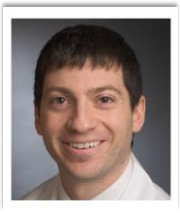
What's on the Horizon for Chronic Lymphocytic Leukemia?



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Disclosures

Matthew S. Davids, MD, MMSc has affiliations with: AbbVie, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, Janssen, MEI, Merck, Pharmacyclics, Surface Oncology, and TG Therapeutics.

What's on the Horizon for Chronic Lymphocytic Leukemia?

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May 8, 2018

Disclosures for **Matthew S. Davids, MD, MMSc**

Employment	**None**
Consultancy/Advisory Committee	**Janssen, Genentech, Pharmacylics, Abbvie, Roche, TG Therapeutics, Merck, Astra-Zeneca, MEI Pharma, Verastem, InCyte**
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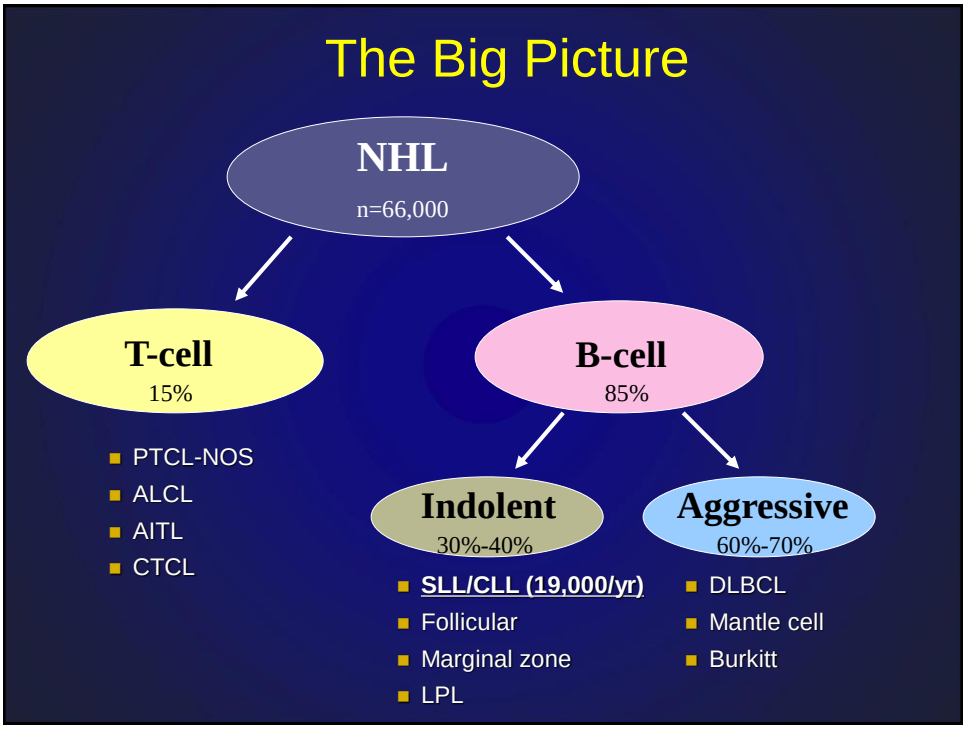
Speakers Bureau	**None**
Other	**None**
Presentation includes a description of the following off-label use of a drug or medical device	**Venetoclax, lenalidomide**



CLL | Fast Facts

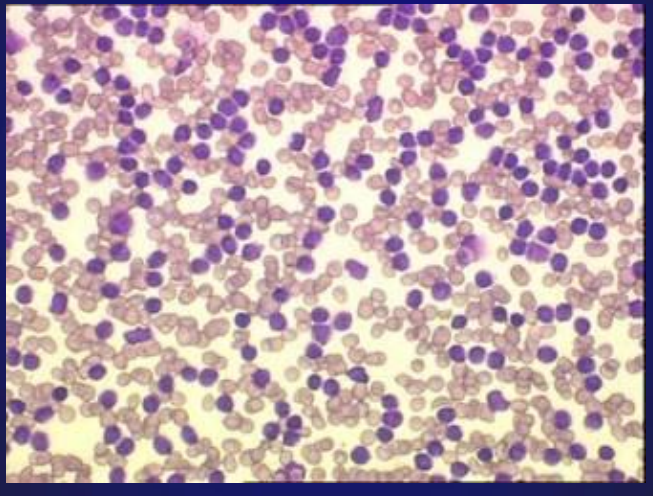
- Median age at diagnosis is 72
- Patients often diagnosed on routine blood work
- Powerful biologic predictors of response
- Early stage patients without symptoms observed
- Advanced stage, symptomatic patients treated with chemoimmunotherapy
- Highly treatable, but historically most therapies not curative
- Bone marrow transplant may lead to long term survival
- Novel oral agents have begun to revolutionize the field

CLL | Diagnosis

- Peripheral blood flow cytometry:
  - ABC ct. >5,000 (CD5+CD23+CD19+dimCD20+dimIg+)
  - N.B. ABC ct. <5,000, same markers = monoclonal B cell lymphocytosis (MBL)
- Lymph node biopsy (excisional or core) (SLL)
- Bone marrow biopsy (rarely)

Key point: small lymphocytic lymphoma (SLL) is part of the same disease continuum as CLL

CLL | Pathology



Courtesy of the Ohio State University CLL Center

CLL | Staging

Clinical staging systems (Rai)*

- Stage 0 (elevated lymphocyte count)
- Stage I (enlarged lymph nodes)
- Stage II (enlarged spleen or liver)

- Stages III (anemia) and IV (low platelets)

*Bone marrow biopsy and CT not required

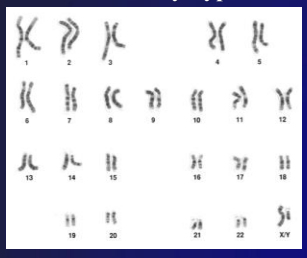
Rai et al., *Blood,* 1975

Key Prognostic Factors

- Beta-2 microglobulin
- Cytogenetic abnormalities (FISH)
- Immunoglobulin gene mutation (*IGHV*)
- Somatic mutations (*TP53*, *SF3B1*, *NOTCH1)*
- ZAP-70
- CD38

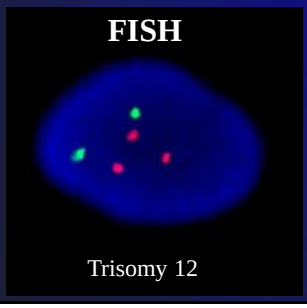
CLL | Prognostic Factors: Cytogenetics

"Routine Karyotype"



vs.

FISH



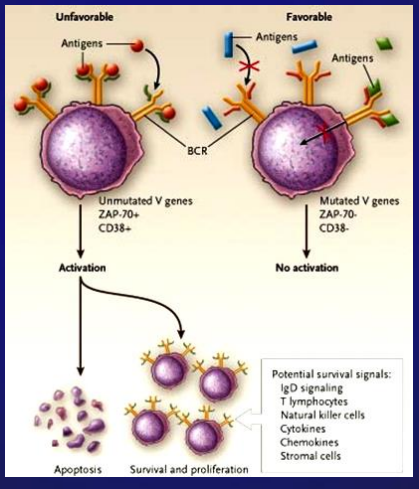
Trisomy 12

	No. patients (%)
• 13q deletion	178 (55)
• 11q deletion	58 (18)
• Trisomy 12	53 (16)
• 17p deletion	23 (7)
• 6q deletion	21 (6)
• Normal	57 (18)

Döhner, et al., *NEJM*, 2000

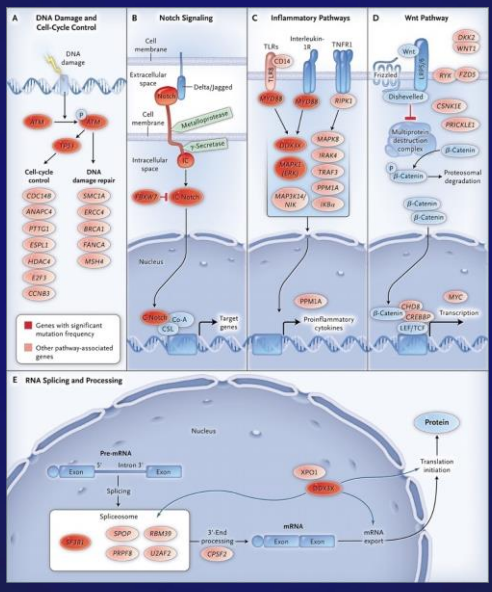
CLL | Prognostic Factors: *IGHV*

***IGHV* mutation status**



Reviewed in Chiorazzi et al., *NEJM*, 2005

CLL | Prognostic Factors: Somatic Mutations



Wang L et al. *N Engl J Med* 2011

Treatment

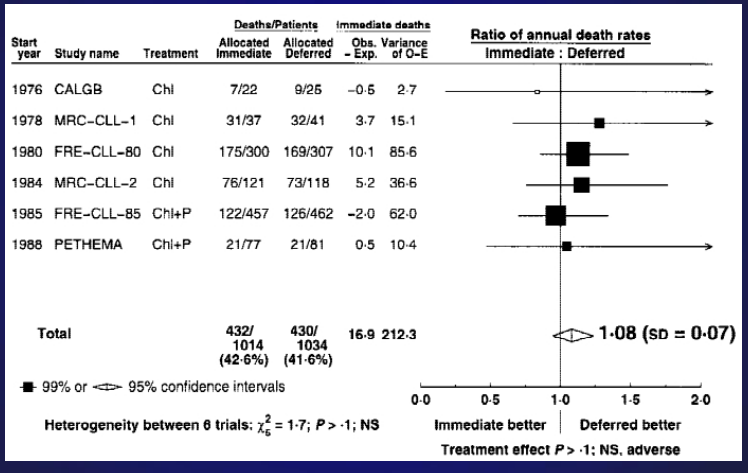
"Why can't you just cut it out, doc?"

CLL | When to Treat

- Indications for treatment
  - Low blood counts
  - Bulky or rapidly enlarging lymph nodes or spleen
  - Symptoms (fevers, night sweats, unintentional weight loss, fatigue, pain)
  - Refractory autoimmune conditions
  - +/- LDT <6 months

If none of the above… → OBSERVATION

CLL | When to Treat



CLL Trialists' Group Meta-analysis, *JNCI*, 1999

Revisiting early intervention in the modern era

CLL7 Trial

Diagnosed within 1 year
No prior treatment
Planned enrollment ~ 600

↓

17p-, 11q- deletion, trisomy 12
Unmutated IGHV, TK > 10 U/L
Predicted LDT < 12 months

↓

≥ 2 risk factors
Planned n = 150

↙ ↘

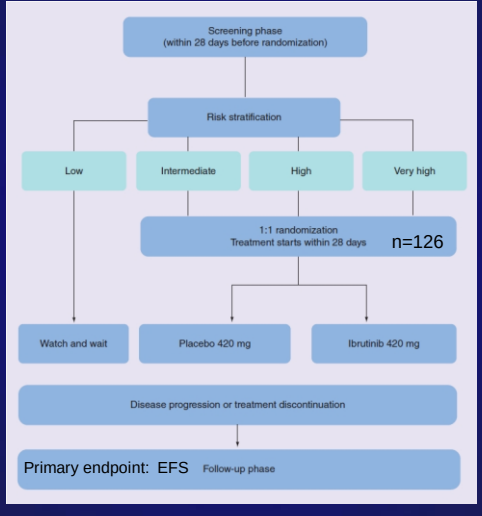
COHORT I
FCR x 6

COHORT II
Watch & wait

- Some serious side effects such as infections seen in FCR arm
- NO DIFFERENCE IN OS

Schweighofer et al., *ASH,* 2013

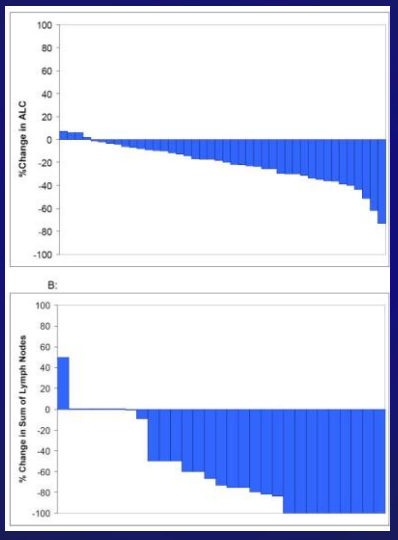
CLL12 is the first study of ibrutinib for high risk watch/wait patients



Langerbeins et al., Future Oncol, 2015

"What can I do to slow this down?"

Polyphenon E: The Mayo Clinic Study



Shanafelt et al., *Cancer,* 2013

CLL | Initial Treatment

1960s

- Alkylating agents
  - Chlorambucil
  - Cytoxan

  5% CR

1970s

- Purine nucleosides
  - Fludarabine
  - Pentostatin
  - Cladribine

  5%-20% CR

1980s

- Purine nucleosides and alkylators

  30% CR

1990s

- -Alemtuzumab monotherapy
  24% CR
- -Bendamustine
  30% CR
- -Chemo-immunotherapy (CIT)
  41%-70% CR

2000s

- -obinutuzumab
- -ibrutinib
- -idelalisib
- -venetoclax
- -next generation molecules

%CR: variable

2010s

FCR

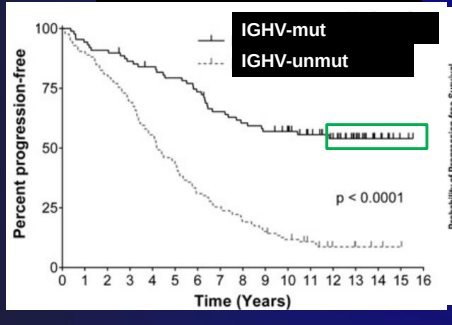
- **F**ludarabine (days 1-3)
- **C**yclophosphamide (days 1-3)
- **R**ituximab (day 1)

Plus Neulasta on day 4

-- above given in 6 monthly cycles --

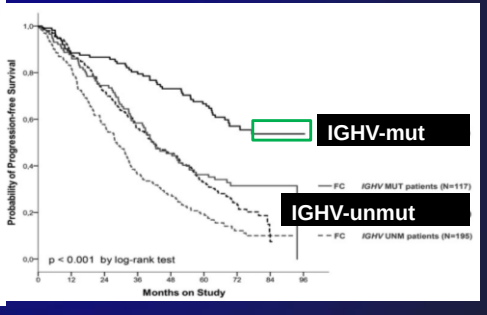
FCR has curative potential in mutated *IGHV* CLL

MDACC – FCR



Thompson et al., *Blood*, 2016

GCLLSG – CLL8



Fischer et al., *Blood*, 2016

22

BR

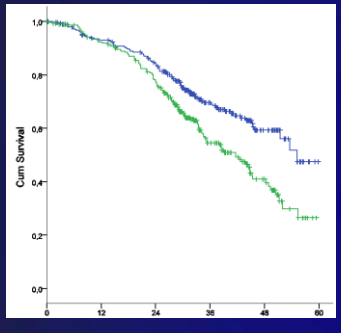
- **B**endamustine (days 1-2)
- **R**ituximab (day 1)

Plus Neulasta on day 3

-- above given in 6 monthly cycles --

CLL10 Study: FCR vs. BR in Frontline

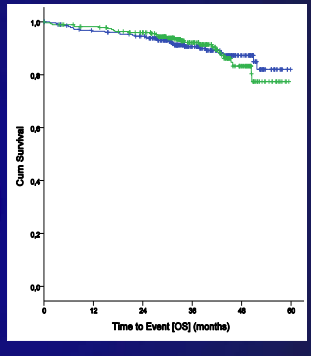
Progression free survival



Median PFS
FCR 55.2 months
BR 41.7 months

***P* < 0.001**
HR = 1.626 = > 1.388

Overall survival



OS at 36 months:
FCR 90.6%
BR 92.2%

***P* = 0.897**

Eichhorst et al., ASH, 2014

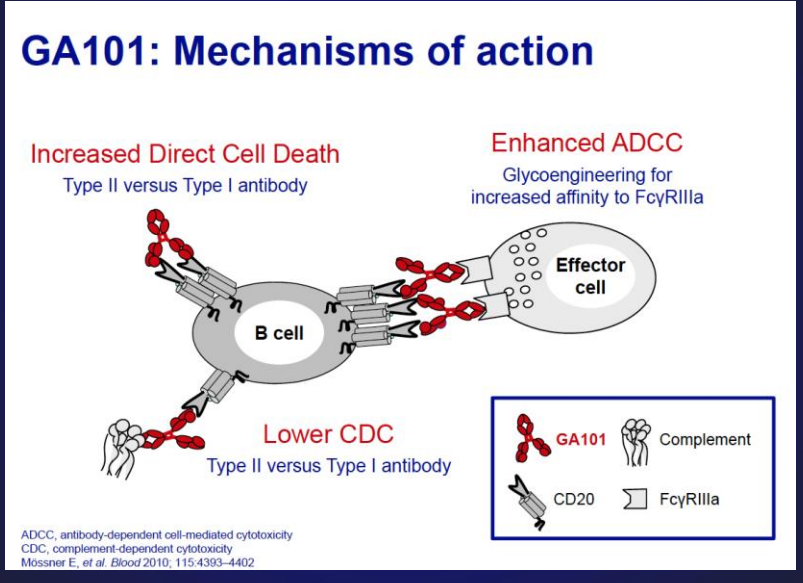
CLL10 Study: FCR vs. BR Frontline Side Effects

Adverse event	FCR (%) N= 279	BR (%) N=278	p value
Neutropenia	84.2	59.0	<0.001
Anemia	13.6	10.4	0.20
Thrombocytopenia	21.5	14.4	0.03
Infection	39.1	26.8	<0.001
All infections in patients ≤ 65 years	35.2	27.5	0.1
All infections in patients > 65 years	47.7	20.6	<0.001
Sec Neoplasm*	6.1	3.6	0.244
TRM	4.6	2.1	0.107

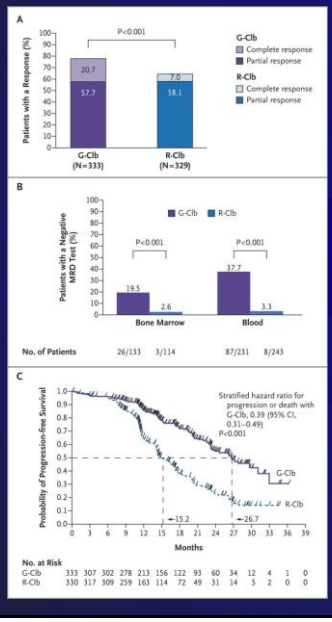
*sAML/MDS: FCR=6, BR = 1

Eichhorst et al., ASH, 2014

Can We do Better than Rituximab in CLL?



Obinutuzumab is Highly Active in CLL



Toxicities of note: infusion reactions, neutropenia, infection

Time to next treatment: 42.7 mo.

Goede et al., *NEJM, 2014*
Goede et al., Leukemia, 2015

CLL | Treatment of Relapsed/Refractory Disease

“Refractory” definition:

- < 24 mo. response to chemoimmunotherapy

“Relapsed” definition

- Achieved >24 mo. response but then disease came back

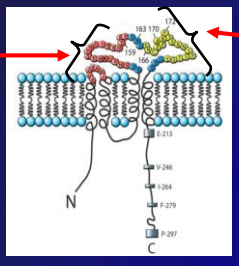
Further evaluation:

- Recheck peripheral blood FISH to rule out clonal evolution
- No need to recheck *IGHV* status (stable marker)

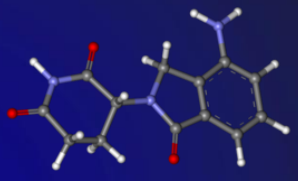
Older Agents

Ofatumumab binding site

Rituximab binding site



ofatumumab (Arzerra)

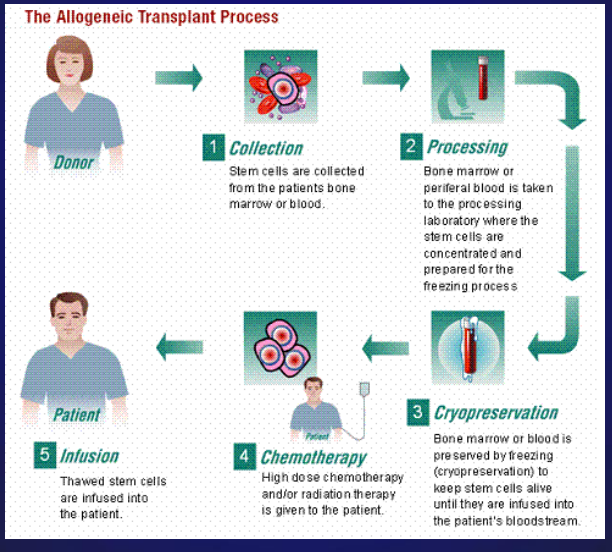


lenalidomide (Revlimid)

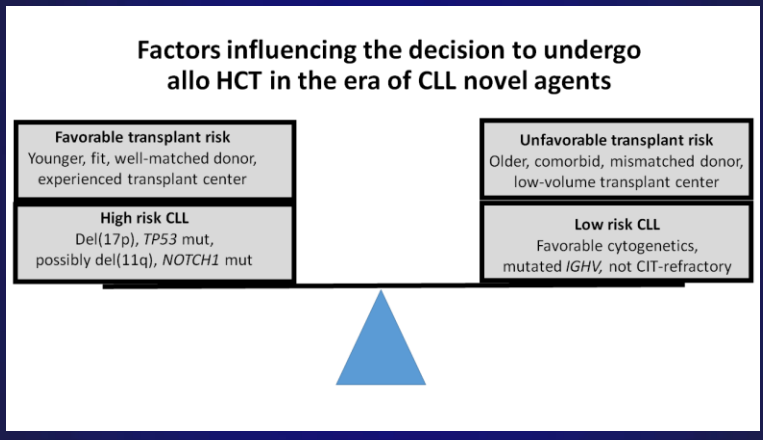
alemtuzumab (Campath)

high-dose methylprednisolone (HDMP)

Hematopoietic Cell Transplantation

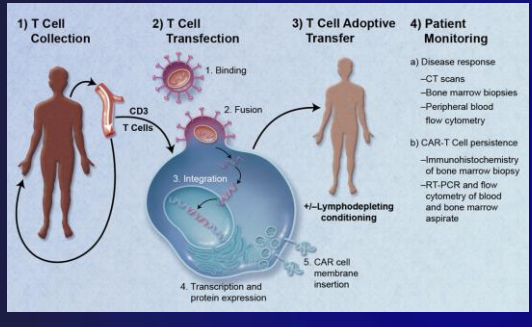


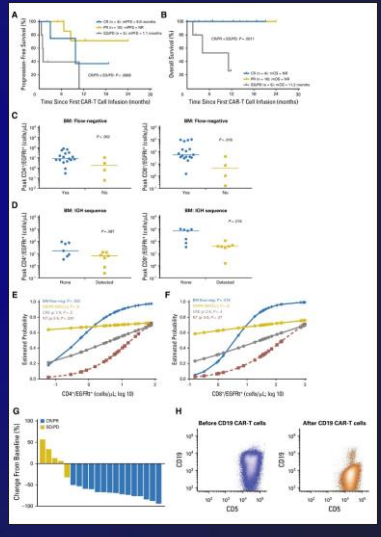
Transplant guidelines are in flux given the novel agents



Davids and Alyea, *Curr Hematol Malig Rep*, 2015

Immune-based Therapies: CARs ('Serial Killers')





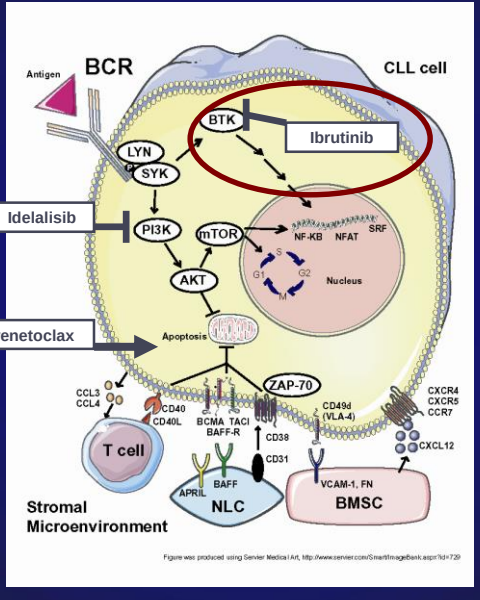
- 24 patients treated with CD19 CAR-T
- ORR 71%, CR 21%, 88% with marrow clearance
- 83% CRS
- 33% neurotoxicity (reversible in all but 1 case)
- Median PFS 8.5 mo., median OS not reached

Turtle et al., *J Clin Oncol*, 2017

“Hide and seek”

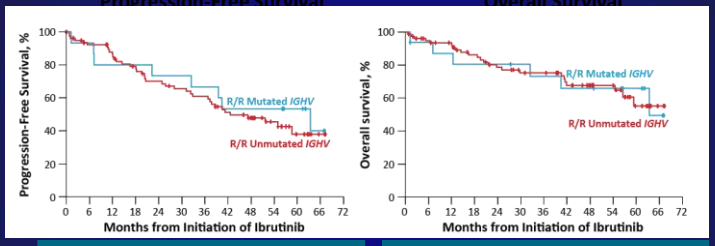
William Merritt Chase

Novel Targeted Agents



Reviewed in Davids and Brown, *Leuk & Lymph*, 2012

The BTK inhibitor ibutinib leads to comparable PFS/OS regardless of *IGHV* status (PCYC-1102 study)

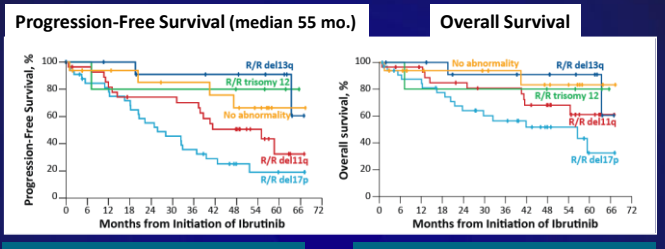


	Median PFS	5-year PFS
Mutated *IGHV* (n=16)	63 mo	53%
Unmutated *IGHV* (n=79)	43 mo	38%

	Median OS	5-year OS
Mutated *IGHV* (n=16)	63 mo	66%
Unmutated *IGHV* (n=79)	NR	55%

O'Brien et al., 2016 ASH Annual Meeting

Ibrutinib leads to durable response in most FISH subgroups



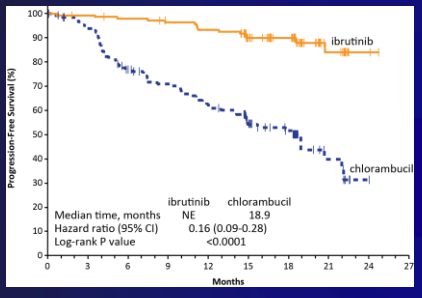
	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

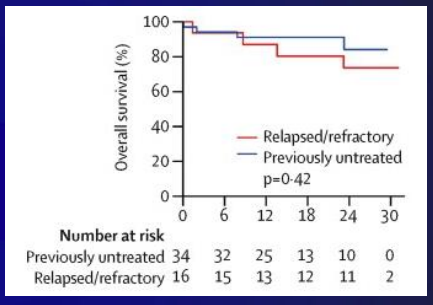
O'Brien et al., 2016 ASH Annual Meeting

Frontline ibrutinib is effective even in pts with TP53 dysfunction

RESONATE-2: no del(17p)



NIH: Del(17p)/*TP53* mut

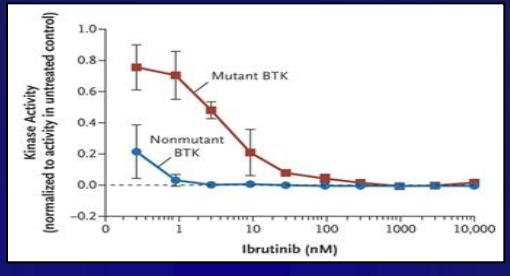


Toxicities of note: diarrhea, bruising, bleeding, hypertension, atrial fibrillation, infection

Burger et al., *N Eng J Med*, 2015

Farooqui et al., *Lancet Oncol*, 2015

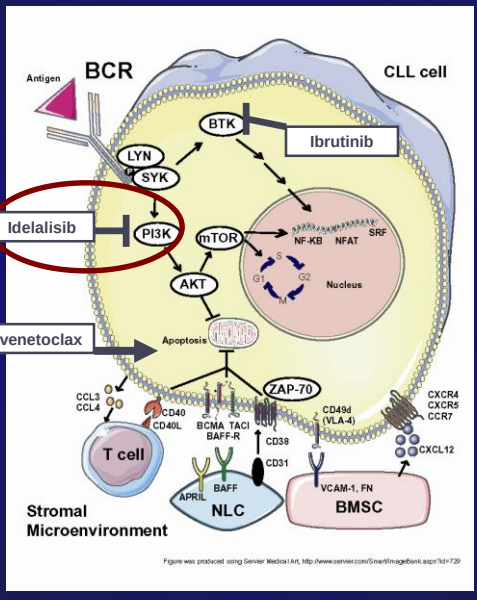
Why not use indefinite ibrutinib monotherapy?



- Achievement of CR is rare
- Duration of response in del(17p)/del(11q)/ complex karyotype is shorter
- Resistance mutations already described
- Long term adherence issues
- Co$t

O'Brien et al., *ASH Annual Meeting*, 2016
Woyach et al., *NEJM*, 2014

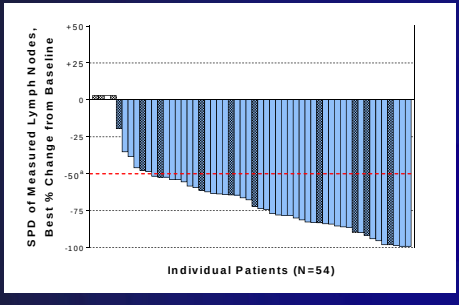
Novel Targeted Agents



Reviewed in Davids and Brown, *Leuk & Lymph*, 2012

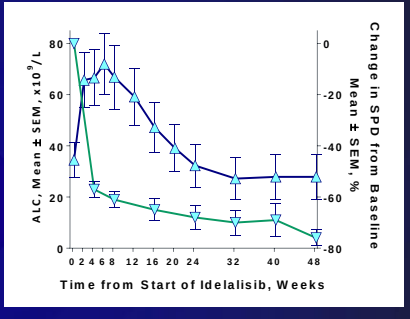
PI3K Inhibitor: Idelalisib (GS1101/CAL-101) -δ-specific

Best Lymph Node Response



☐ Presence of del17p or TP53 mutation

Lymphocyte and Nodal Response

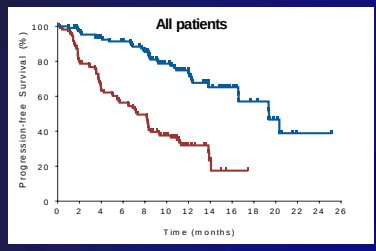


▲ ALC (N=54)
▼ SPD (N=51)

Common side effects	
Diarrhea	30%
Elevated liver function tests	24%
Pneumonia	22%

Brown et al., *ASCO*, 2013

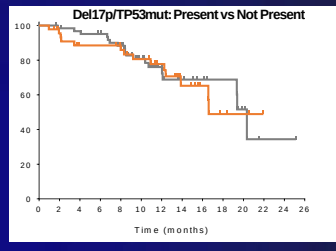
The PI3K-δ inhibitor idelalisib is active in R/R CLL, including those with TP53 dysfunction



N at risk

IDELA + R	110	102	95	92	83	64	43	26	19	12	7	1	1	0
PBO + R	110	86	66	58	51	33	15	5	1	0	-	-	-	-

	Median PFS (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)	

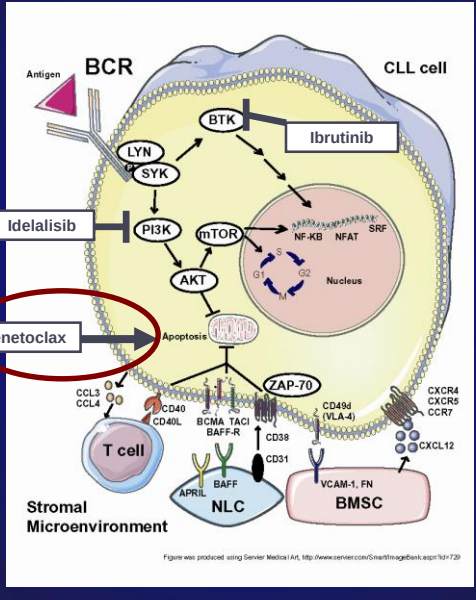


No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0		

	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, –)	0.94
Del	16.6 mo (13.9, –)	

Sharman et al., *ASH Annual Meeting*, 2014

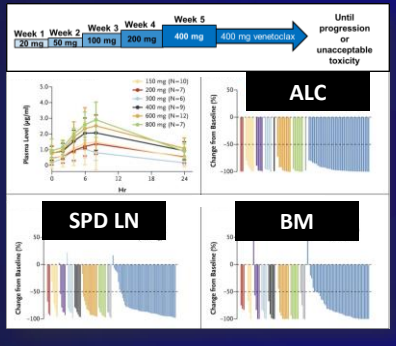
Novel Targeted Agents



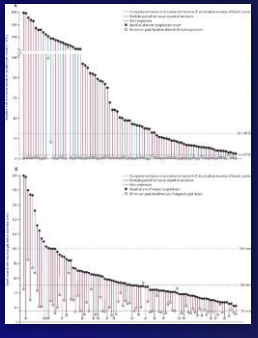
Reviewed in Davids and Brown, *Leuk & Lymph*, 2012

Venetoclax causes profound disease reduction even in pts with TP53 dysfunction, with some risk of TLS

Phase 1



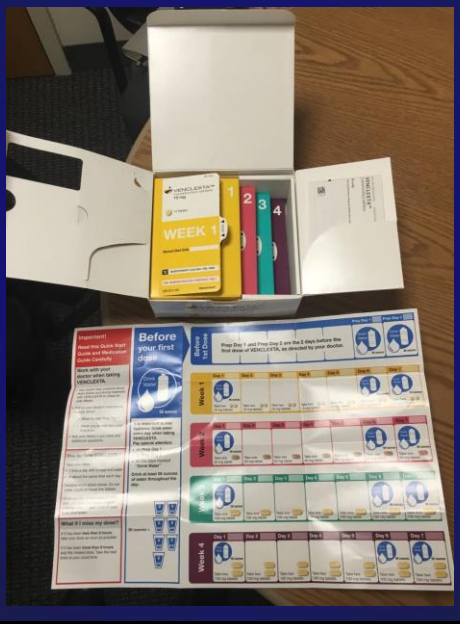
Roberts, Davids, et al., *NEJM*, 2016



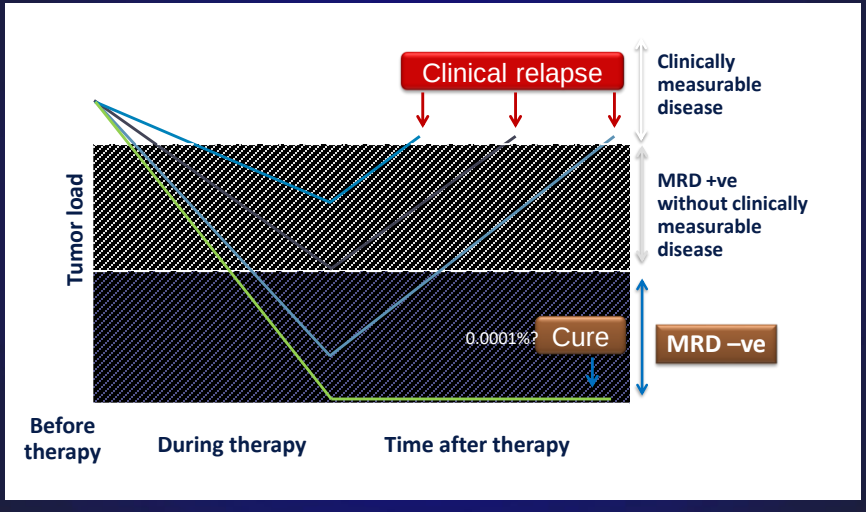
Phase 2

Stilgenbauer, et al., *Lancet Oncol.*, 2016

Venetoclax dosing: follow the directions!

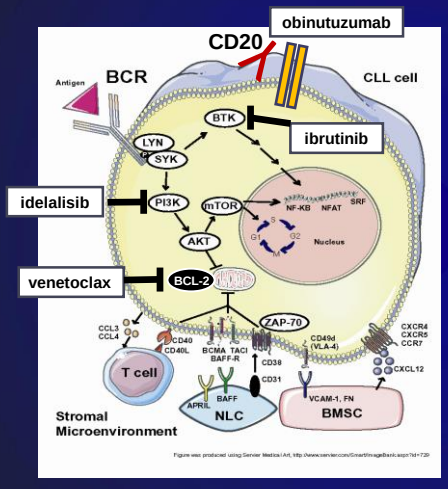


Impact of MRD levels on long-term outcomes in CLL



(courtesy of Peter Hillmen)

Diverse mechanisms allow for many possible combinations

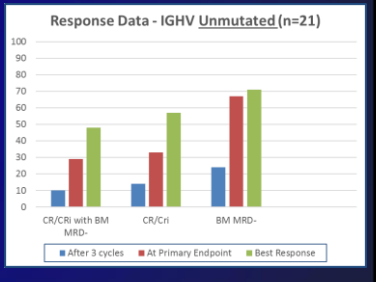


- NA + CIT
- NA + CD20 mAb
- NA-NA combos

NA + CIT

Ibrutinib + FCR (iFCR) is a promising new frontline approach for young, fit CLL patients

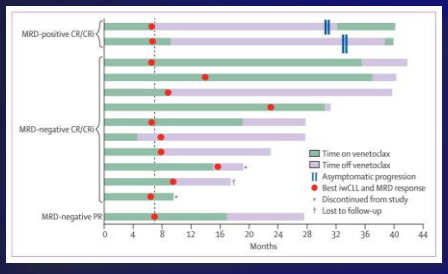
- Best BM MRD neg: 83%, higher than any prior CIT or NA regimen for 1L CLL therapy
- Response deepens over time in both *IGHV* mutated and <u>unmutated</u> patients with ibrutinib maintenance
- Ibrutinib discontinuation after 2 years of maintenance now being explored in patients who are BM MRD neg.

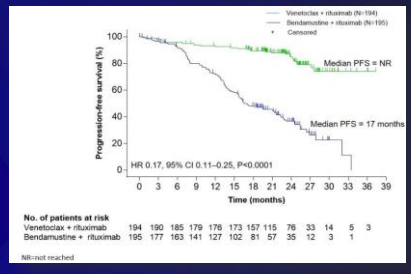


Davids et al., *ASH Annual Meeting*, 2017

NA + CD20 mAb

Venetoclax + rituximab is highly active in R/R CLL





- **Phase 1b: CR rate 51%, marrow MRD-neg. (57%)**
  -MRD neg. pts who discontinued venetoclax have not recurred a median of 9.7 mo. after discontinuation
- **Phase 3 (MURANO): CR rate 27%, peripheral blood MRD-neg. (84%)**
  -This positive registrational study is likely to lead to full approval in R/R CLL

Seymour, Ma, et al., *Lancet Oncol.*, 2017

Seymour et al., *NEJM*, 2018

Venetoclax + obinutuzumab is safe and active in frontline CLL

GP28331

- **All 32 patients responded**
- **CR/Cri: 56%**
- **BM MRD-neg: 62.5%**
- **No clinical TLS observed**
- **56% rate of infusion reactions**

CLL14

Overall response rate (%)	**(N=12)**
Complete response	58
Partial response	42
Minimal residual disease in peripheral blood (%)	(N=11)
Negative ($<10^{-4}$)	91
Intermediate ($\geq 10^{-4}$ and $<10^{-2}$)	9

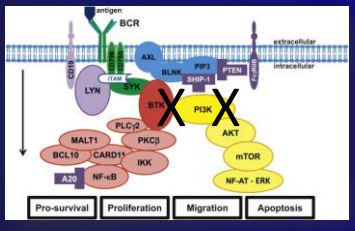
Flinn et al., ASH Annual Meeting, 2017

Fischer et al., Blood, 2017

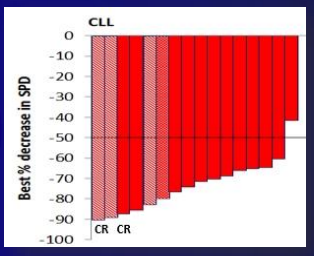
NA + NA

A PI3K-δ/BTK doublet has shown promising efficacy and safety in R/R CLL

A phase I/Ib study of umbralisib (TGR-1202) plus ibrutinib in R/R CLL and MCL



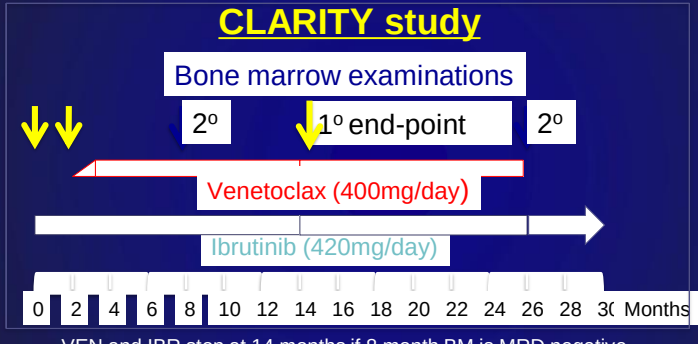
Reviewed in Niemann et al., *Sem. Cancer Biol.*, 2013



- **ORR: 16/18 (89%)**
  - **-PR or PR-L: 15/18 (83%)**
  - **-IW-CLL CR: 1/18 (6%), radiographic CR: 4/18 (22%)**
  - **-1 year PFS and OS: 94%**

Davids et al., IW-CLL, 2017

Several ongoing studies of ibrutinib + venetoclax have shown early promising data



- VEN and IBR stop at 14 months if 8 month BM is MRD negative
- VEN and IBR stop at 26 months if 14 month BM is MRD negative
- IBR alone continues if 26 month BM is MRD positive

Hillmen *et al.* ASH 2017; Abst 428

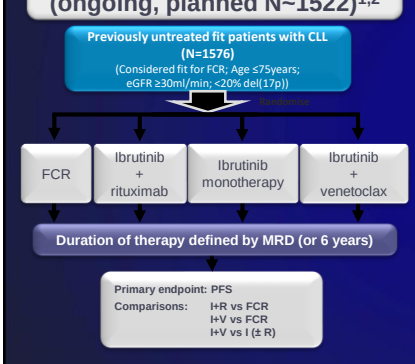
QUESTION

What new and emerging therapies are you most excited about:

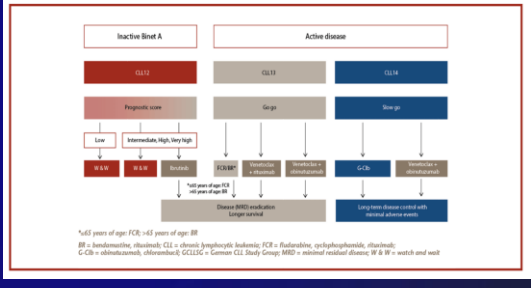
a) CAR T-cell Therapy
b) Novel targeted monotherapy (ibrutinib, idelalisib, venetoclax)
c) Combing existing and novel targeted therapies
d) Combining novel targeted therapies with each other

Ongoing randomized trials may define a new standard of care for frontline CLL treatment

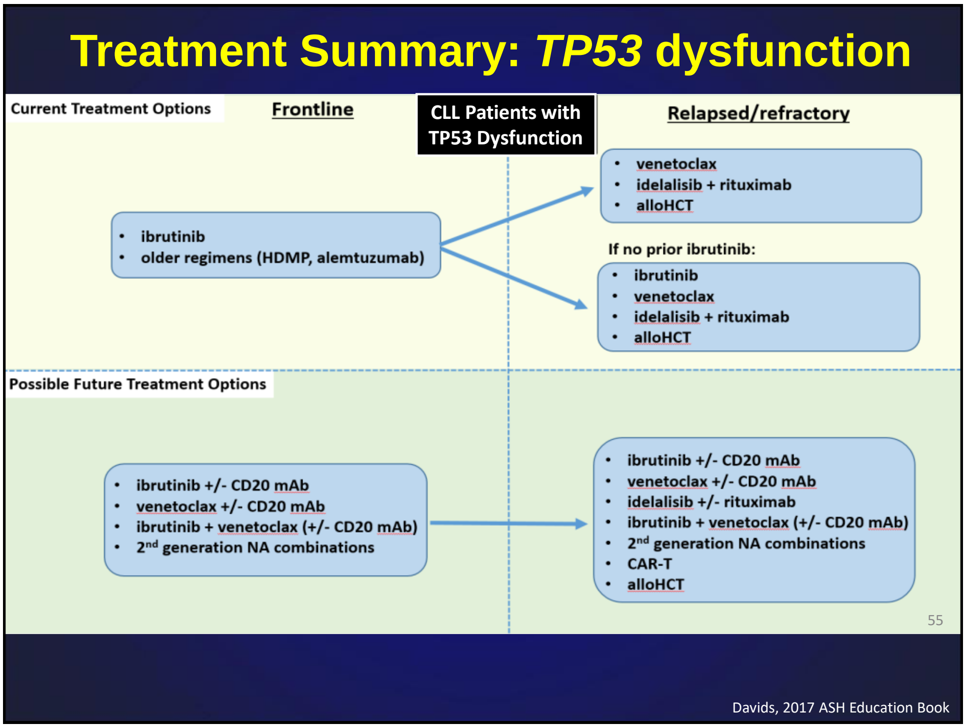
UK NCRI FLAIR trial (ongoing, planned N~1522)[1,2]

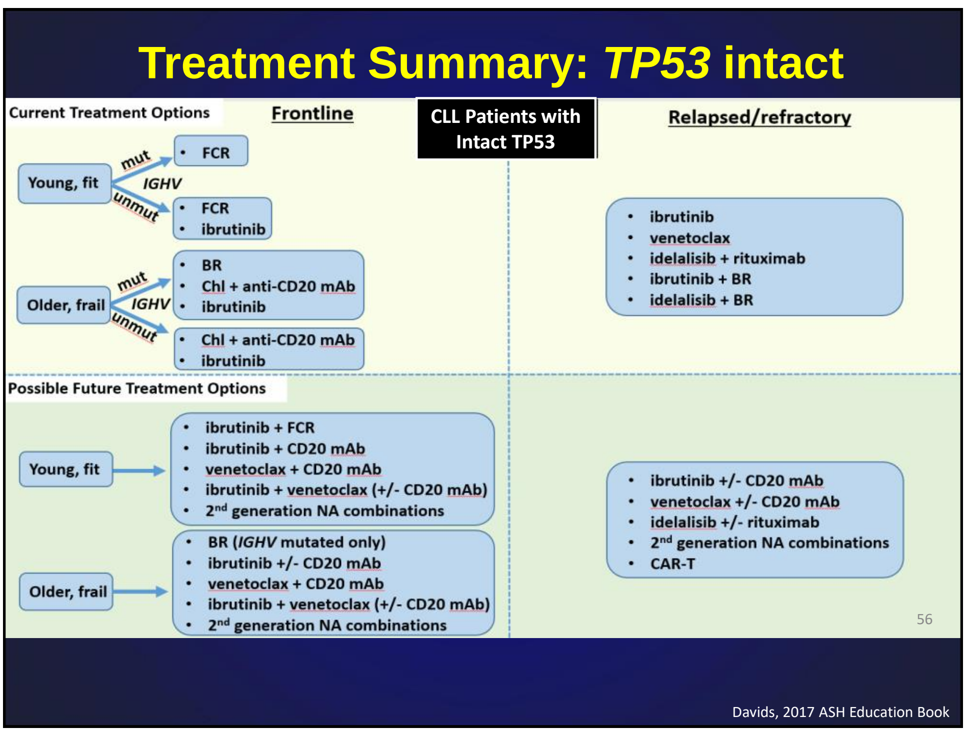


GCLLSG: CLL 13



1. EudraCT. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-001944-76/GB (accessed June 2017);
2. Derby-Burton Local Cancer Network. Available at: http://www.derbyhospitals.nhs.uk/EasysiteWeb/getresource.axd?AssetID=288688&type=full&servicetype=Attachment (accessed June 2017).


Treatment Summary: TP53 dysfunction
Current Treatment Options
Frontline
CLL Patients with TP53 Dysfunction
Relapsed/refractory
• venetoclax
• idelalisib + rituximab
• alloHCT
• ibrutinib
• older regimens (HDMP, alemtuzumab)
If no prior ibrutinib:
• ibrutinib
• venetoclax
• idelalisib + rituximab
• alloHCT
Possible Future Treatment Options
• ibrutinib +/- CD20 mAb
• venetoclax +/- CD20 mAb
• ibrutinib + venetoclax (+/- CD20 mAb)
• 2nd generation NA combinations
• ibrutinib +/- CD20 mAb
• venetoclax +/- CD20 mAb
• idelalisib +/- rituximab
• ibrutinib + venetoclax (+/- CD20 mAb)
• 2nd generation NA combinations
• CAR-T
• alloHCT
55
Davids, 2017 ASH Education Book


Treatment Summary: TP53 intact
Current Treatment Options
Frontline
CLL Patients with Intact TP53
Relapsed/refractory
Young, fit
mut
IGHV
unmut
• FCR
• FCR
• ibrutinib
Older, frail
mut
IGHV
unmut
• BR
• Chl + anti-CD20 mAb
• ibrutinib
• Chl + anti-CD20 mAb
• ibrutinib
• ibrutinib
• venetoclax
• idelalisib + rituximab
• ibrutinib + BR
• idelalisib + BR
Possible Future Treatment Options
Young, fit
• ibrutinib + FCR
• ibrutinib + CD20 mAb
• venetoclax + CD20 mAb
• ibrutinib + venetoclax (+/- CD20 mAb)
• 2nd generation NA combinations
Older, frail
• BR (IGHV mutated only)
• ibrutinib +/- CD20 mAb
• venetoclax + CD20 mAb
• ibrutinib + venetoclax (+/- CD20 mAb)
• 2nd generation NA combinations
• ibrutinib +/- CD20 mAb
• venetoclax +/- CD20 mAb
• idelalisib +/- rituximab
• 2nd generation NA combinations
• CAR-T
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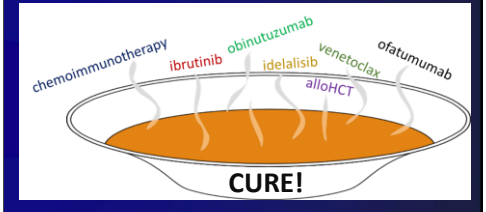
Davids, 2017 ASH Education Book

Conclusions

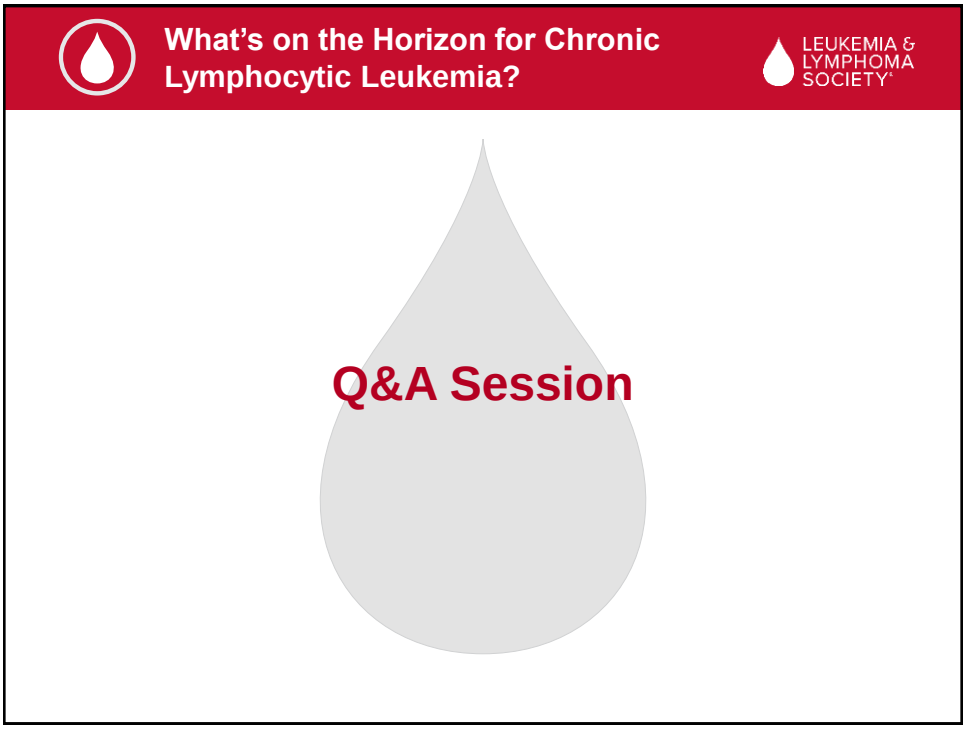
- We have reached the end of the beginning of the NA era
- We now have a powerful toolkit of NAs, with more coming
- Sequencing should be guided by patient characteristics, prognostic markers, and response to prior therapy
- NA monotherapy may be appropriate for frail patients
- Fit patients (especially those with high risk markers) should consider combination therapy
- Active participation in clinical trials is critical

Combination chemotherapy can cure hematologic malignancies



Adapted from DeVita and Chu, *Cancer Res*, 2008

Questions?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LEUKEMIA & LYMPHOMA SOCIETY
Q&A Session

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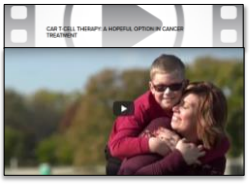
- **Information on leukemia:** For information about chronic lymphocytic leukemia, visit www.LLS.org/leukemia
- **Patti Robinson Kaufmann First Connection Program:** Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition
- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask
- **Support Resources**: LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support




THANK YOU FOR PARTICIPATING!
We have one goal:
A world without blood cancers
LEUKEMIA & LYMPHOMA SOCIETY