Ibrutinib Combos in B-NHL

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May 19, 2026

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Disclosures

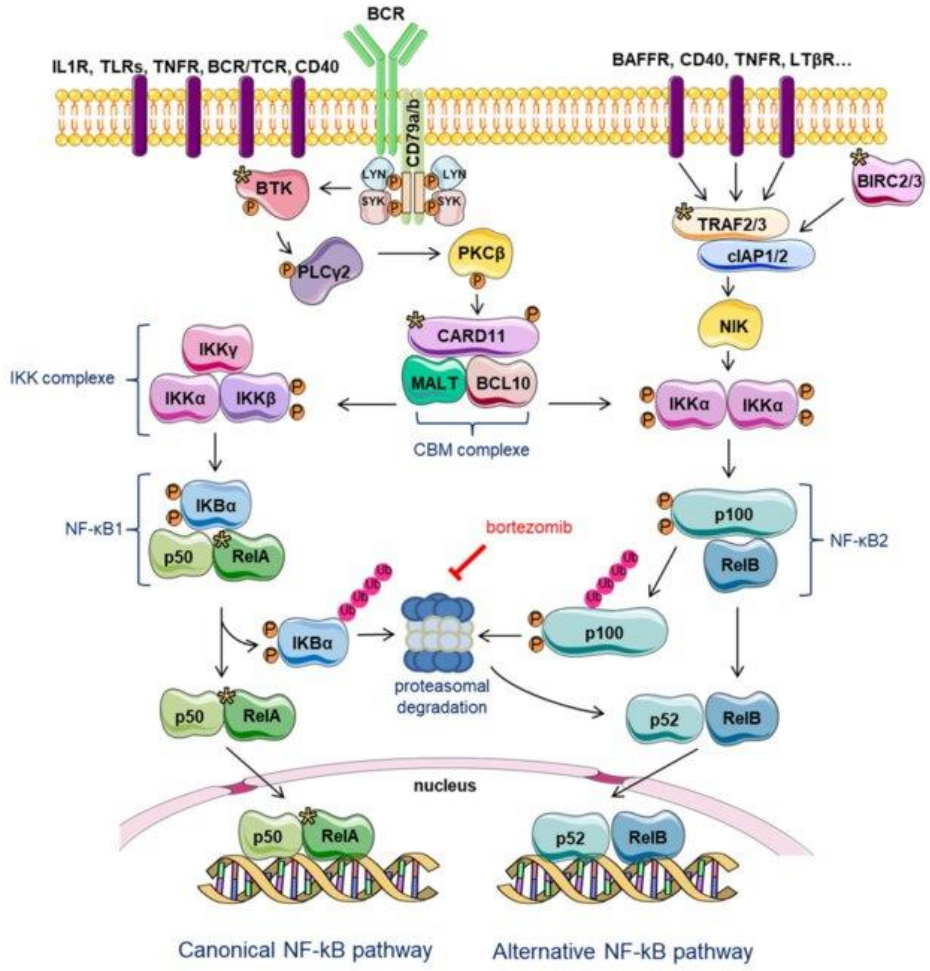
Consultancy (to institution)	Abbvie, Adaptive, ADC, AstraZeneca, Avencell, BeOne, BMS, Caribou, Genentech/Roche, Janssen, Legend, Lilly/Loxo, Merck, Pfizer, Sanofi
Research Funding (to institution)	Abbvie, AstraZeneca, Avencell, BMS, Genentech/Roche, Janssen, Kite, Lilly/Loxo, Merck, Nurix, Pfizer, Sanofi
Stock	None
Employment	N/A

Why revisit ibrutinib combinations in 2026?

- Ibrutinib in B-NHL is being supplanted by 2nd gen cBTKi (acalabrutinib, zanubrutinib) and non-covalent (pirtobrutinib) BTKis based on tolerability
- However…ibrutinib has extensive combination dataset: BTKi + X (anti-CD20, BCL2, chemo) remains a useful paradigm to extend depth and duration of response
- Do ibrutinib combinations represent SOC or proof-of-concept that should now migrate to next-gen BTKis?

Rationale for BTKi combinations

- Chronic active BCR signaling drives NF-κB dependence in ABC-DLBCL, MCL, MZL, WM, and PCNSL (MYD88 / CD79B mutations)
- Synergy with BCL2 inhibition (apoptotic priming), anti-CD20 (ADCC), and chemotherapy via NF-κB blockade
- Why combinations help:
  - mitigate primary resistance
  - increase CR / MRD-negative depth
  - enable fixed duration



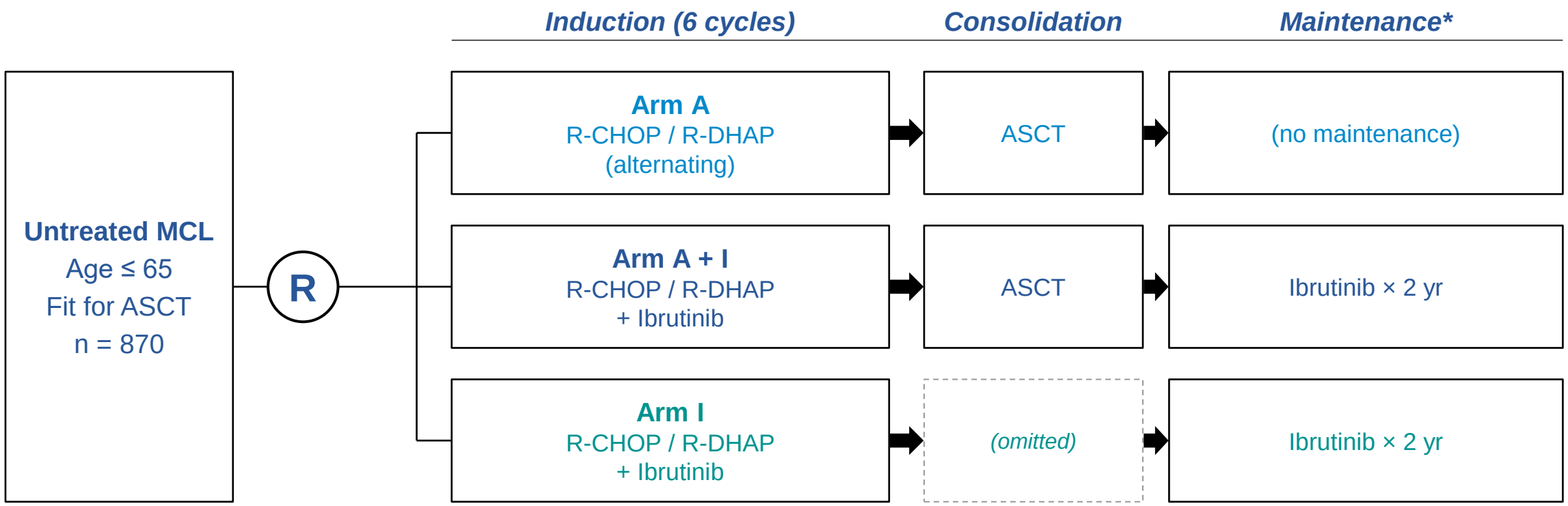
Wilson WH et al. Cancer Cell 2021

Landscape of select ibrutinib combo trials in NHL

Setting	Trial	Comparator	Status	Signal
MCL frontline (young / fit)	TRIANGLE	R-CHOP/R-DHAP + ASCT	Positive Ph3	ASCT may be omitted
MCL frontline (older)	ENRICH	R-chemo (R-CHOP or BR)	Positive Ph 2/3	IR beats R-CHOP
MCL R/R	SYMPATICO	Ibr + placebo	Positive ph 3	Fixed-duration Ibrutinib + Ven superior to Ibrutinib alone
DLBCL frontline (non-GCB)	PHOENIX + biomarker reanalyses	R-CHOP	Missed primary; reanalyzed	Benefit in young MCD/N1
PCNSL	Ibr + HD-MTX / rituximab combos	Various	Phase 1b/2	High response rates in disease with high unmet need

TRIANGLE: Schema

3-arm randomized open-label phase 3 · frontline MCL, fit / ASCT-eligible



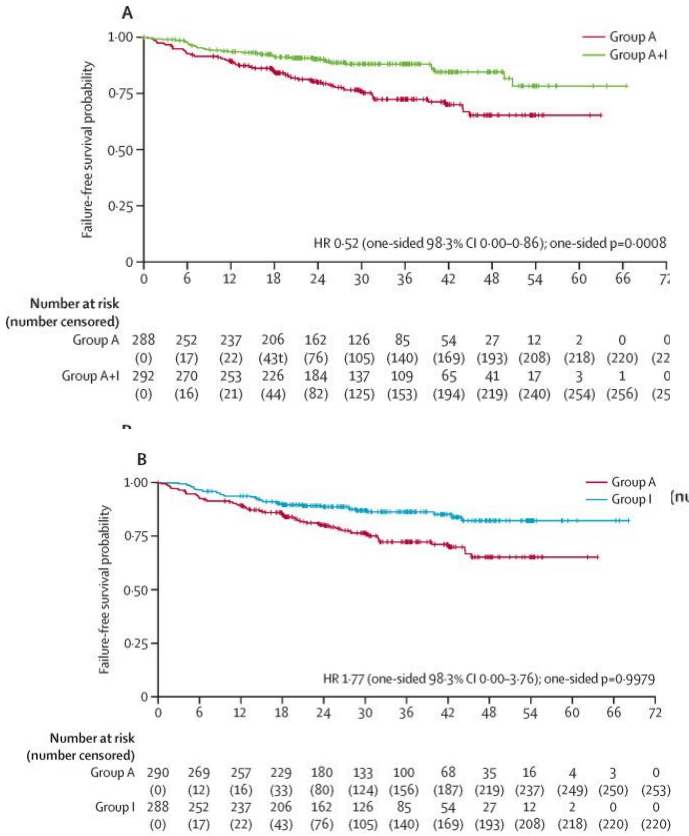
*Rituximab maintanence was allowed but not mandated

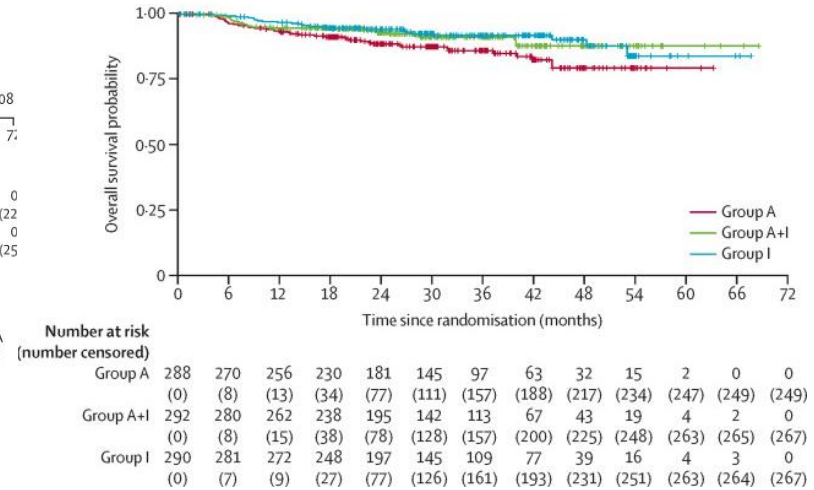
Primary endpoint: failure-free survival (FFS)

Dreyling M et al. Lancet 2024

TRIANGLE: efficacy & the ASCT question

- A+I vs A: **superior FFS**
- I vs A: ibrutinib arm non-inferior / favorable on FFS
- A+I vs I
  - no clear FFS benefit of adding ASCT to an ibrutinib-containing regimen
  - ASCT likely omittable when ibrutinib is used in induction + maintenance
- Increased toxicity (infections, hematologic) in the A+I arm; ASCT adds morbidity without clear efficacy gain





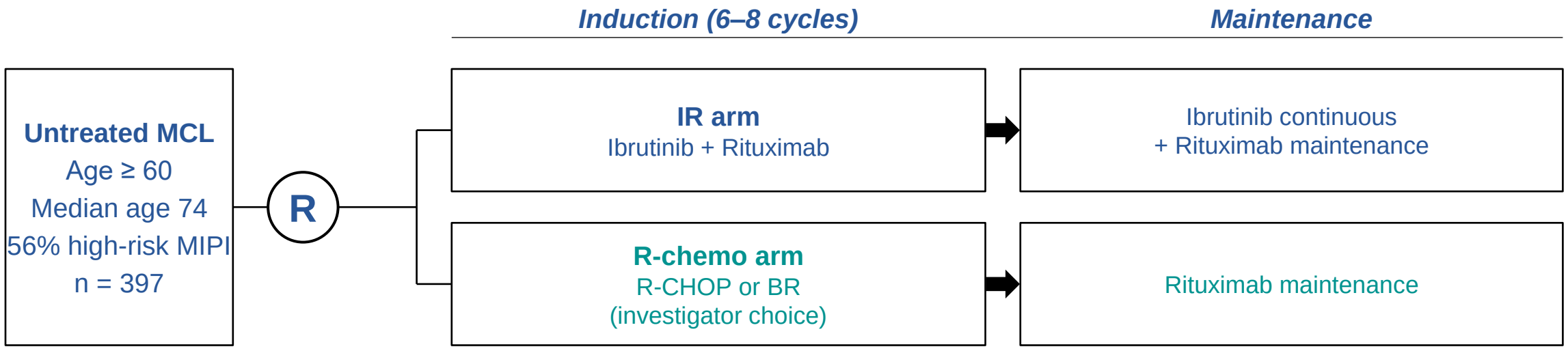
Reference: Dreyling M et al. Lancet 2024;403:2293–2306; Dreyling et al. ASH 2024 abstract #240

TRIANGLE: Takeaways

- First trial to credibly challenge ASCT in fit MCL
- Ibrutinib arms used 2-year maintenance — unclear how much benefit comes from induction vs. maintenance
- TP53-mutated subgroup: ibrutinib-containing arms outperformed A, but outcomes remain poor — these patients still need different strategies (e.g., BOVen, frontline CAR-T trials)
- EMA approval (June 2025), this is the new fit-MCL frontline standard — expect ongoing migration to next-gen BTKis

ENRICH (older MCL frontline): Schema

Randomized open-label phase 2/3 · chemo-free vs immunochemotherapy

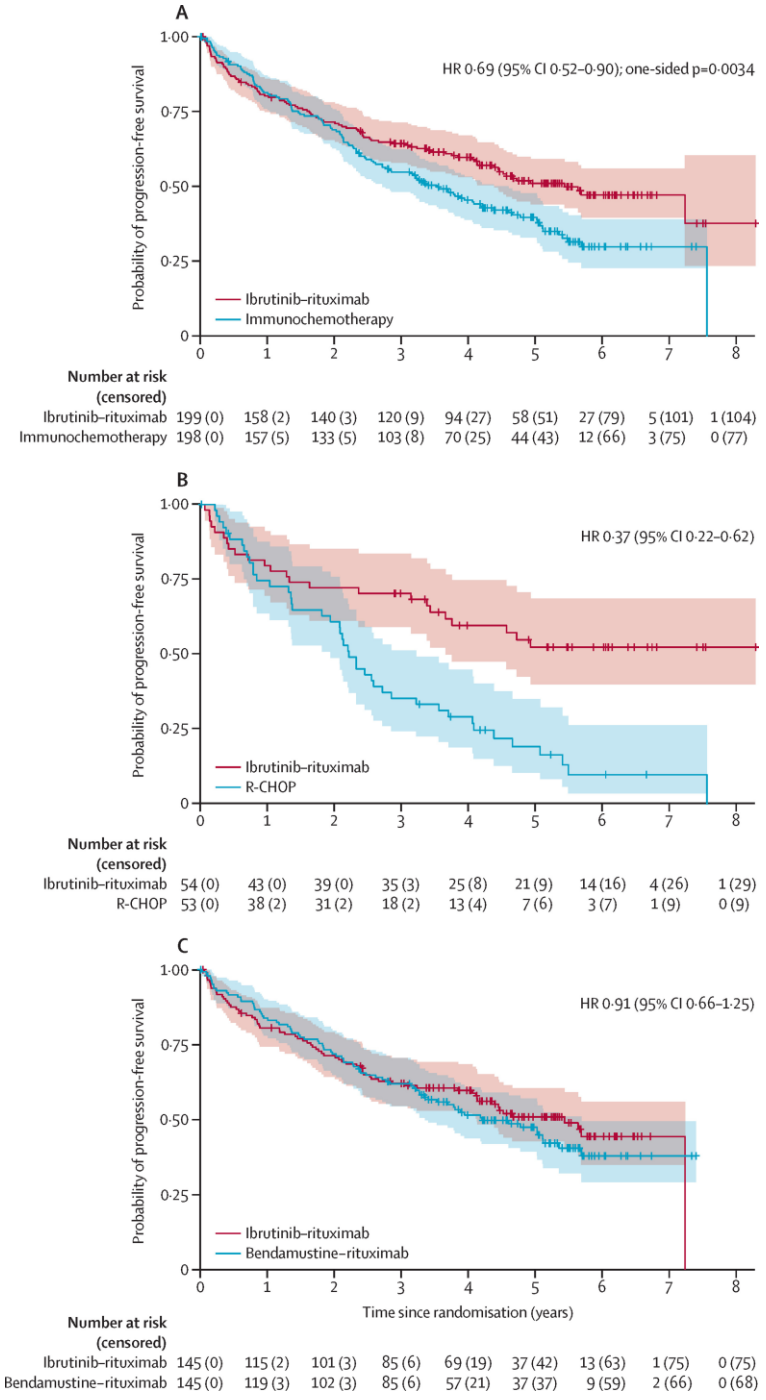


Primary endpoint: progression-free survival (PFS)

Lewis DJ, Jerkeman M, Sorrell L, et al. Lancet 2025

ENRICH: Efficacy

- Median PFS: IR 65.3 mo vs R-chemo 42.4 mo (HR 0.69; 95% CI 0.52–0.90; p = 0.003)
- Median follow-up 47.9 mo
- Key subgroup interaction (p = 0.004): IR superior to R-CHOP (HR 0.37; median PFS NR vs 26.6 mo) but comparable to BR
- Better hematologic toxicity and better mid-treatment QoL with IR; more COVID events with IR
- No OS difference



Lewis et al. Lancet 2025

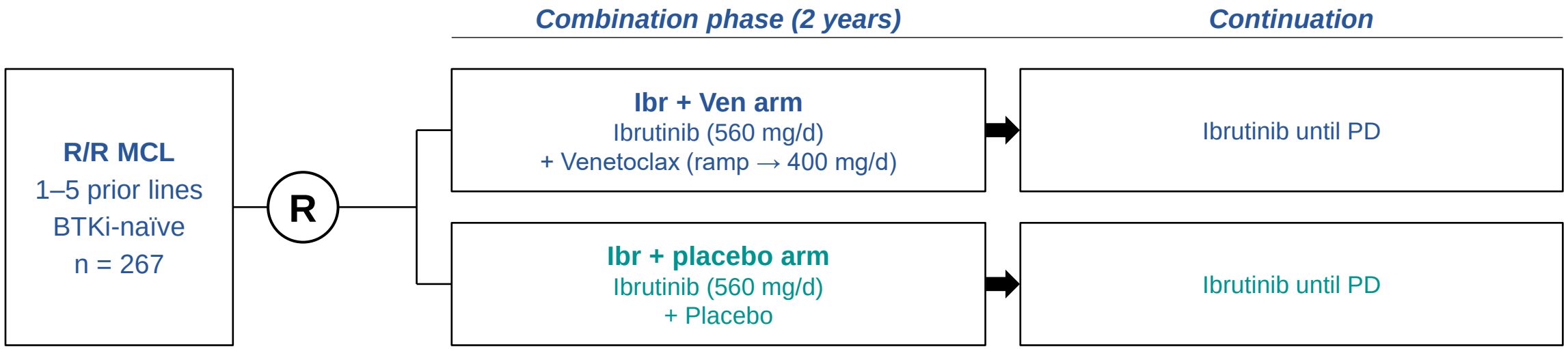
ENRICH: Takeaways

- 1st chemo-free regimen to beat CIT in 1L MCL — but largely vs. R-CHOP; vs. BR (the real-world standard in older patients) it's a wash
- Continuous therapy vs fixed duration (BR) – not necessarily desirable
- TP53-mutated:PFS data still suboptimal
  - SYMPATICO IR + Ven TP53mut median PFS 19.8 mo
  - SHINE BR + I TP53mut 28.8 mo
- Same caveat as TRIANGLE: regimen will likely migrate to acalabrutinib / zanubrutinib (e.g., ALTAMIRA, ECHO data, MANGROVE to come) given cardiac AE profile

Lewis et al. Lancet 2025

SYMPATICO: design recap

Phase 3 randomized double-blind · fixed-duration combination in R/R MCL

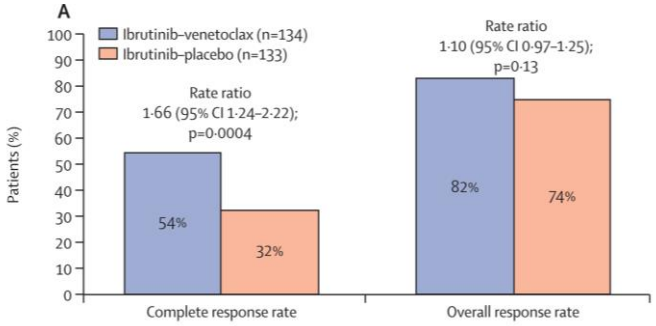


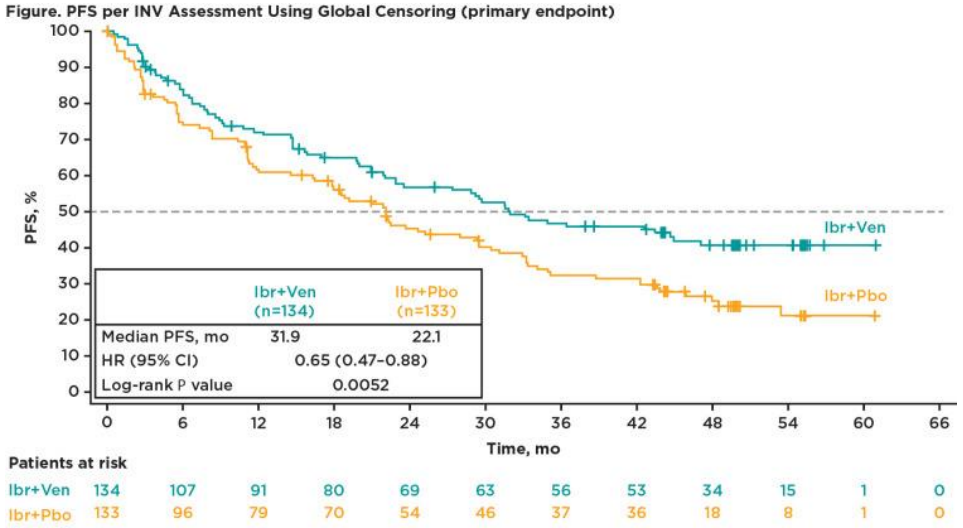
Primary endpoint: progression-free survival (PFS)

Wang M, Jurczak W, Trneny M, et al. Lancet Oncol 2025

SYMPATICO: ibrutinib + venetoclax in R/R MCL

- ORR 82% vs 74%
- CR 54% vs 32%
- Median follow-up 51.2 mo
- Median PFS: 31.9 mo vs 22.1 mo (HR 0.65; 95% CI 0.47–0.88; p = 0.0052)
- Safety: no clinical TLS; expected AEs (diarrhea, neutropenia, COVID); no new signals





Wang M, Jurczak W, Trneny M, et al. Lancet Oncol 2025

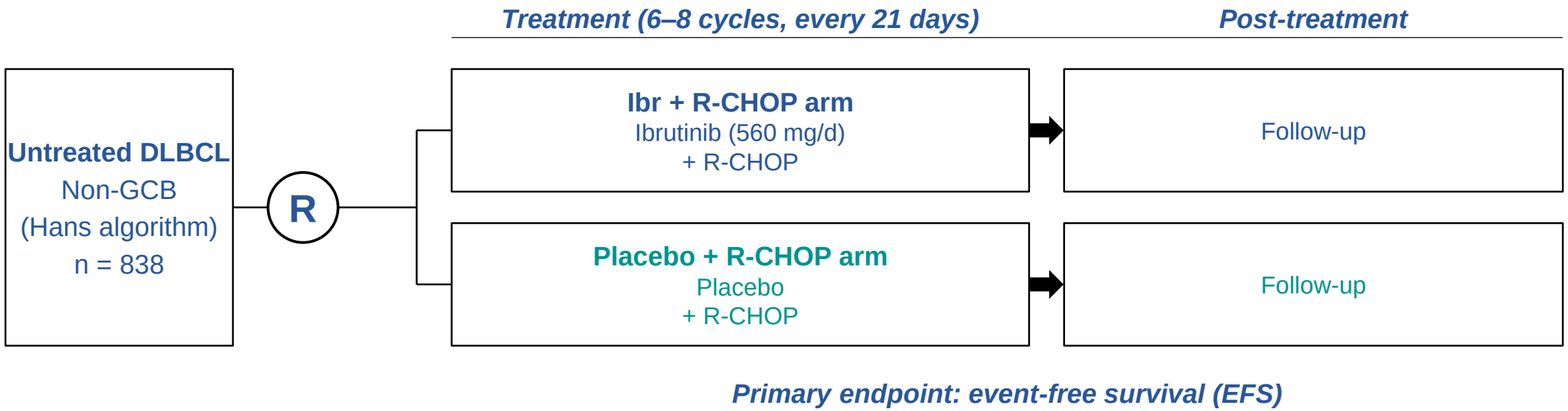
SYMPATICO: Takeaways

- First positive phase 3 of all-oral, targeted doublet in R/R MCL
- Real-world relevance limited: many R/R MCL patients in 2026 may have prior BTKi exposure (post-ENRICH / TRIANGLE adoption) — SYMPATICO enrolled BTKi-naïve patients. Generalizability to current R/R landscape in future may be questionable
- TP53-mutated subgroup (R/R cohort): meaningful but shorter PFS — consistent with BTKi + BCL2i overcoming some, not all, TP53 effect
- Frontline SYMPATICO cohort (ASCO 2025): treatment-naïve MCL incl. TP53mut — high CR, durable responses; potentially a path forward in TP53mut frontline (along with BOVen)
- AIM trial 7-year follow-up: durable PFS 30%, OS 43%, treatment-free remission feasible in MRD-negative CR — proof of concept for fixed duration

Wang et al. Lancet Oncol 2025; Hoffmann MS et al. JCO 2025; Handunnetti SM et al. Blood 2024

PHOENIX: design recap

Phase 3 randomized double-blind · frontline non-GCB DLBCL



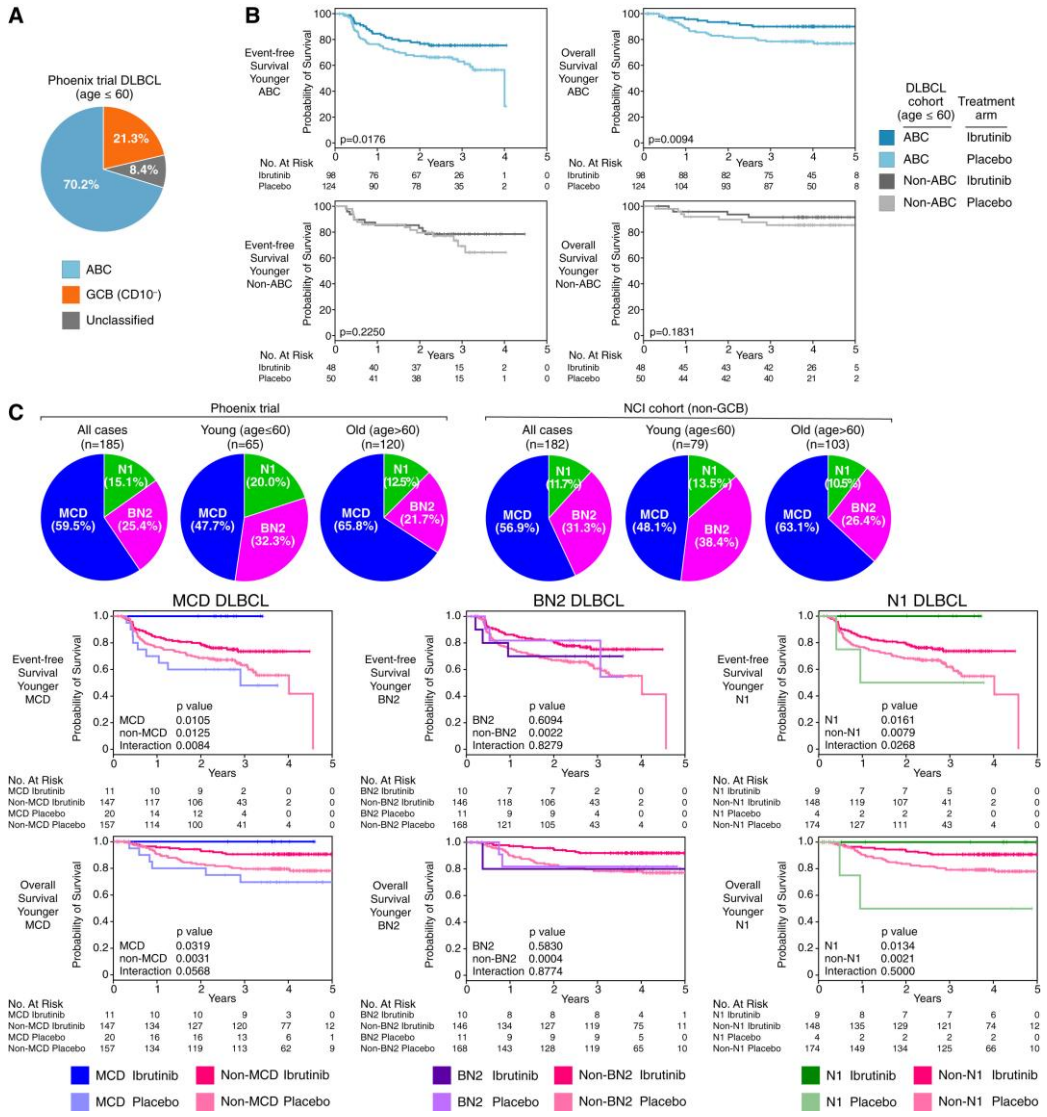
- Missed primary endpoint (EFS) in ITT: HR 0.93 (95% CI 0.73–1.20; p = 0.59)
- Critical age interaction: patients < 60 → improved EFS, PFS, and OS with ibrutinib; patients ≥ 60 → worse outcomes, driven by tolerability and early discontinuation

Younes A, Sehn LH, Johnson P, et al. J Clin Oncol 2019

PHOENIX reanalyzed: the LymphGen story

Patient selection, not drug failure?

- Wilson / Staudt reanalysis (Cancer Cell 2021): LymphGen subtyping of 773 PHOENIX biopsies
- Patients ≤ 60 with MCD or N1 subtype: 3-yr EFS = 100% with Ibr + R-CHOP vs 42.9% / 50% with R-CHOP alone
- BN2 subtype: also signal of benefit
- Other subtypes (incl. GCB): no benefit
- MYC / BCL2 co-expressing non-GCB (double expressors): subanalysis suggests benefit
- Is the right question 'MCD / N1 genotype + age ≤ 60?'
- Real-world implication: biology-driven precision medicine —should we be ordering molecular subtyping in young non-GCB DLBCL…we mostly aren't
- A framework for how future BTKi-in-DLBCL trials should be designed?



Wilson WH, Wright GW, Huang DW, et al. Cancer Cell 2021; Younes et al. JCO 2019

Ibrutinib in PCNSL: signal in a high-unmet-need disease

MCD-like biology + CNS penetration

- Rationale: ~60–80% of PCNSL harbor MYD88 L265P and / or CD79B mutations (MCD-like genotype)
- Grommes et al. (MSKCC) phase 1b, R/R PCNSL / SCNSL: ibrutinib + HD-MTX + rituximab — RP2D ibrutinib 840 mg; high response rates, manageable toxicity (note aspergillosis signal with concurrent steroids)
- Phase 2 MIT regimen (HD-MTX + ibrutinib + temozolomide), newly diagnosed PCNSL: published Blood Cancer Discovery 2025;6(3):191 — strong CR rates, durable PFS (verify topline)
- Small frontline IRM (ibrutinib / rituximab / MTX) pilots: ORR ~100%, 5-yr PFS / OS ~78% (small n, single-center, hypothesis-generating)
- Ibrutinib has CNS penetration, but next-gen CNS-penetrant BTKis (tirabrutinib in Japan; pirtobrutinib in development) may displace ibrutinib here too

Grommes C et al. Blood 2019; Lewis KL et al. Blood Cancer Discov 2025; Guo Y et al. Front Oncol 2025

Synthesis: where does ibrutinib still belong?

- Possible roles today:
  - Frontline MCL — TRIANGLE-style for fit, ENRICH-style for older —acala / zanu have no phase 3 data …but substitution is likely….
  - Possibly frontline non-GCB DLBCL in selected younger MCD / N1 patients if you can get the genotyping…but maybe not with Pola-RCHP…
  - PCNSL combination regimens, particularly MIT / IRM-style
  - R/R MCL fixed-duration with venetoclax in BTKi-naïve patients

- The combinations framework is the durable lesson:
  - BTKi + anti-CD20 → backbone of chemo-free disease control
  - BTKi + BCL2i → fixed-duration, deep MRD-negative remissions
  - BTKi + chemo → only useful where biology predicts BCR dependence
  - Expect these combinations to migrate to next-gen BTKis with better tolerability — ibrutinib's data legacy increasingly becomes acalabrutinib's and zanubrutinib's clinical practice

Conclusions

- TRIANGLE and ENRICH have reshaped frontline MCL; ASCT and chemotherapy are both genuinely challenged
- SYMPATICO validates fixed-duration BTKi + BCL2i but is most relevant for BTKi-naïve R/R MCL — a shrinking population
- PHOENIX is a precision-medicine teaching case: the right combination in the wrong population
- The path forward maybe biomarker-selected combinations on next-gen BTKi backbones (DLBCL, PCNSL)

Thank you.

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