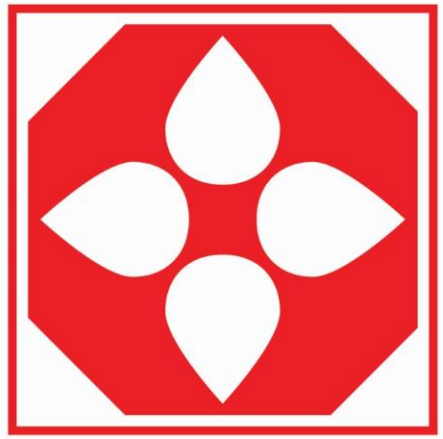
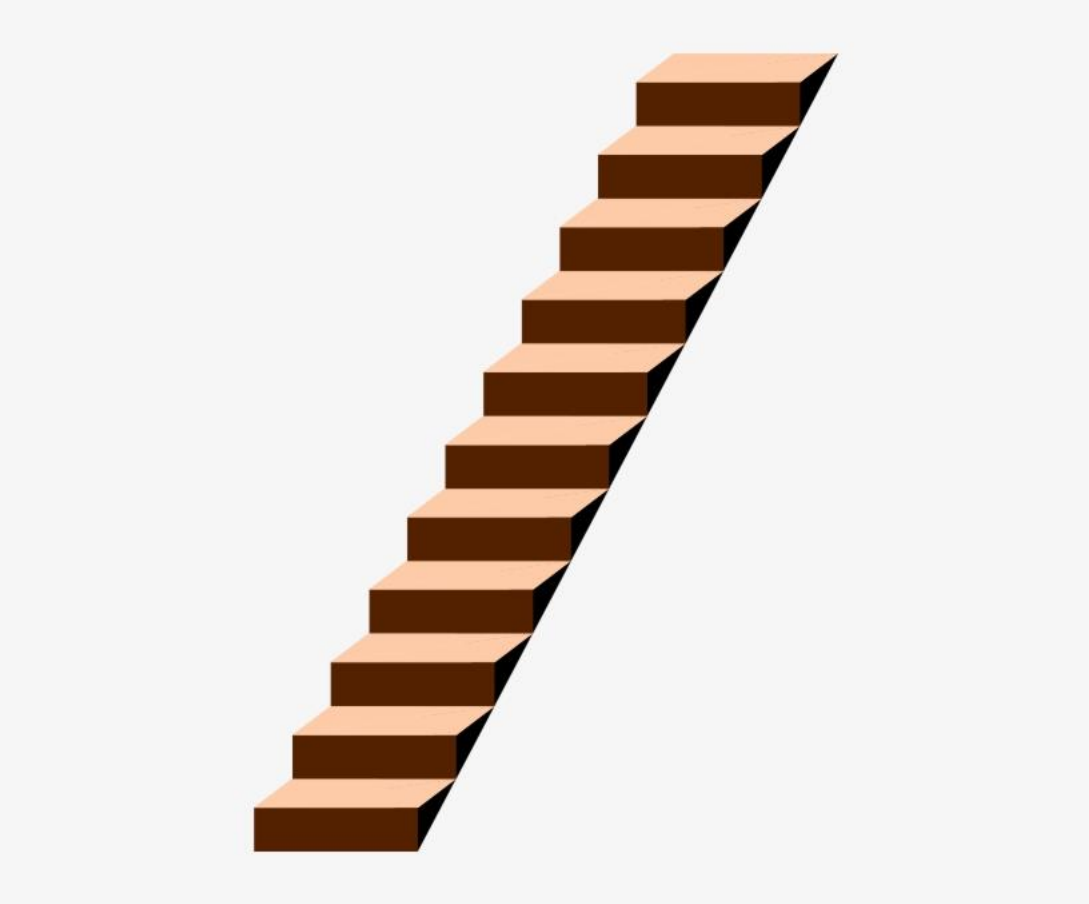


Smart Patients Get Smart Care™

PI3K Inhibitors for the Treatment of CLL

Ian W. Flinn, MD, PhD
Sarah Cannon Research Institute and
Tennessee Oncology

CLL is Driven by Signaling Pathways



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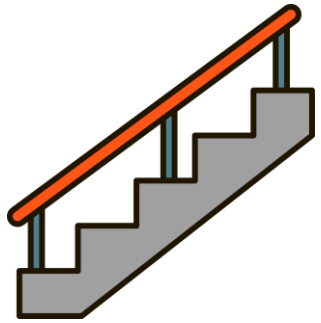
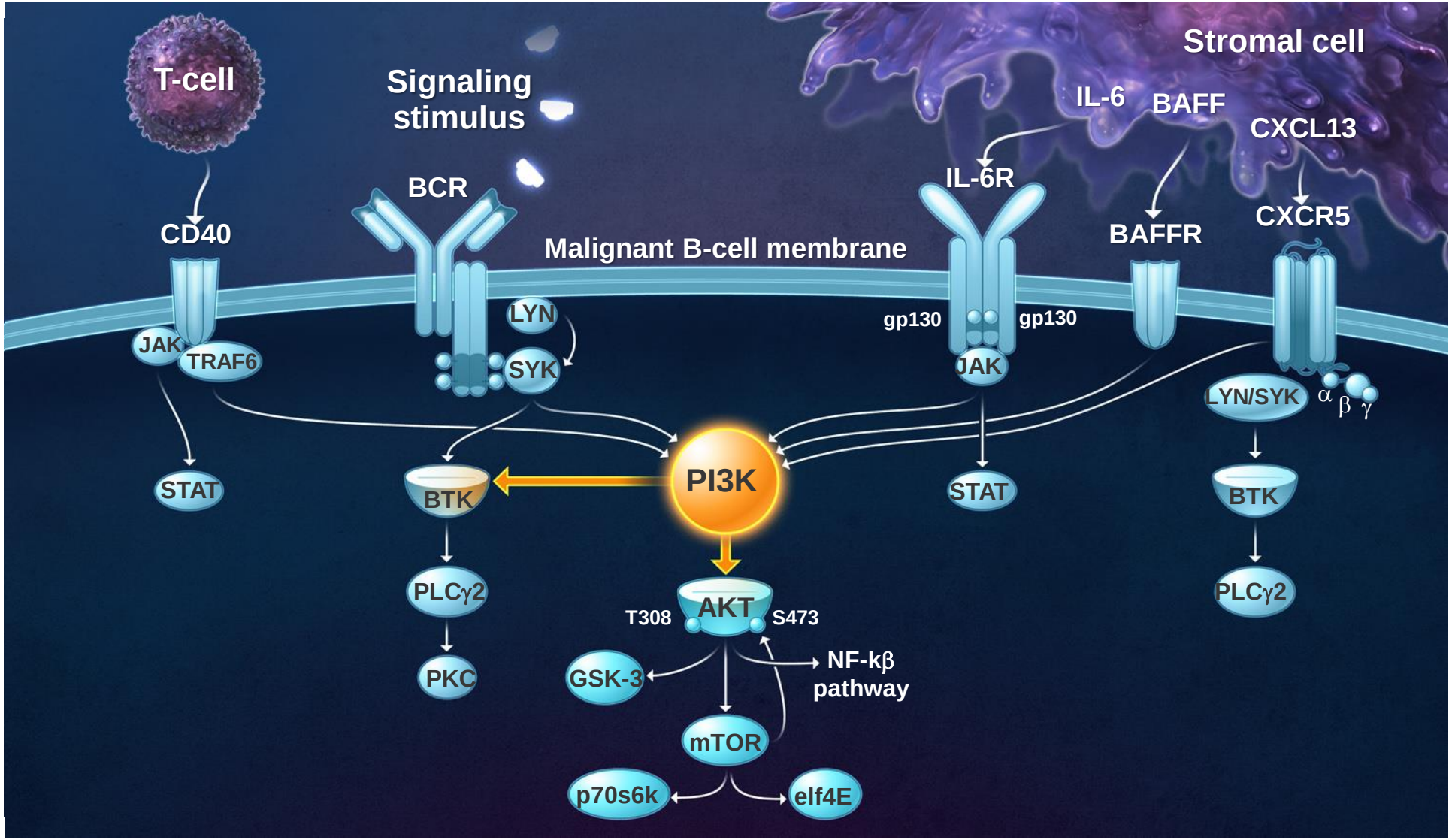
Imagine Many Different Pathways All Driving CLL

CLL SOCIETY



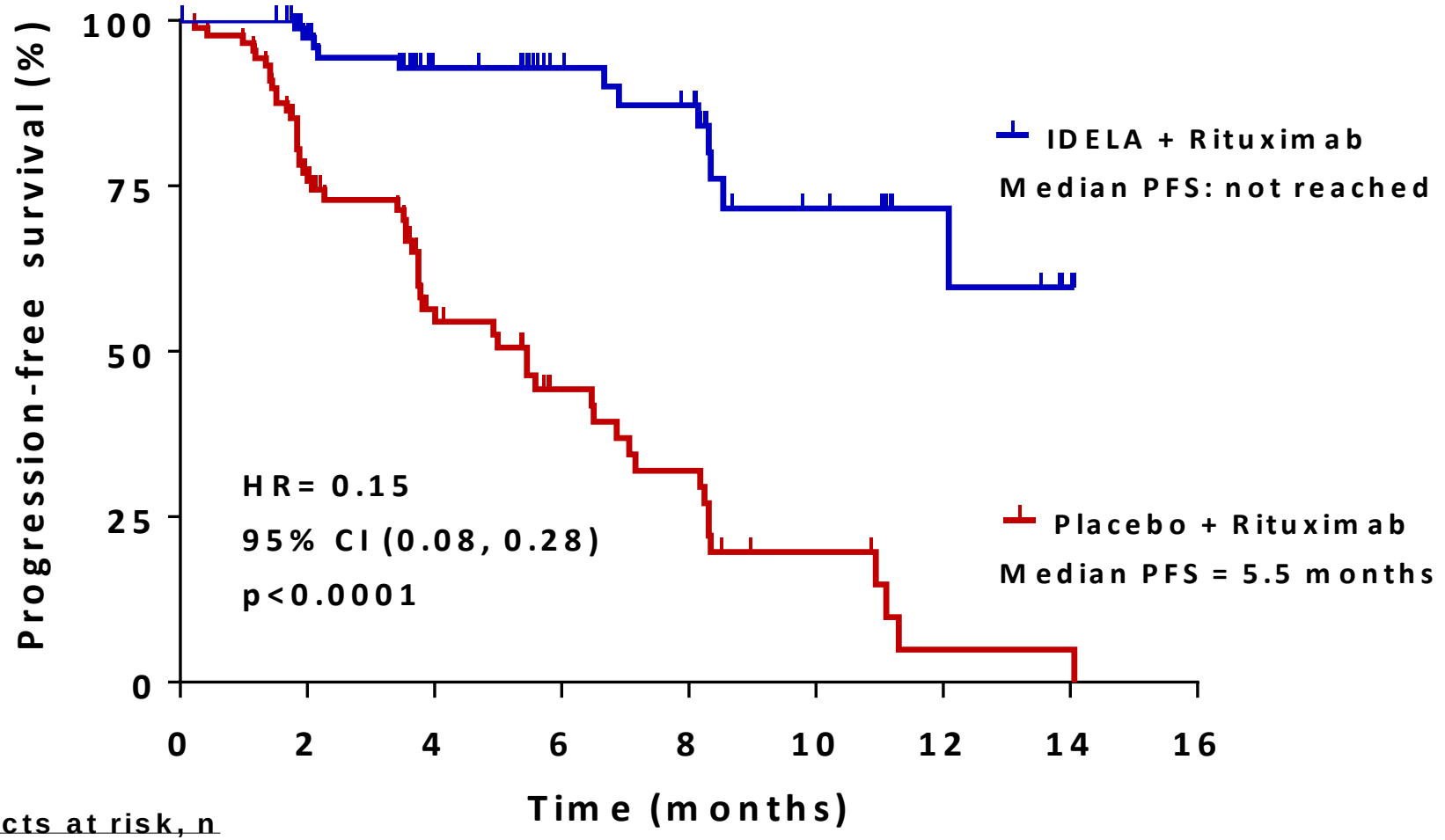
PI3K is at the Crossroads of Critical Signaling Pathways That Drive CLL



There are Several FDA Approved PI3K Inhibitors

- Idelalisib- approved with rituximab in CLL
- Duvelisib- approved as single agent in CLL
- Copanlisib-approved for follicular lymphoma
- Umbralisib- approved for follicular and marginal zone lymphoma

Progression-Free Survival (PFS): Idelalisib (IDELA) + Rituximab versus Placebo + Rituximab



Subjects at risk, n									
IDELA + R:	110	69	44	34	30	14	6	2	0
Placebo + R:	110	62	30	18	13	6	1	1	0

Furman RR, et al. *N Engl J Med.* 2014;370(11):997-1007.

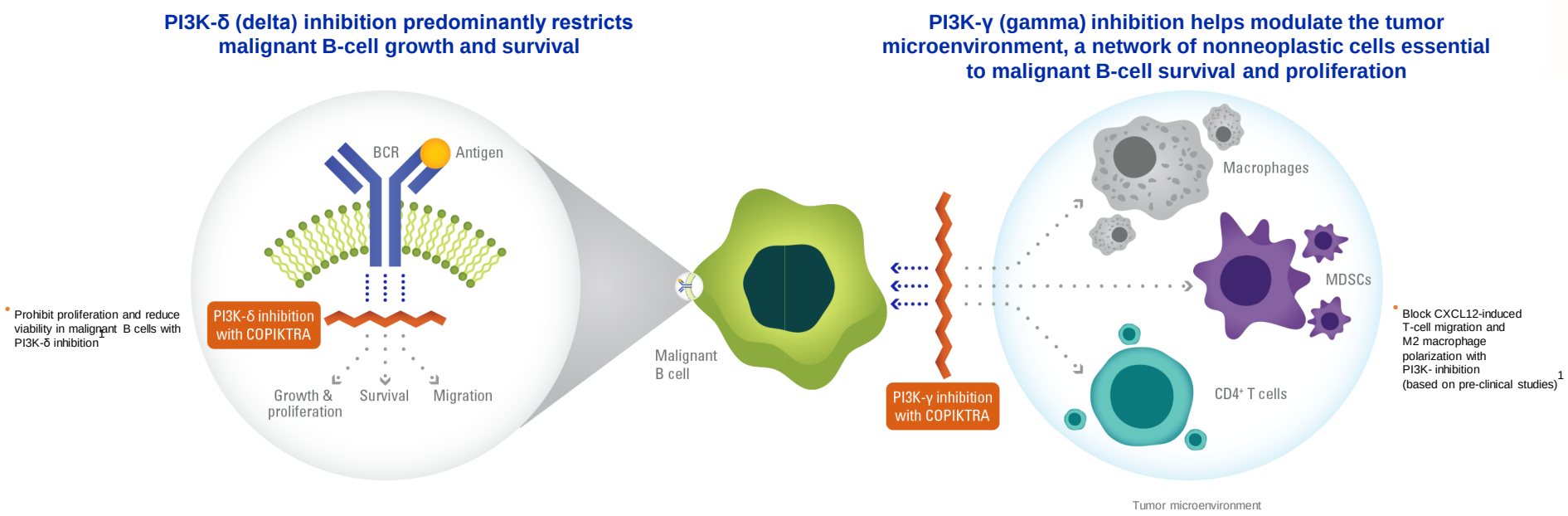
Select Lab Abnormalities
Idelalisib + Rituximab

- Liver inflammation with elevation of the liver enzymes ALT and AST*
  - 53%
- Low Neutrophil count
  - 66%
- Anemia
  - 33%
- Low platelets
  - 29%

*ALT, alanine aminotransferase; AST, aspartate aminotransferase

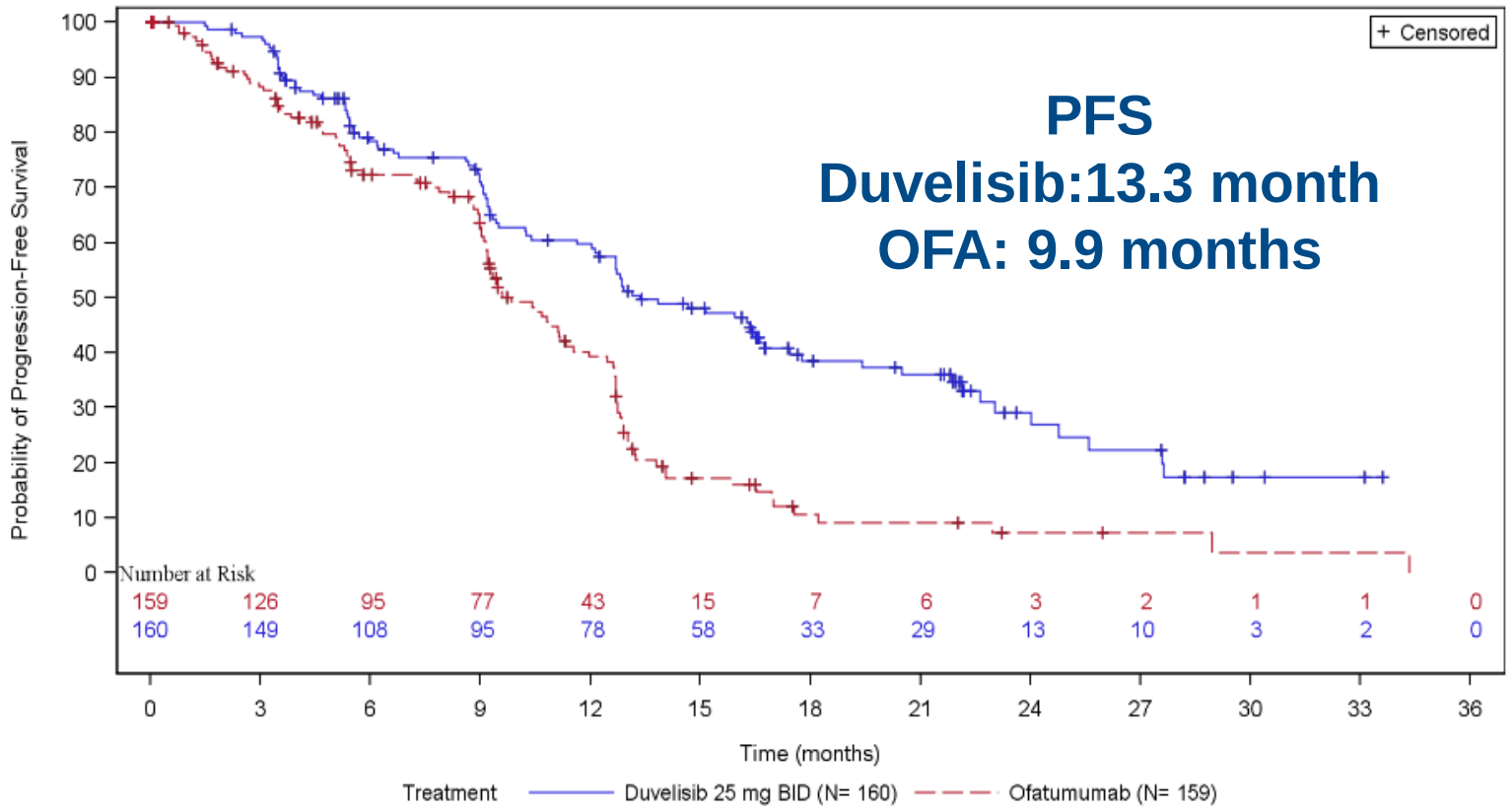
Sharman J, et al. *Blood.* 2014;124: Abstract 330.

Duvelisib Targets CLL and Disrupts the Cells That Support Them



Flinn, I et al Blood. 2018;131(8):877-887

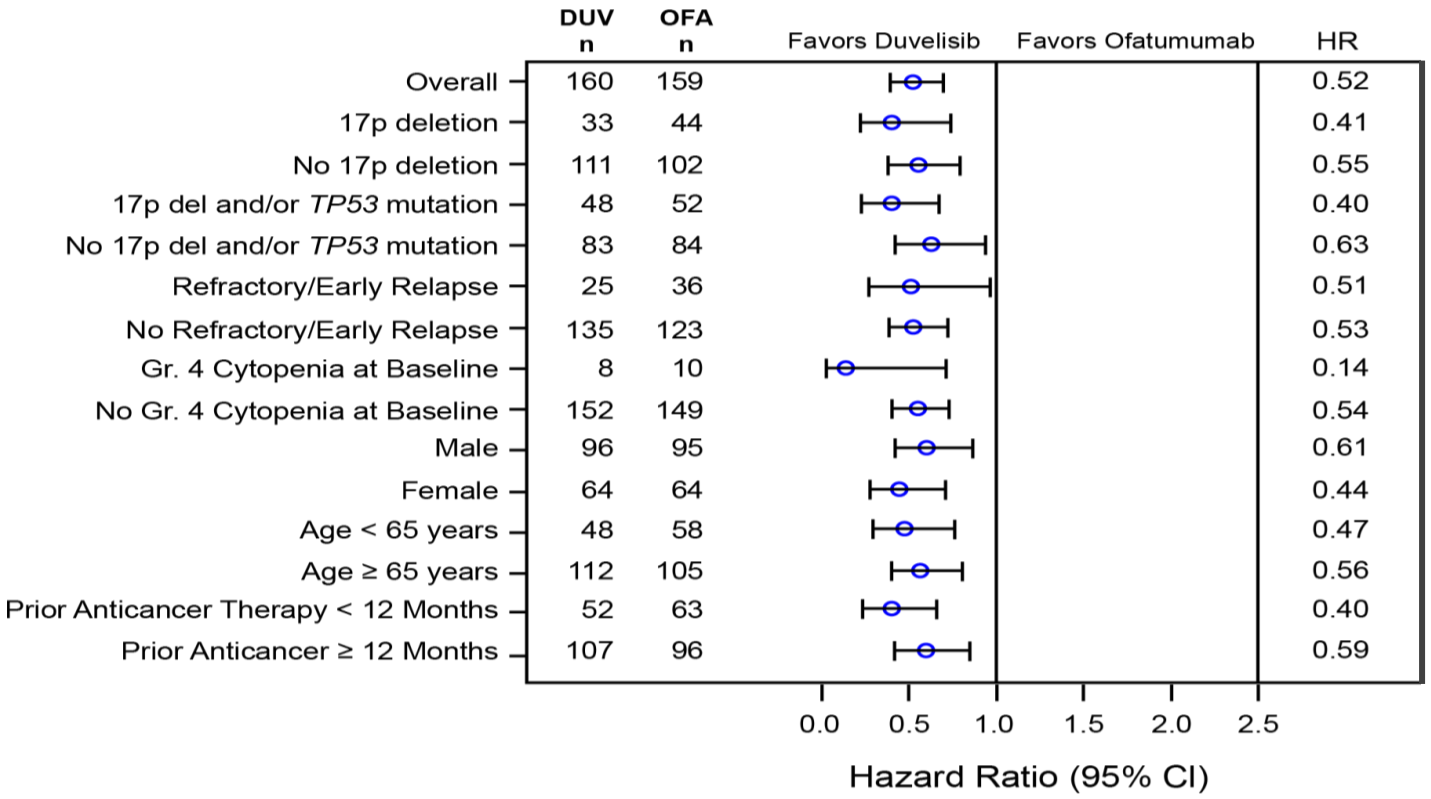
Duvelisib vs. Ofatumumab: Randomized Control Study Showed Improved Progression Free Survival (PFS) with Duvelisib



- 89 patients on OFA arm received duvelisib in crossover study, achieving an ORR of 73% and a median PFS of 15 months per Investigator assessment

Flinn et al., Blood Oct 4 2018 Epub ahead of print

Duvelisib Maintained PFS Advantage in All Subgroups Analyzed



Flinn et al., Blood Oct 4 2018 Epub ahead of print

Incidence of Serious Adverse Experiences and Time to Onset

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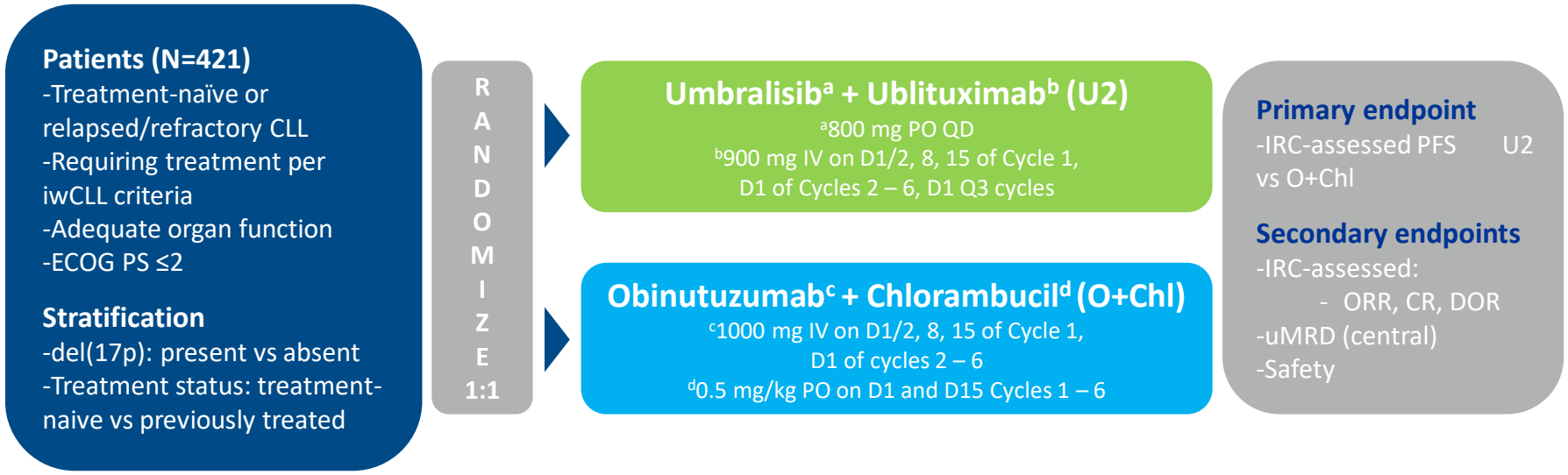
Adverse Experience N= 442	Serious (including fatal)	Fatal	Median Onset (all grades)	Range of Onset	75% of events occurred by	Median Event Duration and Range
Infections	31%	18/442, 4%	3 months	1 day to 32 months	6 months	Not reported
Diarrhea or Colitis	18%	1/442, <1%	4 months	1 day to 33 months	8 months	Duration: 0.5 months Range: 1 day to 29 months, 75th Percentile: 1 month
Cutaneous Reactions*	5%	2/442, <1%	3 months	1 day to 29 months	6 months	Duration: 1 month Range: 1 day to 37 months, 75th Percentile: 2 months
Pneumonitis	5%	1/442, <1%	4 months	9 days to 27 months	9 months	Duration: 1 month 75% resolve by 2 months

*Included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN).

- The most common serious infections were pneumonia, sepsis, and lower respiratory tract infections. Serious, including fatal, *Pneumoncystis jirovecii pneumonia* (PJP) occurred in 1% of patients. CMV reactivation/infection occurred in 1% of patients
- Presenting features for cutaneous reaction serious events were primarily described as pruritic, erythematous, or maculo-popular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash.

UNITY-CLL Study Design (UTX-TGR-304)

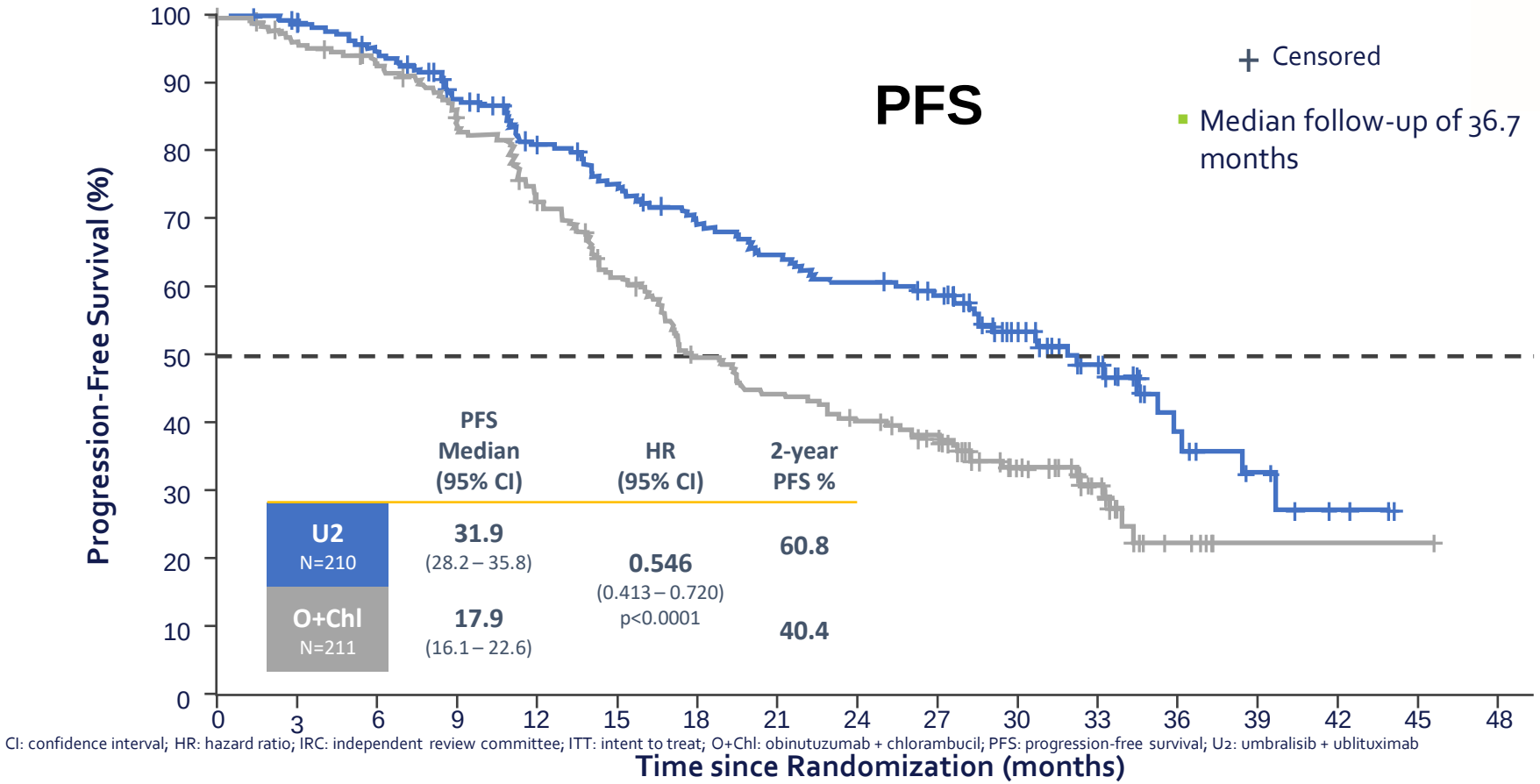
Presentation will focus on primary analysis:U2 vs O+Chl (n=421)



- Interim analyses for PFS were performed at:
  - 50% IRC-assessed PFS events to assess futility only
  - 75% IRC-assessed PFS events to evaluate superiority of U2 vs O+Chl

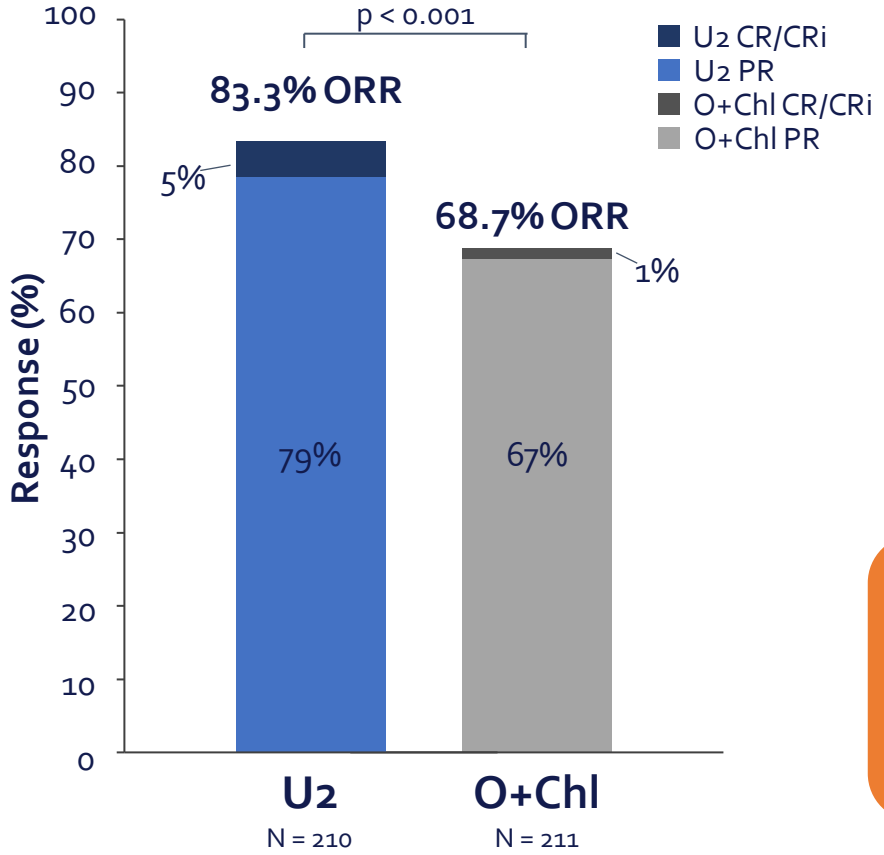
CR: complete response; DOR: duration of response; DSMB: data safety monitoring board; ECOG PS: Eastern Cooperative Oncology Group performance status; IRC: independent review committee; IV: intravenously; ORR: overall response rate; PFS: progression-free survival, PO: orally; Q3: every 3; QD: daily; uMRD: undetectable minimal residual disease; D1/2 signifies split doses ublituximab (150 mg / 750 mg) obinutuzumab (100 mg /900 mg); cycles were 28 days. U2 combination continued until progressive disease, unacceptable toxicity, or withdrawal of consent.

UNITY-CLL Trial: Umbralisib+Ublituximab (U2) vs Obinutuzumab+Chlorambucil (O+Chl)



CI: confidence interval; HR: hazard ratio; IRC: independent review committee; ITT: intent to treat; O+Chl: obinutuzumab + chlorambucil; PFS: progression-free survival; U2: umbralisib + ublituximab

IRC-Assessed Response Rates



ORR (%)	U2	O+Chl
Treatment Naïve	84%	78%
Previously treated	82%	57%
Prior BTK inhibitor	57%	25%

- U2 produced higher IRC – assessed response rates across subgroups
- U2 responses were durable with **62%** maintaining response at **2 years**
- **93%** disease control rate achieved by U2

CR: complete response; CRi: complete response with incomplete marrow recovery; Disease control rate = (CR+CRi+nPR+PR+PR-L+SD); IRC: independent review committee; ITT: intent to treat; nPR: nodular partial response; O+Chl: obinutuzumab + chlorambucil; ORR: overall response rate; PR: partial response; PR-L: partial response with lymphocytosis; SD: stable disease; U2: umbralisib + ublituximab

Events of Clinical Interest – PI3K Specific

AEs, n (%)	U2 N=206 Any	U2 N=206 Grade ≥3	O+Chl N=200 Any	O+Chl N=200 Grade ≥3
ALT elevation	35 (17.0)	17 (8.3)	9 (4.5)	2 (1.0)
AST elevation	28 (13.6)	11 (5.3)	9 (4.5)	4 (2.0)
Colitis (non-infectious)[a]	10 (4.9)	4 (1.9)	0	0
Colitis (infectious)[a]	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)
Pneumonitis	6 (2.9)	1 (0.5)	1 (0.5)	0
Rash[a]	26 (12.6)	5 (2.4)	10 (5.0)	1 (0.5)
Opportunistic Infections[a]	29 (14.1)	12 (5.8)	11 (5.5)	3 (1.5)

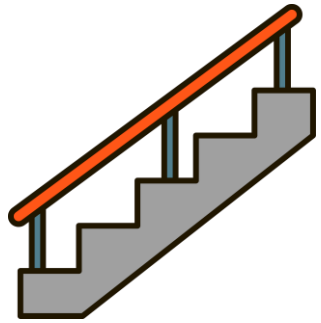
[a]Group includes multiple MedDRA terms. AE: adverse event; O+Chl: obinutuzumab + chlorambucil; U2: umbralisib + ublituximab.

Events of Clinical Interest or Serious Side Effects

- All the approved PI3K inhibitors carry the risk of adverse events
- Most of these can be managed by holding or reducing the dose, but can be serious if not properly handled
  - Liver inflammation
  - Pneumonitis
  - Diarrhea
  - Colitis
  - Infection

Imagine Many Different Pathways All Driving CLL but Going in Different Directions

CLL SOCIETY



New Directions with PI3K Inhibitors

- Combinations
  - Venetoclax and CD20 antibodies
  - Fixed duration gets the patient off the drug, avoids long term toxicities

- Dose and schedule
  - Do we need continuous dosing?
    - Could intermittent dosing lower the auto-immune side effects?
  - Can a lower dose be used?

PI3K in CLL- Summary

- Potent oral medications that target the same B-cell receptor (BCR) targeted by BTKi such as ibrutinib and acalabrutinib, but by a different pathway
- Very effective in controlling CLL, even when patients have failed a BTKi or venetoclax
- Use has been limited by patients not being able to tolerate their side effects but that may be helped by:
  - New drugs in development for CLL
  - Innovative dosing schedules to lower side effects
  - Combinations that would allow a finite duration of therapy