How I Approach Treatment-Naïve CLL/SLL

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Disclosures

- Advisory Boards/Consulting:
  - Abbvie, AstraZeneca, Beigene, Celegene, Eli Lilly, Genentech, J & J, Pharmacyclics
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Cases – Newly Diagnosed CLL/SLL

1. Asymptomatic – High Risk
2. Older – High Risk
3. Younger – Low Risk
4. Younger – Intermediate Risk

Case #1

Ms. Organa: 54F newly diagnosed CLL, Rai Stage 1, currently asymptomatic and without cytopenias

- Del(17p) and *TP53* mutation = **0**
- B2M = 4.0mg/L = **2**
- Unmutated IGHV = **2**
- Rai Stage 1 = **1**
- Age >65 = **0**

CLL-IPI Score = 5 = High Risk

Median TTFT: 28 months (95% CI, 4–53)

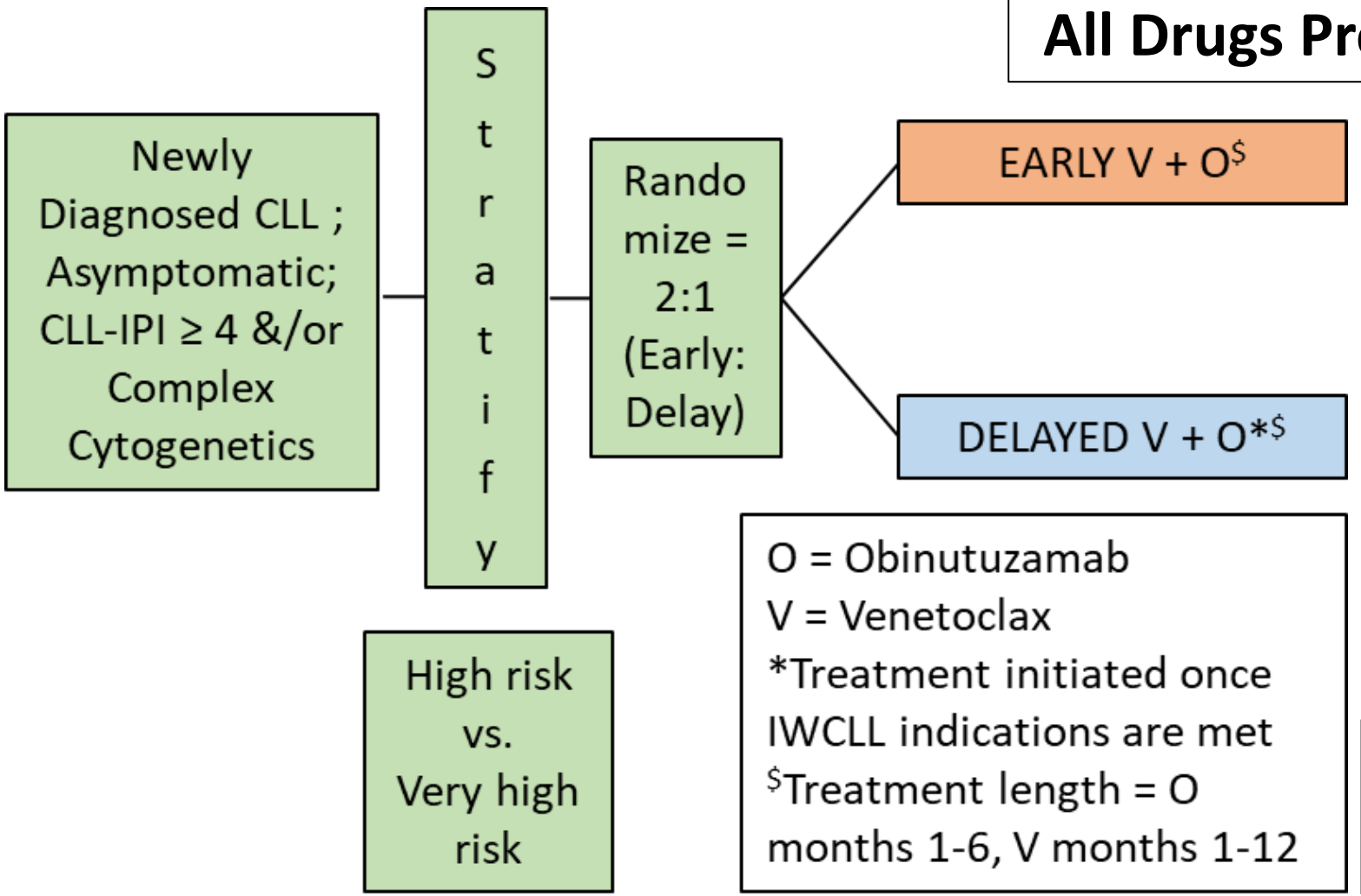
CLL-IPI Characteristic	Pts
Del(17p) or TP53 mutation	4
Serum beta-2-microglobulin ≥ 3.5mg/L	2
Un-mutated IgVH status	2
Rai Stage I-IV	1
Age > 65 years	1

CLL-IPI Group, Lancet Oncol 2016; Molica, Am J Hematol 2016; https://www.reddit.com/r/StarWars/comments/1cdv4e5/our_princess_our_general_our_leia/?rdt=34432

S1925: EVOLVE Study

1◦ Endpoint: Overall Survival

All Drugs Provided by Study



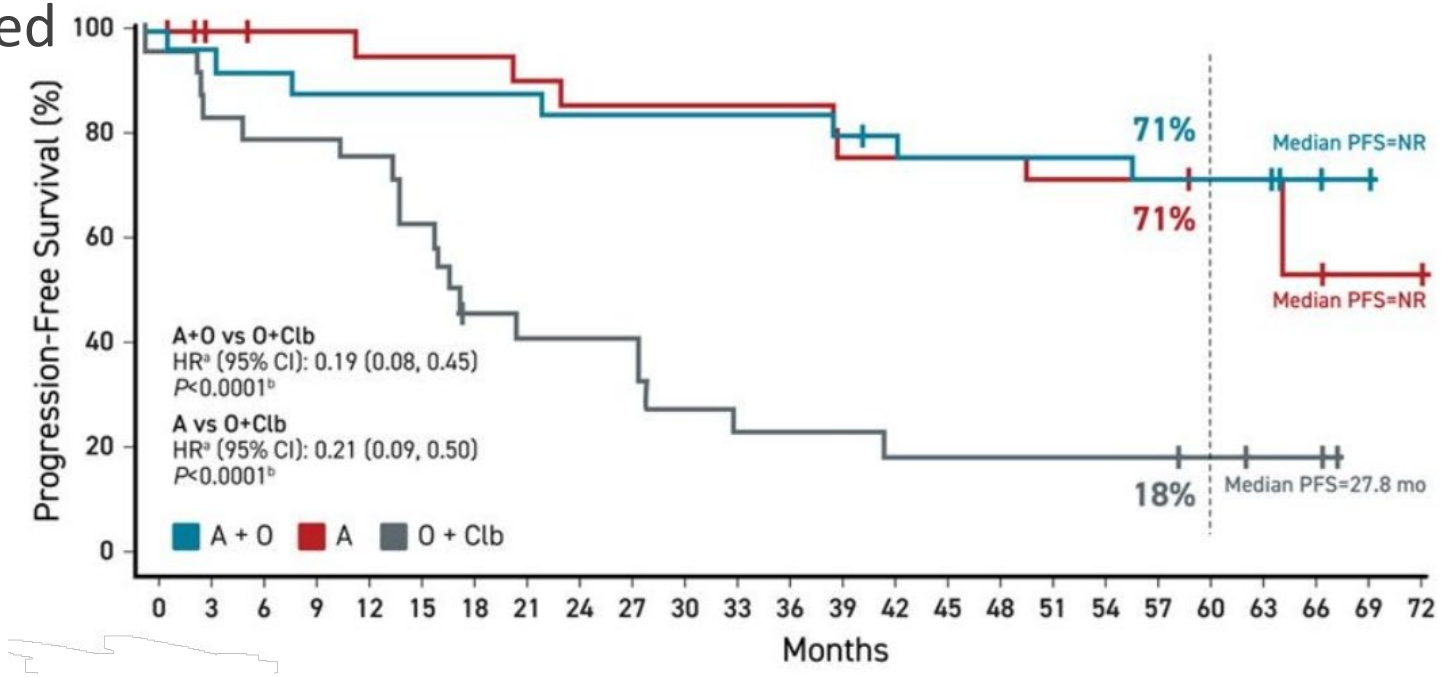
O = Obinutuzamab
V = Venetoclax
*Treatment initiated once IWCLL indications are met
$Treatment length = O months 1-6, V months 1-12

Study Ongoing: Need Accruals!

Case #2

Mr. Yoda: 867M newly diagnosed CLL, fit, HTN, GERD.

- Risk Factors: Del17p, TP53m, IGHVu
- Symptoms: Drenching night sweats, unplanned weight loss, significant fatigue
- Comorbidities: CKD Stage 3-4 – CrCl baseline 25-35ml/min
- Logistics: Lives in swamp ~2 hours from nearest cancer center



ELEVATE TN: Great efficacy in TP53m
No indication to add obinutuzumab in this setting

Sharman, ASCO 2022; https://starwars.fandom.com/wiki/Yoda

How to Choose Between BTKi?

ACALABRUTINIB

- Older patients
- Patients with hypertension
- No longer has formulary issue with proton-pump inhibitors

ZANUBRUTINIB

- Option for once daily dosing
- Most others

IBRUTINIB

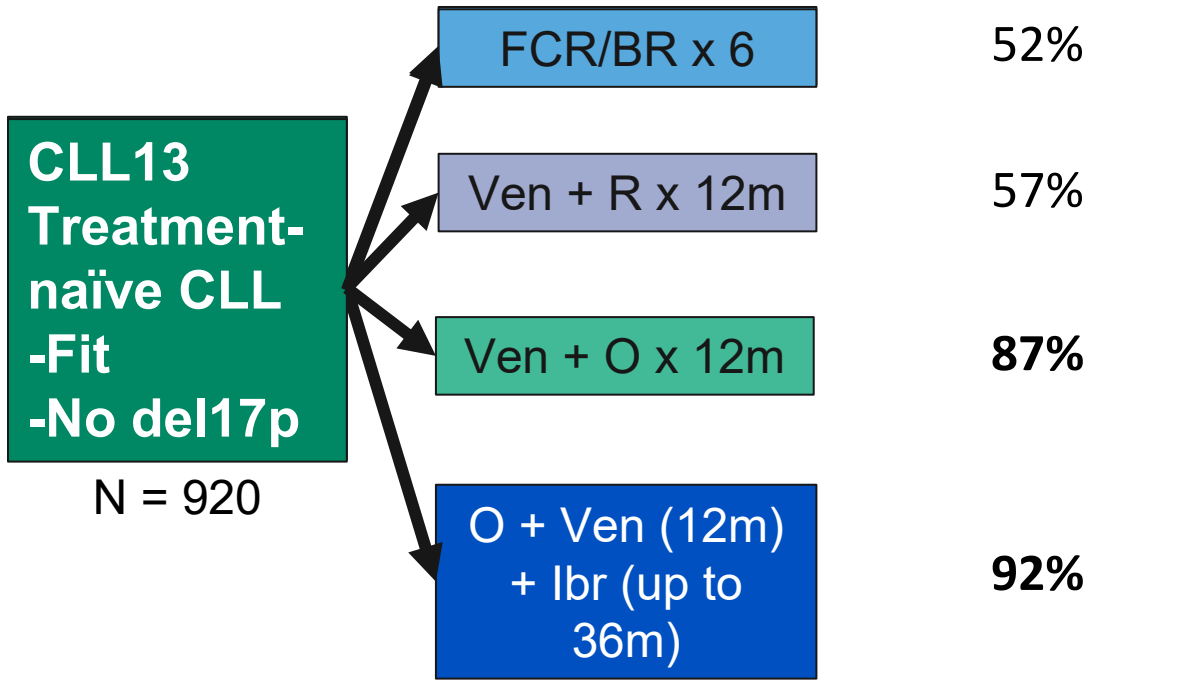
- Patients already tolerating the drug
- Patients with extensive history of other cancers?

Byrd, JCO 2021; Brown, NEJM 2023

Case #3

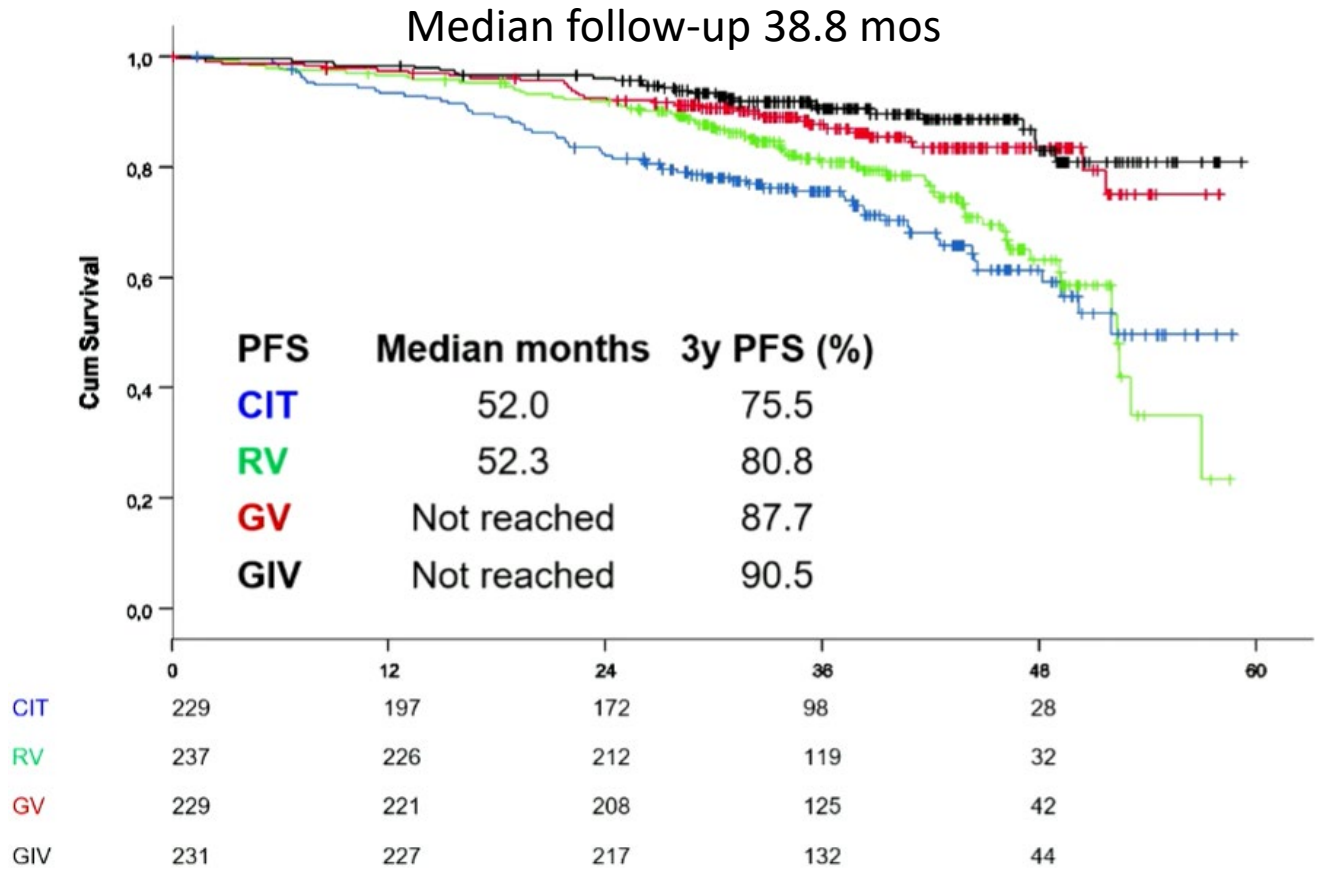
Mr. Solo: 62M newly diagnosed CLL, fit, no comorbidities

- Risk Factors: Del13q, IGHVm
- Symptoms: Early satiety and SOB from anemia (non-hemolytic)
- Comorbidities: None
- Logistics: Travels for work a lot but mostly controls his own schedule. Lives near treating facility



Eichhorst, NEJM 2023; https://charactercommunity.fandom.com/wiki/Han_Solo

CLL13



Significant benefit to adding ibrutinib?

- At this point, no.
- Longer follow-up may show benefit as ibrutinib can extend to 36 mo.

Will toxicity of adding ibrutinib outweigh any efficacy benefit?

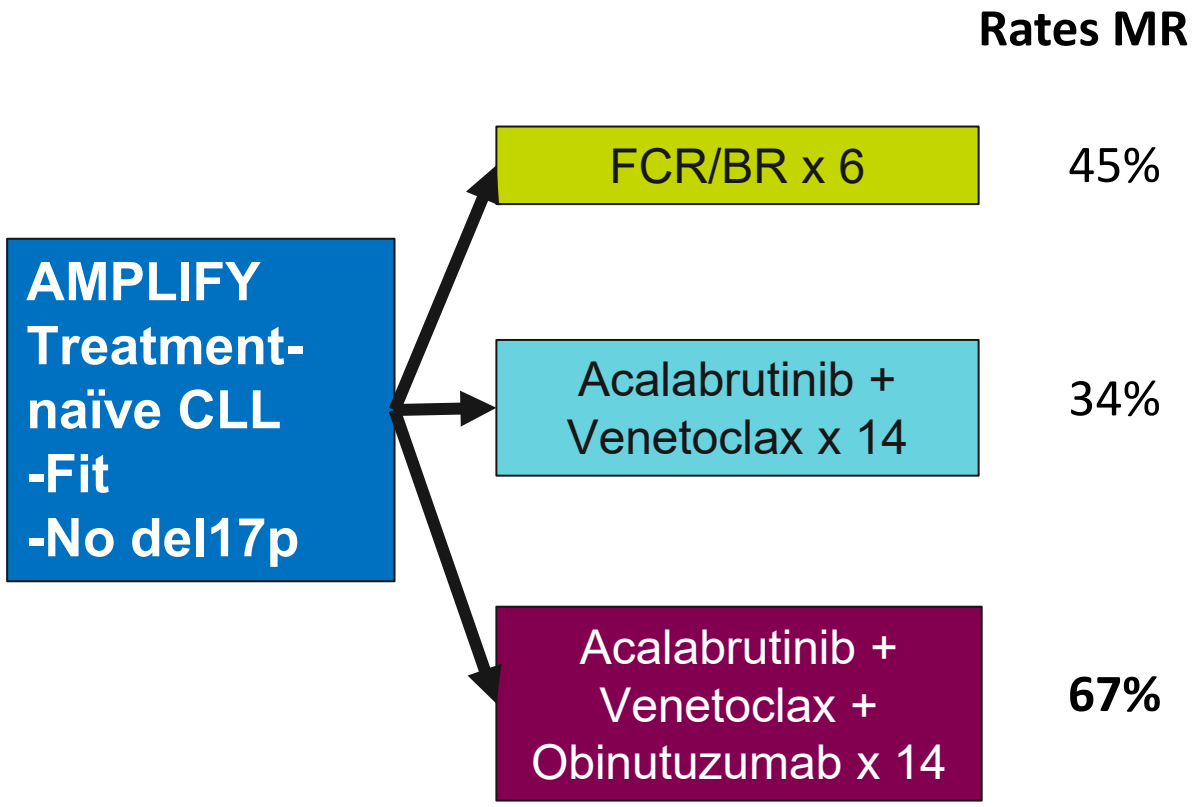
- Unclear, longer follow-up needed.
- **A041702** (I+O vs I+V+O) reported interim analysis with no PFS benefit of I+V+O.
- **CLL17** ongoing: I vs V+O vs I+V

Eichhorst, NEJM 2023; Woyach, ASCO 2023

Case #4

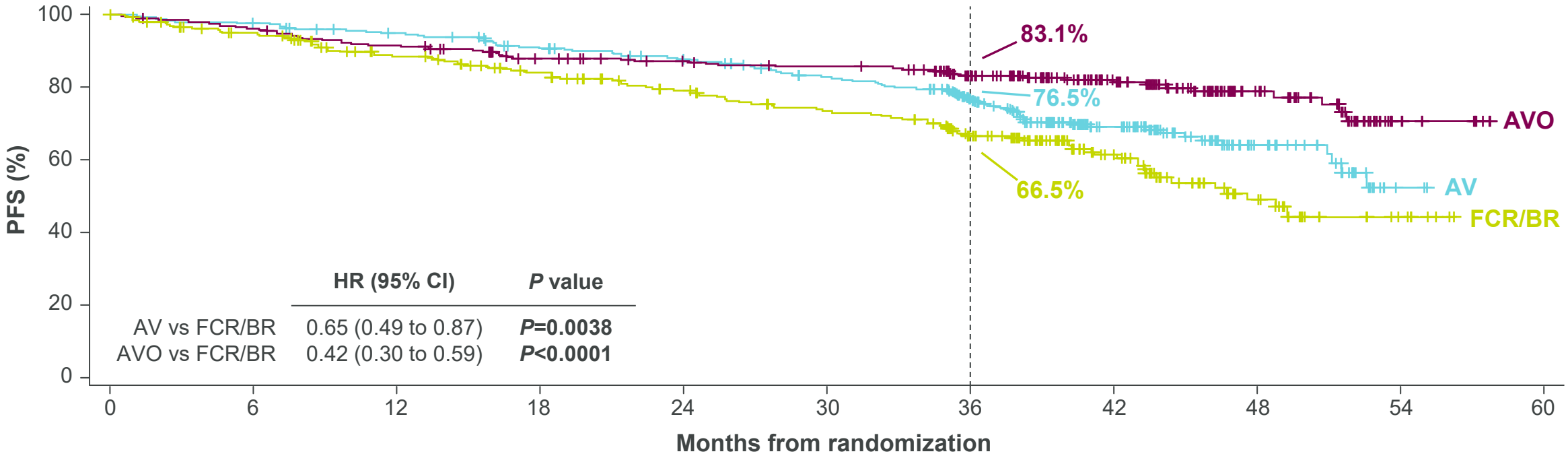
Mr. Skywalker: 54M newly diagnosed CLL, fit, no comorbidities

- Risk Factors: Del13q, IGHVu
- Symptoms: Very bulky adenopathy
- Comorbidities: None
- Logistics: Works as a farmer in the desert ~ 5 hours from closest cancer center



Brown, ASH 2024; https://www.starstills.com/luke-skywalker-white-robe-from-star-wars-cardboard-cutout-official-standee/

AMPLIFY



More COVID-19 Deaths in AVO (25) and CIT (21) Arms than AV (10) Arm

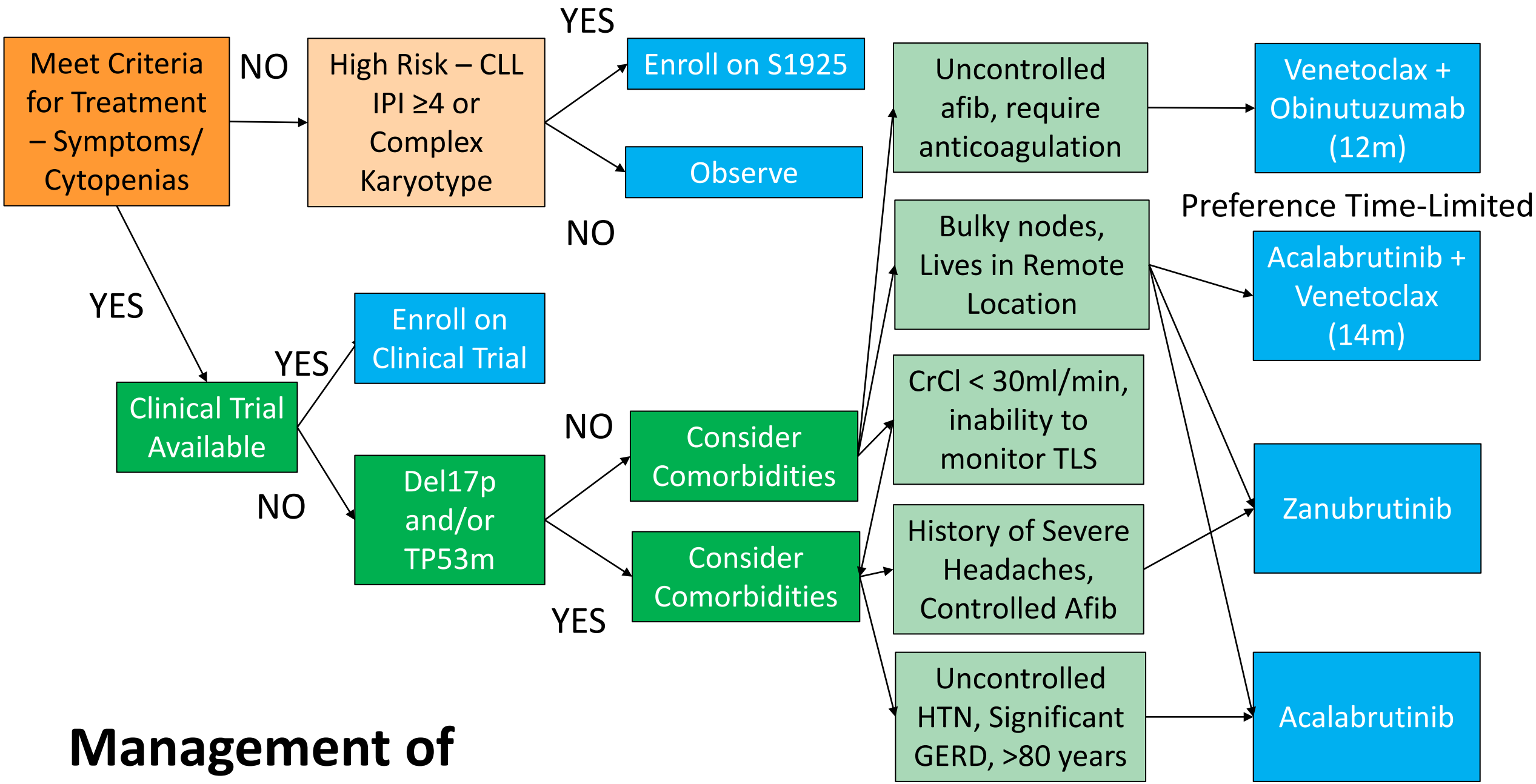
When COVID-19 deaths were censored, there was a bigger improvement in PFS of AVO arm

AMPLIFY Take-Home Points

- Significantly improved PFS with fixed-duration AV and AVO vs FCR/BR
- uMRD rates highest in the AVO arm
- Prolonged OS with AV versus FCR/BR (primary analysis), and with both AV and AVO vs FCR/BR (censoring COVID-19 deaths)
- AV and AVO had tolerable safety profiles, with low incidence of cardiac AEs typically associated with BTKis (ie, atrial fibrillation, hypertension)
- AVO had higher toxicity rates than AV

Impact: AMPLIFY will likely be the basis of submission for approval of AV+/- O

Where to use? Young? High-risk? Bulky Disease?



Management of Newly Diagnosed CLL

May the Force Be With You

TWITTER: @DEBBIEMSTEPHENS