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How do I manage a CLL patient refractory to BTK and BCL-2 inhibitors?

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Disclosures

AstraZeneca – Research funding, advisory board participation, speaking engagements

Abbvie – Advisory board participation

BeiGene – Research funding

BMS – Consulting

Eli Lilly – Advisory board participation, speaking engagements

Janssen – Speaking engagements

Galapagos – Advisory board participation

Agenda

Review a case

Sequencing

Definition of Relapsed/Refractory

Go over options for patients with Relapsed/Refractory CLL

My treatment algorithm

A case:

A 72 yo M with **del17p, IGHV unmutated RR CLL** presents for a second opinion.

He was diagnosed with CLL in 10 years ago. At diagnosis he had **unmutated IGHV, but no FISH or Karyotypic abnormalities**. He was on watch+wait for 2 years, and then developed cytopenias, and was placed on **ibrutinib**.

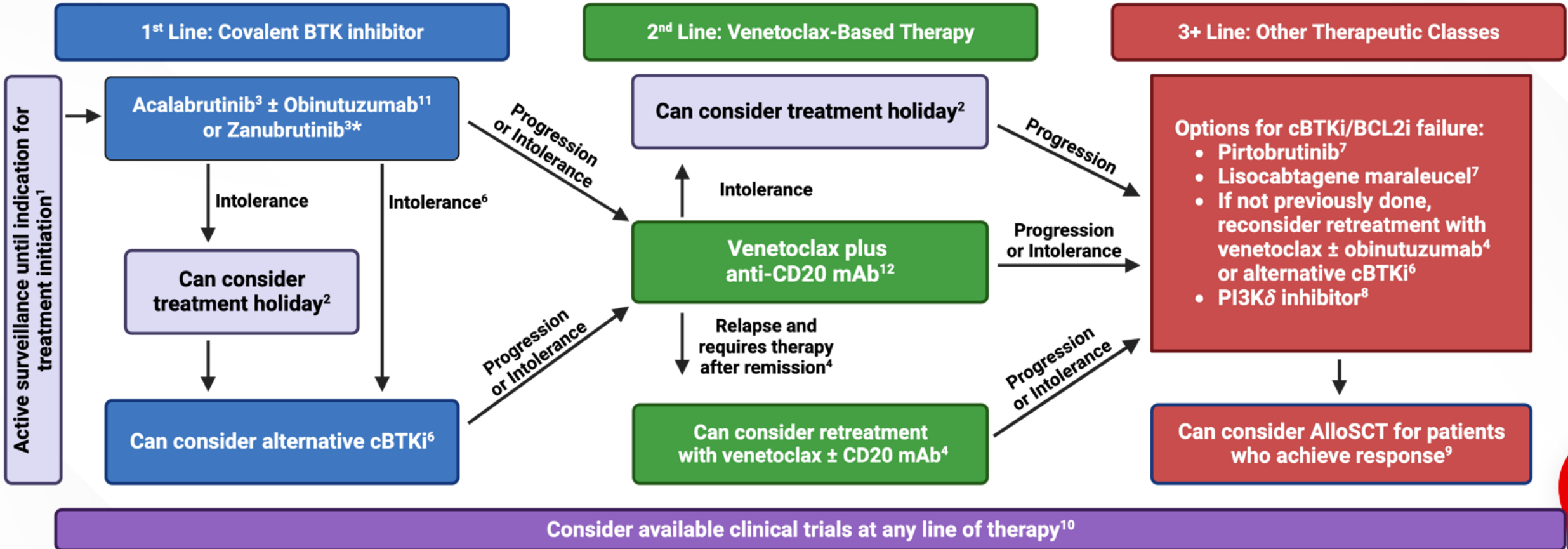
Ibrutinib for 5 years.

He then developed lymphocytosis again, with worsening cytopenias, and **repeat FISH testing showed a new del17p**.

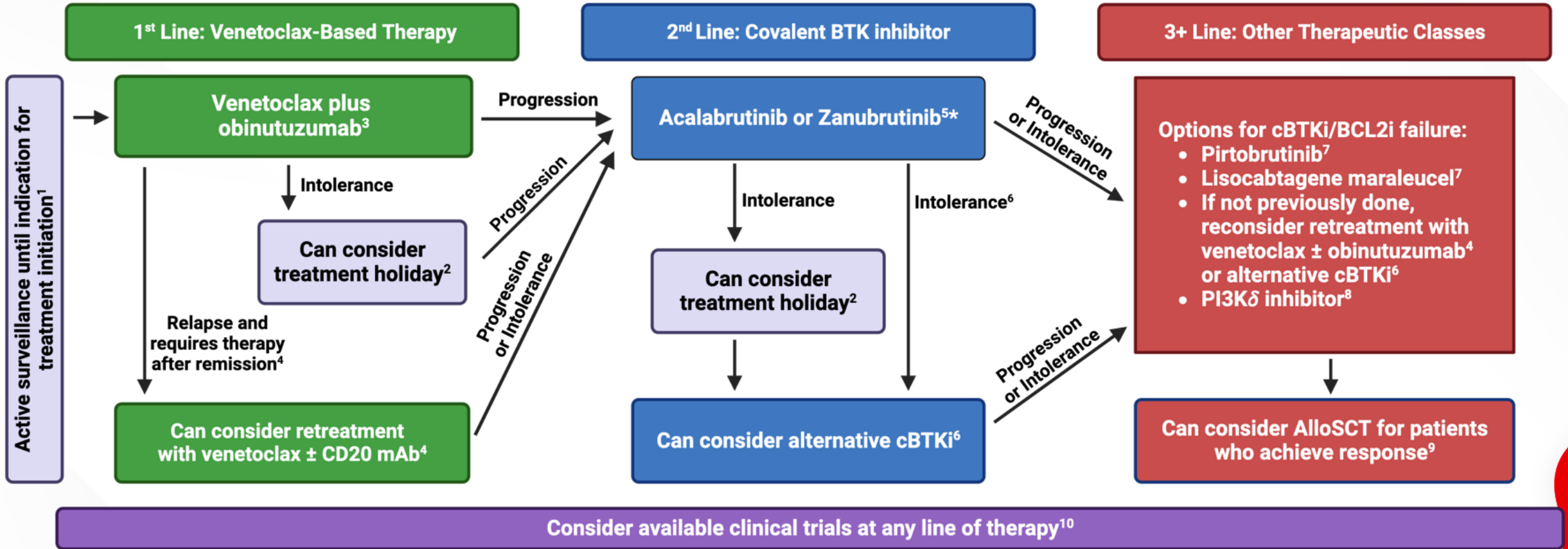
He was then started on **venetoclax + rituximab**. He had been treated with **VR for 2 years**, and stopped therapy.

Unfortunately, his **WBC began to rise 6 months after stopping VR**. He comes to you to ask what to do next.

BTKi First



Venetoclax First



Defining relapsed/refractory disease:

What I consider refractory to covalent BTK inhibitors:

- 1) Progressed while receiving a covalent BTK inhibitor
- 2) Developed toxicity where you wouldn't feel comfortable retreating
- 3) Switched cBTKi, and toxicity remains unmanageable
- 4) Stopped BTKi but developed a BTK mutation

What I consider refractory to venetoclax-based regimens:

- 1) Progressed while receiving venetoclax regimen
- 2) Progressed within 1-2 years of receiving time-limited venetoclax
- 3) Received time limited venetoclax x2
- 4) Developed toxicity where you wouldn't feel comfortable retreating

Thinking about our patient

What I consider refractory to covalent BTK inhibitors:

- 1) Progressed while receiving a covalent BTK inhibitor
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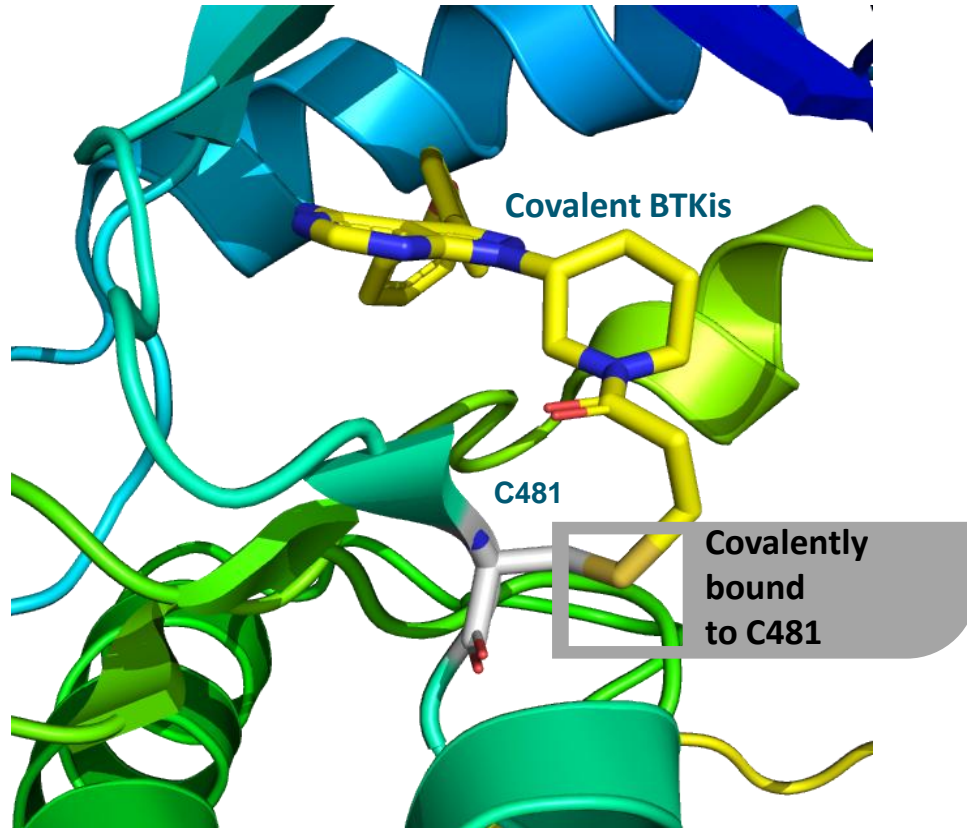
- 1) Progressed while receiving venetoclax regimen
- 2) Progressed within 1-2 years of receiving time-limited venetoclax
- 3) Received time limited venetoclax x2
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What are our options?

- Pirtobrutinib – ncBTKi
- Lisocabtagene maraleucel – CAR T-cell Therapy
- Allogeneic Stem Cell Transplant
- Retreatment with a Venetoclax-based regimen
 - > Trial BTKi + Ven especially if hasn't received it before
- Chemotherapy? PI3Ki?

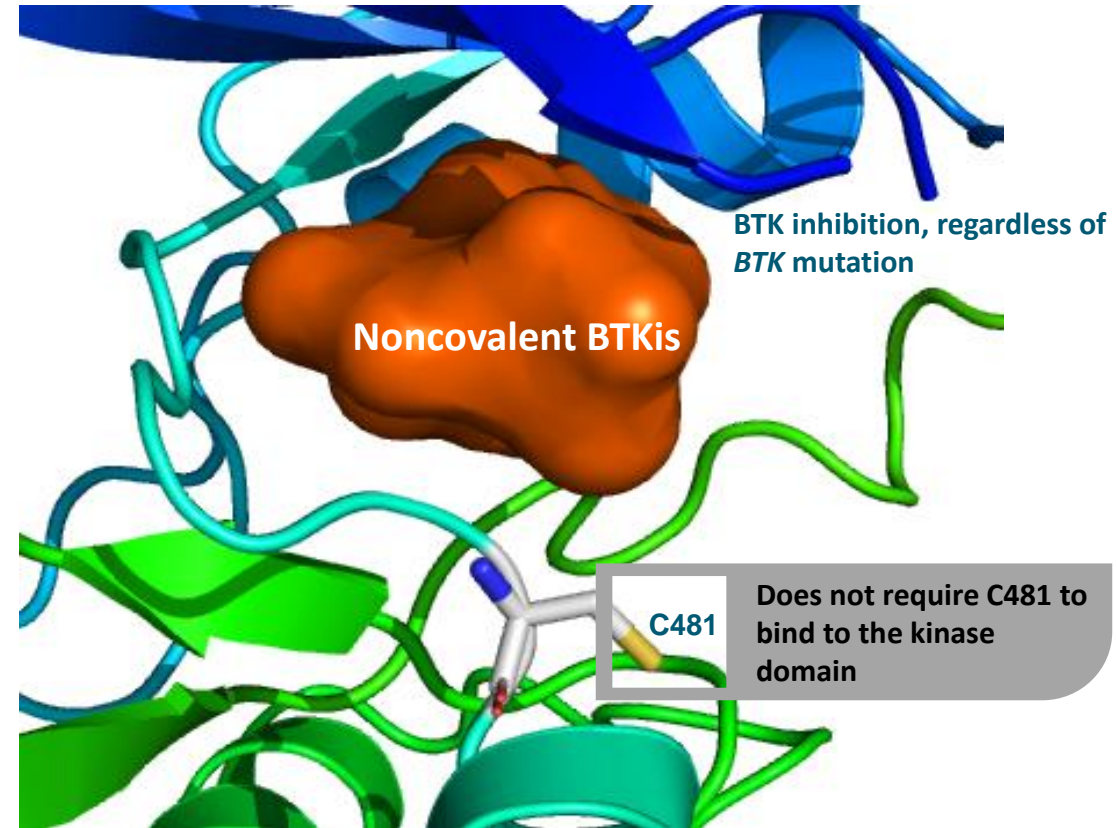
Noncovalent BTK Inhibitors Can Overcome BTK Resistance

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib) Require WT *BTK* for Activity

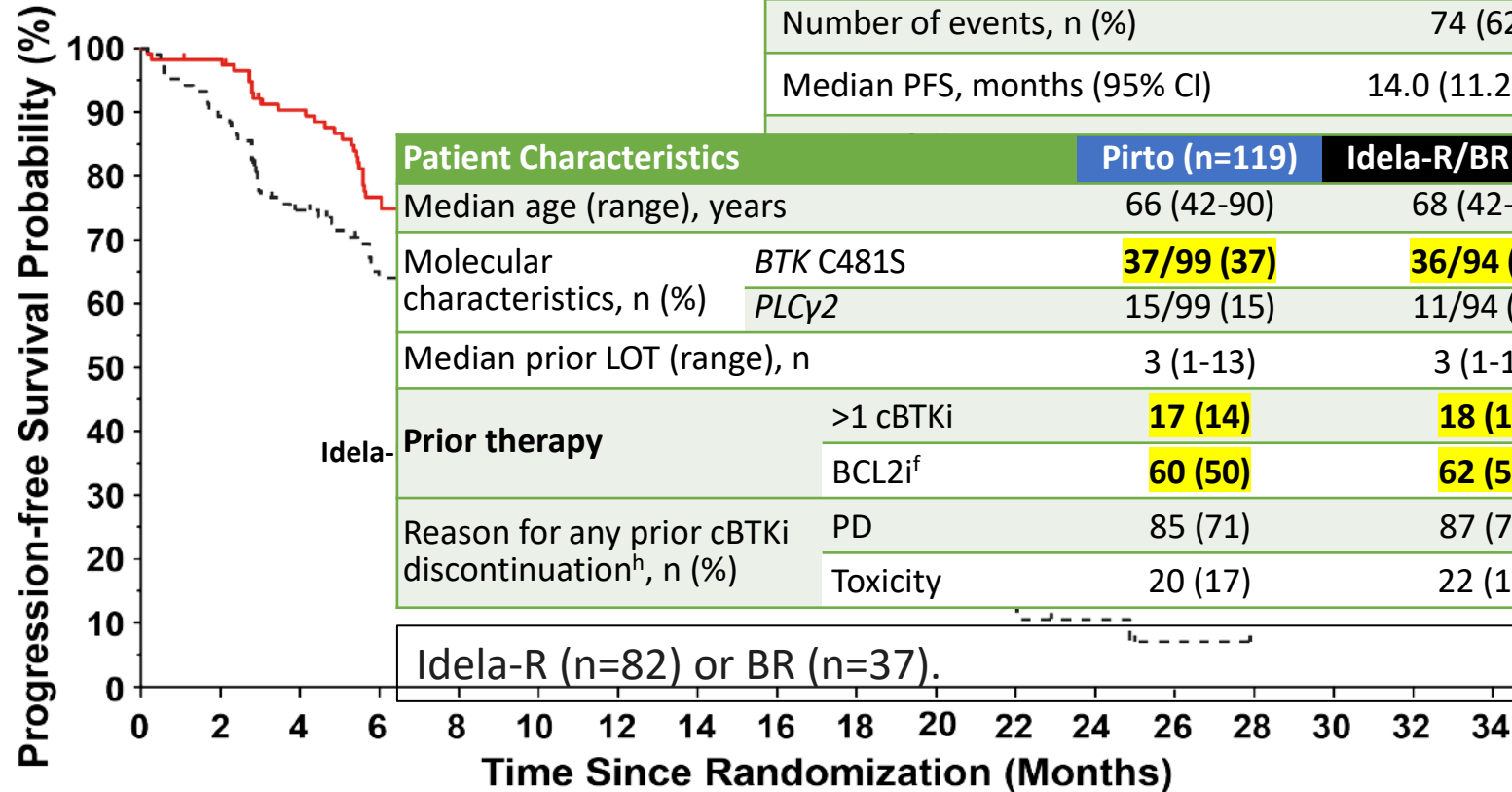


When *BTK* C481 mutations are present, resistance is conferred to all covalent BTKi

Noncovalent BTK Inhibitors (Pirtobrutinib, Nemtabrutinib) Are Active Against Both WT and C481-Mutated *BTK*



Phase 3 BRUIN CLL-321 - Pirto vs Idela-R or BR in BTKi-Pretreated CLL/SLL



| PFS by IRC | Pirto (n=119) | Idela-R/BR(n=119) |
|-----------------------------|------------------|-------------------|
| Number of events, n (%) | 74 (62) | 79 (66) |
| Median PFS, months (95% CI) | 14.0 (11.2-16.6) | 8.7 (8.1-10.4) |
| | | 17.7 |
| | | 0.75); 0.0002 |

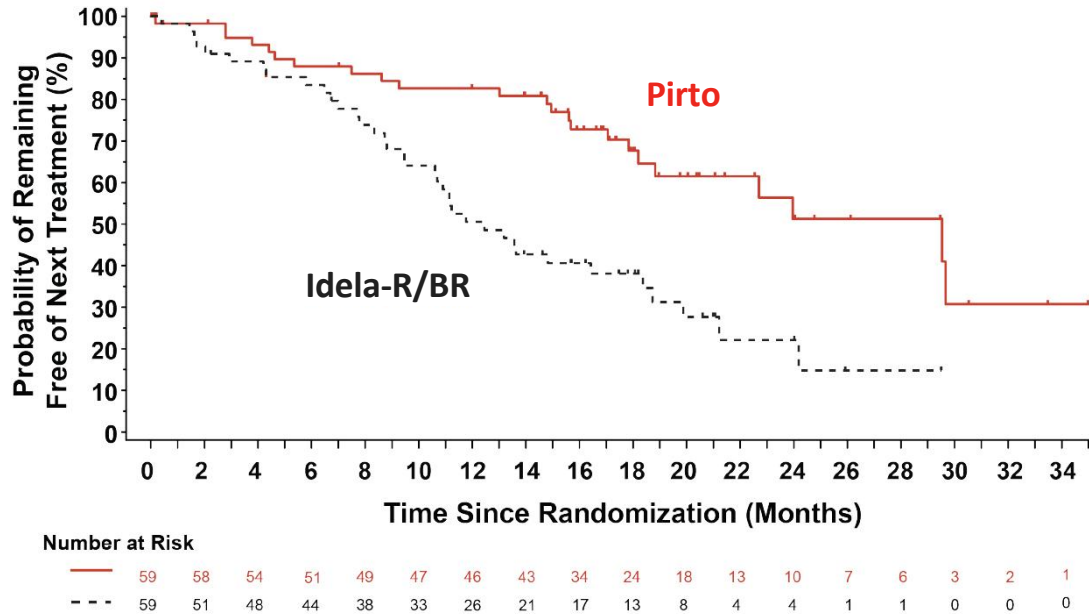
| Patient Characteristics | | Pirto (n=119) | Idela-R/BR (n=119) |
|---|---------------------------|-------------------|--------------------|
| Median age (range), years | | 66 (42-90) | 68 (42-85) |
| Molecular characteristics, n (%) | <i>BTK</i> C481S | 37/99 (37) | 36/94 (38) |
| | <i>PLCγ2</i> | 15/99 (15) | 11/94 (12) |
| Median prior LOT (range), n | | 3 (1-13) | 3 (1-11) |
| Prior therapy | >1 cBTKi | 17 (14) | 18 (15) |
| | <i>BCL2</i> ^{if} | 60 (50) | 62 (52) |
| Reason for any prior cBTKi discontinuation ^h , n (%) | PD | 85 (71) | 87 (73) |
| | Toxicity | 20 (17) | 22 (18) |

Number at Risk

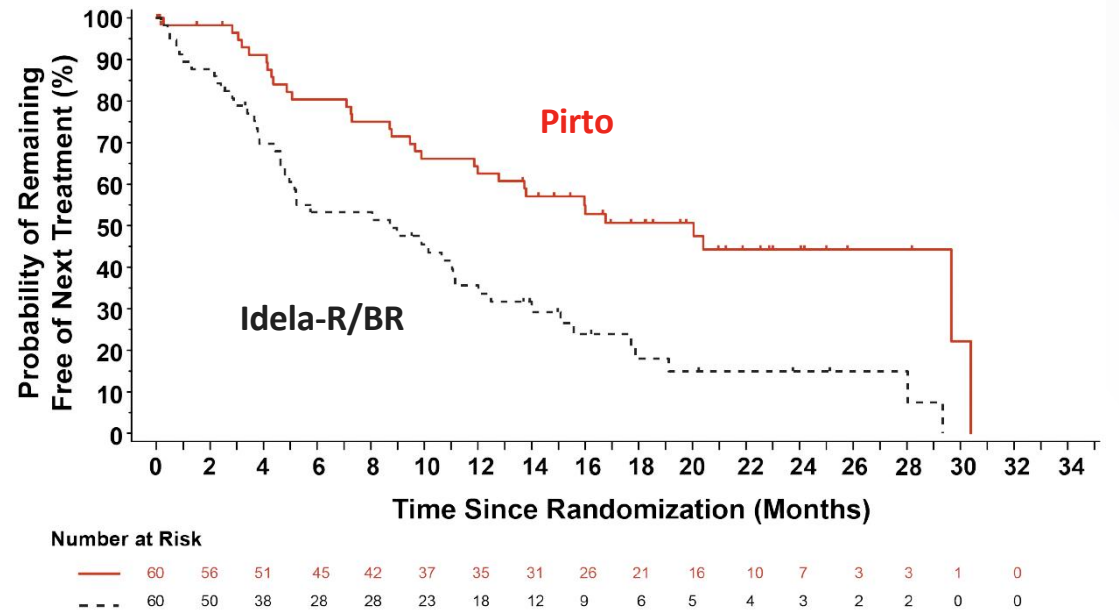
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|-------|-----|-----|-----|----|----|----|----|----|----|----|----|----|---|---|---|---|---|---|
| — | 119 | 113 | 100 | 84 | 79 | 69 | 54 | 44 | 36 | 19 | 12 | 10 | 4 | 3 | 3 | 3 | 2 | 0 |
| - - - | 119 | 92 | 73 | 60 | 57 | 37 | 25 | 18 | 16 | 10 | 7 | 5 | 3 | 1 | 0 | 0 | 0 | 0 |

Data split on whether patient received prior venetoclax

No Prior Venetoclax



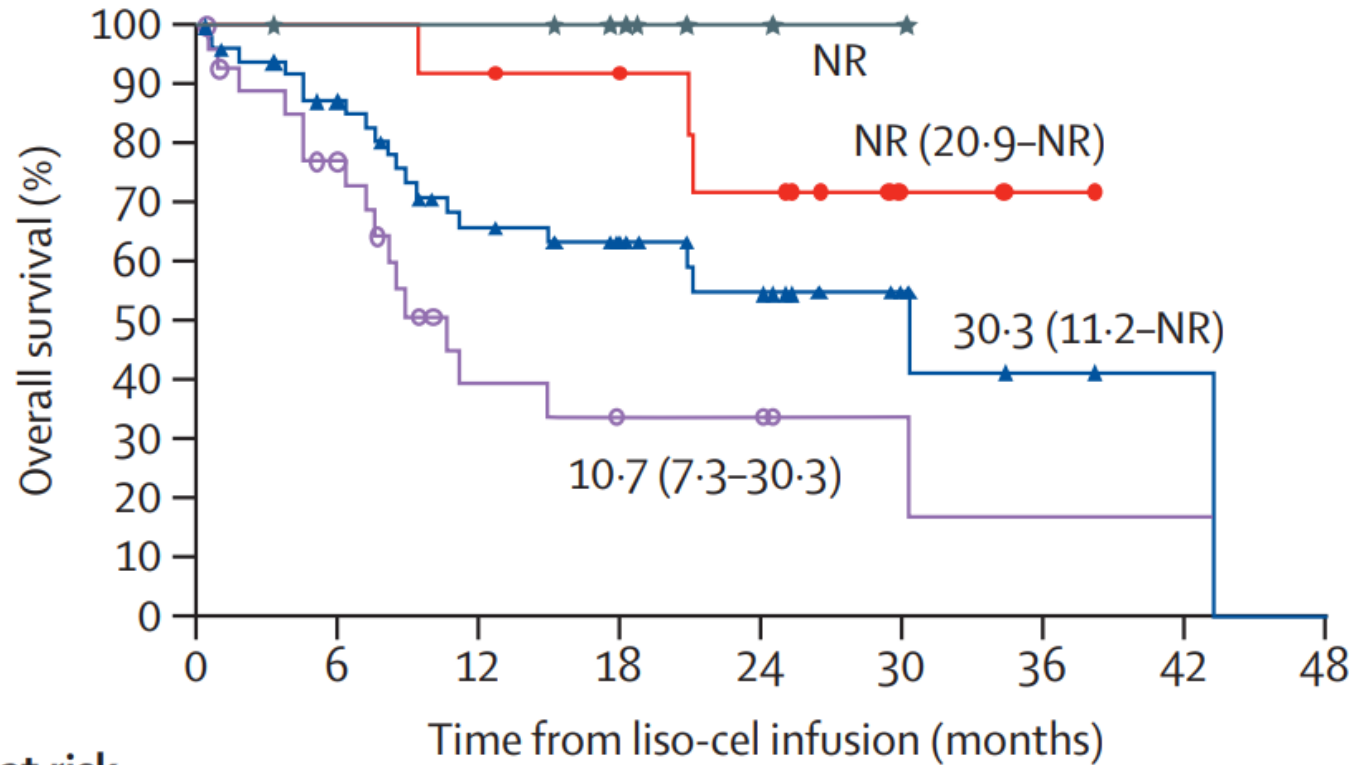
Prior Venetoclax



| TTNT | Ven-Naive Patients | | Ven-Treated Patients | |
|------------------------------|--------------------------|-------------------|--------------------------|-------------------|
| | Pirto (n=59) | Idela-R/BR (n=59) | Pirto (n=60) | Idela-R/BR (n=60) |
| Median TTNT, months (95% CI) | 29.5 | 12.5 | 20.0 | 8.7 |
| HR (95% CI); P value | 0.36 (0.21-0.61); 0.0001 | | 0.37 (0.23-0.60); 0.0001 | |

TRANSCEND-004 – Liso-cel for RR CLL

Median follow-up 20.8 months (95% CI 17.8–25.2)



Number at risk

| | | | | | | | | | |
|---------------|----|----|----|----|----|---|---|---|---|
| CR or CRi | 9 | 8 | 8 | 6 | 2 | 1 | 0 | 0 | 0 |
| PR or nPR | 12 | 12 | 11 | 9 | 7 | 2 | 1 | 0 | 0 |
| Non-responder | 28 | 18 | 7 | 4 | 4 | 2 | 1 | 1 | 0 |
| Total | 49 | 38 | 26 | 19 | 13 | 5 | 2 | 1 | 0 |

Liso-Cel + Ibr Cohort of the TRANSCEND CLL-004 Phase 1/2 Study in R/R CLL/SLL

Key Eligibility Criteria

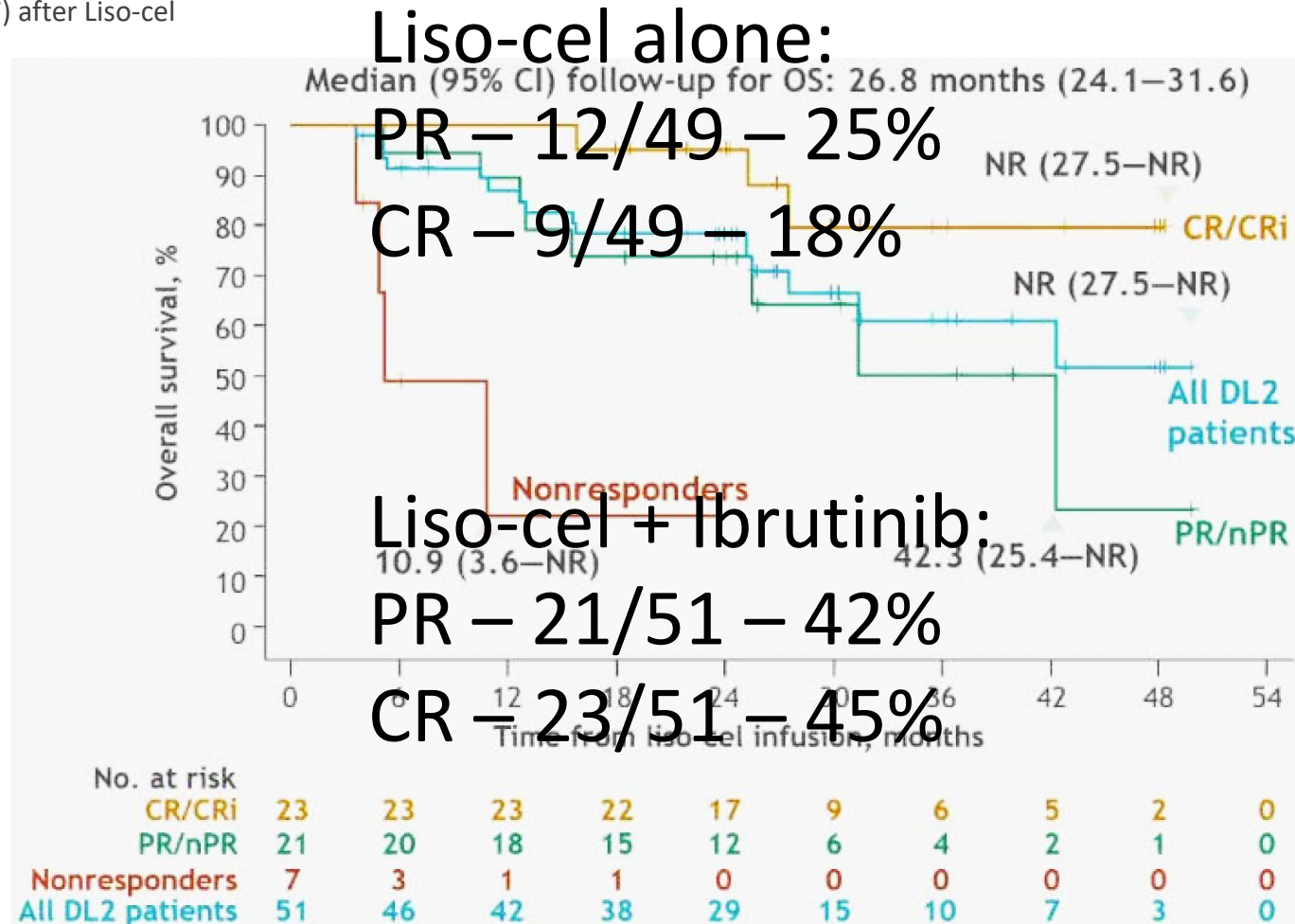
- R/R CLL/SLL with no RT; ECOG PS -1
- ≥1 of the following: Receiving BTKi with PD at study entry; High-risk features with <CR after ≥6 months on BTKi; *BTK/PLCγ2* mutation ± Ibr PD; Prior BTKi with no contraindications to restart BTKi
- PD on BTKi and received Ven (per amendment 5)

| Patient Characteristics | | DL2 + Ibr (n=51) | Liso-cel + Ibr (n=56) |
|--------------------------------|----------------------------------|---------------------|--------------------------|
| Median age (range), years | | 65 (44-77) | 65 (44-77) |
| Median prior LOT (range), n | | 5 (1-13) | 5 (1-13) |
| ≤3 prior LOT, n (%) | | 19 (37) | 20 (36) |
| Prior therapy, n (%) | BTKi | 51 (100) | 56 (100) |
| | Ven | 39 (76) | 42 (75) |
| | BTKi and Ven | 39 (76) | 42 (75) |
| | BTKi PD/Ven failure ^a | 28 (55) | 31 (55) |
| High-risk cytogenetics, n (%) | Overall | 50 (98) | 55 (98) |
| | del(17p) | 23 (45) | 25 (45) |
| | Mutated <i>TP53</i> | 23 (45) | 24 (43) |
| | Unmutated <i>IGHV</i> | 37 (73) | 39 (70) |
| Complex karyotype ^b | | 25 (49) | 29 (52) |

PFS and OS of Ibrutinib + Liso-cel

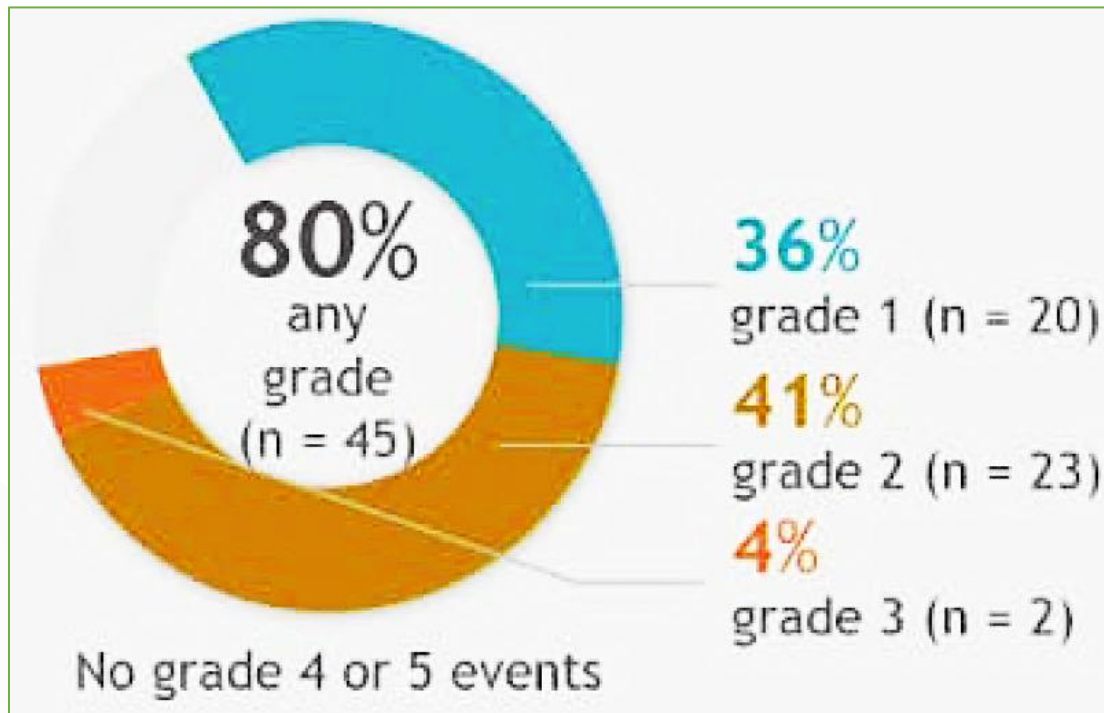
Treatment

- Median Ibr exposure (in the total combination-treated set)
 - 34 days (range, 15-188) before Liso-cel
 - 95 days (range, 6-1517) after Liso-cel

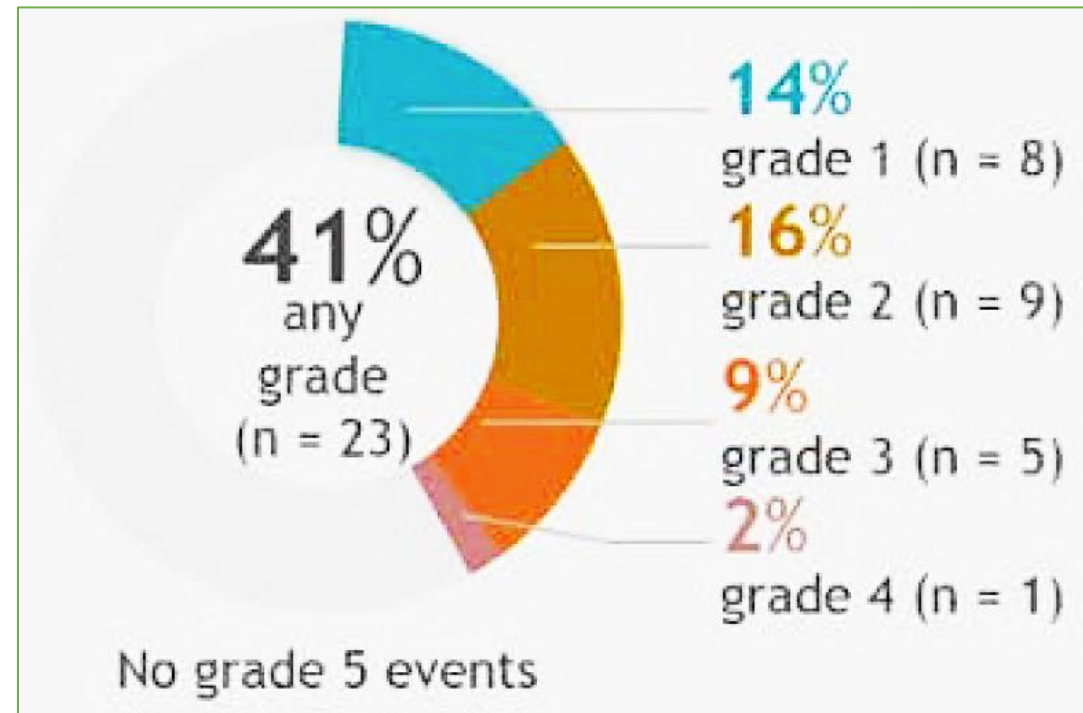


Safety of Liso-cel + Ibrutinib

CRS



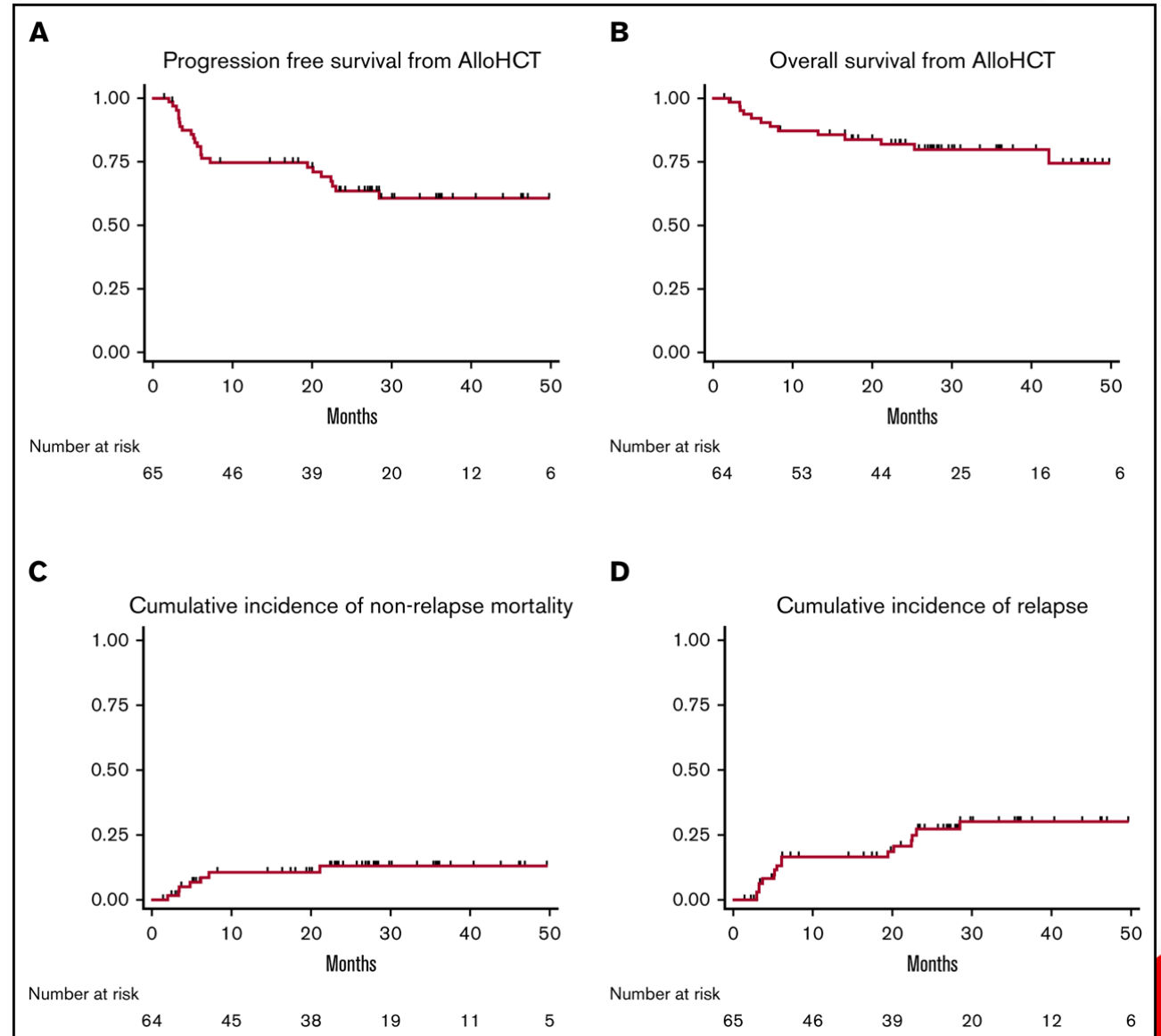
ICANS



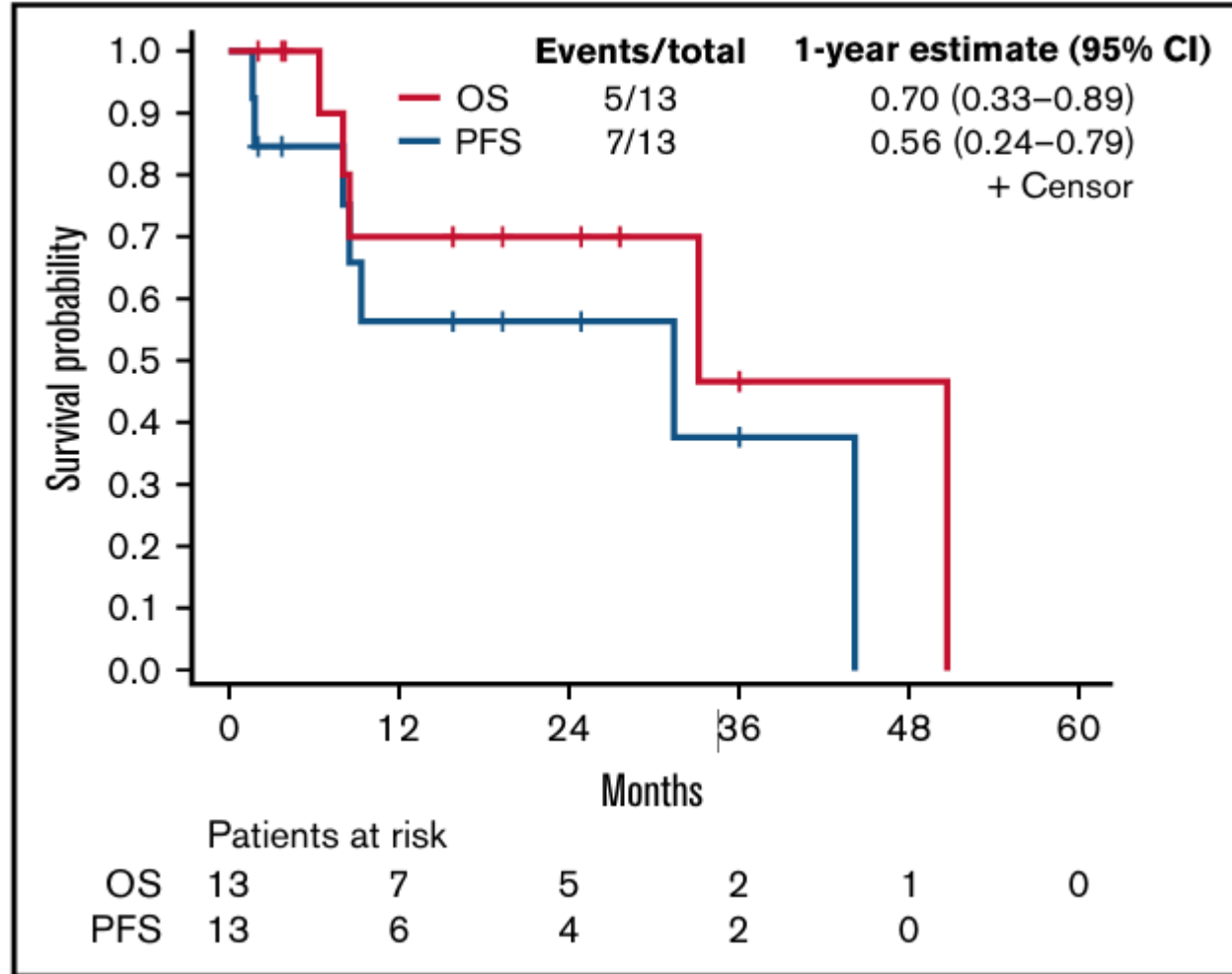
AlloHCT for R/R CLL/SLL

Data-free zone in the era of targeted agent.

- 2020 retrospective study
- (n = 65)
 - PFS - 63%
 - OS - 81%
- 29% of patients (n=19) received novel agents alone



BTKi + Ven in patients who both BTKi and Ven



My treatment approach:

Clinical trial #1

Most patients will get:

-Pirtobrutinib

Can consider:

-BTKi + Venetoclax

-Venetoclax + anti-CD20

Pirto PFS - 1-2 years

What next?

At best response:

Young/Fit?

- Allo-SCT

Old/Unfit?

- CAR T-cell + BTKi

Continue Pirto/BTKi?

What next?

Pirto + Ven?

PI3Ki

Supportive

Care



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