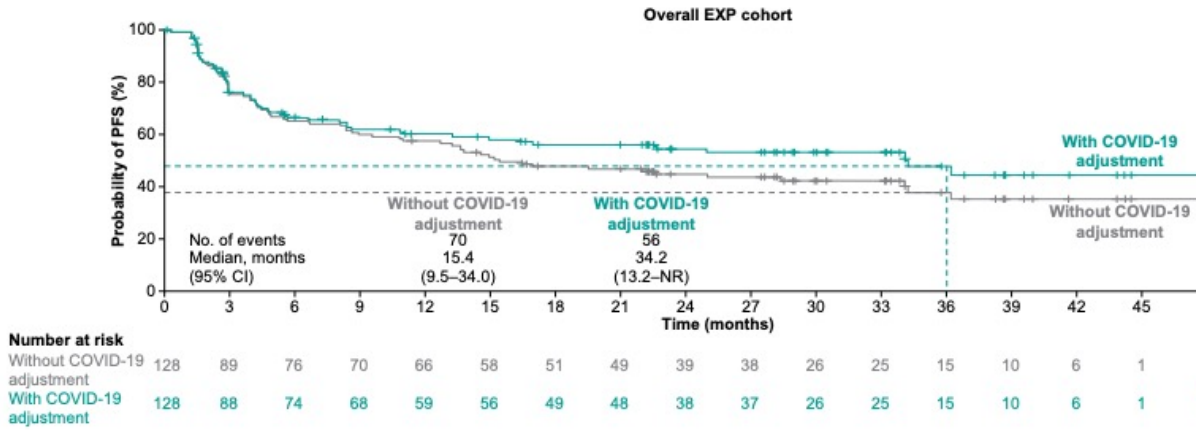
Surovatamig	**61**	**3**	**NR**	**NR**	**96%**	**92%**	**Median PFS – NR** **1-year PFS 88%**	Hou, ASH 2025

Continual risk of relapse?

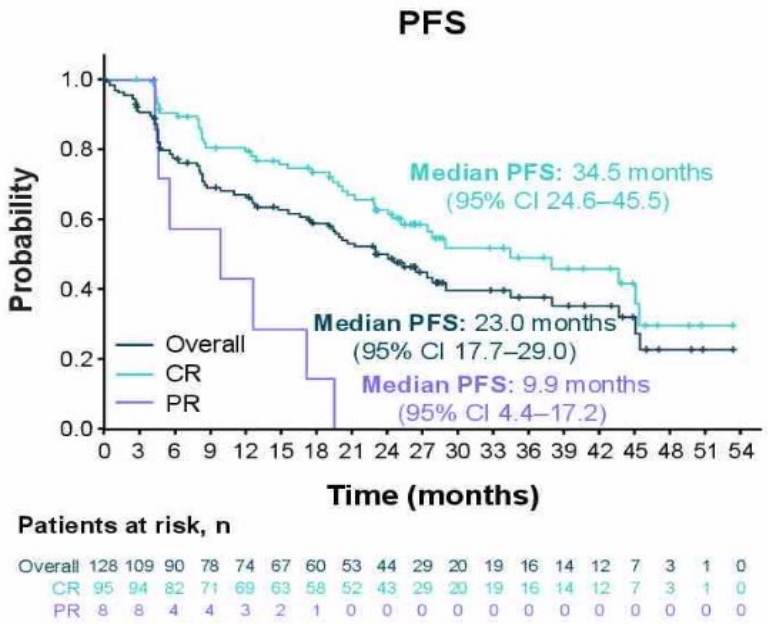
Mosunetuzumab



Epcoritamab



Odronextamab



Sehn, Blood 2024
Linton, Lancet 2024
Kim, Annals Onc 2024

BsAbs - Safety

	N	Any grade CRS	G2+ CRS	ICANS	Grade 3+ Infections	Citations
Mosunetuzumab	90	**44%**	**21%**	3% (all G1-2)	14%	Budde, Lanc Onc 2022
Epcoritamab	149 EXP (2 SUDs)	**67%**	**27%**	6% (all G1-2)	35% (7% G5)	Linton, ICML 2025
	86 C1 OPT (3 SUDs)	**49%**	**9%**	0%	21% (1% G5)	
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Surovatamig	43 (for pts receiving 2 SUDs)	**51%**	**2%**	5% (G1-G2)	NR	Hou, ASH 2025

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Other novel agents

	Duration	N	Median prior lines	POD24	High-risk FLIPI	Citations
Zanubrutinib + obinutuzumab	Indefinite Zanubrutinib treatment	145	3	37%	53%	Zinzani JCO 2023. Zinzani, ASH 2025
Loncastuximab + Rituximab	7-13 cycles of lonca	39	1	51%	62%	Alderuccio, Lanc Haem 2025
Golcadomide	Up to 2 years of golcadomide	60 (n=22 0.2 mg, n=38 0.4 mg)	3	NR	NR	Chavez, ASH 2025

Other novel agents

	N	ORR	CMR	PFS	Safety	Citations
Zanubrutinib + obinutuzumab	145	70%	42%	Median PFS 22.1 m 3-year PFS 39%	Any grade infections 55%. 8% fatal TEAEs	Zinzani JCO 2023. Zinzani, ASH 2025
Loncastuximab + Rituximab	39	100%	75%	12-month PFS 95%	G3AEs and G3 infections rare. 3% discontinued tx due to AEs	Alderuccio, Lanc Haem 2025
Golcadomide + rituximab	60	97% (0.4 mg) 77% (0.2 mg)	78% (0.4 mg) 41% (0.2 mg)	mDOR 9-10 months	9% F+N G3 infections “rare”	Chavez, ASH 2025

Agenda

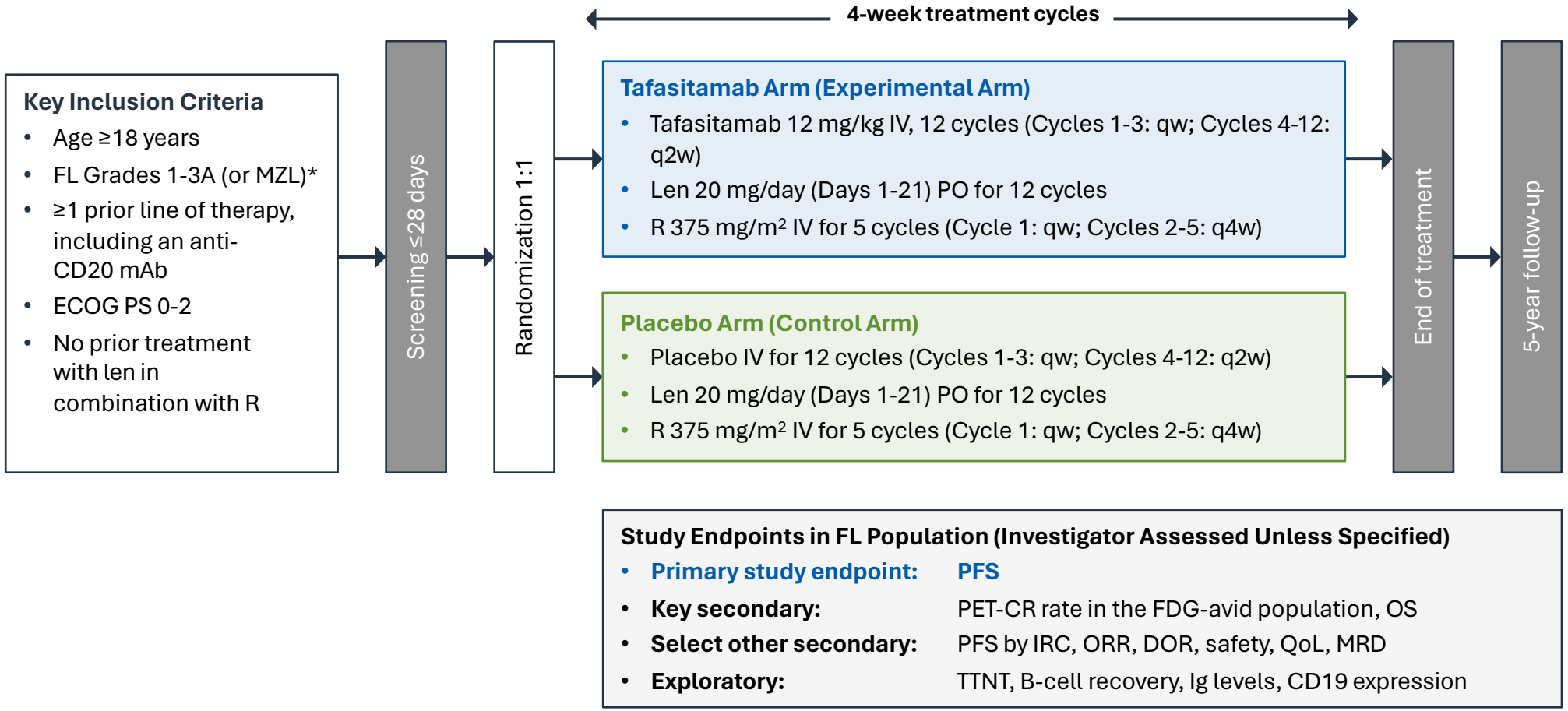
- Novel agents are challenging traditional treatments across all lines
- Where are novel agents now?
  - BsAbs
  - Other (Zanubrutinib, Loncastuximab, Golcadomide)
  - CD19 CAR T cell therapy
- **Where will novel agents be in the (near) future?**
  - **2L treatment**
  - 1L treatment

Phase III Trials 2L FL

	Treatment (experimental)	Treatment (control)	Patients	N	Start/Primary endpoint dates
INMIND*	R2 + tafa (12 cycles)	R2 (12 cycles)	Grade 1-3A FL or **MZL** with at least 1 prior CD20-containing regimen	654	4/2021 2/2024
EPCORE FL-1*	R2 + epcoritamab (12 cycles)	R2 (12 cycles)	Grade 1-3A FL with at least 1 prior CD20 combination treatment	500	9/2022 11/2029
CELESTIMO	Mosun-len (12 cycles)	R2 (12 cycles)	Grade 1-3A FL with 1+ prior line containing R	474	10/2021 8/2025
OLYMPIA-5	Odronextamab + len (12 cycles)	R2 (12 cycles)	Grade 1-3A FL or **MZL** 1+ prior line including CD20	422	12/2023 1/2029
SY[redacted]Y-1	R2 + tazemetostat (1 year of len, **tazemetostat up to 2 years**)	R2 (12 cycles)	Grade 1-3A FL with 1+ prior line	540	12/2019 3/2026
MAHOGANY	Zanubrutinib + obinutuzumab (**Zanubrutinib given continuously**)	R2 (12 cycles)	Grade 1-3A FL or **MZL** with at least 1 prior CD20-containing regimen	750	3/2022 7/2028
GOLSEEK-4	R-golca (1-year)	R2 (12 cycles), RCHOP, or BR	Grade 1-3A FL with at least 1 prior CD20 mAb and alkylator-containing regimen	400	7/2025 7/2030

- Primary endpoint for all trials is PFS; *Met primary endpoint
- Not showing ZUMA-22, a Phase III trial comparing axi-cel to SOC in high-risk 2L and all 3L+ FL pts

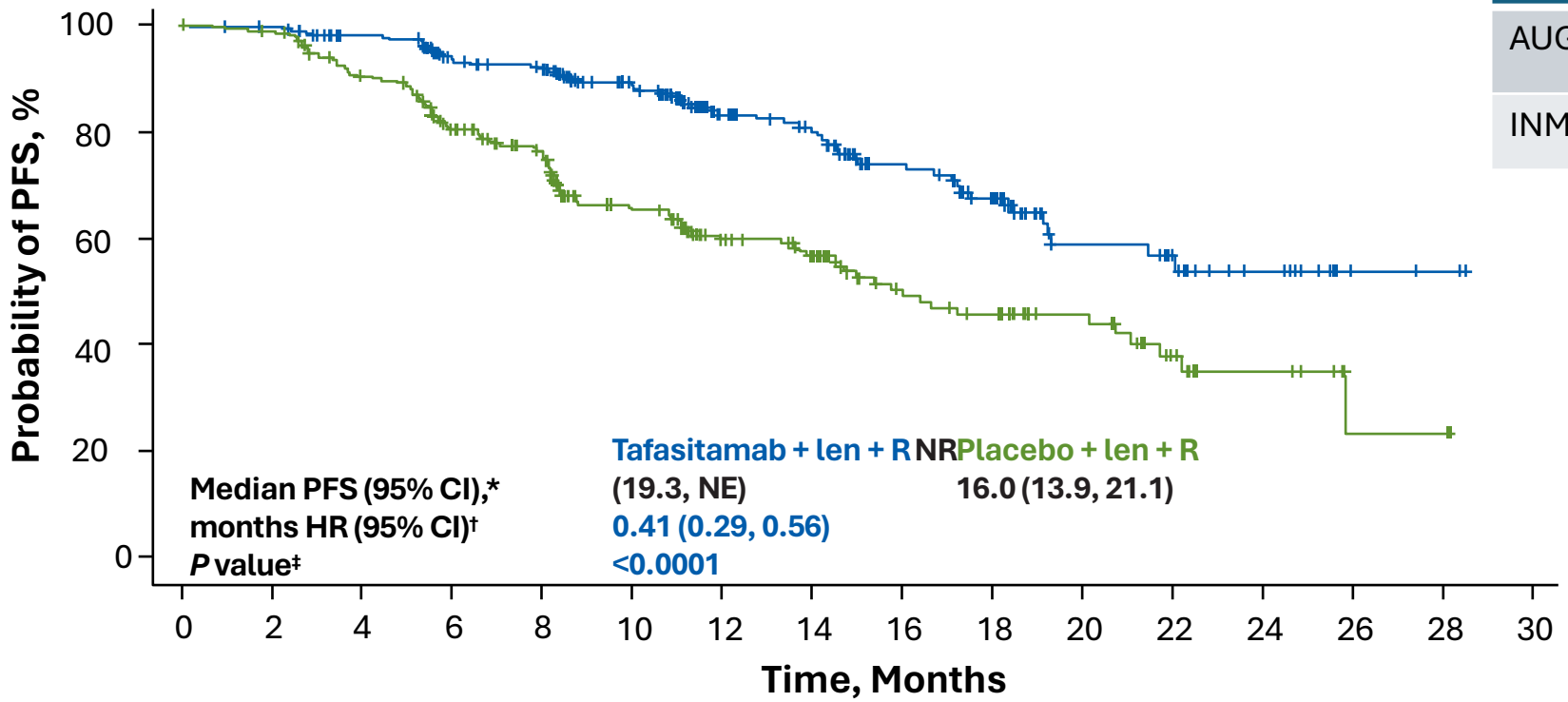
INMIND – Tafasitamab + R2



Study Endpoints in FL Population (Investigator Assessed Unless Specified)

- **Primary study endpoint:** **PFS**
- **Key secondary:** PET-CR rate in the FDG-avid population, OS
- **Select other secondary:** PFS by IRC, ORR, DOR, safety, QoL, MRD
- **Exploratory:** TTNT, B-cell recovery, Ig levels, CD19 expression

INMIND – PFS



No. at Risk																
Tafasitamab + len + R	273	260	246	210	200	162	113	98	72	58	28	20	12	3	2	0
Placebo + len + R	275	260	230	193	170	120	79	67	44	38	26	15	8	2	2	0

	Median PFS for R2
AUGMENT	39.4 months
INMIND	16.0 months

Sehn, Lanc 2026
Leonard, JCO 2019

Phase III Trials 2L FL

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- Primary endpoint for all trials is PFS; *Met primary endpoint
- Not showing 3 Phase III trials for CAR T cells

EPCORE FL-1

Study design

Key inclusion criteria

- 2L+ FL patients
- Histologically confirmed CD20+ Grade 1-3A, Stage II-IV
- ≥1 prior treatment which must include anti-CD20 mAb + chemotherapy

N=488

Randomized 1:1

Epcoritamab + R2
- Epcoritamab[a] 48 mg SC: C1-12 (3-SUD in C1)
- Rituximab 375 mg/m^2 IV: C1-5
- Lenalidomide 20 mg PO: C1-12

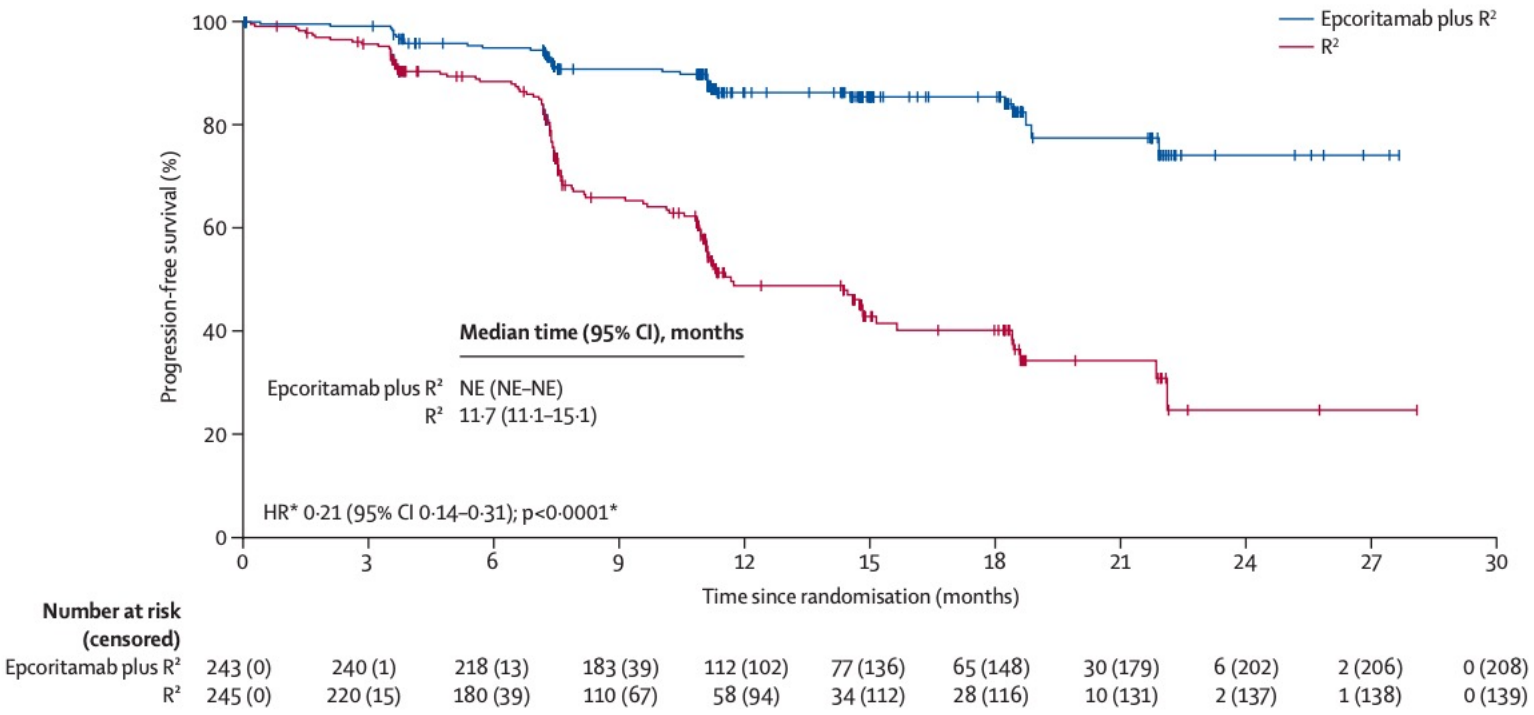
R2
- Rituximab 375 mg/m^2 IV: C1-5
- Lenalidomide 20 mg PO: C1-12

Primary endpoints:
- ORR and PFS by IRC

Secondary endpoints:
- CR by IRC
- MRD negativity
- OS

EPCORE FL-1

A



Efficacy endpoints	Epco-R2	R2
ORR	95%	83%
CRR	83%	50%
Median PFS	NR	11.7 mo
16-month OS	96%	89%

Falchi, Lanc 2026

EPCORE FL-1 - Safety

Adverse Event, n (%)	Epcoritamab+R² (N = 243)		R² (N = 238)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any adverse event	242 (100)	219 (90)	235 (99)	161 (68)
Serious adverse event	135 (56)	-	69 (29)	-
Adverse event leading to treatment discontinuation	46 (19)	-	29 (12)	-
Epcoritamab	21 (9)	-	-	-
Rituximab	7 (3)	-	12 (5)	-
Lenalidomide	45 (19)	-	29 (12)	-
Adverse event of clinical interest > 20%[a,b]				
Infections[c]	188 (77)	81 (33)	125 (53)	37 (16)
Neutropenia	180 (74)	167 (69)	123 (52)	100 (42)
Cytokine release syndrome	85 (35)	-	1 (< 1)	-
Anemia	68 (28)	19 (8)	41 (17)	11 (5)
Thrombocytopenia	67 (28)	23 (9)	44 (18)	15 (6)
Pyrexia	58 (24)	1 (< 1)	33 (14)	3 (1)
Rash	58 (24)	19 (8)	53 (22)	9 (4)
COVID-19	54 (22)	7 (3)	32 (13)	4 (2)

- 3 SUDs significantly lowers the risk of high grade CRS
- High grade infections are very common.

Falchi, Lanc 2026

Key Questions

With so many potential 2L regimens, which will “win”?

Differentiating features:

Key Questions

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Differentiating features:

- Duration of therapy

1- year	More than 1 year
EPCORE FL-1 (Epcoritamab)	**MAHOGANY** (Zanubrutinib given indefinitely)
CELESTIMO (Mosunetuzumab)	
OLYMPIA-5 (Odronextamab)	
INMIND (Tafasitamab)	
GOLSEEK-4 (Golcadomide)	

Key Questions

With so many potential 2L regimens, which will “win”?

Differentiating features:

- Duration of therapy
- Frequency of dosing

Frequent infusions (more than once every 3 weeks)	Less frequent infusions
EPCORE FL-1 (Epcoritamab)	**MAHOGANY** (Zanubrutinib)
OLYMPIA-5 (Odronextamab)	**GOLSEEK-4** (Golcadomide)
INMIND (Tafasitamab)	**CELESTIMO** (Mosunetuzumab)

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Differentiating features:

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- Frequency of dosing
- Efficacy - BsAbs have higher single agent response rates than other agents…

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Differentiating features:

- Duration of therapy
- Frequency of dosing
- Efficacy - BsAbs have higher single agent response rates than other agents…
- Safety – BsAbs are also associated with more frequent AEs

Key Questions

With so many potential 2L regimens, which will “win”?

Is lenalidomide the optimal combination partner for BsAbs?

- Activity of R2 in non-"cherry-picked" populations is poor
- Lenalidomide is associated with significant toxicities, particularly in older patients
- Alternative combination partners may be better
  - Zanubrutinib*
  - Loncastuximab*
  - Golcadomide*
  - Polatuzumab vedotin*
  - Others?

*Ongoing phase II studies in combination with a CD3/CD20 BsAb

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Current 1L FL treatment

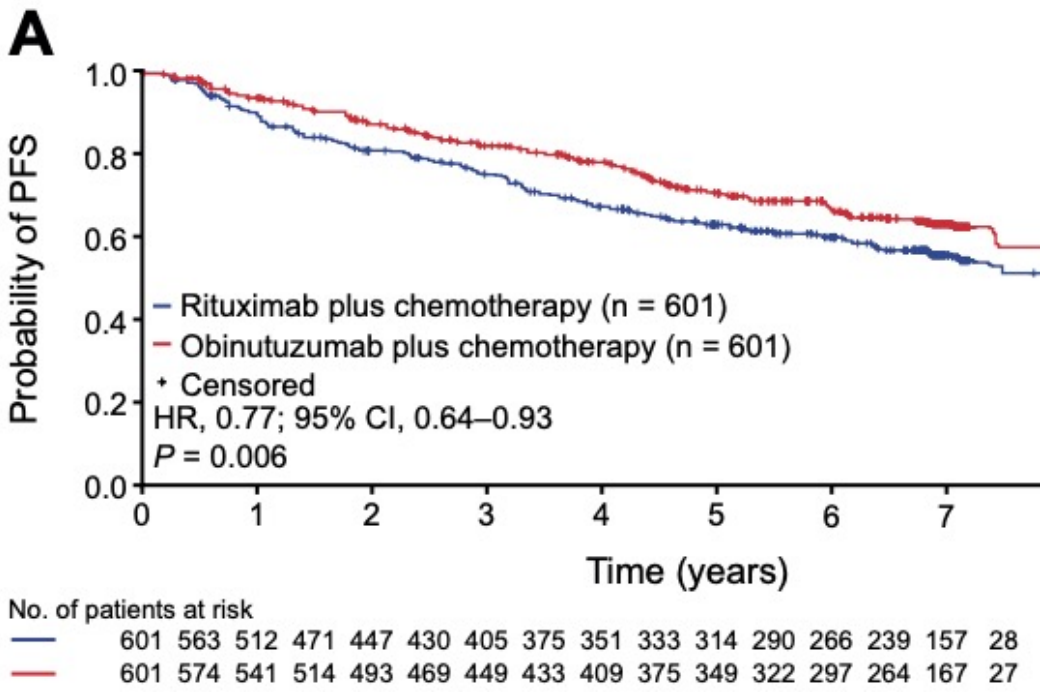
First-line treatment

High tumor burden

- Chemoimmunotherapy (R or G + bendamustine, CHOP or CVP)*
- Lenalidomide + rituximab (R2)

Low tumor burden

- Rituximab*
- Watchful waiting

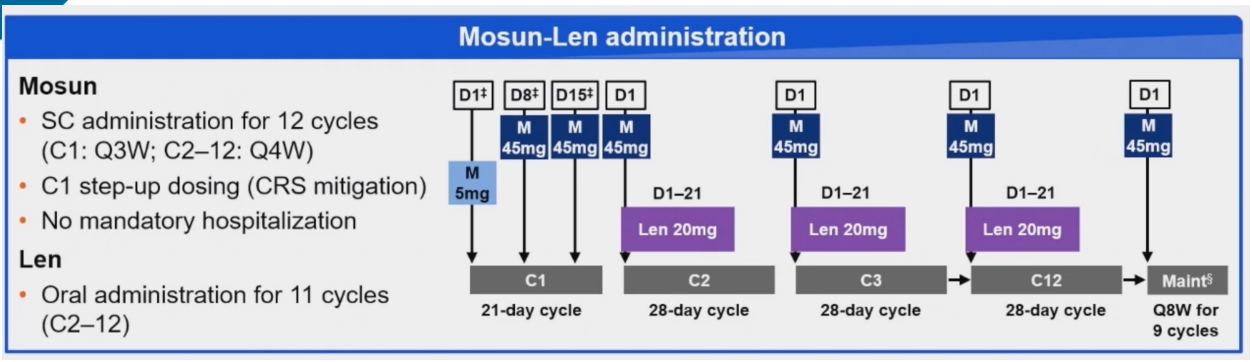


Benchmarking for CIT

- EOI CMR – 75.6% (Lugano 2014)
- PFS (rituximab-arm)
  - 1 year - ~90%
  - 2 year – ~81%
  - 3 year – ~73%

Townsend, HemaSphere 2023

BsAb + lenalidomide 1L combinations



	Treatment Regimen Epcoritamab SC 48 mg + R²						
Agent	**C1**	**C2**	**C3**	**C4**	**C5**	**C6–C12**	**C13+**
Epcoritamab SC 48 mg	QW	QW	Q4W	Q4W	Q4W	Q4W	Q4W Up to 2 years
R² Rituximab IV 375 mg/m²	QW	Q4W	Q4W	Q4W	Q4W		
R² Lenalidomide oral 20 mg	Daily for 21 d (for 12 cycles)						

	Mosu+len	Epco+R2
N	40	41
High FLIPI score	43%	39%
ORR	92%	95%
CMR	89%	88%
PFS	Only 5.2m median follow-up	3-year PFS 86%
Citations	*Morschhauser, ASH 2023*	*Leslie, ASH 2025*

1L FL Phase 3 trial Landscape

	Treatment (Experimental)	Treatment (control)	Patients	N
EPCORE FL-2 (4-way randomization)	Epcoritamab + R2 (All arms 120 weeks of treatment)	1. CIT (w/ CD20 maintenance) *2. R2* *3. Epco R2 (no maintenance)*	Stage 2-4, GELF+, Grade 1-3A	1080
MorningLyte	Mosunetuzumab + len (30 months w/ maintenance)	CIT (R or G with CHOP or benda) (30 months w/ maintenance)	Grade 1-3A, GELF+, **FLIPI 2-5 FL**	790

Primary endpoint either CR30 or PFS for all trials.

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	Treatment (Experimental)	Treatment (control)	Patients	N
EPCORE FL-2 (4-way randomization)	Epcoritamab + R2 (All arms 120 weeks of treatment)	1. CIT (w/ CD20 maintenance) *2. R2* *3. Epco R2 (no maintenance)*	Stage 2-4, GELF+, Grade 1-3A	1080
MorningLyte	Mosunetuzumab + len (30 months w/ maintenance)	CIT (R or G with CHOP or benda) (30 months w/ maintenance)	Grade 1-3A, GELF+, **FLIPI 2-5 FL**	790
OLYMPIA-1	Odronextamab followed by Odro maintenance	CIT (RCVP, RCHOP, or BR), all followed by R maintenance	Stage 3-4 or stage II bulky FL (grade 1-3A)	478
OLYMPIA-2 (1:1:1 randomization)	1. O-Chemo (CVP or CHOP) with O maintenance 2. O-chemo without maintenance or	R-chemo with R maintenance	Stage 3-4 or stage II bulky FL (grade 1-3A)	733

Primary endpoint either CR30 or PFS for all trials.

1L FL Phase 3 trial Landscape

	Treatment (Experimental)	Treatment (control)	Patients	N
EPCORE FL-2 (4-way randomization)	Epcoritamab + R2 (All arms 120 weeks of treatment)	1. CIT (w/ CD20 maintenance) *2. R2* *3. Epco R2 (no maintenance)*	Stage 2-4, GELF+, Grade 1-3A	1080
MorningLyte	Mosunetuzumab + len (30 months w/ maintenance)	CIT (R or G with CHOP or benda) (30 months w/ maintenance)	Grade 1-3A, GELF+, **FLIPI 2-5 FL**	790
OLYMPIA-1	Odronextamab followed by Odro maintenance	CIT (RCVP, RCHOP, or BR), all followed by R maintenance	Stage 3-4 or stage II bulky FL (grade 1-3A)	478
OLYMPIA-2 (1:1:1 randomization)	1. O-Chemo (CVP or CHOP) with O maintenance 2. O-chemo without maintenance or	R-chemo with R maintenance	Stage 3-4 or stage II bulky FL (grade 1-3A)	733
SOUNDTRACK-F1 (1:1:1 randomization)	Surovatamig + rituximab (with two different surovatamig schedules)	R-chemo (CVP, CHOP, B) with R maintenance	Grade 1-3A, GELF+	1015

Primary endpoint either CR30 or PFS for all trials.

1L FL Phase 3 trial Landscape

	Treatment (Experimental)	Treatment (control)	Patients	N
EPCORE FL-2 (4-way randomization)	Epcoritamab + R2 (All arms 120 weeks of treatment)	1. CIT (w/ CD20 maintenance) *2. R2* *3. Epco R2 (no maintenance)*	Stage 2-4, GELF+, Grade 1-3A	1080
MorningLyte	Mosunetuzumab + len (30 months w/ maintenance)	CIT (R or G with CHOP or benda) (30 months w/ maintenance)	Grade 1-3A, GELF+, **FLIPI 2-5 FL**	790
OLYMPIA-1	Odronextamab followed by Odro maintenance	CIT (RCVP, RCHOP, or BR), all followed by R maintenance	Stage 3-4 or stage II bulky FL (grade 1-3A)	478
OLYMPIA-2 (1:1:1 randomization)	1. O-Chemo (CVP or CHOP) with O maintenance 2. O-chemo without maintenance or	R-chemo with R maintenance	Stage 3-4 or stage II bulky FL (grade 1-3A)	733
SOUNDTRACK-F1 (1:1:1 randomization)	Surovatamig + rituximab (with two different surovatamig schedules)	R-chemo (CVP, CHOP, B) with R maintenance	Grade 1-3A, GELF+	1015
S2308	Mosu x 8 cycles	Rituximab (4 weekly doses, 5 doses q8 weeks)	Grade 1-3A FL, low GELF	600

Primary endpoint either CR30 or PFS for all trials.

Key Questions

> Do most patients with FL need 30 months of frontline therapy?

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No! Less may be more.

- It’s likely that most patients can have durable remission with (much) less therapy.
- Prolonged therapy could increase the risk of toxicity (infections, etc). BsAb maintenance may have a different side effect profile than rituximab maintenance
- Can we select patients for de-intensification?
  - EPCORE-FL2 and OLYMPIA-2 include arms without maintenance therapy.
  - Risk-adapted trial designs?

Key Questions

> Do most patients with FL need 30 months of frontline therapy?

Is lenalidomide the optimal combination partner for BsAbs?

	Epcor-R2 (NHL-2)[1]	R-Epcor (DFCI IST)[2]	Epcor-Len (COH IST)[3]
N	41	35	18
ORR	95%	97%	100%
CMR	85%	94%	89%

BsAbs, bispecific antibodies; CMR, complete metabolic response; COH, City of Hope; DFCI, Dana-Farber Cancer Institute; IST, investigator sponsored trial; len, lenalidomide; NHL, non-Hodgkin lymphoma; ORR, overall response rate; R, rituximab; R2, rituximab + lenalidomide

1. Lori LA, et al. ASH 2025; Abstract 465 ; 2. Merryman R, et al. ASH 2025. Abstract 464; 3. Thiruvengadam SK, et al. ASH 2025. Abstract 5373

Alternative combination partners in 1L

	Treatment	N	CMR rate	Citations
Mosu + **polatuzumab** (WUSTL IST)	Ph II. Initial dose of step up is 5mg then 45 mg. 6 cycles of pola	34	83%	Russler-Germain, ASH 2024
Response adapted Mosu +/- **polatuzumab/obin** (UW IST)	Mosu C 1-8. Pola/obin added if not in CR	41	76% (to mosu alone) 6/7 achieved a CR to combination tx	Lynch, ASH 2025
Mosun alone or with **zanubrutinib** (MSKCC)	Cohort 1 - mosun alone Cohort 2 - mosun + zanu (12 months)	47	74% (n=27 response-evaluable)	Falchi, ASH 2025
Rituximab + Epco (DFCI IST)	4 doses of R, 9 cycles of epco	100	94% (35 response-evaluable)	Merryman, ASH 2025
Obinutuzumab + Glofit (DFCI IST)	4 doses of obin, 12 cycles of glofit	35	88%	Merryman, ASH 2025

Conclusions

- Novel agents (particularly BsAbs) will likely dramatically change standard treatments for FL, but many questions remain.
- What is the optimal role and combination partner(s) for BsAbs?
- Can we personalize therapy?
    - Can we de-escalate therapy for some patients?
    - Could more intensive novel agent approaches be curative for some patients
    - Biomarkers needed!
- How should we select length of treatment? Should this vary by patient?

Thanks!

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