2020 Year in Review: Follicular Lymphoma (FL) and Mantle-Cell Lymphoma (MCL)

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Follicular Lymphoma

Phase II Trial of the Oral EZH2 Inhibitor Tazemetostat for R/R FL - Response

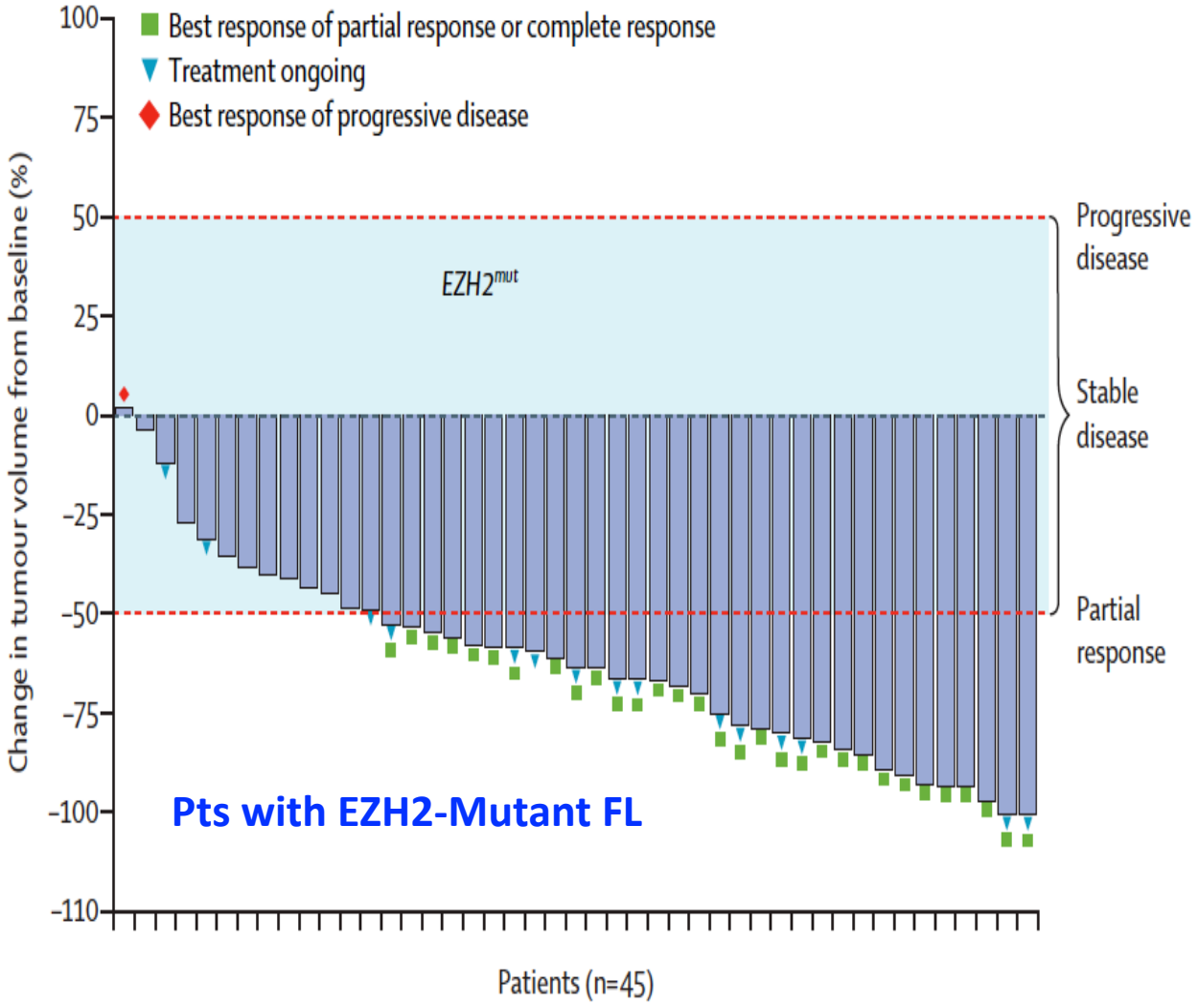
Tumor Response by EZH2 mutation status	*EZH2*^{mut} (n=45)		*EZH2*^{WT} (n=54)	
	IRC-assessed	Investigator-assessed	IRC-assessed	Investigator-assessed
Objective response rate*	31 (69%; 53–82)	35 (78%; 63–89)	19 (35%; 23–49)	18 (33%; 21–48)
Overall disease control rate†	44 (98%)	45 (100%)	37 (69%)	34 (63%)
Best overall response				
Complete response	6 (13%)	4 (9%)	2 (4%)	3 (6%)
Partial response	25 (56%)	31 (69%)	17 (31%)	15 (28%)
Stable disease	13 (29%)	10 (22%)	18 (33%)	16 (30%)
Progressive disease	1 (2%)	0	12 (22%)	16 (30%)
Not estimable or unknown	0	0	5 (9%)	4 (7%)

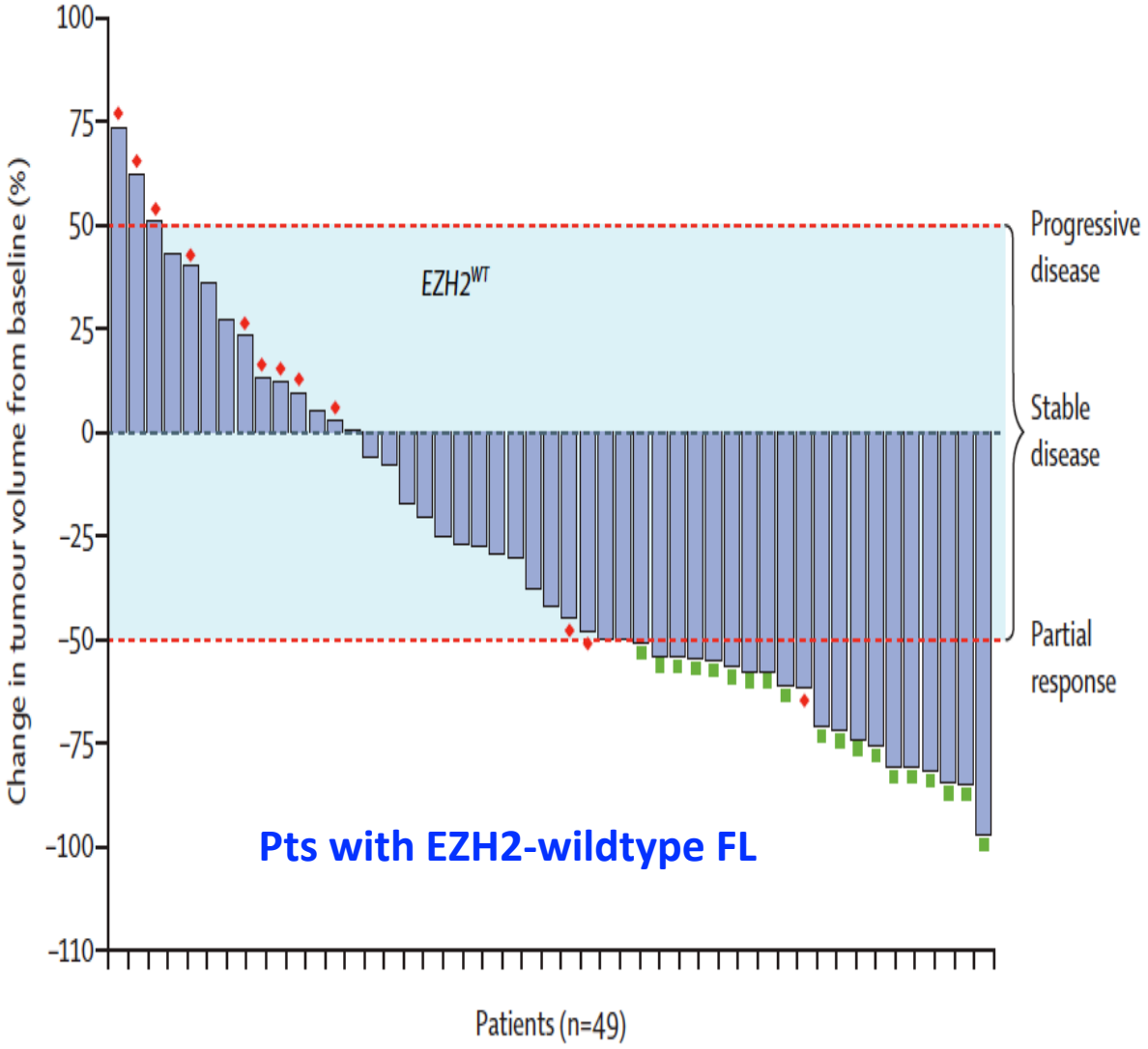
Data are n (%; 95% CI) or n (%). IRC=independent radiology committee. *Objective response rate includes patients with a complete or partial response. †Overall disease control rate includes patients with a complete response, partial response, or stable disease.

Morschhauser F et al. *Lancet Oncol* 2020;21(11):1433-1442.

Courtesy of Christopher R Flowers, MD, MS

Phase II Trial of Tazemetostat in R/R FL – Change in Tumor Volume from Baseline

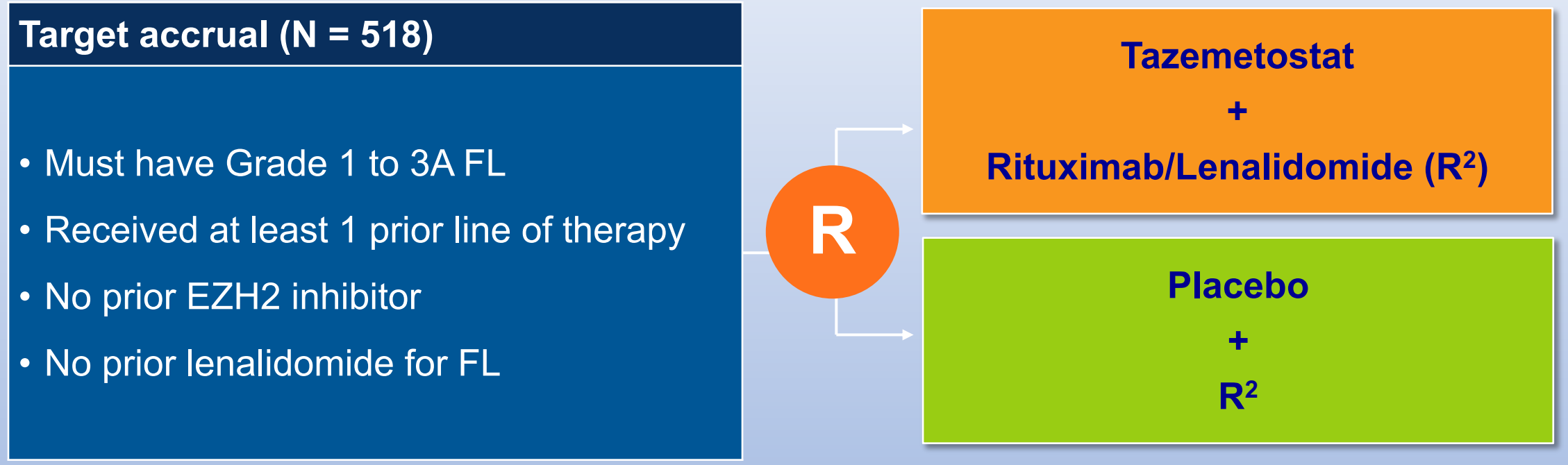




Morschhauser F et al. *Lancet Oncol* 2020;21(11):1433-1442.

Courtesy of Christopher R Flowers, MD, MS

Ongoing Phase Ib/III Trial of Tazemetostat + Len/Rituximab in R/R FL



- **Primary endpoint:**
  - **Stage 1: RP3D of tazemetostat in combination with R^2**
  - **Stage 2: PFS**

Batlevi CL et al. ASH 2020; Abstract 2052; Clinicaltrials.gov; NCT04224493 (Accessed January 2021).

Courtesy of Christopher R Flowers, MD, MS

Morschhauser F et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol 2020 Nov;21(11):1433-1442

Impact on Patient Care and Treatment Algorithm

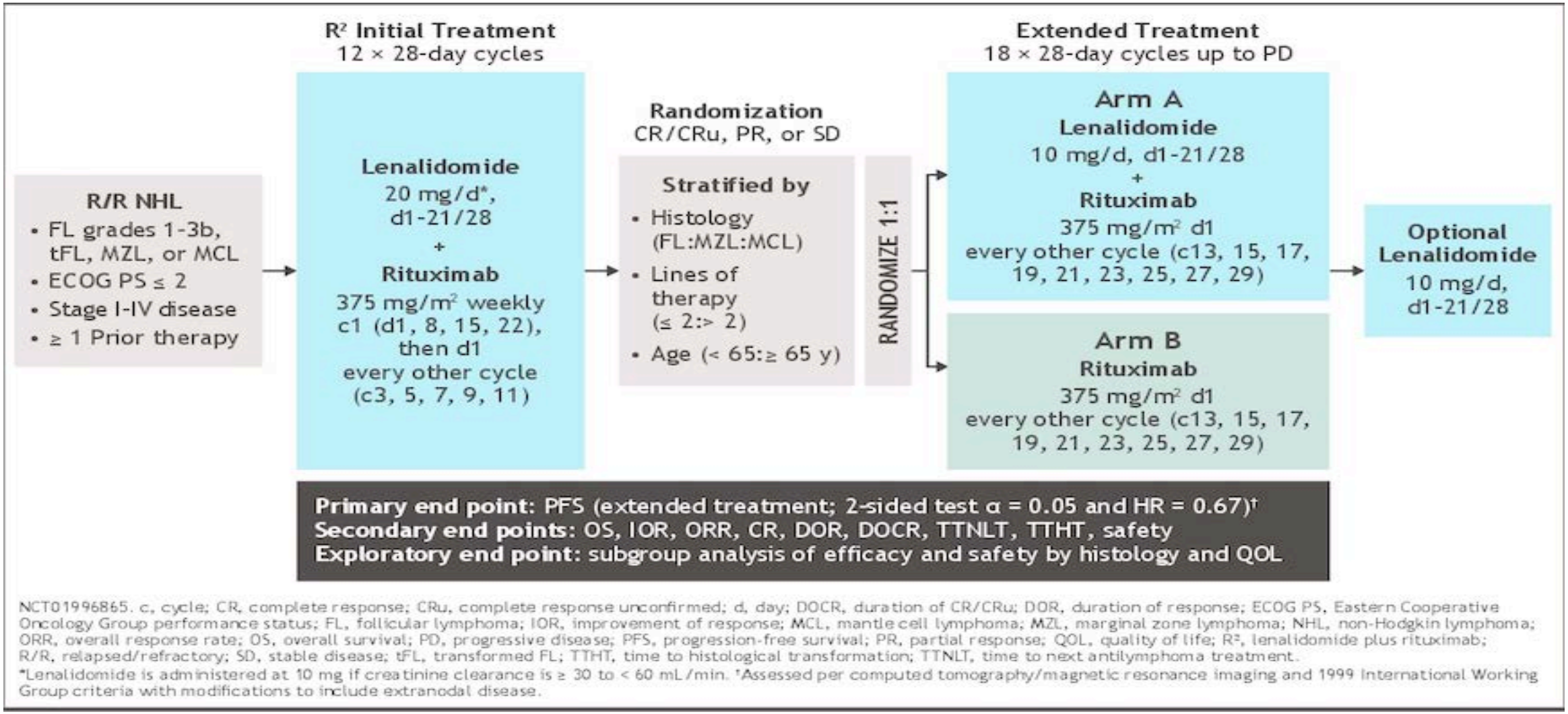
- Tazemetostat, a first-in-class, oral EZH2 inhibitor, is approved and available as monotherapy for patients with relapsed/refractory FL after 2 lines
- EZH2 mutation status should be tested where available
  - Response rate 69% $EZH2^{mut}$ and 35% $EZH2^{WT}$

Implications for Future Research

- Evaluation of EZH2 mutation test (panels, cfDNA)
- Integration of tazemetostat into first line and relapsed combination regimens
  - Phase 1b/3 Randomized, Double-Blind, 3-Stage Study of Tazemetostat or Placebo Plus Lenalidomide and Rituximab in Patients with Relapsed/Refractory Follicular Lymphoma (Batlevi et al. ASH 2020; Abstract 2052)

Courtesy of Christopher R Flowers, MD, MS

Phase IIIb MAGNIFY Trial Design



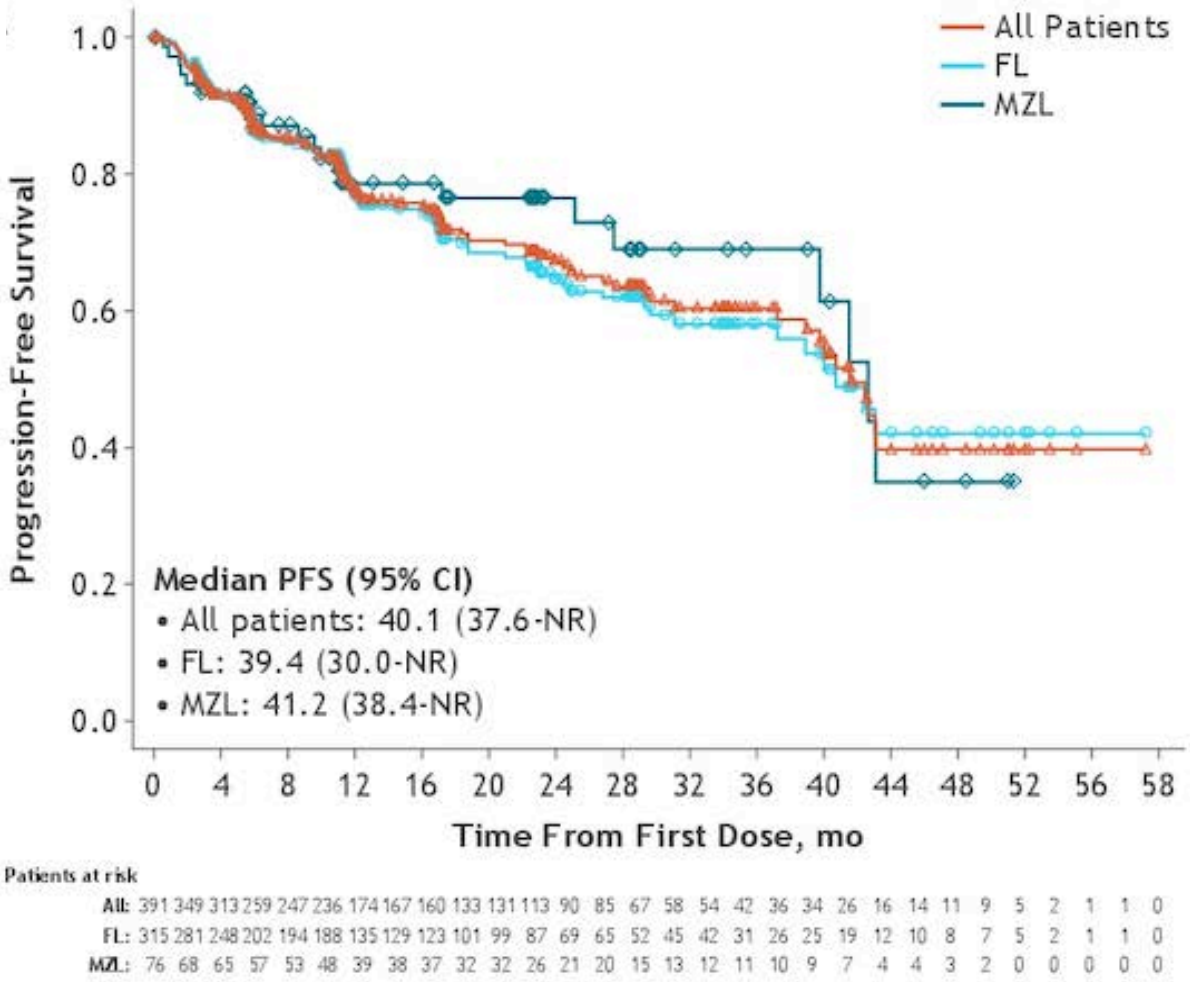
NCT01996865. c, cycle; CR, complete response; CRu, complete response unconfirmed; d, day; DOCR, duration of CR/CRu; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IOR, improvement of response; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QOL, quality of life; R², lenalidomide plus rituximab; R/R, relapsed/refractory; SD, stable disease; tFL, transformed FL; TTHT, time to histological transformation; TTNLT, time to next antilymphoma treatment.

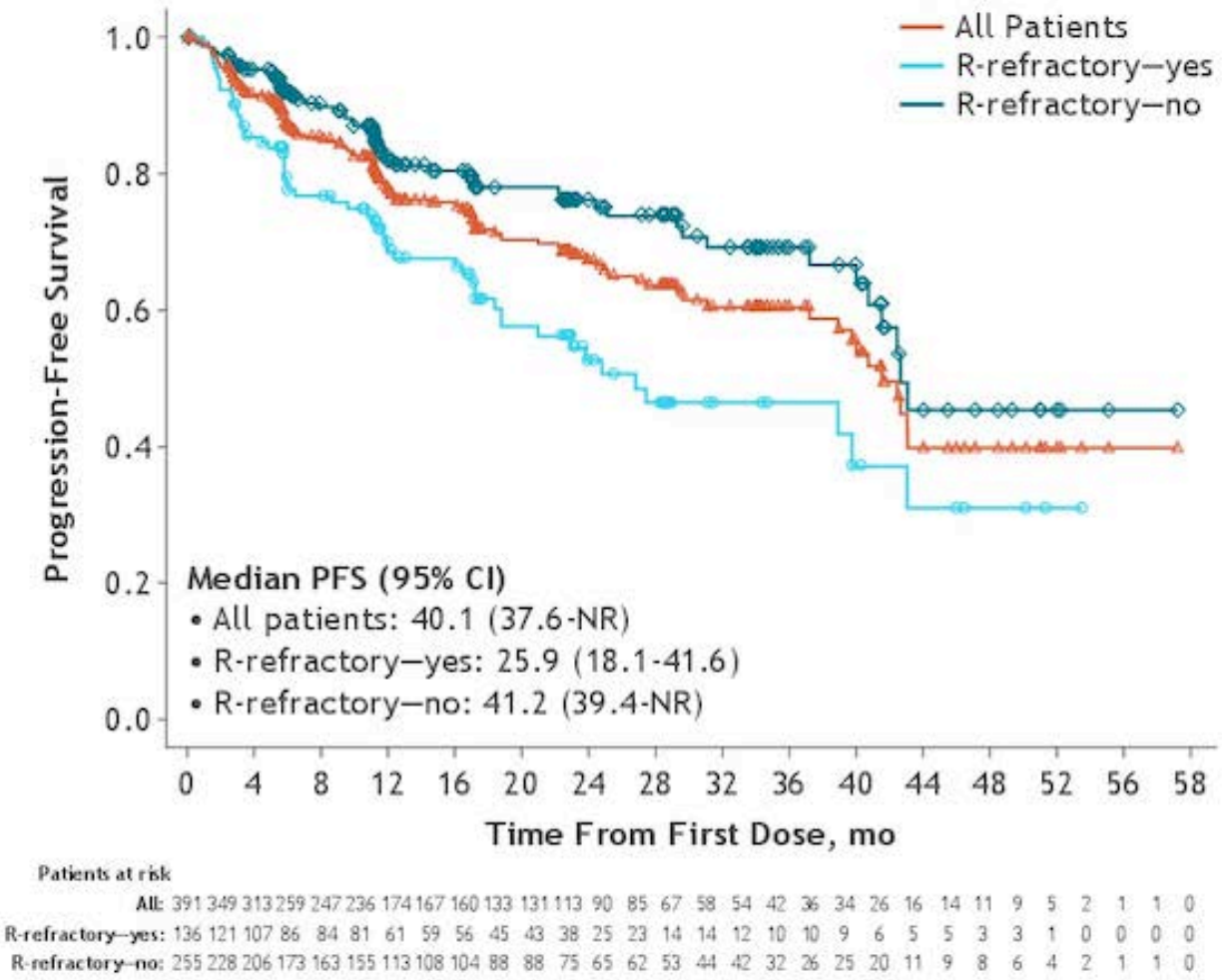
*Lenalidomide is administered at 10 mg if creatinine clearance is ≥ 30 to < 60 mL/min. †Assessed per computed tomography/magnetic resonance imaging and 1999 International Working Group criteria with modifications to include extranodal disease.

Andorsky DJ et al. ASCO 2020; Abstract 8046.

Courtesy of Christopher R Flowers, MD, MS

MAGNIFY Trial Design – PFS by Disease Type

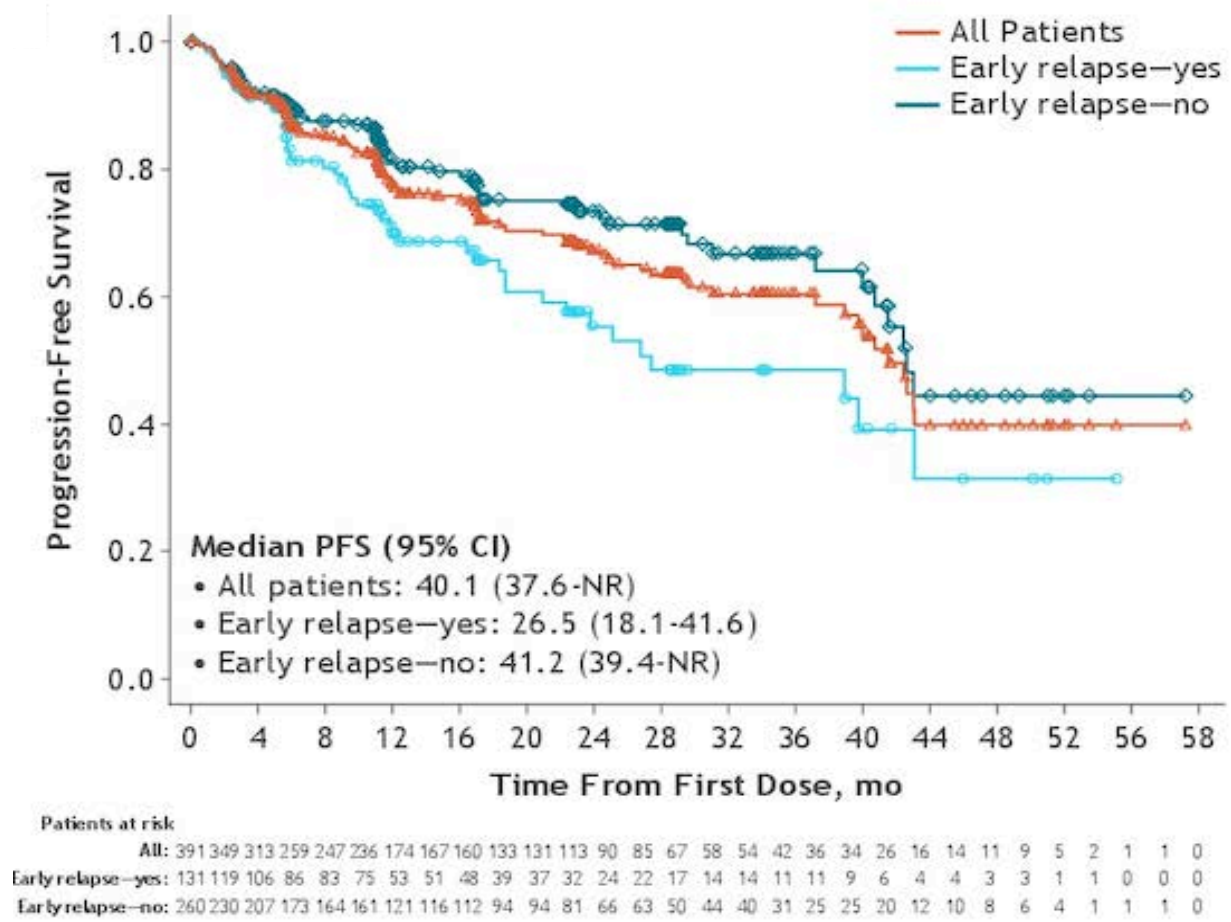


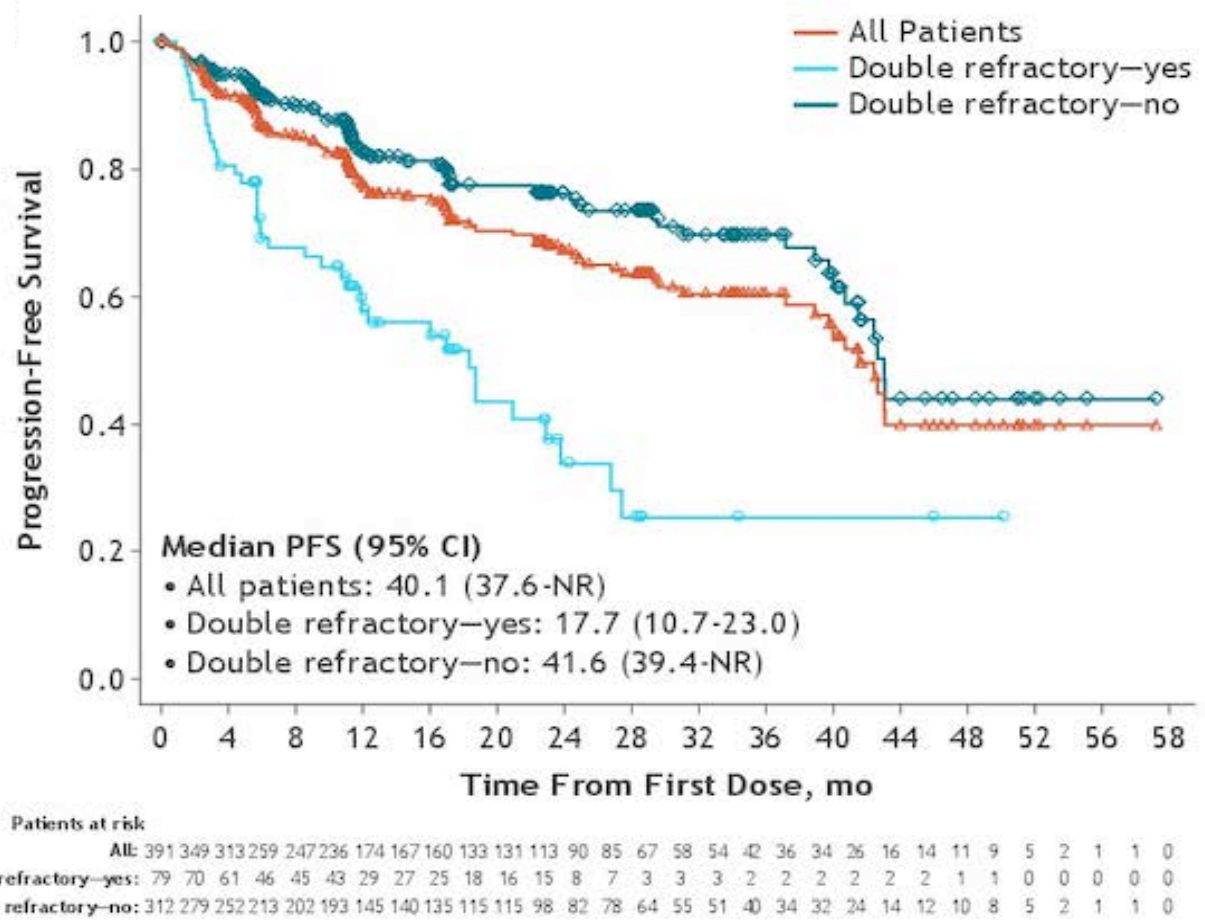


Andorsky DJ et al. ASCO 2020; Abstract 8046.

Courtesy of Christopher R Flowers, MD, MS

MAGNIFY Trial Design – PFS by Relapse or Refractory Status





Andorsky DJ et al. ASCO 2020; Abstract 8046.

Courtesy of Christopher R Flowers, MD, MS

Andorsky DJ et al. MAGNIFY phase IIIb interim analysis of induction R2 followed by maintenance in relapsed/refractory indolent NHL. ASCO 2020; Abstract 8046.

Impact on Patient Care and Treatment Algorithm

- Confirmation of activity of R^2 in rel/ref FL
- After 12 cycles of R^2, 48% of pts entered maintenance phase
  - 13% discontinued prematurely due to AE
  - Most common AEs: fatigue, neutropenia, diarrhea, nausea

Implications for Future Research

- Follow-up on this trial to determine benefit of R^2 vs. R maintenance
- Development of biomarker predictors for benefit of maintenance

Courtesy of Christopher R Flowers, MD, MS

Phase III AUGMENT Trial of R^2 vs R/Placebo in R/R iNHL: Subgroup Analyses of Elderly Patients

	≥70y		<70y		Total	
	R^2 (n = 47)	R-Placebo (n = 44)	R^2 (n = 131)	R-Placebo (n = 136)	R^2 (n = 178)	R-Placebo (n = 180)
mPFS, mo (95% CI)	24.9 (16.4-NE)	14.3 (11.3-27.7)	39.4 (22.9-NE)	13.9 (9.6-16.7)	39.4 (22.9-NE)	14.1 (11.4-16.7)
ORR, n (%)	38 (81)	26 (59)	100 (76)	70 (51)	138 (78)	96 (53)
CR, n (%)	12 (26)	7 (16)	48 (37)	26 (19)	60 (34)	33 (18)
mTTNLT, mo (95% CI)	NE (22.9-NE)	NE (20.8-NE)	NE (NE-NE)	28.2 (21.5-NE)	NE (NE-NE)	32.2 (23.2-NE)

CR, complete response; mPFS, median progression-free survival; mTTNLT, median time to next antilymphoma treatment; NE, not evaluable; ORR, overall response rate.

Trneny M et al. ASH 2019; Abstract 347.

Courtesy of Christopher R Flowers, MD, MS

Trneny M et al. Subgroup Analyses of Elderly Patients Aged ≥ 70 Years in AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R2) vs Rituximab Plus Placebo (R-Placebo) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL). ASH 2019; Abstract 347.

Impact on Patient Care and Treatment Algorithm

- Lenalidomide + rituximab (R^2) is a treatment option for rel/ref FL
- Efficacy and safety profiles for R^2 in pts ≥ 70 yrs were similar to overall population

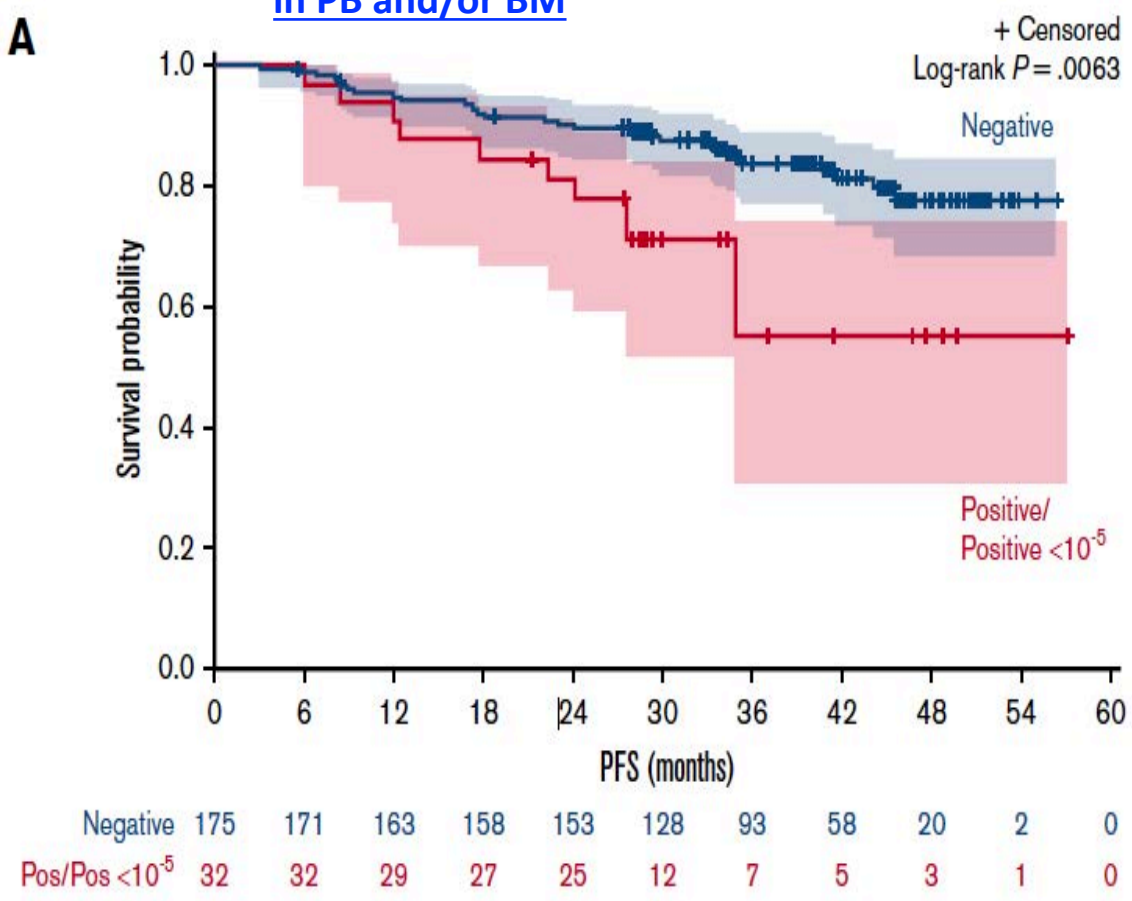
Implications for Future Research

- Comparison of effectiveness in rel/ref FL when R-chemo is considered
- Sequencing of R^2 in FL – first-line (RELEVANCE) or relapse?
- Comparisons or combinations with other agents (e.g. tazemetostat)

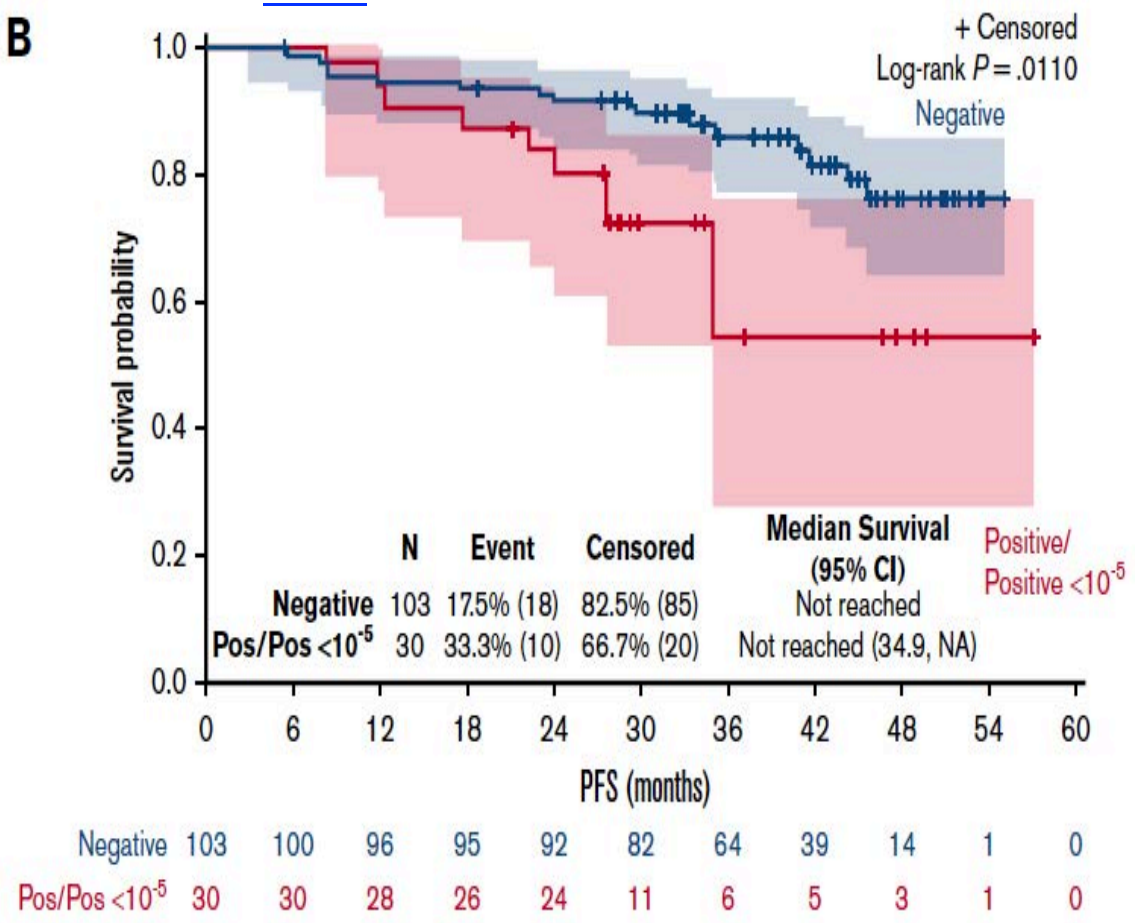
Courtesy of Christopher R Flowers, MD, MS

RELEVANCE Trial: R^2 induces high molecular response in untreated FL

Impact of positive MRD at week 24 on PFS in PB and/or BM



Impact of positive MRD at week 24 on PFS in BM



Delfau-Larue MH et al. *Blood Adv* 2020;4(14):3217-3223.

Courtesy of Christopher R Flowers, MD, MS

Delfau-Larue MH et al. Lenalidomide/rituximab induces high molecular response in untreated follicular lymphoma: LYSA ancillary RELEVANCE study. Blood Adv 2020 Jul 16;4(14):3217-3223.

Impact on Patient Care and Treatment Algorithm

- Quantitative MRD assessment by PCR with a sensitivity of $\leq 10^{-4}$ commonly performed in FL trials in Europe
- Complete molecular response (CMR) at 24 weeks predicts 3-year PFS (84% MRD- 55% MRD+)
- Are we ready for MRD assessment in clinical practice?
- CMR at 24 weeks more common with R^2 (90%) than R-Chemo (77%)

Implications for Future Research

- Need for including MRD assessment in FL trials
- Is PCR better than other approaches (e.g. cfDNA)?
- Use of MRD achievement to select therapy; consolidation, maintenance

Courtesy of Christopher R Flowers, MD, MS

CHRONOS-3 Trial: Copanlisib + Rituximab Meets Primary Endpoint in Relapsed iNHL
Press Release: October 14, 2020

- The Phase III study CHRONOS-3 evaluating copanlisib in combination with rituximab in indolent Non-Hodgkin's Lymphoma (iNHL) patients (n=458) who have relapsed after one or more prior lines of rituximab-containing therapy has met its primary endpoint of prolonged progression-free survival (PFS). The study predominantly included patients with follicular lymphoma (FL) and marginal zone lymphoma, as well as patients with small lymphocytic lymphoma and lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia.
- Safety observed in the trial was generally consistent with previously published data on the individual components of the combination and no new safety signals were identified.

https://bayer2019tf.q4web.com/news/news-details/2020/Aliqopa-copanlisib-in-Combination-With-Rituximab-Meets-Primary-Endpoint-in-Patients-With-Relapsed-Indolent-Non-Hodgkins-Lymphoma/default.aspx.

Courtesy of Christopher R Flowers, MD, MS

CHRONOS-3: Copanlisib in Combination With Rituximab Meets Primary Endpoint in Patients With Relapsed Indolent Non-Hodgkin's Lymphoma
October 14, 2020

Impact on Patient Care and Treatment Algorithm

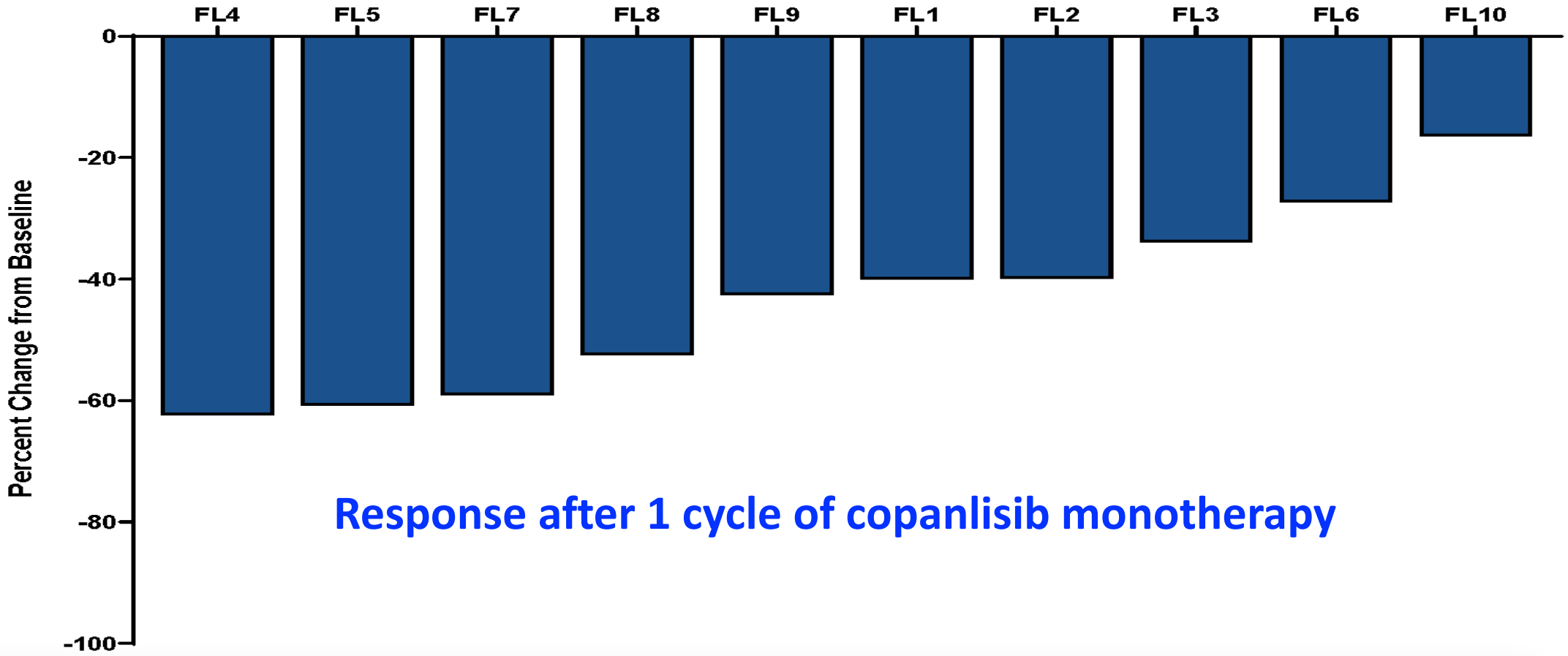
- Copanlisib + rituximab meets primary endpoint of improving PFS compared with rituximab alone in rel/ref FL
- May be another treatment option

Implications for Future Research

- Comparison of effectiveness in rel/ref FL when R-chemo is considered
- Sequencing of copanlisib + R vs. other chemotherapy-free options

Courtesy of Christopher R Flowers, MD, MS

Preliminary Results from a Phase II Study of Response-Adapted Therapy with Copanlisib and Rituximab for Untreated FL



Lakhotia R et al. ASH 2020; Abstract 1137.

Courtesy of Christopher R Flowers, MD, MS

Phase II Study of Response-Adapted Therapy with Copanlisib and Rituximab for Untreated FL – Adverse Events

	Adverse Event	Patients (N=10)		Cycles (N=58)	
		All Grades N (%)	Grade ≥3 N (%)	All Grades N (%)	Grade ≥3 N (%)
Hematologic	Eosinophilia	2 (20)	1 (10)	2 (3.4)	1 (1.7)
	Neutropenia	1 (10)		1 (1.7)	
	Febrile Neutropenia	-		-	
	Thrombocytopenia	1 (10)		1 (1.7)	
	Anemia	-		-	
Non-Hematologic	Diarrhea	5 (50)		6 (10.4)	
	Rash*#	5 (50)		6 (10.4)	
	Mucositis	4 (40)		8 (13.8)	
	Headache	2 (20)		2 (3.4)	
	Nausea	2 (20)		3 (5.2)	
	Abdominal Pain	1 (10)		2 (3.4)	
	Elevated ALT	1 (10)		2 (3.4)	
Adverse Events of Special Interest	Hyperglycemia	2 (20)		3 (5.2)	
	Hypertension	-		-	
	Opportunistic Infections¶	1 (10)		1 (1.7)	

Lakhotia R et al. ASH 2020; Abstract 1137.

Courtesy of Christopher R Flowers, MD, MS

Lakhotia R et al. Preliminary Results from a Phase II Study of Response-Adapted Therapy with Copanlisib and Rituximab for Untreated Follicular Lymphoma. ASH 2020; Abstract 1137. Poster

Impact on Patient Care and Treatment Algorithm

- None yet
- Provocative ongoing trial with early stop of therapy for CR after 6 cycles

Implications for Future Research

- Evaluation of early stopping with other targeted agents
- Approach may require integration of MRD assessment

Courtesy of Christopher R Flowers, MD, MS

Phase II ELARA Trial of Tisagenlecleucel in Adult Patients with R/R FL

- **Overall, 43% of pts received bridging therapy**
  - 18% were treated as outpatient.
- Of the first 52 pts evaluable for efficacy,
  - CRR was 65.4% in the ITT population and 71.1% in the per-protocol (PP) population
  - ORR was 82.7% in the ITT population and 84.8% in the PP population.
- CRR and ORR were consistent across key prognostic subgroups and per investigator assessment.
- Median DOR, PFS, OS, and time to next anti-lymphoma treatment were not reached.
- **Of 97 pts evaluable for safety:**
  - 69% experienced Gr ≥3 adverse events, most commonly neutropenia
  - 48% of pts had CRS-related to tisa-cel (Gr 1, 29%; Gr 2, 20%; Gr ≥3, 0%).
  - To treat CRS, 15% of pts required tocilizumab and 3% required steroids.
  - Any grade serious neurologic events occurred in 10% of pts; 2% had Gr ≥3 and all recovered.

Fowler NH et al. ASH 2020; Abstract 1149.

Courtesy of Christopher R Flowers, MD, MS

Fowler NH et al. Efficacy and Safety of Tisagenlecleucel in Adult Patients with Relapsed/Refractory Follicular Lymphoma: Interim Analysis of the Phase 2 Elara Trial. ASH 2020; Abstract 1149.

Impact on Patient Care and Treatment Algorithm

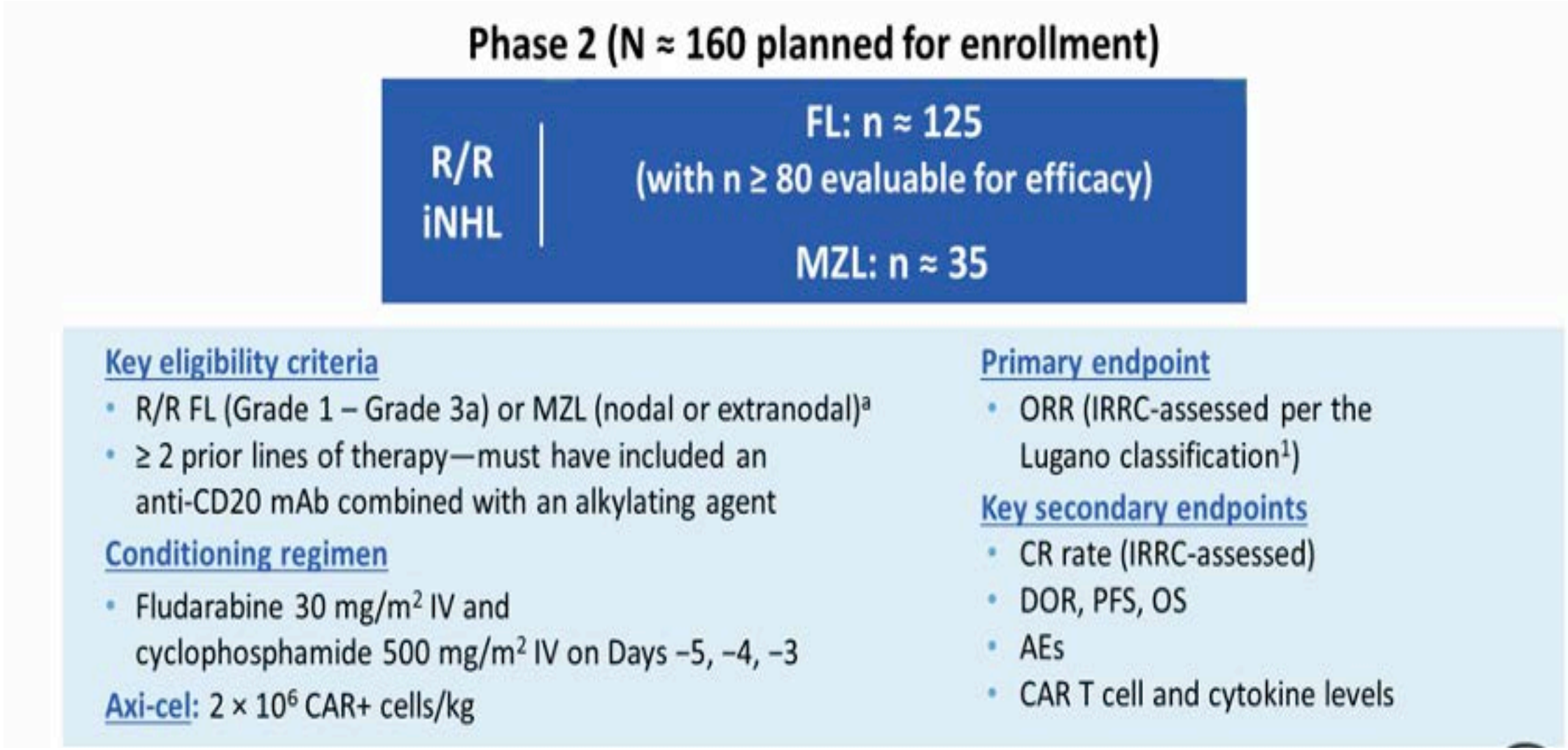
- Tisa-cel produces high CR rate (65%) in relapsed/refractory FL with a short follow-up (median f/u 10 months)
- Limited toxicity - Grade ≥ 3 CRS 0%
- May provide a new treatment option if approved; particularly for older pts or those with comorbidities

Implications for Future Research

- Risk stratification needed to identify patients most likely to benefit from CAR T-cell therapies
- Effects of sequencing with other therapies

Courtesy of Christopher R Flowers, MD, MS

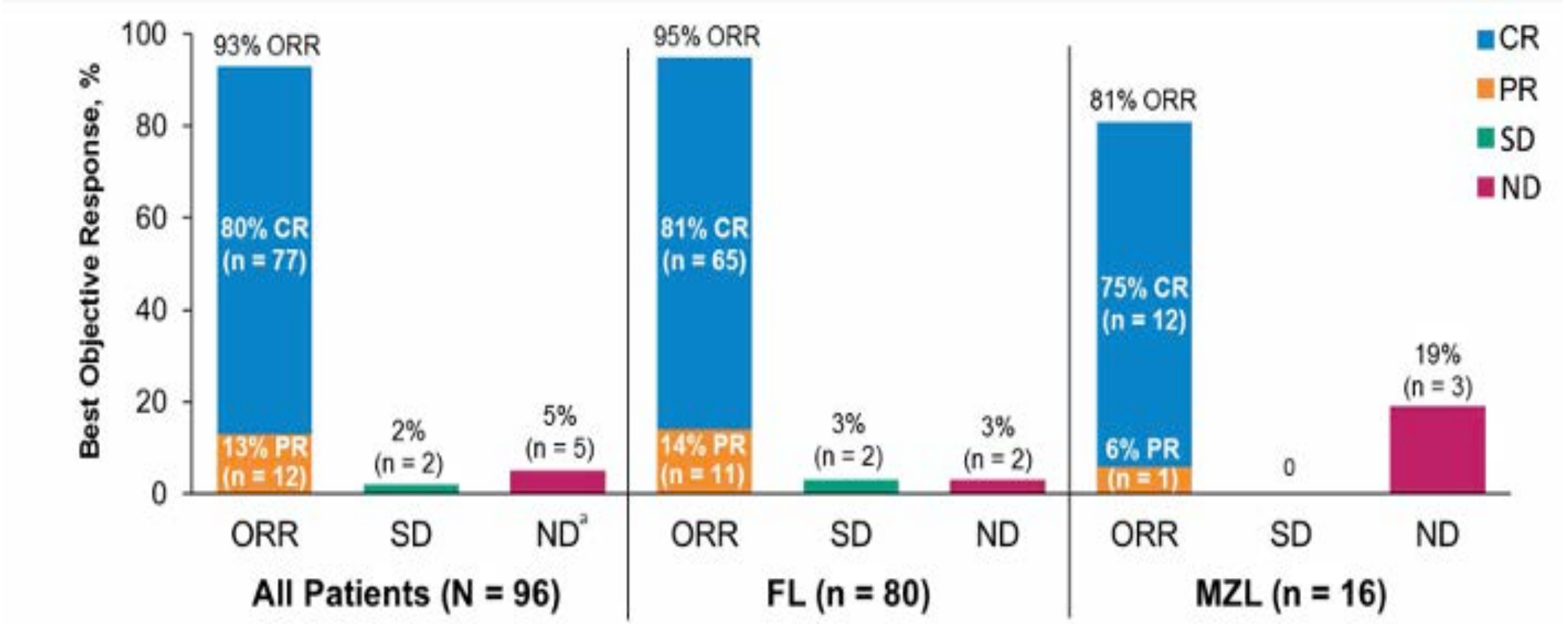
Phase II ZUMA-5 Trial of Axicabtagene Ciloleucel



Jacobson CA et al. ASCO 2020; Abstract 8008.

Courtesy of Christopher R Flowers, MD, MS

ZUMA-5: Response



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Of the 80 patients with FL, 10 (13%) had an initial response of PR at Week 4 and later converted to CR

Jacobson CA et al. ASCO 2020; Abstract 8008.

Courtesy of Christopher R Flowers, MD, MS

ZUMA-5: Primary Analysis

- The median time to peak CAR T was 9 days (range, 8 – 371) in all patients
  - 8 days (range, 8 – 371) in patients with FL
  - 15 days (range, 8 – 29) in patients with MZL
- In efficacy-evaluable patients with FL, median peak CAR T cell levels were numerically greater in those with ongoing response at 12 months than in those who relapsed (P = .057).
- In all treated patients with FL, CAR T cell peak was associated with Grade ≥ 3 CRS (P = .031) and NEs (P = .005).
- **Conclusions:**
  - Axi-cel had considerable and durable clinical benefit in patients with iNHL, with high ORR and CR rates.
  - Axi-cel had a manageable safety profile, with lower rates of Grade ≥ 3 NEs observed in patients with FL vs those in patients with MZL and those previously reported in aggressive NHL

Jacobson CA et al. ASH 2020; Abstract 700.

Courtesy of Christopher R Flowers, MD, MS

Jacobson CA et al. Interim analysis of ZUMA-5: A phase II study of axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory indolent non-Hodgkin lymphoma (R/R iNHL). ASCO 2020; Abstract 8008.

Jacobson C et al. Primary Analysis of Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL). ASH 2020; Abstract 700.

Impact on Patient Care and Treatment Algorithm

- Axi-cel produces a high CR rate (80%) in relapsed/refractory FL that appears durable with short follow-up (68% CR with median f/u 15 months)
- Limited toxicity - Grade ≥ 3 CRS 7%
- May provide a new treatment option if approved

Implications for Future Research

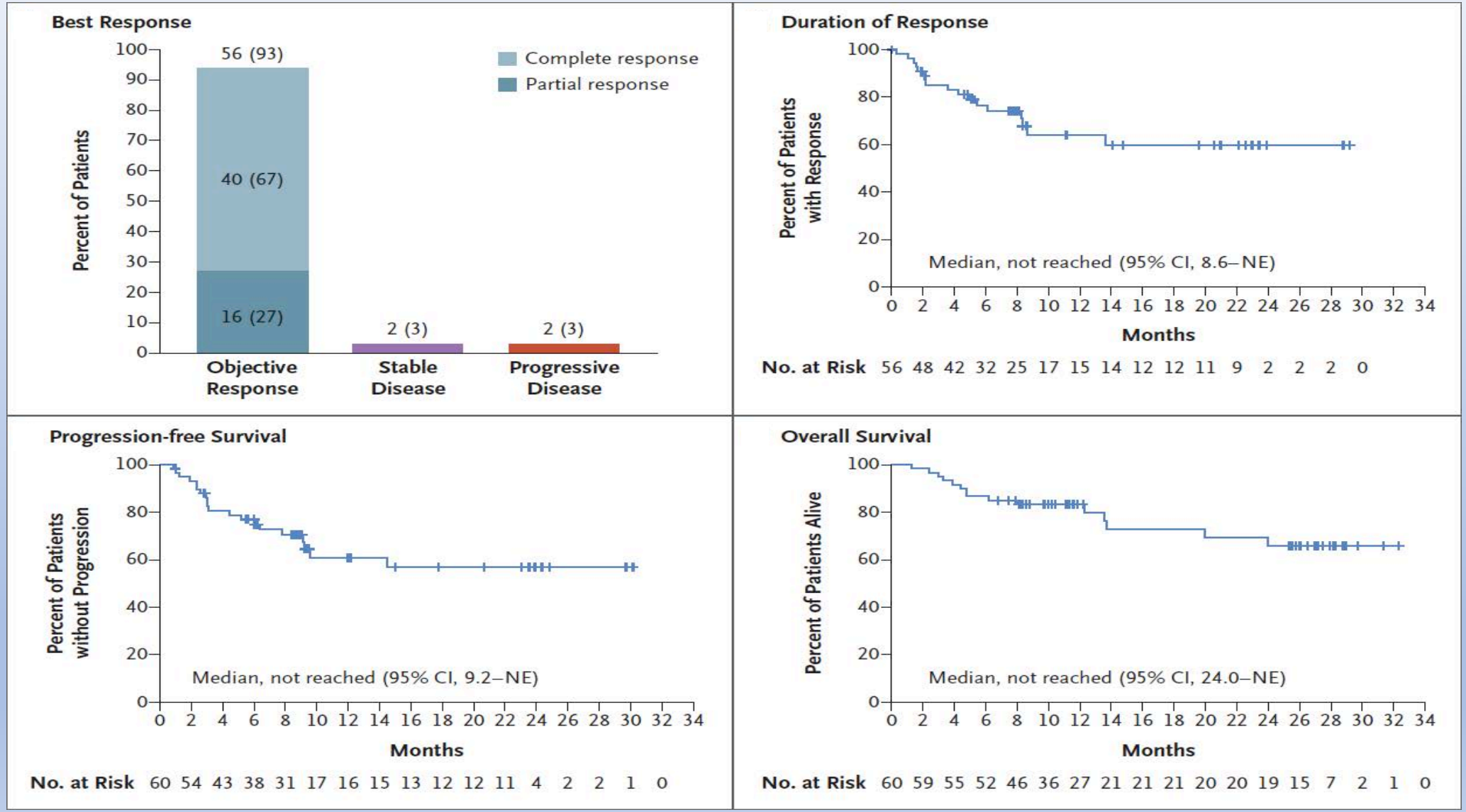
- Risk stratification needed to identify patients most likely to benefit from CAR T-cell therapies
- Effects of sequencing with other therapies

Courtesy of Christopher R Flowers, MD, MS

Mantle Cell Lymphoma

Courtesy of Christopher R Flowers, MD, MS

Results from the ZUMA-2 Trial of KTE-X19 CAR T-Cell Therapy in R/R MCL (7-Month Follow-Up)



Wang M et al. *N Engl J Med* 2020;382(14):1331-1342.

Courtesy of Christopher R Flowers, MD, MS

ZUMA-2: One-Year Follow-Up Results for 60 Pts

- **The ORR = 92%**
  - CR rate = 67%
- Of all efficacy-evaluable patients, 48% had ongoing responses at the data cutoff. Median DoR, PFS and OS = Not reached
  - 15-month PFS = 59.2%
  - 15-month OS = 76.0%
- **Common grade ≥ 3 AEs:** Neutropenia (85%), thrombocytopenia (53%), anemia (53%), and infections (34%).
- Grade ≥ 3 cytopenias were reported in 60% of patients ≥ 30 days post-infusion.
- Grade ≥ 3 CRS occurred in 15% of patients; 59% received tocilizumab
- Grade ≥ 3 neurologic events (NEs) were reported in 31% of patients; 8% received steroids
- All CRS events and most NEs (37/43) resolved, as previously reported.
- There were no Grade 5 CRS events or NEs, and no new Grade 5 events occurred with additional follow-up.

Wang M et al. ASH 2020; Abstract 1120.

Courtesy of Christopher R Flowers, MD, MS

Wang M, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020 Apr 2;382(14):1331-1342.

Wang M et al. One-Year Follow-up of ZUMA-2, the Multicenter, Registrational Study of KTE-X19 in Patients with Relapsed/Refractory Mantle Cell Lymphoma. ASH 2020; Abstract 1120.

Impact on Patient Care and Treatment Algorithm

- KTE-X19 produces durable remissions in pts with rel/ref MCL and provides a new approved treatment option
- Grade ≥ 3 cytopenias occurred in 60% of pts ≥ 30 days post-infusion
- Grade ≥ 3 CRS occurred in 15% of pts; 59% received tocilizumab
- Grade ≥ 3 neurologic events occurred in 31% of pts

Implications for Future Research

- Need to define biomarkers to predict patients likely to respond
- Sequencing of KTE-X19 with first line and relapsed combination regimens

Courtesy of Christopher R Flowers, MD, MS

Phase II Trial of Zanubrutinib, a Selective BTK Inhibitor, in R/R MCL

Efficacy variable	*N* = 86
Objective response, *n* (%)	
Complete	59 (68.6)
Partial	13 (15.1)
No response	14 (16.3)
Overall	72 (84)
95% CI for overall response	(74, 91)
Time to response (months)	
Median (range)	2.7 (2.5–16.6)
Response duration (months)	
Median (range)	19.5 (0.9–19.5)
95% CI	(16.6, NE)
Event-free rates at 12 months (%)	78.3
95% CI	(67, 86)
PFS (months)	
Median (range)	22.1 (0.0+, 22.3+)
95% CI	(17.4, NE)
Event-free rates at 12 months (%)	75.5
95% CI	(65, 83)

Song Y et al. *Clin Cancer Res* 2020;26(16):4216-4224.

Courtesy of Christopher R Flowers, MD, MS

Phase II Trial of Zanubrutinib: Adverse Events

Event	All grades, *n* (%)	Grade ≥3, *n* (%)
Patients with at least one adverse event	83 (96.5)	34 (41.9)
Hematologic events		
Neutropenia	42 (48.8)	17 (19.8)
Leukopenia	30 (34.9)	6 (7.0)
Thrombocytopenia	28 (32.6)	4 (4.7)
Anemia	13 (15.1)	5 (5.8)
Nonhematologic events		
Upper respiratory tract infection	30 (34.9)	0
Rash	29 (33.7)	0
Hypokalemia	14 (16.3)	1 (1.2)
Diarrhea	13 (15.1)	0
Hypertension	13 (15.1)	3 (3.5)
Alanine aminotransferase increased	12 (14.0)	1 (1.2)
Lung infection	11 (12.8)	8 (9.3)

Song Y et al. *Clin Cancer Res* 2020;26(16):4216-4224.

Courtesy of Christopher R Flowers, MD, MS

Song Y, et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. Clin Cancer Res. 2020 Aug 15;26(16):4216-4224.

Impact on Patient Care and Treatment Algorithm

- High and durable CR rates, and zanubrutinib provides a treatment option for pts with rel/ref MCL
- Typical grade ≥3 BTK toxicities (bleeding, HTN, a-fib.) were uncommon

Implications for Future Research

- Need to distinguish pts for whom a particular BTKi would be preferred
- Development of strategies for time-limited therapy in patients who achieve CR/ MRD negativity

Courtesy of Christopher R Flowers, MD, MS

Phase I/II BRUIN Trial of LOXO-305 in Previously Treated MCL, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas

- LOXO-305 is a highly selective, non-covalent BTK inhibitor that inhibits both wild type and C481-mutated BTK with equal low nanomolar potency
- Median number of prior lines of therapy was 2 for MCL (range 2-8)
- Responses were observed at the first dose level of 25 mg QD.
- RP2D of 200 mg QD was selected for future studies.
- **Among 35 evaluable pts with MCL**
  - ORR = 51%
  - CR = 9 (25.7%)
  - Among the 20 efficacy evaluable pts who started at RP2D, ORR was 65% with 7 CRs
- Responses in MCL were observed in pts who received prior cell therapy, including 3 of 7 patents with prior SCT, and 1 of 2 with prior CAR-T
- There were no DLTs or dose reductions.
- The only TEAEs regardless of attribution or grade seen in ≥10% of pts (n=186) were fatigue (n=29, 16%) and diarrhea (n=28, 15%).

Wang M et al. ASH 2020; Abstract 117.

Courtesy of Christopher R Flowers, MD, MS

Wang M et al. LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study. ASH 2020; Abstract 117.

Impact on Patient Care and Treatment Algorithm

- LOXO-305 is a selective, non-covalent BTKi active in WT and C481-mutated-BTK that has promising efficacy in heavily pretreated relapsed/refractory MCL after 2 lines
- Can be a useful addition to therapeutic options if approved

Implications for Future Research

- Would benefit from identification of pts more likely to respond to LOXO-305 compared with other BTKis
- Can consider trials involving combinations in MCL and WM

Courtesy of Christopher R Flowers, MD, MS