Low grade Non-Hodgkin Lymphoma: New Therapies & Updates

Craig A. Portell MD
Assistant Professor of Medicine
Division of Hematology/Oncology
University of Virginia

Friday, April 28, 2017

Disclosures

- I have no personal financial relationships or interests with any proprietary entity producing healthcare goods/or services
- I do have research funding from below:
  - AbbVie: investigator initiated trial
  - AbbVie/Roche/Genentech: Institutional PI on industry sponsored trial
  - Infinity: Institutional PI on industry sponsored trial
  - Acerta: Intuitional PI on industry sponsored trial
  - TG Therapeutics: Institutional PI on industry sponsored trial
- I have received support from:
  - Lymphoma Research Foundation
- I will be discussing non-FDA approved treatments and off-label treatments

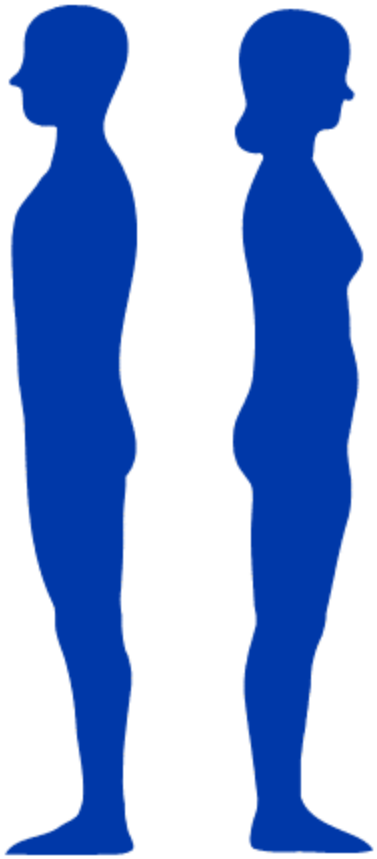
Outline

- Overview of indolent Non-Hodgkin Lymphomas
- Controversies in follicular lymphoma
  - Best front-line therapy?
  - Maintenance rituximab after Bendamustine?
  - Will chemotherapy become obsolete?
- New up-dates in Marginal Zone lymphoma
- Ibrutinib in Mantle cell lymphoma: the good and the bad

Overview of NHL

Estimated New Cancer Cases* in the US in 2017

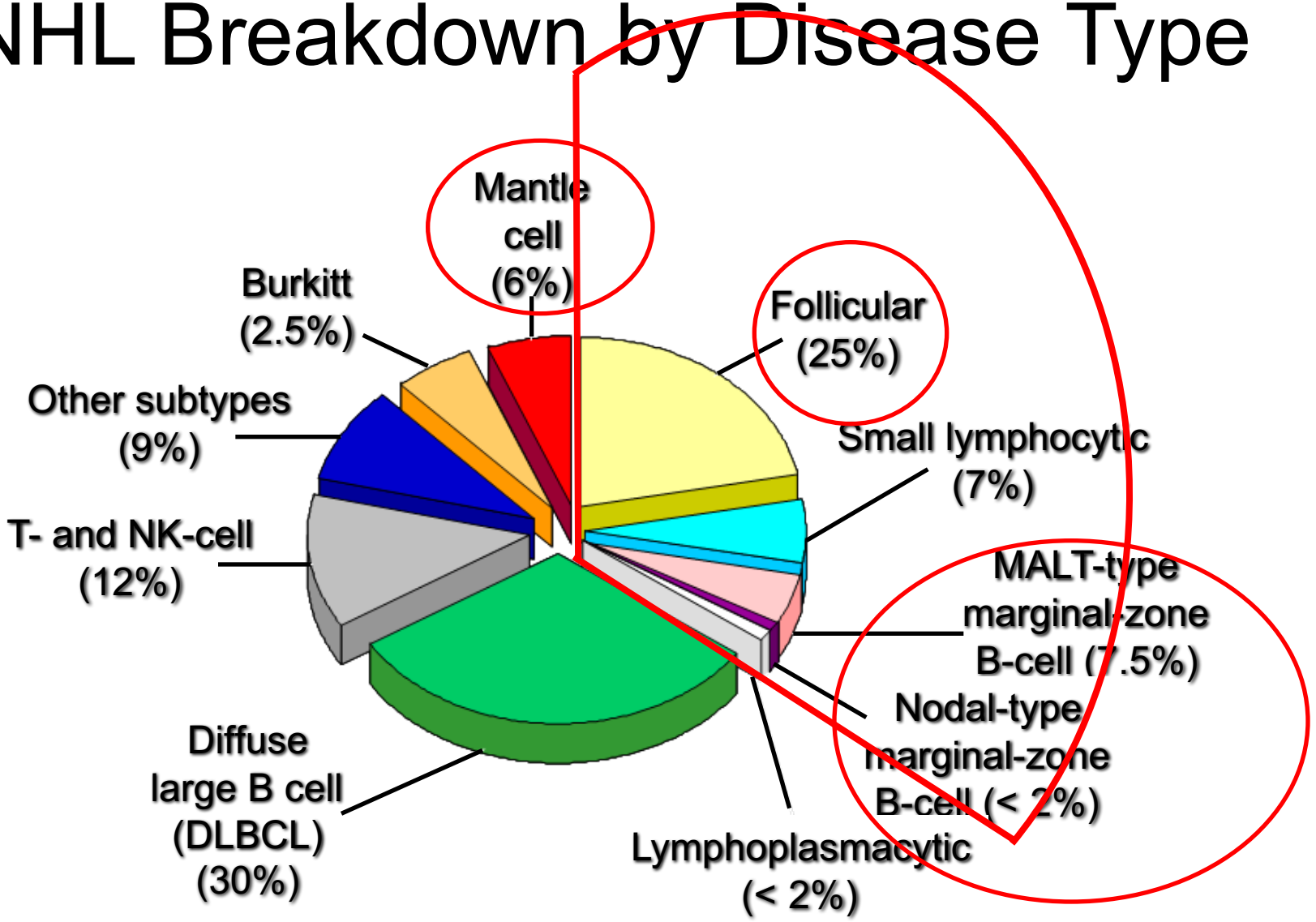
Males 836,150		Females 852,630	
Prostate	19%	30%	Breast
Lung & bronchus	14%	12%	Lung & bronchus
Colon & rectum	9%	8%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	6%	5%	Thyroid
Kidney & renal pelvis	5%	4%	Melanoma of skin
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Leukemia	4%	3%	Leukemia
Oral cavity & pharynx	4%	3%	Pancreas
Liver & intrahepatic bile duct	3%	3%	Kidney & renal pelvis
All other sites	23%	22%	All other sites



72,000 new cases of NHL per year (stable)
60% indolent NHL
20,000 deaths per year from NHL (declining)

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

NHL Breakdown by Disease Type



Lichtman MA. *Williams Hematology, 7th Ed*. The McGraw-Hill Companies;2006;1408..

Follicular lymphoma

Frontline treatment

FL: frontline treatment considerations

- Asymptomatic, low tumor burden
  - Observation is still reasonable
  - Single agent rituximab also reasonable
    - No maintenance per RESORT study
- Symptomatic or high tumor burden
  - Single agent rituximab per SAKK 35/03 study
    - 4 weekly doses followed by 4 every other month doses
    - 40% did not go to maintenance
  - Chemo-immunotherapy

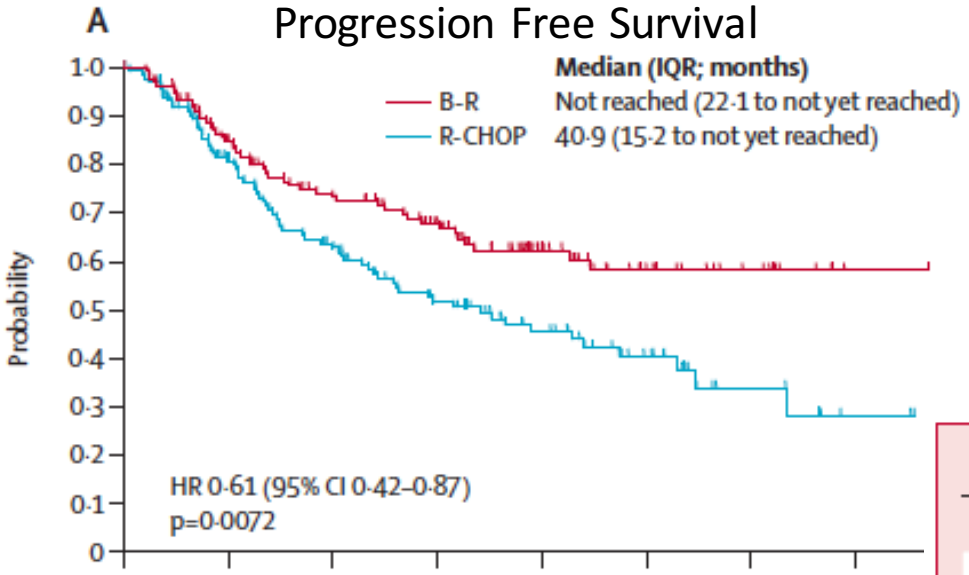
GELF Criteria

- Involvement of 3 nodal sites, each with a diameter of 3cm
- Any nodal of extranodal tumor mass with a diameter of 7cm
- B symptoms
- Splenomegaly
- Effusions or ascites
- Cytopenias (WBC <1 or Platelelts <100)
- Leukemia (>5K malignant cells)

RESORT: Kahl et al, JCO 2014
SAKK: Taverna JCO 2016

Chemoimmunotherapy

- Before ASH 2016: STiL Study of BR vs. RCHOP



We generally feel that BR is superior to RCHOP for PFS and improved safety

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: **All grades of non-haematological toxic events in patients receiving at least one dose of study treatment**

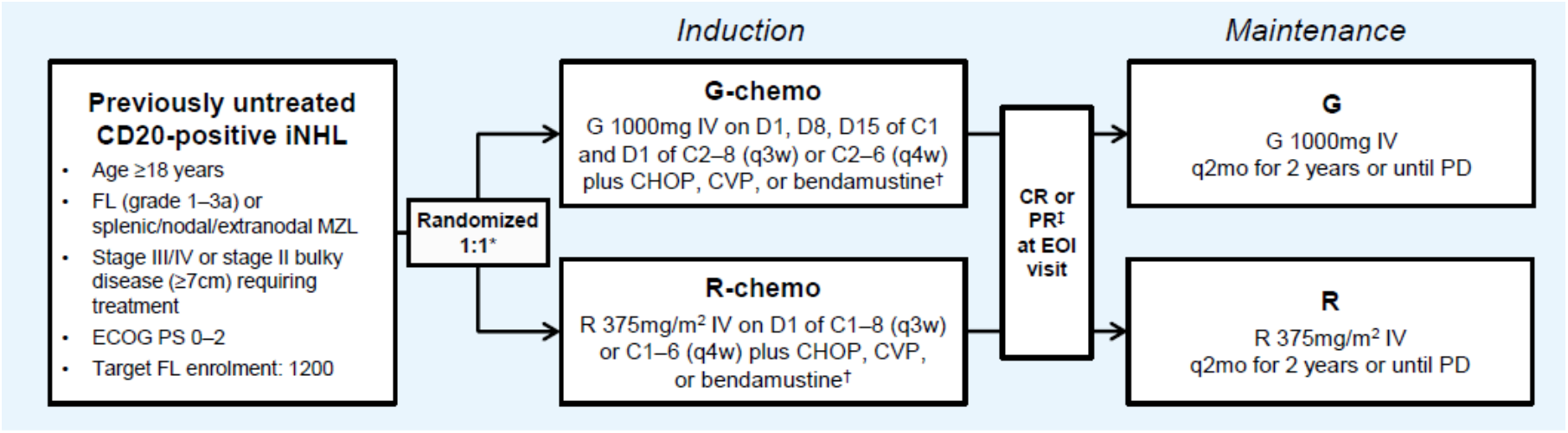
Rummel, Lancet 2015

Bendamustine and rituximab

- Became the standard
- BR vs. RCHOP study showed us that BR is safer during treatment
- BUT Growing concern in community about later, odd infections occurring after BR
- Newer CD20 monoclonal antibodies are being developed
  - Obinutuzumab, type II glycoengineered monoclonal Ab
    - Increased direct cell kill
    - Increased effector mediated cell kill
    - Decreased complement mediated cell kill

GALLIUM study

- Phase III randomized study of Obinutuzumab + chemo vs. rituximab + chemo in front line iNHL



Primary endpoint

- PFS (INV-assessed in FL)

Secondary and other endpoints

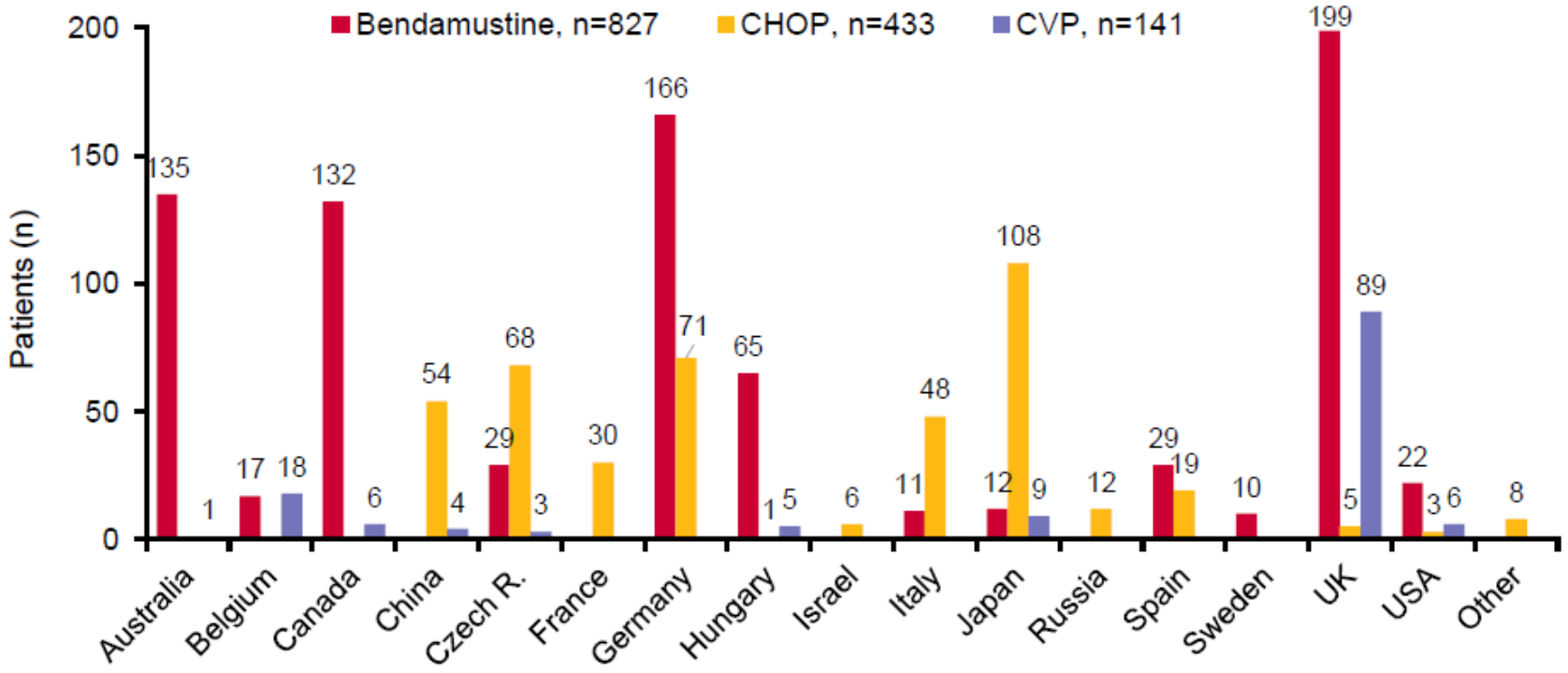
- PFS (IRC-assessed)§
- OS, EFS, DFS, DoR, TTNT
- CR/ORR at EOI (+/− FDG-PET)
- Safety

Note there is about double the amount of obinutuzumab as rituximab given

Marcus R, ASH 2016

GALLIUM Cont

- Allowed 3 different chemotherapy backbones
  - Sites had to select which they would use



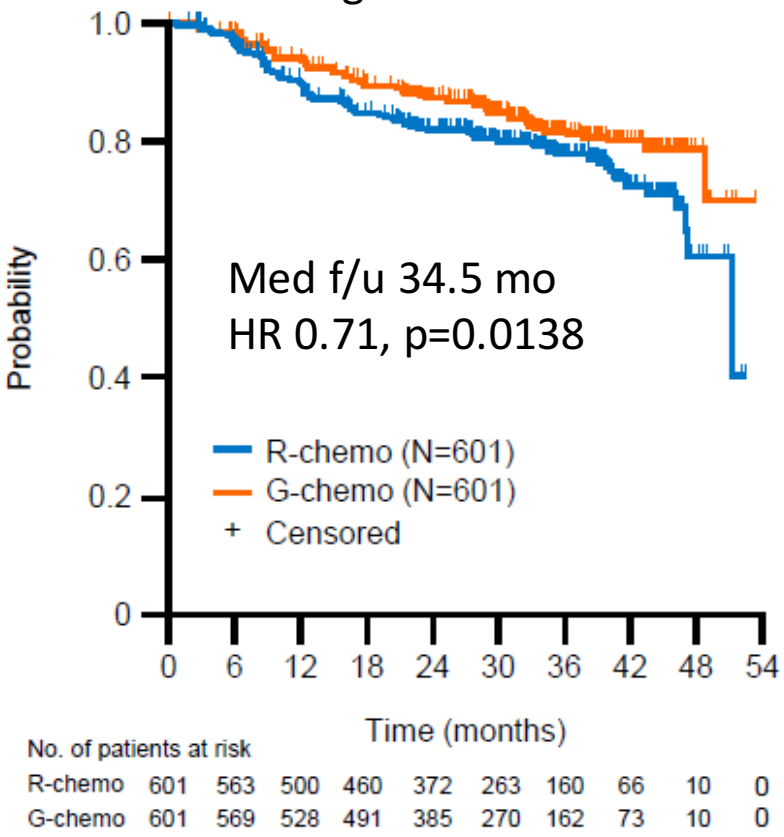
Marcus R, ASH 2016

GALLIUM, Follicular

Response after treatment

% (n)	Ritux-chemo (n=601)	Obinu-Chemo (n=601)
ORR	86.9 (522)	88.5 (532)
CR	23.8 (143)	19.5 (117)
PR	63.1 (379)	69.1 (415)
SD	1.3 (8)	0.5 (3)
PD	4 (24)	2.3 (14
UNK	7.8 (47)	8.6 (52)

Progression free survival



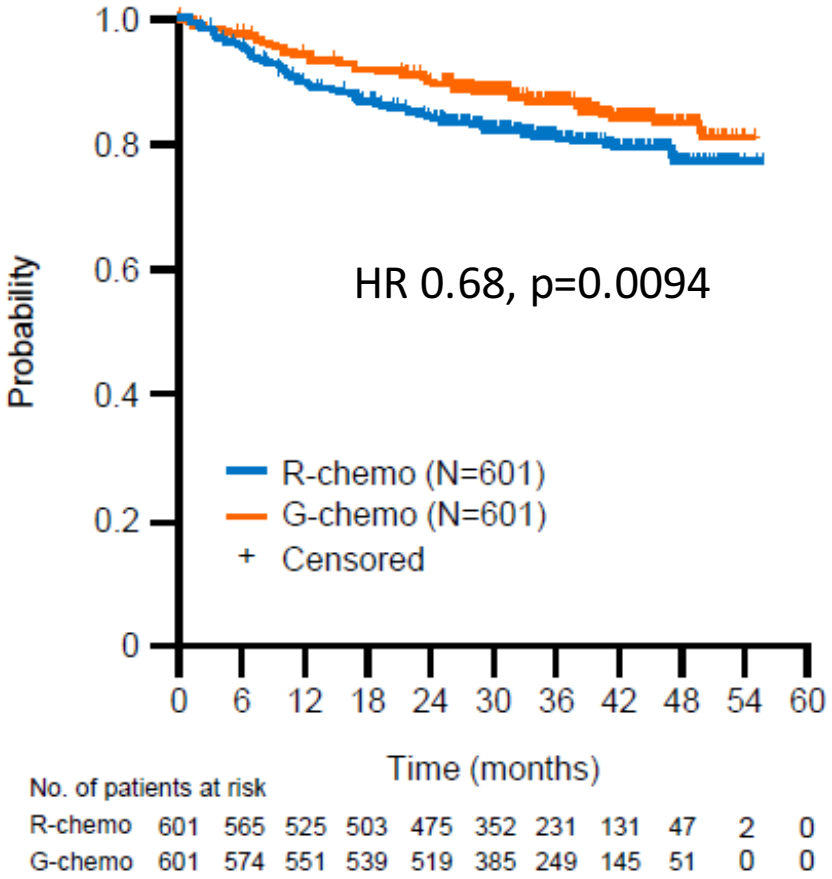
3 yr PFS 77.9 vs. 81.9 %

Marcus R, ASH 2016

GALLIUM, Follicular

University of Virginia Health System | Cancer Center

Time to next treatment

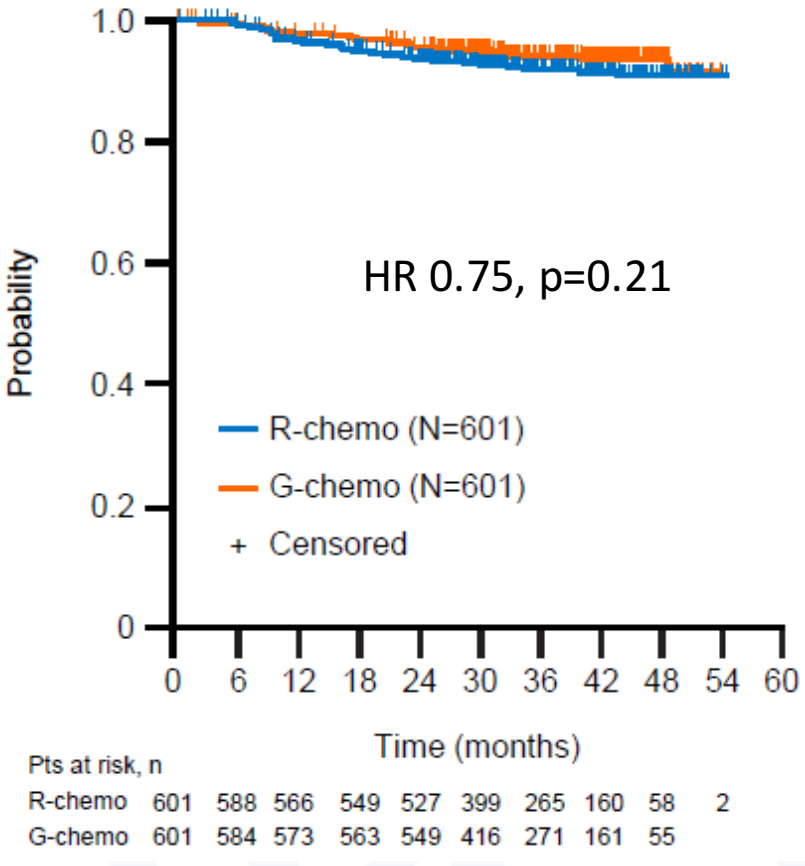


No. of patients at risk

R-chemo	601	565	525	503	475	352	231	131	47	2	0
G-chemo	601	574	551	539	519	385	249	145	51	0	0

3 yr TTNT 81.2 vs. 87.1 %

Overall survival



Pts at risk, n

R-chemo	601	588	566	549	527	399	265	160	58	2
G-chemo	601	584	573	563	549	416	271	161	55	

3 yr OS 92.1 vs. 94.0%

Marcus R, ASH 2016

Obinutuzumab

- The costs (obinu vs. ritux):
  - Increased febrile neutropenia (6.9 vs 4.9%)
  - Increased infections (20 vs. 15.6%)
  - Increased infusion related reactions (12.4 vs. 6.7%)
  - Increased fatal AEs (4 vs. 3.4%)
    - Per chemo regimen
      - Benda (5.6 vs. 4.4%)
      - CHOP (1.6 vs. 2.0%)
      - CVP (1.6 vs. 1.8%)

Marcus R, ASH 2016

- Thus, obinutuzumab appears to be more active but more toxic
- Questions remain
  - Is it safe with bendamustine?
  - Could ritux be as effective with the same dosing schedule?

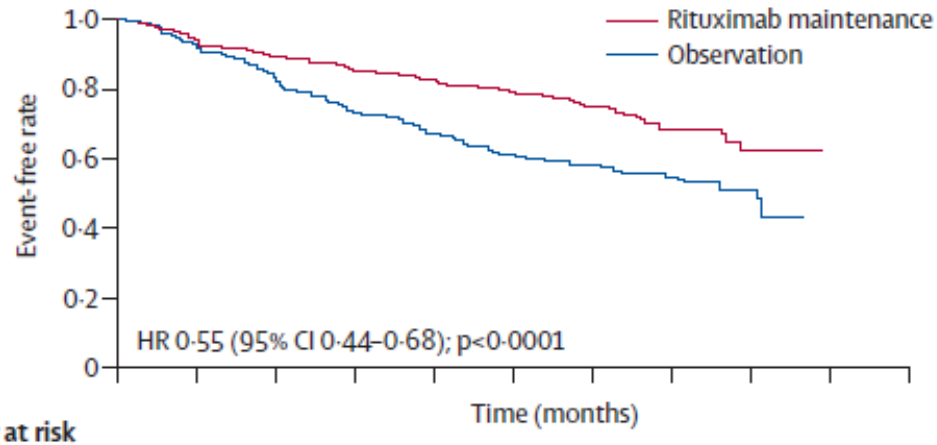
Follicular lymphoma

Maintenance rituximab after bendamustine

Maintenance rituximab

- Based on results of the PRIMA study
  - Restricted to high tumor burden
  - Bendamustine induction not included in PRIMA study
    - Induction regimens included
      - RCHOP (75.5%)
      - RCVP (21.8%)
      - RFCM (2.8%)

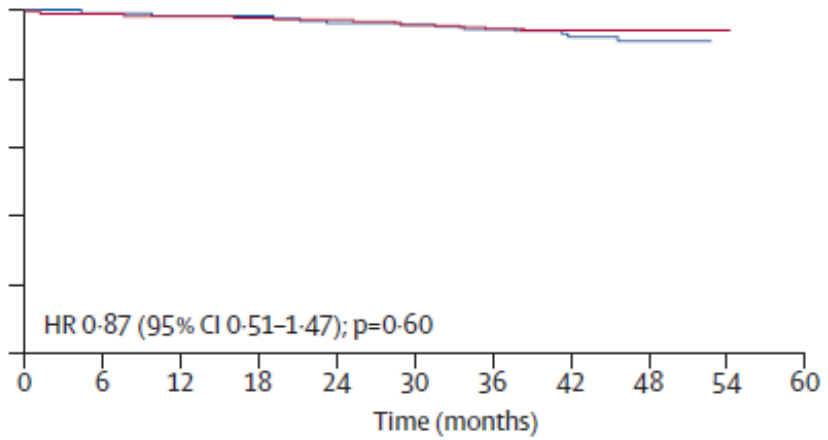
PFS



Number at risk

Rituximab	505	472	445	423	404	307	207	84	17	0
Observation	513	469	415	367	334	247	161	70	16	0

OS

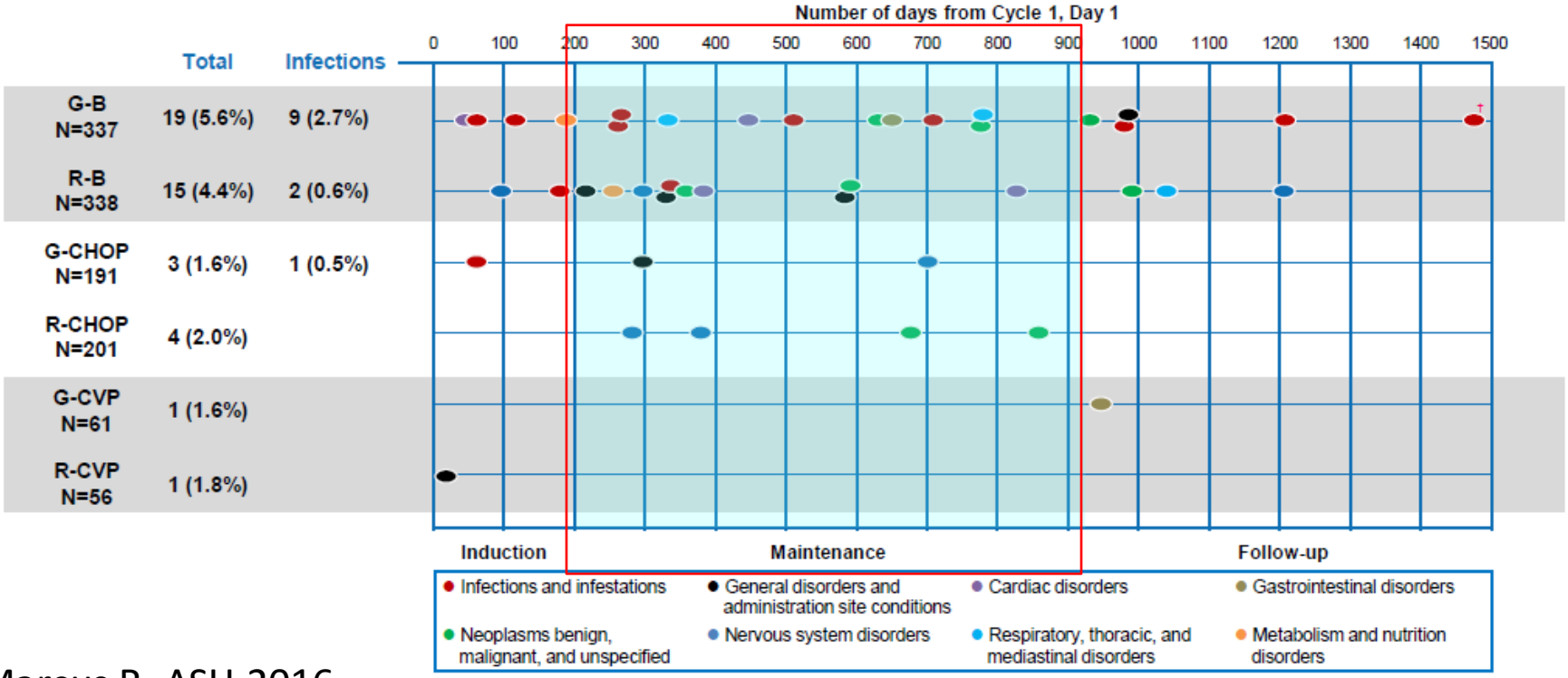


	505	499	492	483	474	365	246	108	22	1
	513	507	501	492	472	381	243	97	26	0

Salles, G, Lancet 2011

Maintenance rituximab

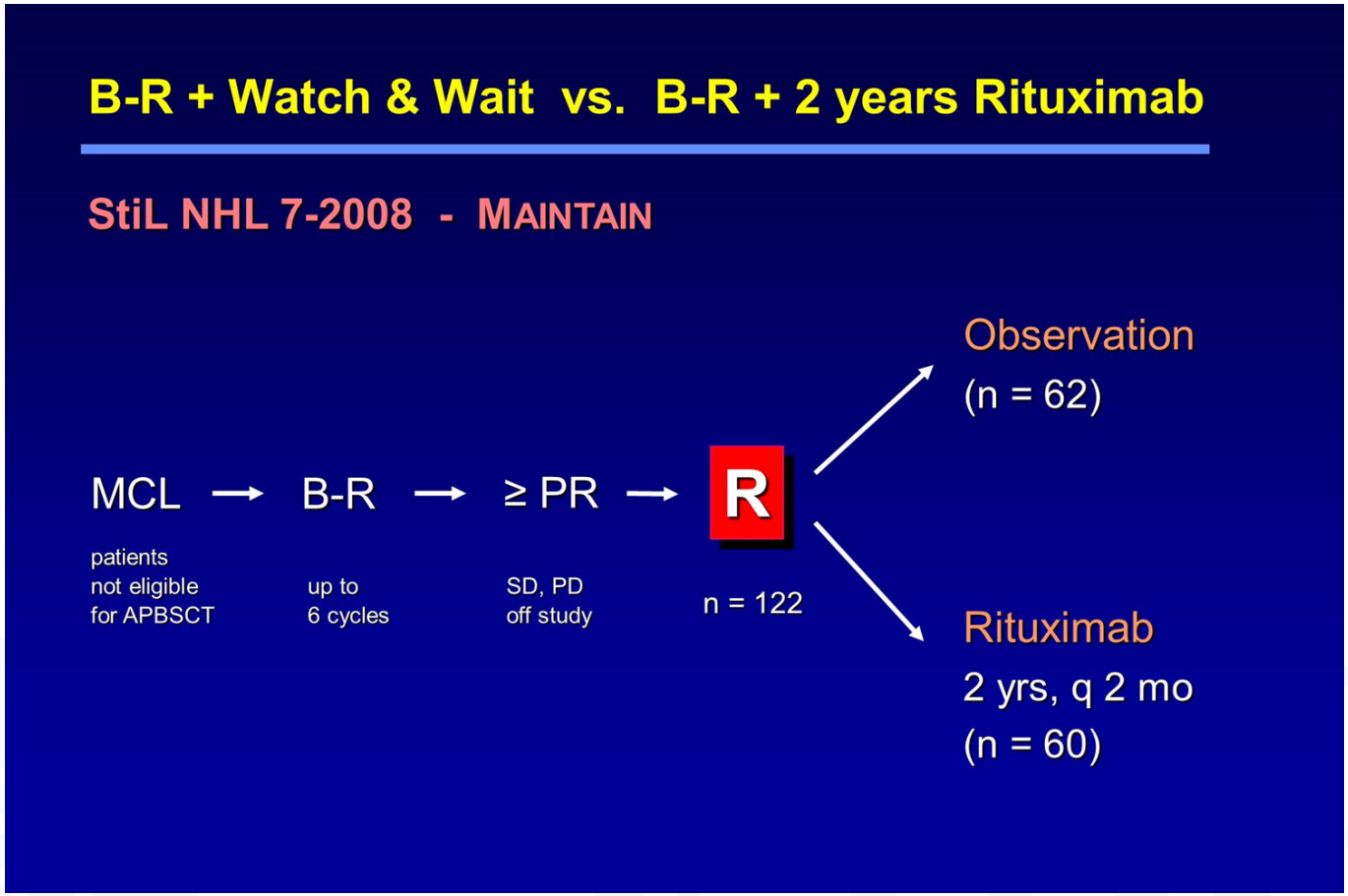
- Many of us, myself included, have extended this to bendamustine induction
  - Though it is a discussion without an OS benefit.
- BUT, the increased risk of infections with bendamustine has caused some speculation
- Back to the GALLIUM data, fatal AEs on study:



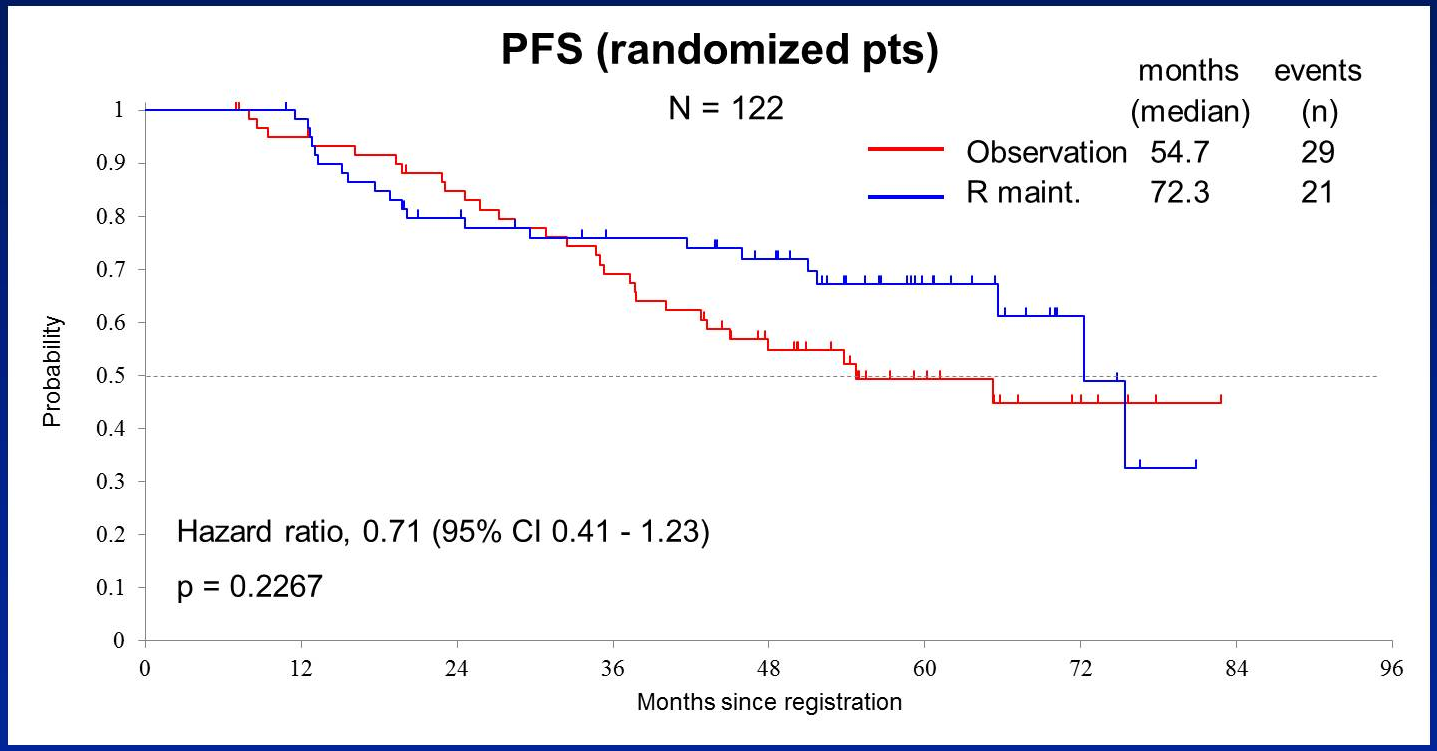
Marcus R, ASH 2016

Maintenance after Bendamustine

- In elderly Pts with MCL, there was a small study out of Germany
  - 122 Pts responding to BR were randomized to observation or R-maintenance



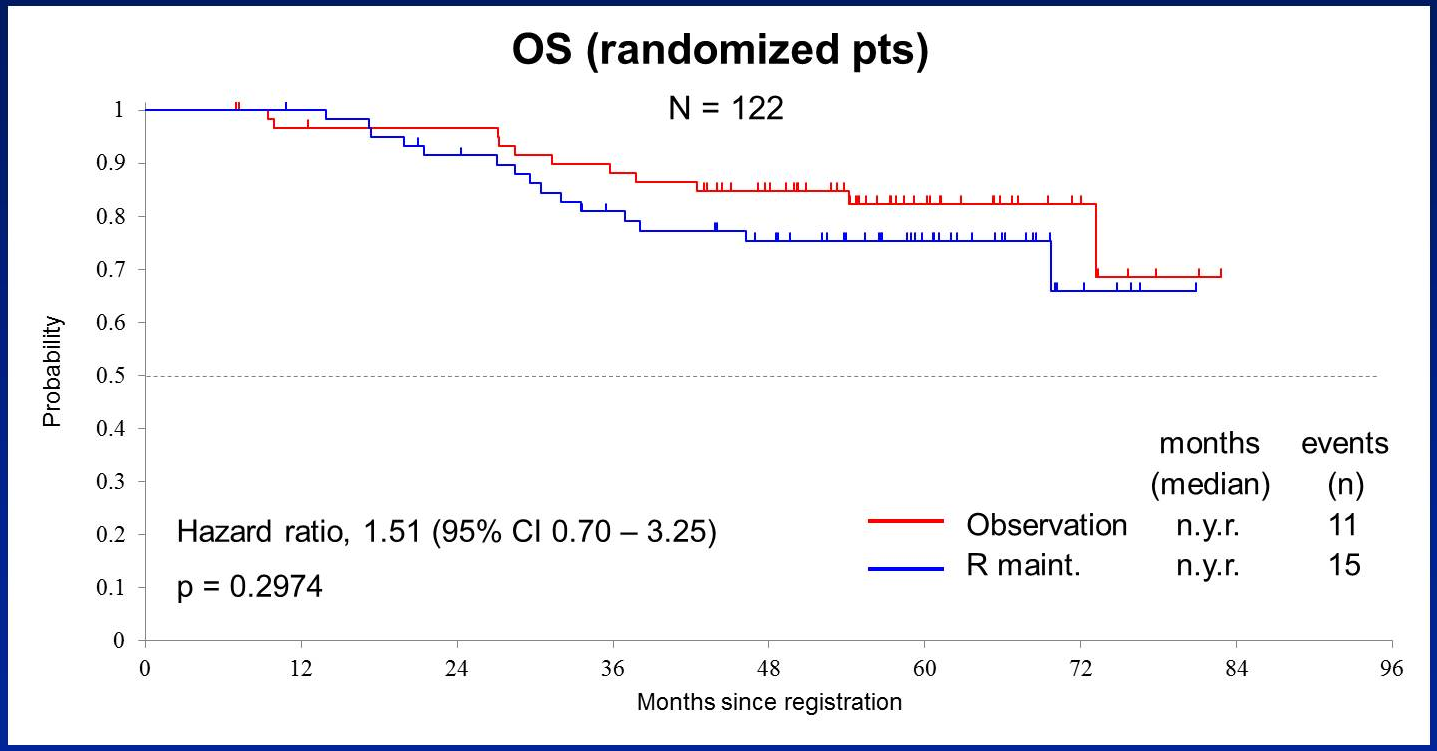
Progression free survival (58.6 months median follow-up)



Pts at risk							
Observ	62	57	49	40	26	13	5
R maint	60	58	45	39	24	18	5

Overall survival

(58.6 months median follow-up)



Pts at risk							
Observ	62	58	57	52	43	21	8
R maint	60	59	53	44	38	23	5

Causes of death

	R-maintenance n = 60	Observation n = 62
OS events, n (%)	15 (25%)	11 (18%)
– Lymphoma	10 (67%)	2 (18%)
– Infection	4 (27%)	2 (18%)
– Cardial reasons	-	3 (27%)
– Secondary malignancy	-	1 (9%)
– Suicide	1 (7%)	-
– Accident	-	1 (9%)
– Other / unknown	-	2 (18%)

15 deaths in R-maintenance arm: only 1 completed 2 yrs, 9 stopped early due to progression

Median of 4 administered Rituximab cycles in these 15 patients

10 lymphoma deaths: 8 have stopped R-maintenance because of disease progression

MJR

R maintenance after Benda

- Thus
  - There are some concerns of toxicity after bendamustine
  - Prolonged immunosuppression may make this worse
  - At least in MCL, in a small cohort of patients, there is no benefit to Rituximab maintenance after BR.

- So
  - I've still been recommending rituximab maintenance after BR in follicular lymphoma
  - But not as strongly
    - Not if Pts are not tolerating rapid rituximab
    - VERY low threshold to stop

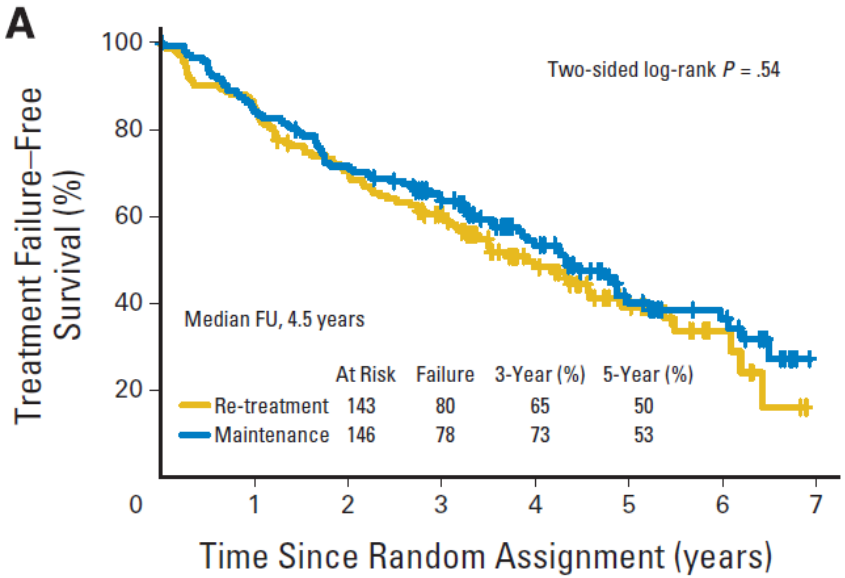
Follicular lymphoma

Will chemotherapy become obsolete?

Follicular lymphoma

In LOW tumor burden FL:

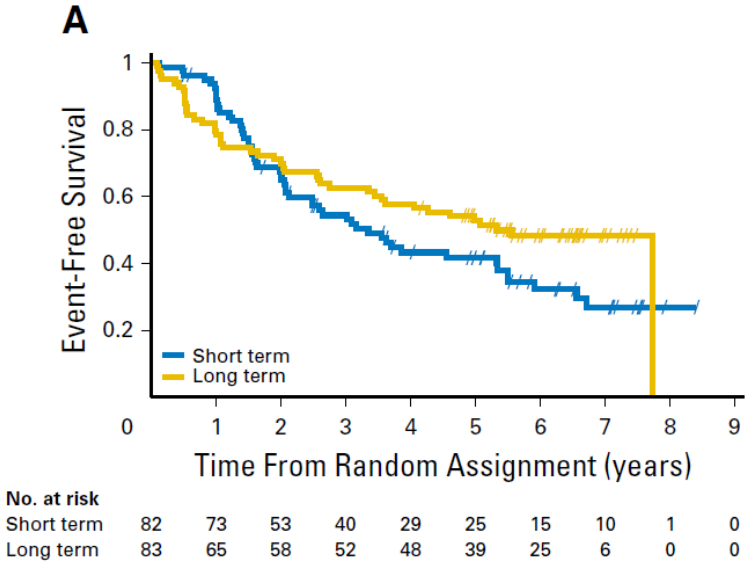
- Rituximab can be very helpful
  - 70% ORR (11% CR)
- Maintenance is not better than retreatment
  - TTF was the same 3.9 vs. 4.3 yrs



RESORT: Kahl et al, JCO 2014

In HIGH tumor burden FL:

- Rituximab can still be very helpful
  - 63% ORR (13% CR)*
- Short term maintenance is used
  - 4 doses every 2 months
  - EFS was not statistically different
    - 3.4 vs. 5.3 yrs (p=0.14)



*Note not all had high tumor burden

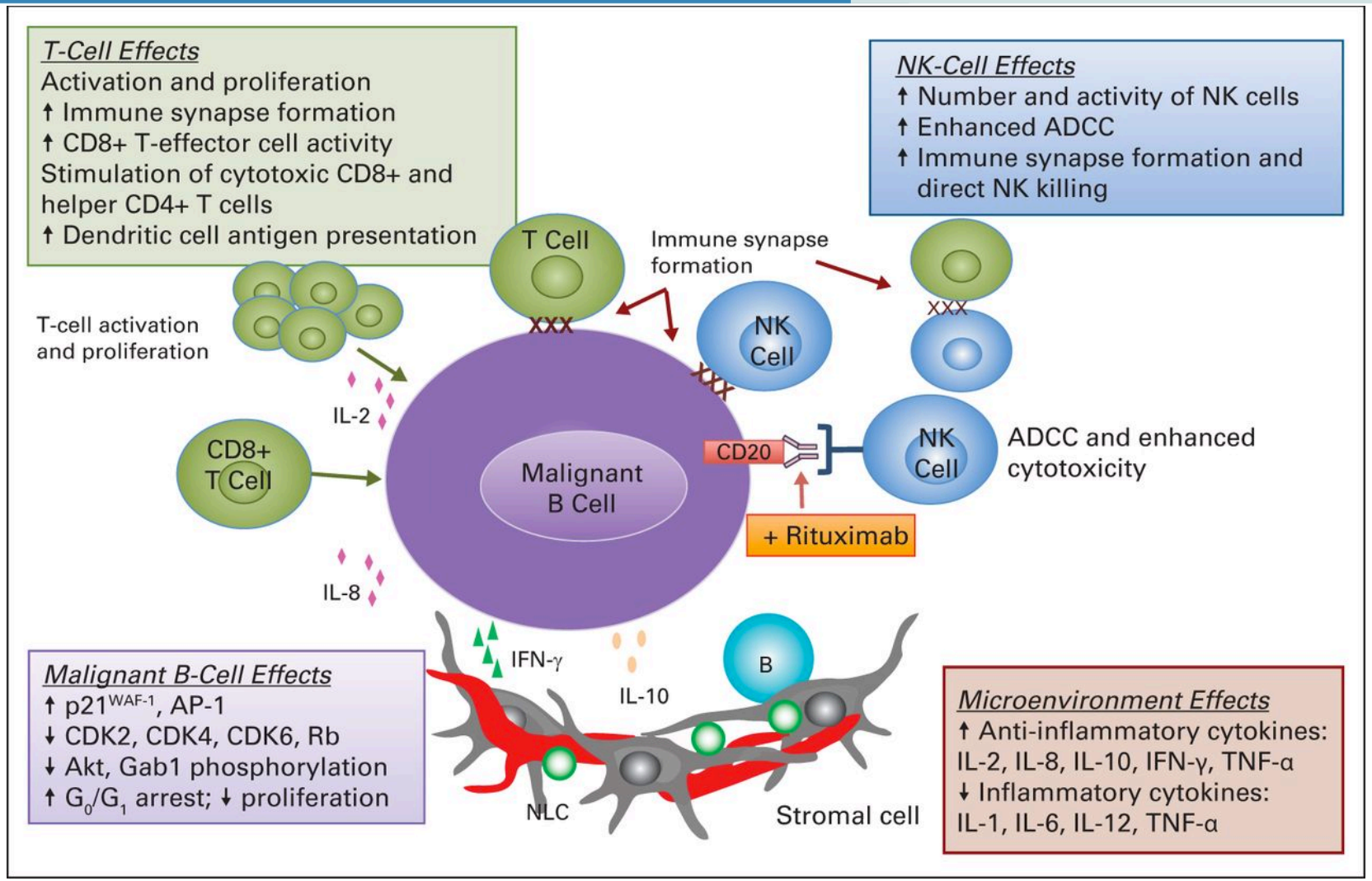
SAKK: Taverna JCO 2016

Follicular lymphoma

Chemotherapy is added to rituximab to get a quicker, more durable response

But, is there something else we can add to rituximab to improve it's efficacy?

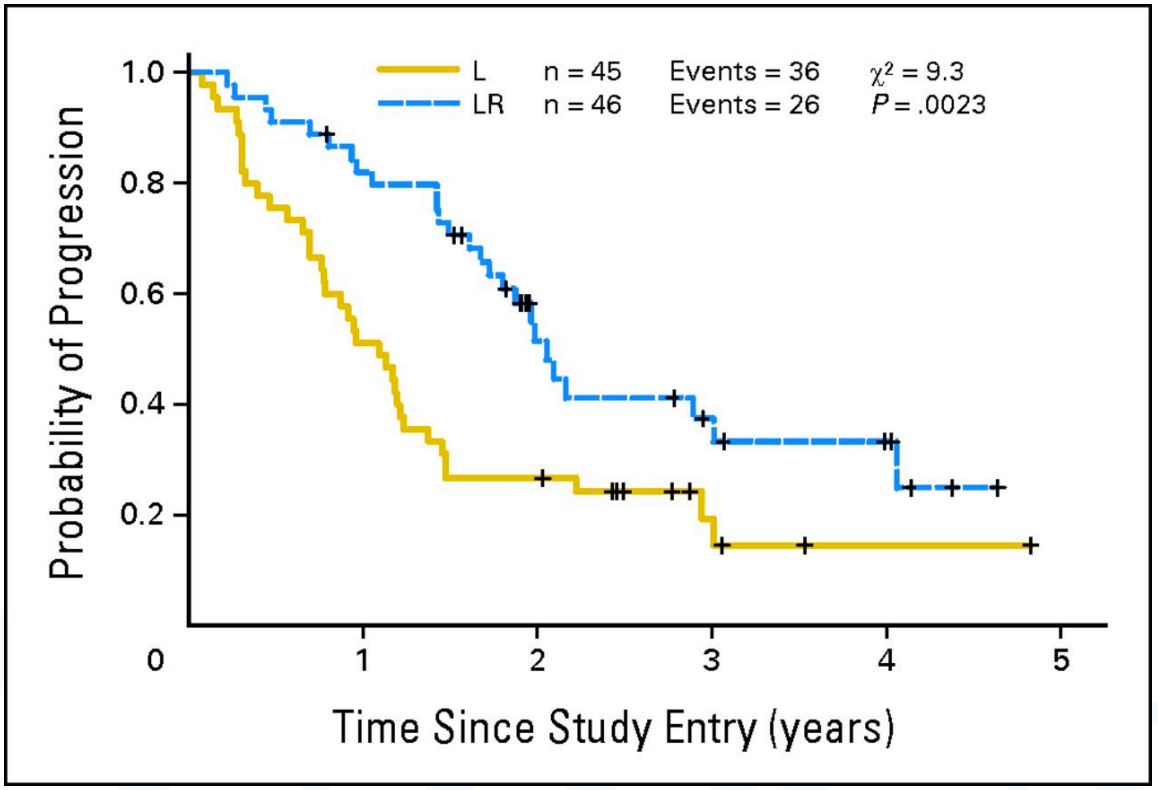
Lenalidomide Mechanism



Gribben JG JCO
2015

Follicular lymphoma-R2 CALGB

- Relapsed FL
- Randomized trial of rituximab+lenalidomide vs. lenalidomide alone
- N=91
- ORR 76 vs. 53%
- CR 18 vs. 9%

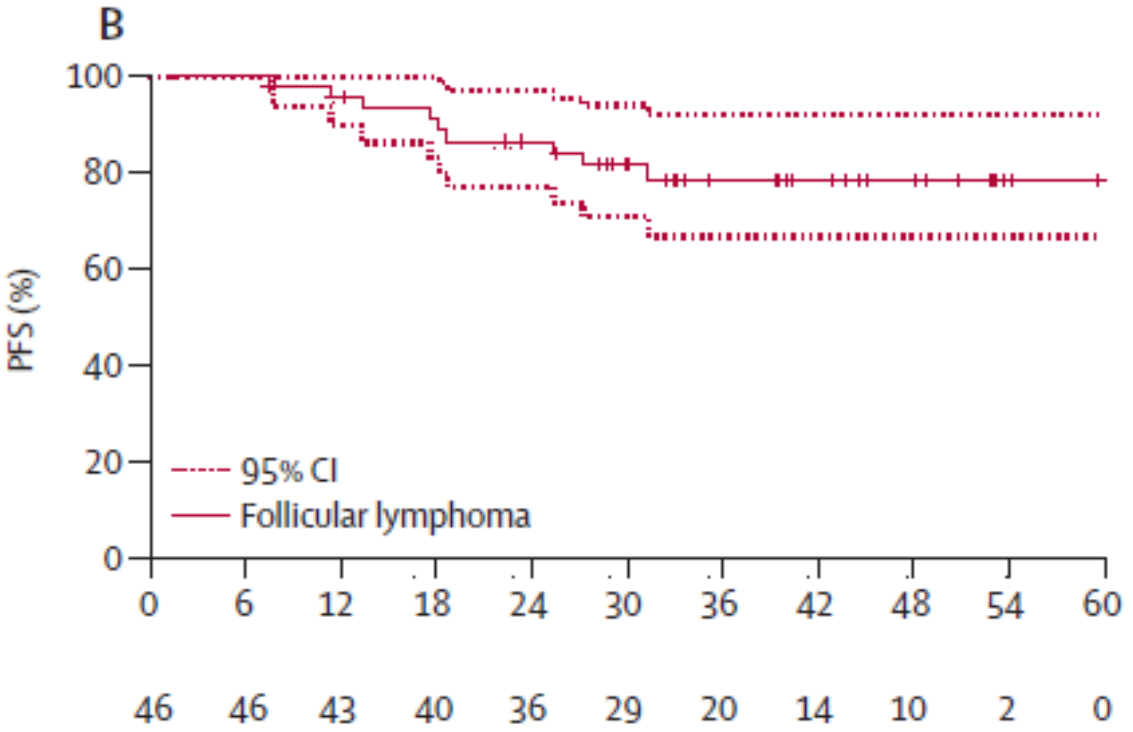


Leonard JP JCO 2015

Follicular lymphoma-R2 MDA

- Upfront FL (other histologyies included)
- Single arm Phase II study Len + Ritux
- N=50 (FL only), 46 evaluable for response
  - 54% with high tumor burden by GELF
  - ORR 98%
  - CR 87%
  - 3 year PFS 78.5%
- Len 20mg/day D1-21
- Ritux 375mg/m2 D1
- Treat for 12, 28-day cycles

3 year PFS for Gallium 77.9 vs. 81.9



Fowler NH Lancet Oncol 2014

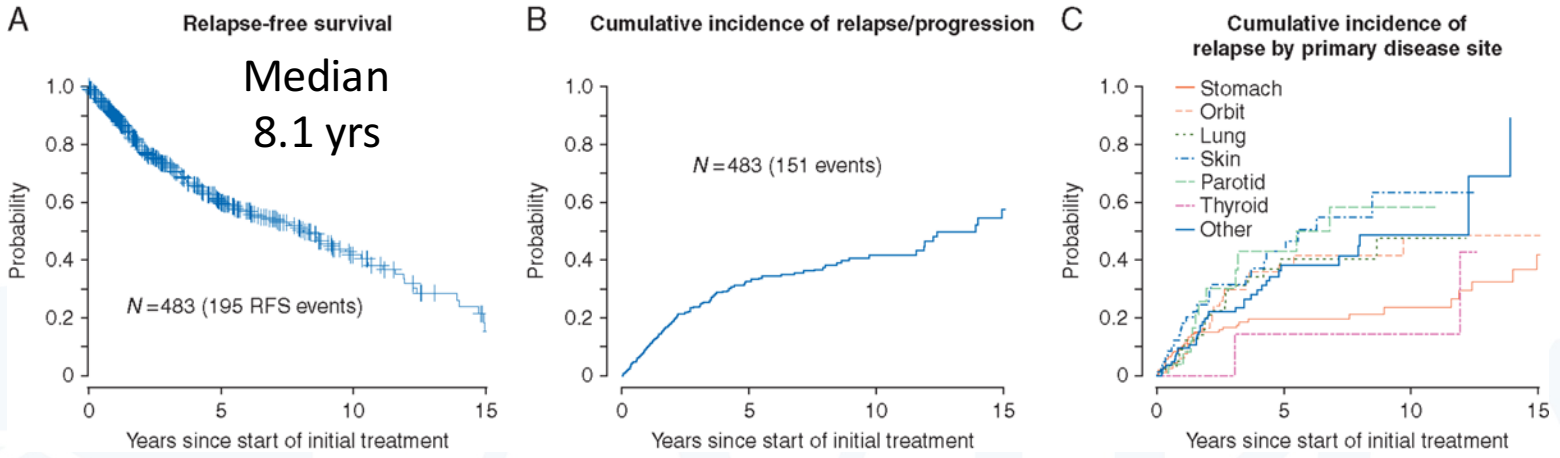
Len Ritux for FL

- Promising but not compared to chemoimmunotherapy
- All phase II studies with limited numbers
- There are Phase III studies which are accrued and/or ongoing but not reported
- I'm not using upfront but can use in relapsed setting.

What is new in Marginal Zone Lymphoma

Extranodal Marginal Zone Lymphoma

- Frontline therapy depends on situation
  - Gastric, H.pylori positive—eradication alone and surviellence
    - If returns, usually radiation
  - Gastric, H.pylori negative—usually try eradication, most need radiation
  - Non-Gastric: local therapy: radiation vs. surgery
- MSK retrospective study showed excellent outcomes.
  - Disease specific death at 5 yrs only 1.3%



Teckie Ann Oncol 2017 (epub)

Extranodal Marginal Zone Lymphoma

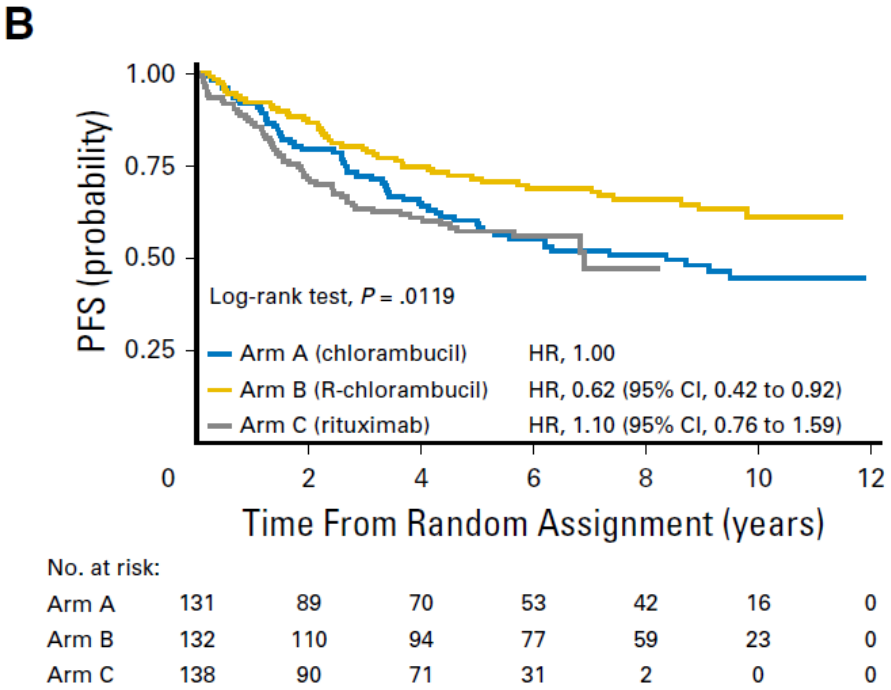
- What if local therapy is not indicated or fails
  - European group evaluated rituximab vs. Chlorambucil vs. ritux + Chlorambucil
    - Note they published ritux vs. ritux + chlorambucil earlier, showed benefit to combo.
    - New study just published adds ritux single agent as an arm
  - Includes MALT lymphoma, newly diagnosed or progressed after local therapy

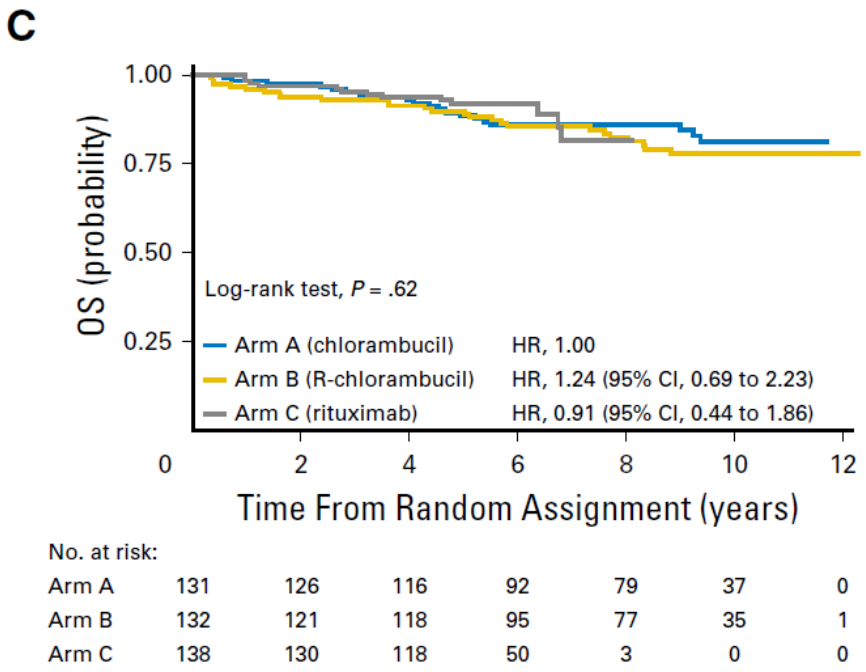
	Chlor (N=131)	Chlor + Ritux (n=132)	Ritux (n=138
ORR (%)	85.5	94.7	78.3
CR Rate (%)	63.4	78.8	55.8
5 yr PFS (%)	59	72	57
5 yr OS (%)	89	90	92

Zucca E, JCO 2017 (epub)

Extranodal Marginal Zone Lymphoma

- Chlorambucil given as 6mg/m2 PO x 42 days, then 6mg/m2 x 14 days every 28 days x 4 cycles
- Rituximab 375mg/m2 IV weekly x 4, then every 4 weeks x 4 cycles

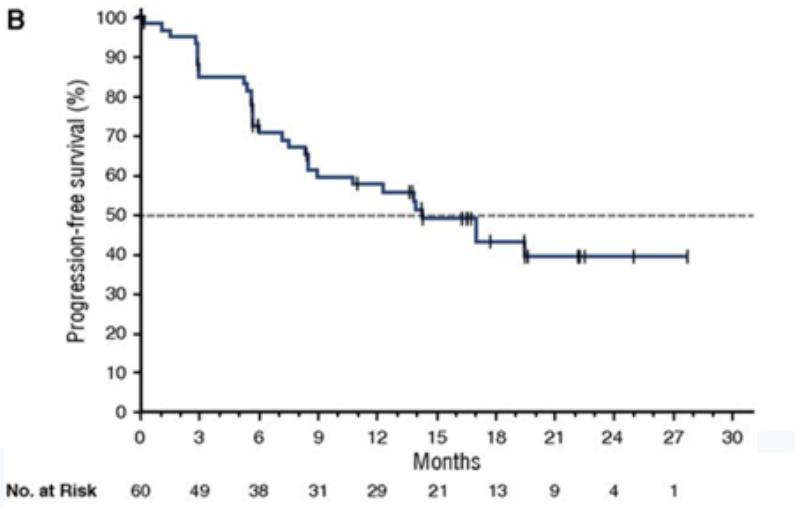


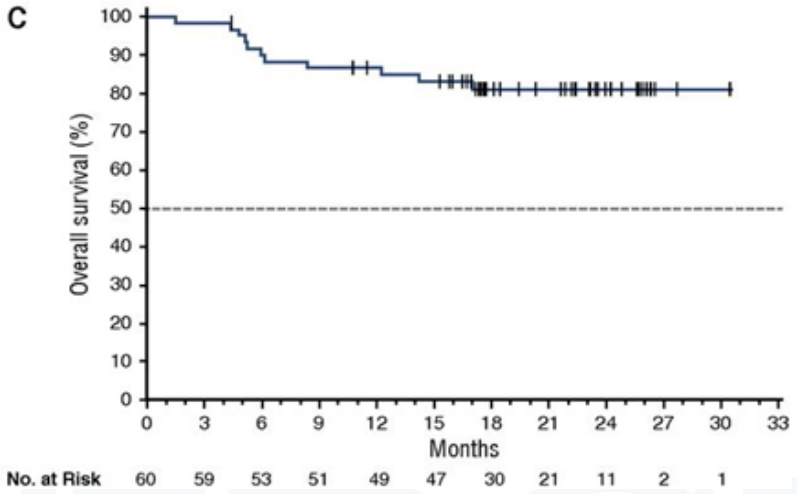


Zucca E, JCO 2017 (epub)

Relapsed

- Phase II study of ibrutinib 560mg daily
- All subtypes of MZL who received at least 1 line of CD20 directed therapy
- N=63 (32 extranodal, 14 splenic, 17 nodal)
- ORR 48%, no difference in subtypes





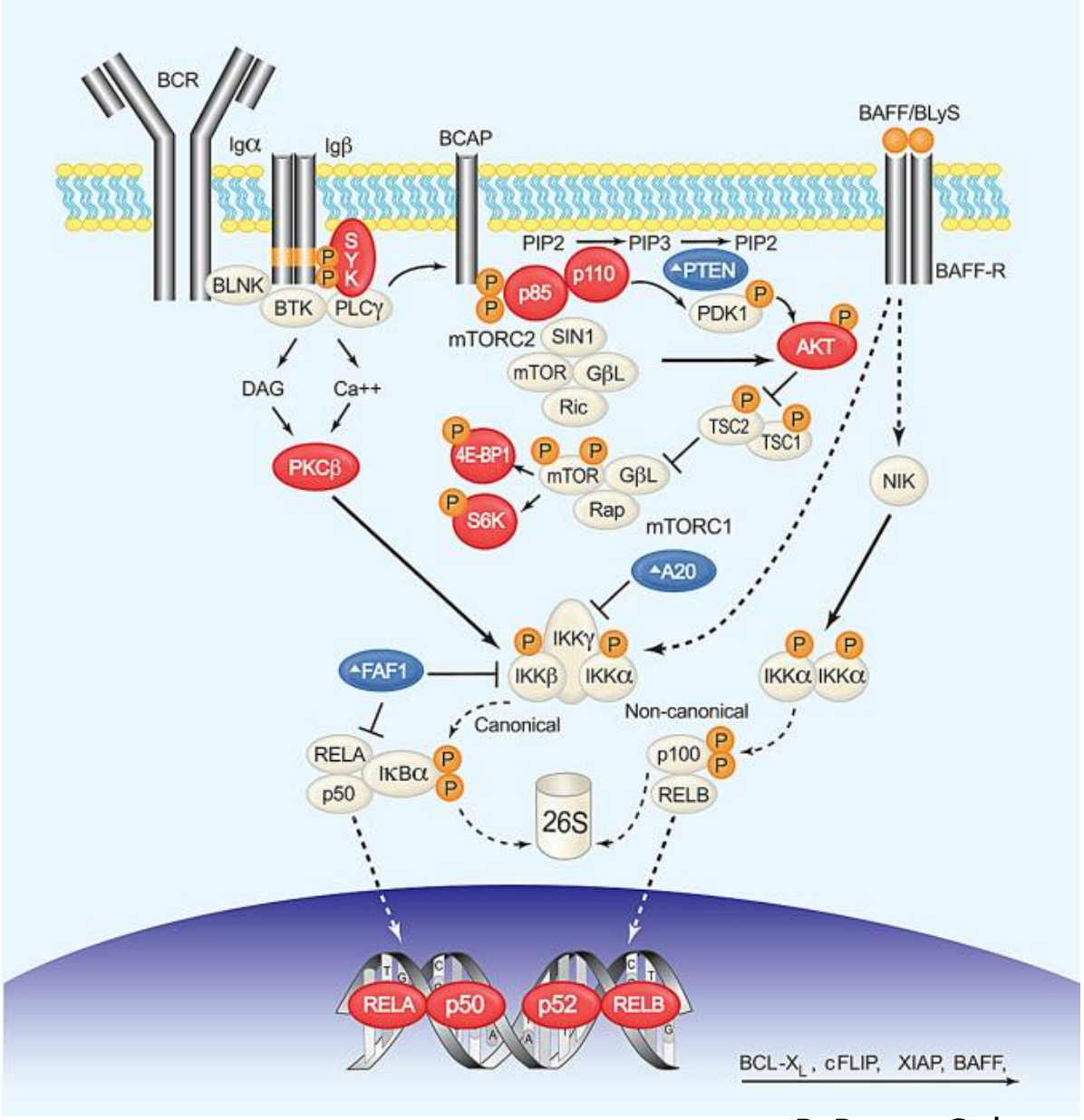
Noy A, Blood 2017

Ibrutinib in Mantle cell lymphoma

The Good and the Bad

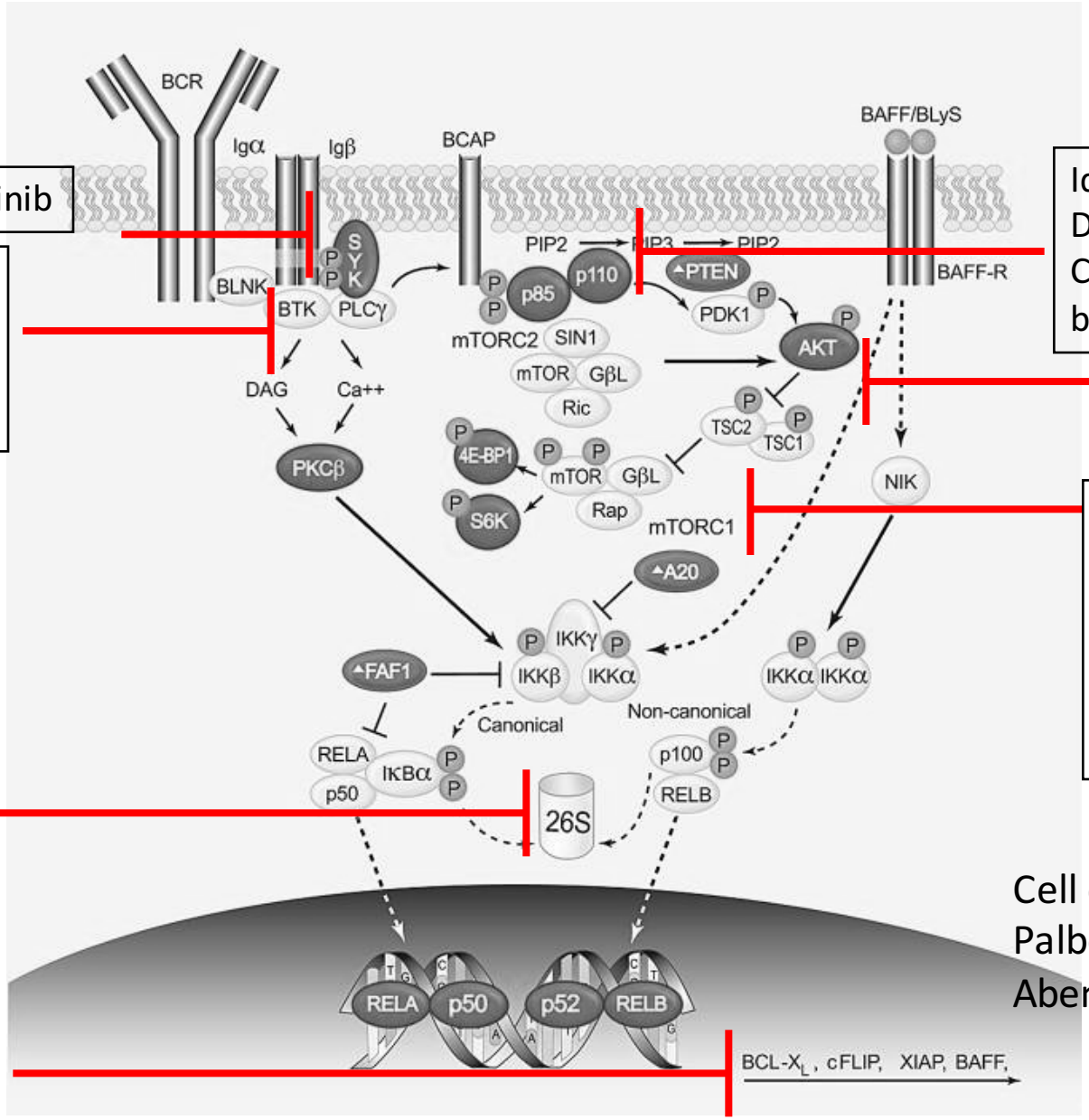
BCR, NF-kB, and PI3K/AKT/mTOR signaling pathways are dysregulated in MCL

- Overexpressed
- Down-regulated



P. Perez-Galan et al. Blood. 2011

BCR, NF-kB, and PI3K/AKT/mTOR signaling pathways: **Selected Inhibitors**



Fostamatinib

Ibrutinib
acalabrutinib
AVL-292
ONO-4059

Idelalisib
Duvelisib
Copanalisib
buparlisib

Perifosine

Everolimus
Temsirolimus
Rapamycin

OSI-027
(dual mTOR inh)

Bortezomib
Carfilzomib

Cell cycle:
Palbociclib
Abemaciclib

Venetoclax
Navitoclax
Obatoclax

Modified from P. Perez-Galan et al. Blood. 2011

Ibrutinib—The good

- Single agent ibrutinib

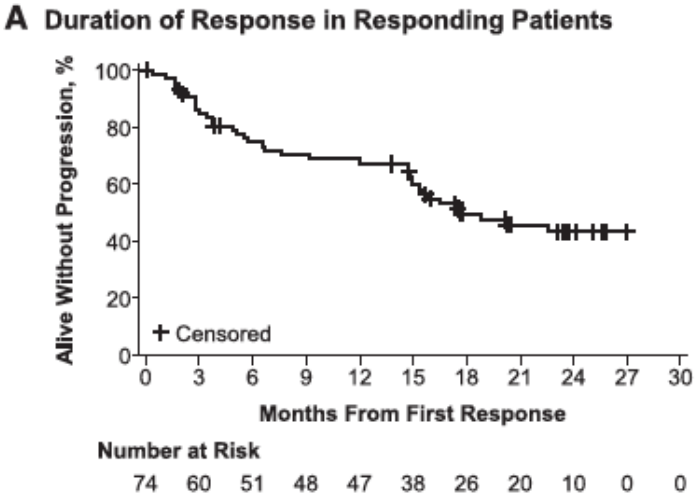
MCL update

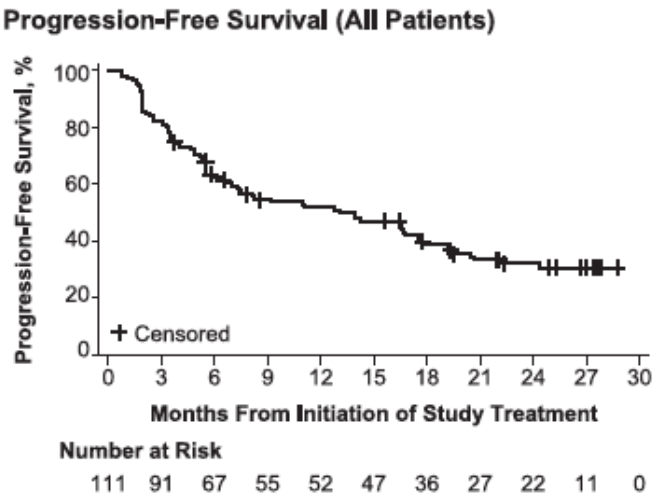
26.7 mo median follow up

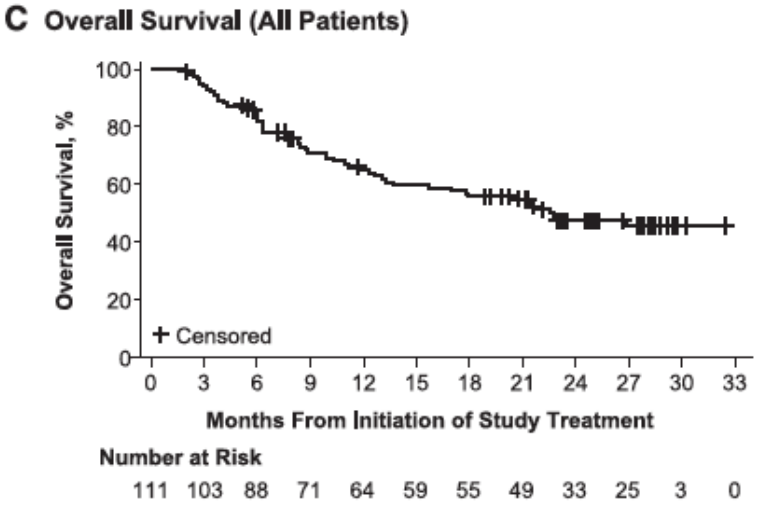
ORR 67%

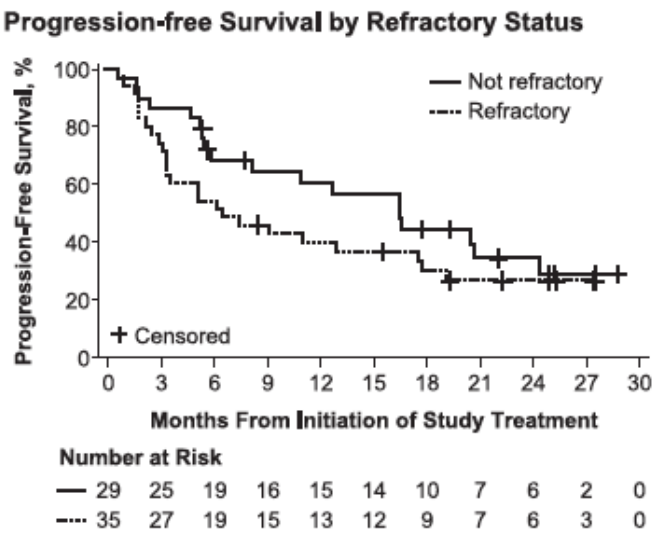
CR rate 23%

DOR 40% at 2 years





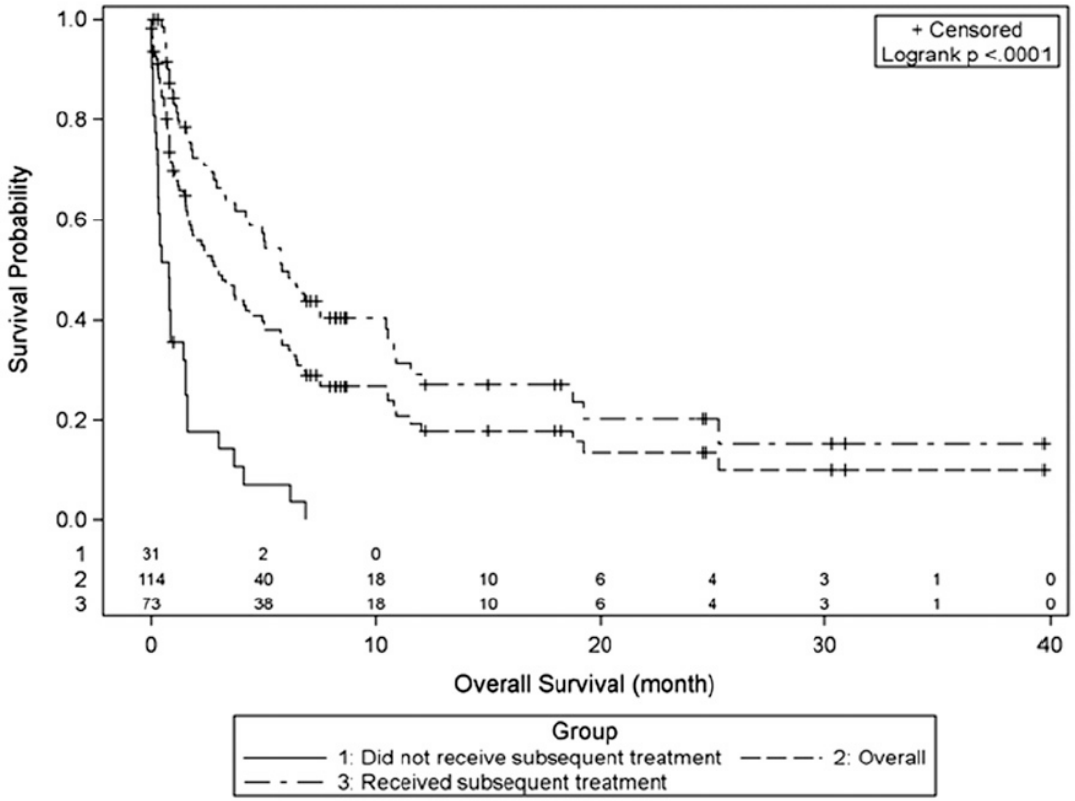




Wang M Blood 2015

Ibrutinib—The bad

- Multicenter cohort (including UVA)
- N=114 pts
- All progressed while on ibrutinib
- Median time on ibrutinib was 4.7 months
- Median OS after stopping ibrutinib was 3 months



Ibrutinib is very active in MCL BUT

- 30% of patients will not respond
- Failures are very difficult to salvage

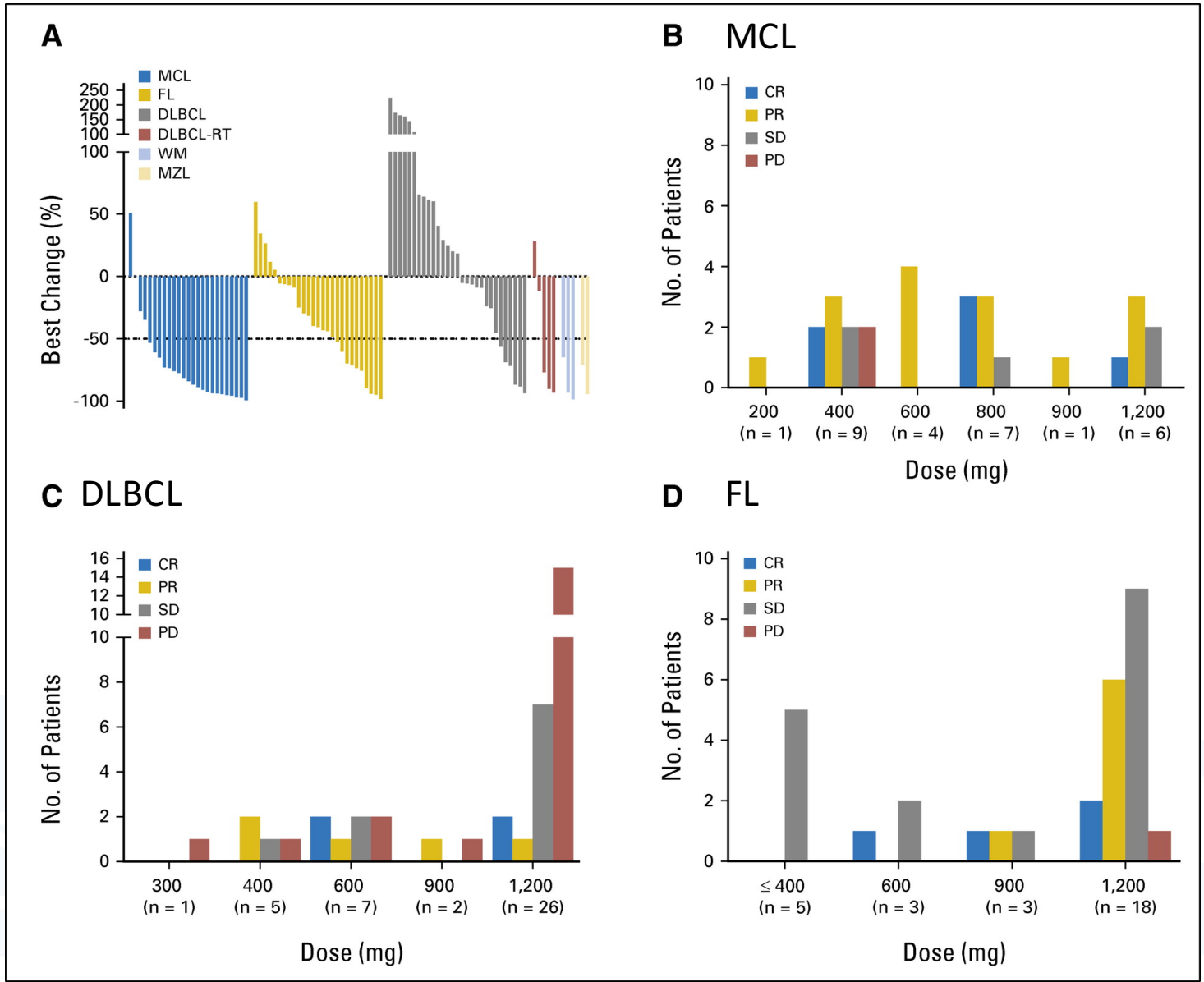
Our preference is clinical trial

Martin P Blood 2016

Venetoclax (ABT-199/ GDC-199)

- Oral Bcl-2 inhibitor with potent therapeutic activity
  - **Requires TLS precautions and monitoring**
- Highly active in very poor-risk CLL
  - **R/R del(17p) CLL**
  - **Fludarabine-refractory CLL**
- Has activity in B-NHL
  - **Less than expected in Follicular lymphoma**
- Combinations under study
  - **Veneto plus ibrutinib in trials for MCL and CLL**

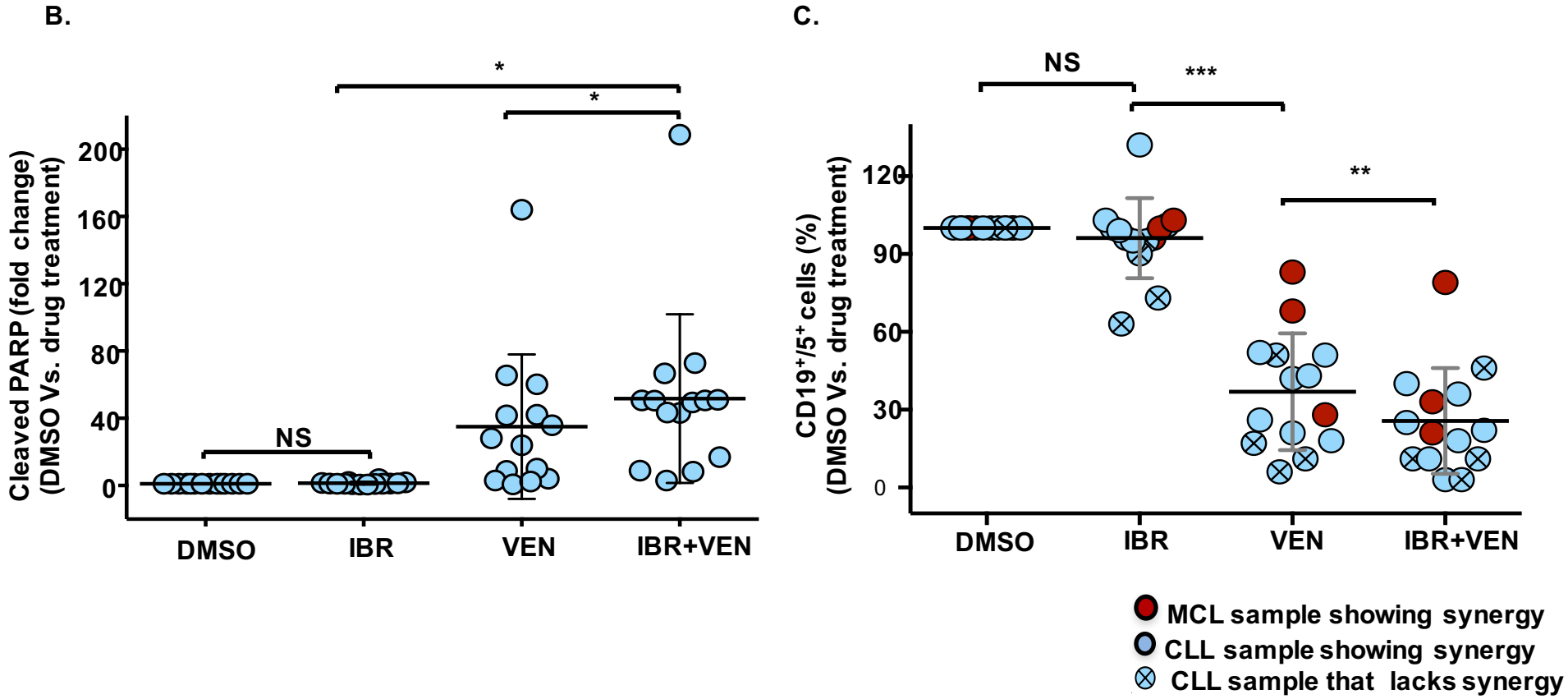
Phase I study of VEN in NHL



Davids M, JCO 2017

Can we rationally combine targeted agents to enhance response and survival in R/R MCL?

- Initial findings at UVA:
  - Ibrutinib synergizes with proteasome inhibitors and venetoclax, a BCL2 inhibitor in MCL and CLL
    - ***Supported by a UVA Cancer Center CaTS Award and the Lymphoma Research Fund***
- Progress in past year:
  - Molecular mechanisms of synergy
  - Mechanisms of resistance, including the role of the tumor microenvironment and cytokines
    - ***Supported by V Foundation grant***
  - Initiation of phase 1b Clinical Trial
    - ***Supported by Abbvie Pharmaceuticals***



Ibrutinib plus venetoclax: Synergistic activity in CLL and MCL patient samples

Jayappa, Portell, Gordon, Bender, Williams, Weber

Blood advances, in press

Phase I/Ib study of Ven and Ibr

University of Virginia Health System | Cancer Center

Table 1: Zone and Arm Designation by Combination

Venetoclax (mg per day)				
400 (week 3+) 200 (week 2) 100 (week 1)	Zone 2/ Arm C	Zone 3/ Arm E	Zone 4/ Arm F
200 (week 3+) 200 (week 2) 100 (week 1)	Zone 1/ Arm A	Zone 2/ Arm B	Zone 3/ Arm D
All Subjects 100 mg Venetoclax (week 0)	280	420	560
	Ibrutinib (week 1+) mg per day		

Major inclusion/exclusion

- Ibrutinib naïve
- not high risk for TLS
- Relapsed to 1 prior chemotherapy containing regimen

UVA run but funded by a grant through AbbVie Inc

- Also open at :
  - Washington University, St. Louis MO
  - Emory University, Atlanta GA
  - City of Hope, Duarte, CA

Continual re-assessment model searching for the optimal dose of ibrutinib and venetoclax.

Clinicaltrails.gov Identifier: NCT02419560

Conclusions

- Follicular lymphoma
  - Standard upfront treatment for high tumor burden:
    - BR vs. Obinu + other chemo?
    - Watch out for Len/Ritux
  - Use of maintenance after bendamustine is becoming questionable

- Marginal zone lymphoma
  - Local therapy first
  - If local therapy fails, chlorambucil+ rituximab
  - If systemic therapy fails, consider ibrutinib

- Mantle cell lymphoma
  - Ibrutinib is very active but relapses occur
    - Consider clinical trials before starting ibrutinb
  - Venetoclax is having an early signal

Questions?

University of Virginia Health System | Cancer Center

Contact/Referral Info:

New patient referrals:
434-924-9333

Craig A. Portell, MD
Office Tele: 434-982-4982
Fax: 434-243-6086
cp4ys@virginia.edu