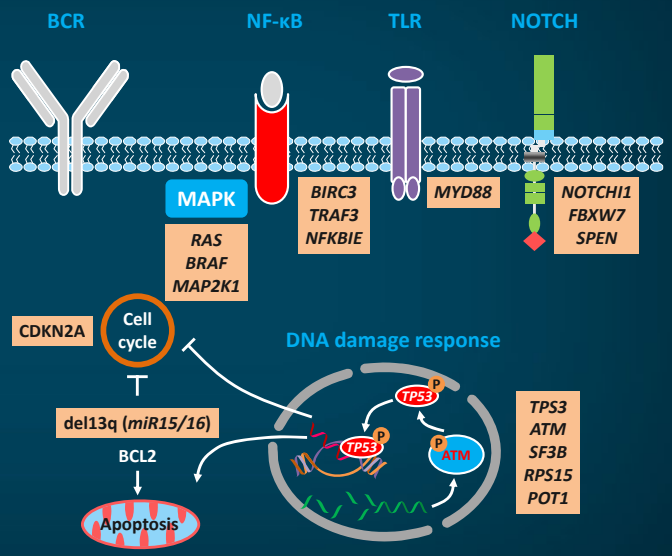
The New BTKids on the Block: Compelling Rationale for Non-Covalent Bruton Tyrosine Kinase Inhibition in B-Cell Cancers

Pre-Read Slides

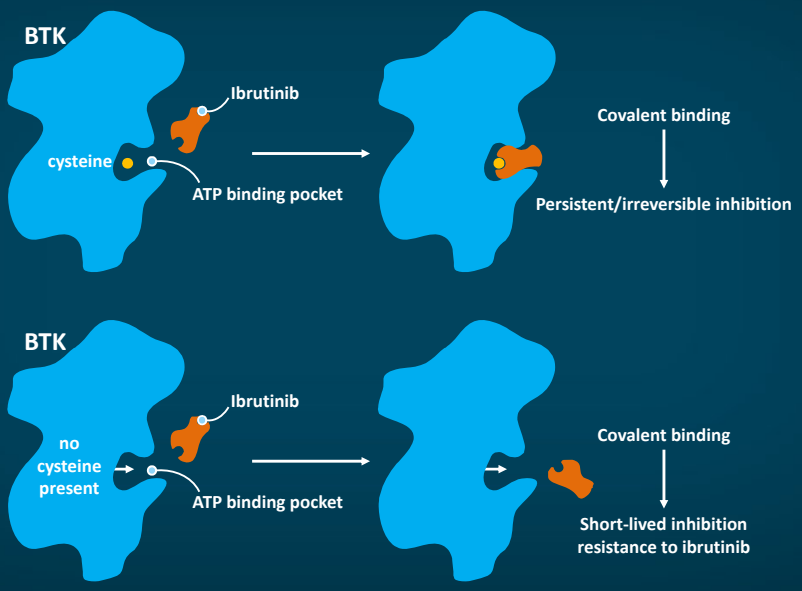
CLL/SLL

- Mature B cell lymphoma/leukemia driven by impaired apoptosis and increased lymphocyte proliferation
  - Impaired immune response
  - Associated autoimmune disorders
- Heterogeneous disease
  - Genetic abnormalities
  - Immunoglobulin heavy chain mutational status
- Majority of patients are diagnosed at 70 years or older



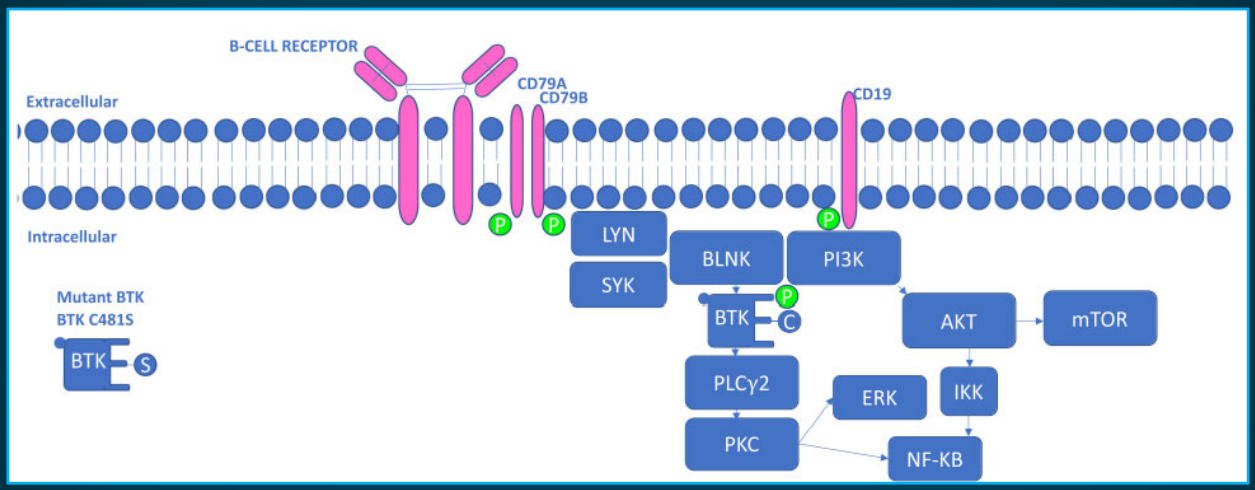
Gaidano G, Rossi D.. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):329-337.

Mechanism of BTK Inhibition



Wiestner A. *Haematologica.* 2021;100(12):1495-1507.

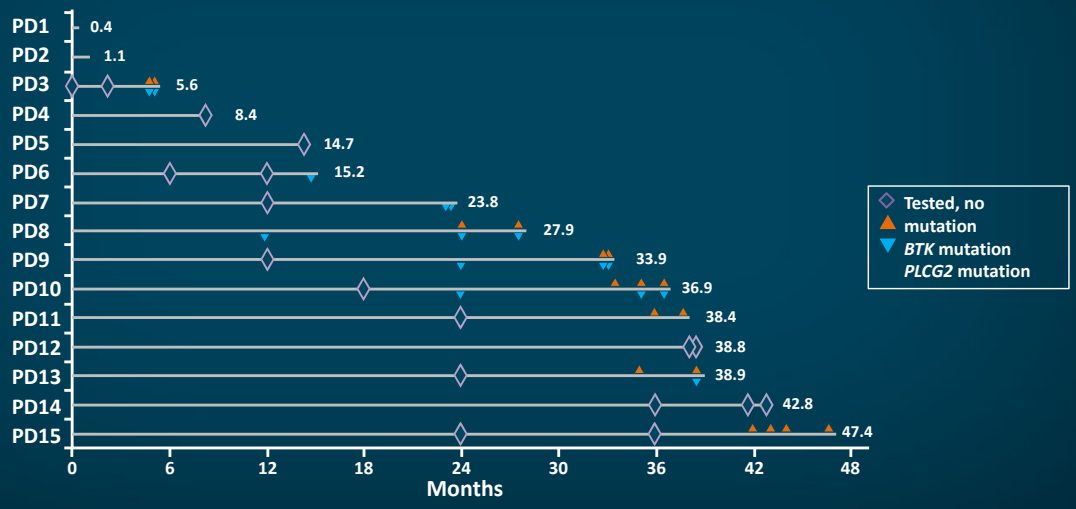
Role of BTK Inhibitors in BCR Signaling in CLL



Tambaro FP, et al. *J Exp Pharmacol.* 2021;13:923-935.

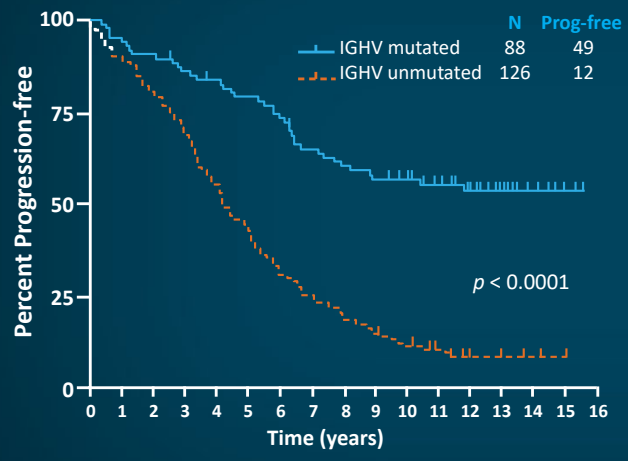
Ibrutinib Resistance: BTK and PLGγ Mutations

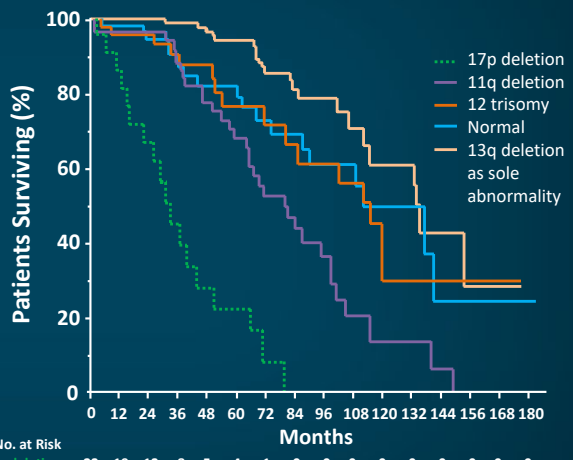
Resistance mutations detected in 9/15 ibrutinib-treated patients up to 15 months before progressive disease



Ahn IE, et al. *Blood*. 2017;129(11):1469-1479.

In the Past: Minority of Patients Experienced Long-Term Disease Control with Chemoimmunotherapy



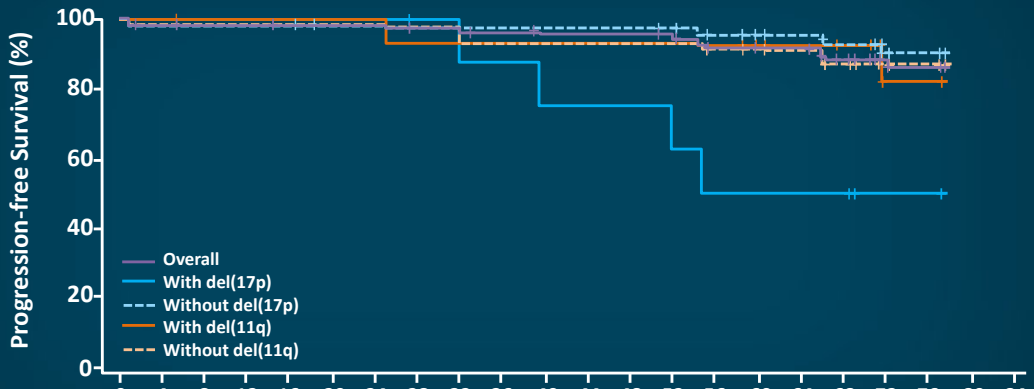


No. at Risk															
17p deletion	23	19	13	8	5	4	1	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0
12 trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1

Thompson PA, et al. *Blood*. 2016; 127 (3):303–309; Döhner H, et al. *N Engl J Med*. 2000;343(26):1910-1916.

ACE-CL-001:
6-Year Follow-up Data of Phase 1/2 Acalabrutinib Monotherapy

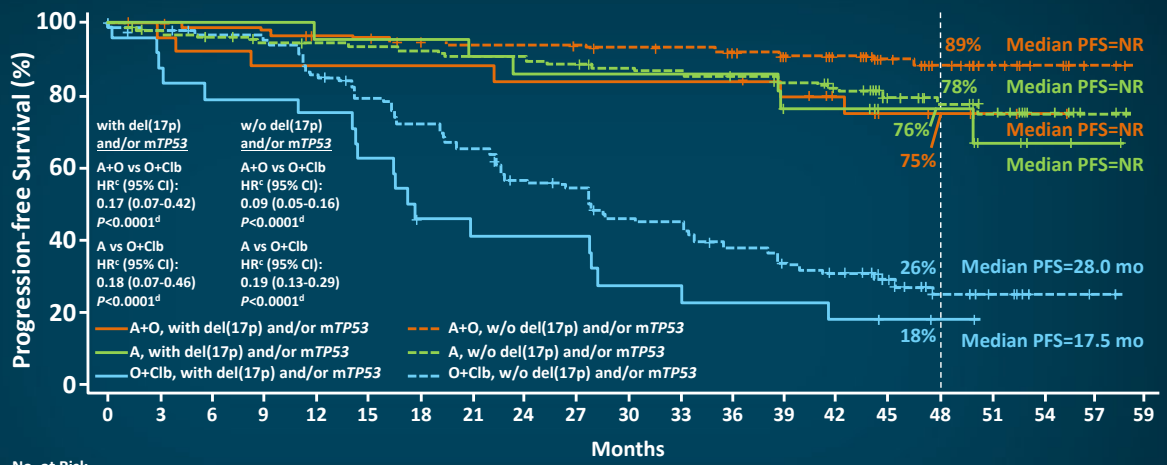
Kaplan-Meier Curves for Progression-Free Survival Overall and by High-Risk Genomic Subgroup



No. at Risk																					
Overall	99	97	96	96	95	93	93	91	91	89	87	87	87	86	78	76	72	62	34	30	0
With del(17p)	9	9	9	9	9	9	9	8	8	7	6	6	6	6	4	4	4	4	2	2	0
Without del(17p)	79	77	76	76	75	73	73	72	72	72	72	72	72	71	65	63	60	51	26	21	0
With del(11q)	16	16	15	15	15	15	15	14	14	14	14	14	14	14	14	13	12	10	6	6	0
Without del(11q)	72	70	70	70	69	67	67	66	66	65	64	64	64	63	55	54	52	45	21	17	0

Qi, J, et al. *Blood*. 2022;140(Supplement 1):9865-9867.

ELEVATE-TN: 4-year Follow-Up of Acalabrutinib +/- Obinutuzumab



No. at Risk																					
A+O, with del(17p) and/or m*TP53*	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A, with del(17p) and/or m*TP53*	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
O+Clb, with del(17p) and/or m*TP53*	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0
A+O, w/o del(17p) and/or m*TP53*	154	152	148	146	142	141	138	135	135	134	132	131	129	122	116	76	51	30	11	2	0
A, w/o del(17p) and/or m*TP53*	156	145	142	137	136	135	133	131	131	128	124	123	118	115	108	68	52	30	14	3	0
O+Clb, w/o del(17p) and/or m*TP53*	152	142	137	134	121	110	100	91	77	73	61	60	50	43	38	19	11	6	2	1	0

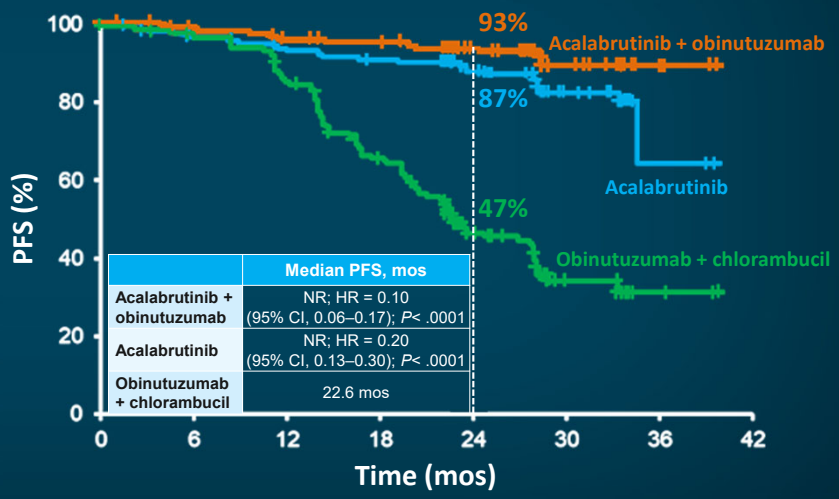
Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175.

ELEVATE-TN: Acalabrutinib ± Obinutuzumab in Treatment-Naïve Patients With Co-existing Medical Conditions

- Phase 3, open-label trial
- Untreated CLL
- Eligible patients were either ≥65 years or 18 to <65 years with comorbidities
- Median FU = 28.3 mos

Post hoc analysis
HR for PFS between acalabrutinib + obinutuzumab and acalabrutinib monotherapy = 0.49 (95% CI, 0.26–0.95)

Acalabrutinib vs acalabrutinib + obinutuzumab vs O-Clb



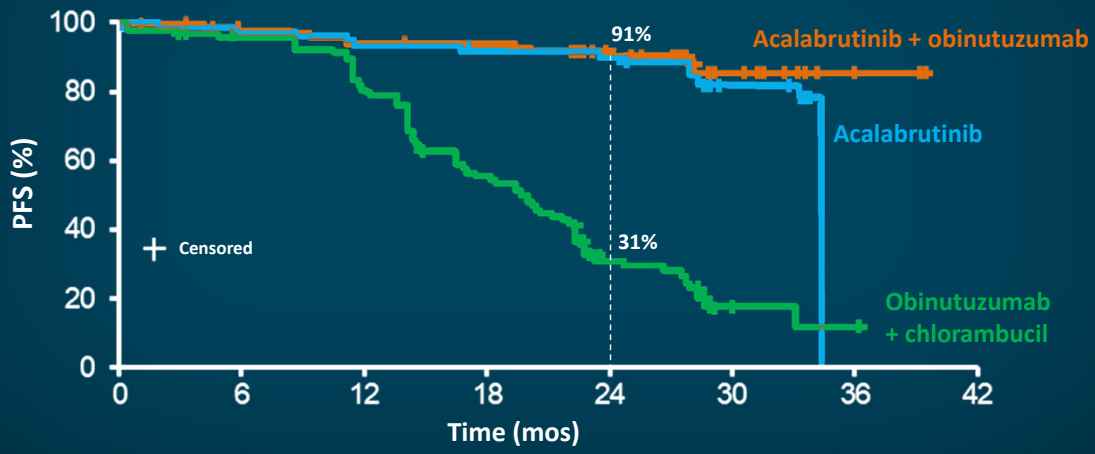
	Median PFS, mos
Acalabrutinib + obinutuzumab	NR; HR = 0.10 (95% CI, 0.06–0.17); *P*< .0001
Acalabrutinib	NR; HR = 0.20 (95% CI, 0.13–0.30); *P*< .0001
Obinutuzumab + chlorambucil	22.6 mos

FU = follow-up; O-Clb = obinutuzumab + chlorambucil.

Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

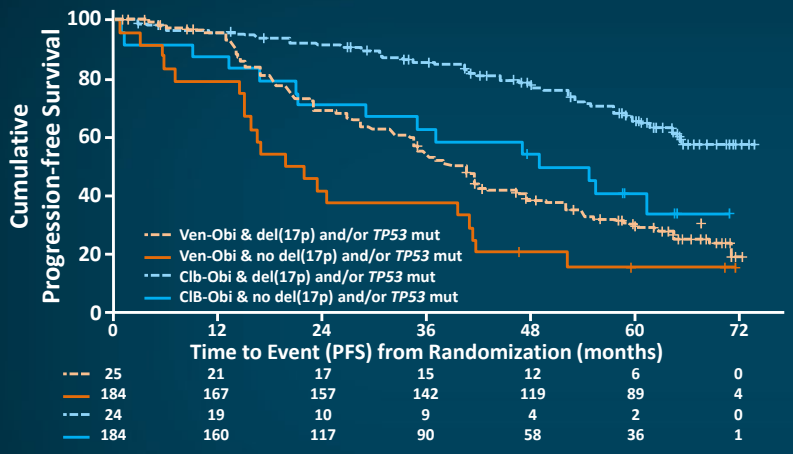
ELEVATE-TN: Acalabrutinib ± Obinutuzumab in Treatment-Naïve Patients With Coexisting Medical Conditions

PFS in *IgHV*-unmutated patients



Modified from Sharman JP, et al. *Lancet*. 2020;395:1278-1291.

CLL14: Venetoclax + Obinutuzumab for Untreated CLL



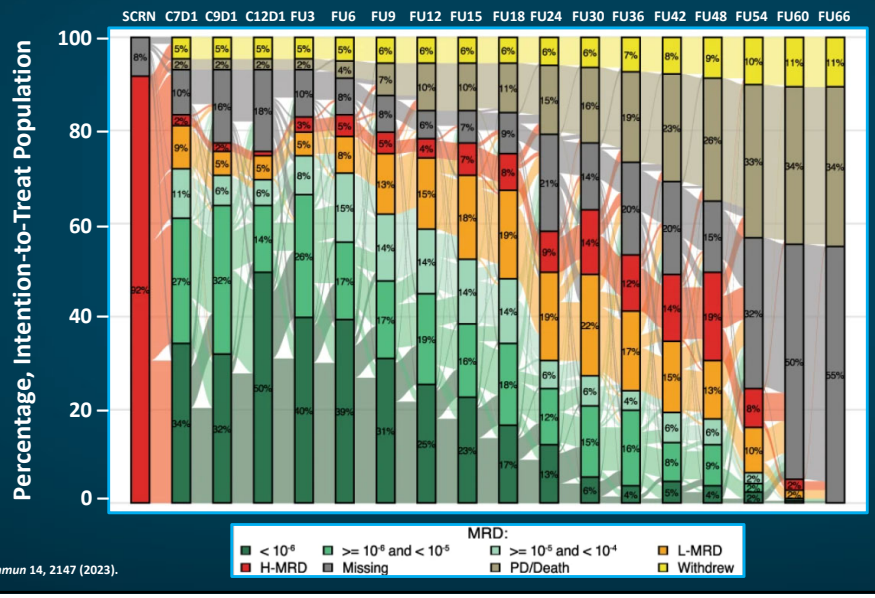
- 5 year PFS: Ven-Obin vs. Chl-Obin
  - Overall: 63% vs. 27%
  - *TP53* aberration: 40.6% vs 15.6%
  - unmutated IgHV = 55.8% vs 12.5%
- TTNT: 72 vs. 43%
- 5 year OS: 82% vs. 77%

Patients negative for MRD for all patients		
	Peripheral blood	Bone marrow
Venetoclax + obinutuzumab	75.5%	56.9%
Obinutuzumab + chlorambucil	35.2%	17.1%

Al-Sawaf, O et al. *Lancet Oncol*. 2020;21:1188-1200. Fischer K, et al. *N Engl J Med*. 2019;380:2225-2236. Al Sawaf, O et al. *Nat Commun* 14, 2147 (2023).

CLL-14: Venetoclax + Obinutuzumab

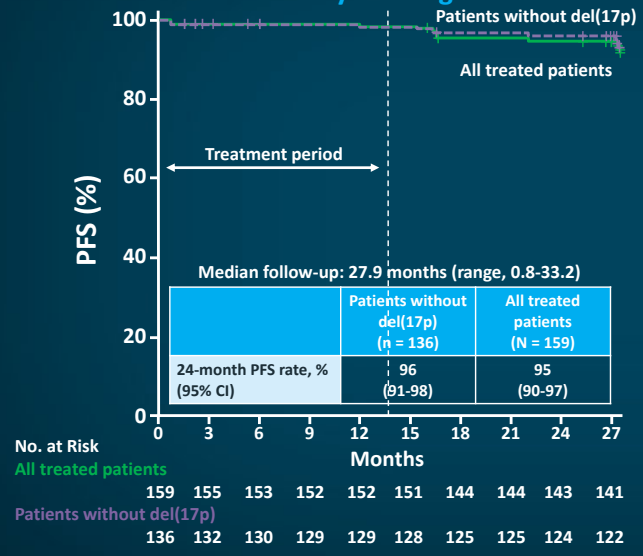
NGS MRD levels, ITT population, Ven-Obi (N=216)



Al-Sawaf O, et al. *Nat Commun* 14, 2147 (2023).

CAPTIVATE: Fixed Duration Ibr + Ven

PFS with Fixed-duration ibrutinib + venetoclax as assessed by investigators



5 year update from CAPTIVATE-MRD cohort

- Sustained uMRD post randomization
  - PBO: 56% year 2→ 58% year 3
  - IBR: 60% year 2 → 63% year 3
- 3 year disease free survival similar in both groups of ≥ 85%

Efficacy outcomes, % (95% CI)	All treated Placebo (N=43)	All treated ibrutinib (N=43)	Del(17p), *TP53* mut, or CK Placebo (n=6)	Del(17p), *TP53* mut, or CK ibrutinib (n=20)
DFS (3-year)	85 (69-93)	93 (80-98)	100 (100-100)	95 (70-99)
PFS (4-year)	88 (74-95)	95 (82-99)	100 (100-100)	95 (70-99)
OS (4-year)	100 (100-100)	98 (84-100)	100 (100-100)	100 (100-100)

Allan JN, et al. ASH 2022; Abstract 92 Tam CS, et al. *Blood.* 2022;139(22):3278–3289.

Patient Tailored Treatment Approach: An Evolving Treatment Paradigm for Indolent NHL

Current Standard of Care

Disease eradication with fixed duration therapies

Disease control with long-term continuous therapies

Future Directions

- Toxicity considerations with combination regimens
- Novel agents with improved side effect profiles
- Long-term survival data with sequential therapies vs combination regimens
- Emerging and evolving Prognostic impact of uMRD and molecular/ cytogenetic features