Year in Review

A Multitumor Regional Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Saturday, February 8, 2020, 8:00 AM – 4:00 PM
Charlotte, North Carolina

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Moderator

Neil Love, MD

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Agenda

Module 1 — Lung Cancer: *Drs Langer and Riely*

Module 2 — Acute Leukemias: *Drs DiNardo and Stone*

Module 3 — Lymphomas and Chronic Lymphocytic Leukemia: *Drs Abramson, LaCasce and Smith*

Module 4 — Gastrointestinal Cancers: *Drs Bendell, Marshall and Wainberg*

Module 5 — Genitourinary Cancers: *Drs Oh and Petrylak*

Module 6 — Gynecologic Cancers: *Drs Armstrong and Liu*

Module 7 — Breast Cancer: *Drs Geyer and Krop*

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Disclosures

Consulting Agreements	AbbVie Inc, Allogene Therapeutics, Celgene Corporation, EMD Serono Inc, Genentech, Janssen Biotech Inc, Karyopharm Therapeutics, Kite Pharma Inc, MorphoSys, Novartis, Roche Laboratories Inc
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Advisory Committee	Humanigen Inc
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Data and Safety Monitoring Board/Committee	Bristol-Myers Squibb Company
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Disclosures

Data and Safety Monitoring Board/Committee	Eastern Cooperative Oncology Group
Speakers Bureau	AstraZeneca Pharmaceuticals LP, EUSA Pharma

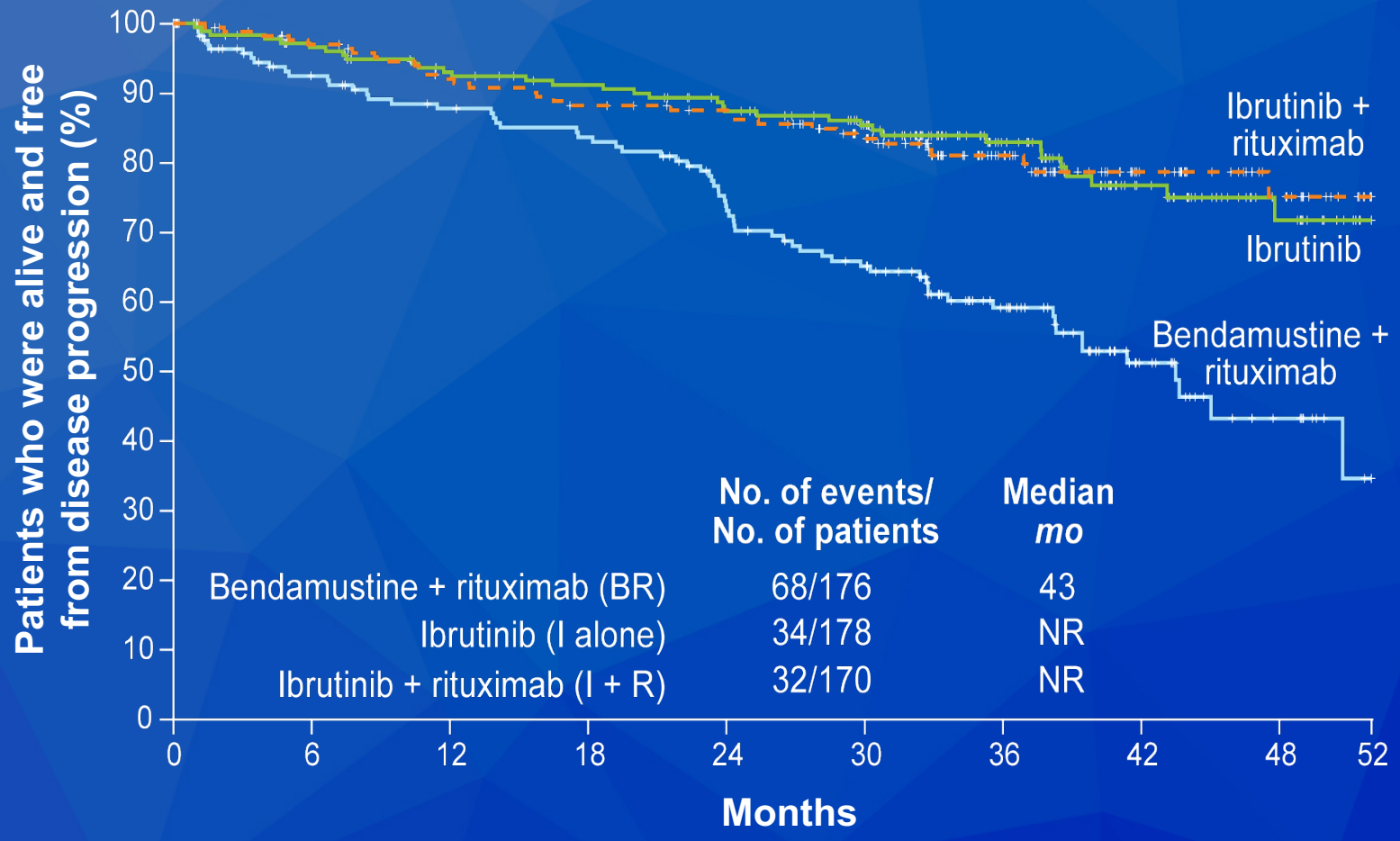
Lymphomas and CLL — Drs Abramson, LaCasce and Smith

- **Chronic Lymphocytic Leukemia**
- Diffuse Large B-Cell Lymphoma
- Hodgkin Lymphoma
- Peripheral T-Cell Lymphoma
- Follicular Lymphoma
- Mantle Cell Lymphoma

Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

Woyach JA et al.
N Engl J Med 2018;379(26):2517-28.

Efficacy and Safety Results with Ibrutinib Alone or in Combination Compared to Bendamustine/Rituximab (BR)



Adverse events	BR (n = 176)	I alone (n = 180)	I + R (n = 181)
Gr ≥3 hematologic, any	61%	41%	39%
Gr ≥3 non-hematologic, any	63%	74%	74%
Gr ≥3 HTN	14%	29%	34%
Atrial fibrillation (any grade)	3%	17%	14%

HTN = hypertension

Woyach JA et al. *N Engl J Med* 2018;379(26):2517-28.

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-up from the E1912 Trial

Shanafelt TD et al.
ASH 2019;Abstract 33.

ECOG-ACRIN-E1912: Extended PFS Follow-Up with Up-Front Ibrutinib and Rituximab (IR) Compared to FCR for Younger Patients with CLL

Three-year PFS rates	IR	FCR	HR	*p*-value
Overall patient population (n = 354, 175)	89%	71%	0.39	<0.0001
IGHV mutation (n = 70, 44)	88%	82%	0.42	0.086
No IGHV mutation (n = 210, 71)	89%	65%	0.28	<0.0001

- With median follow-up of 45 months, 73% of patients randomized to IR remain on ibrutinib.
- With extended follow-up, Grade 3 and higher treatment-related AEs were observed in 70% of IR and 80% of FCR treated patients (OR = 0.56; $p = 0.013$).

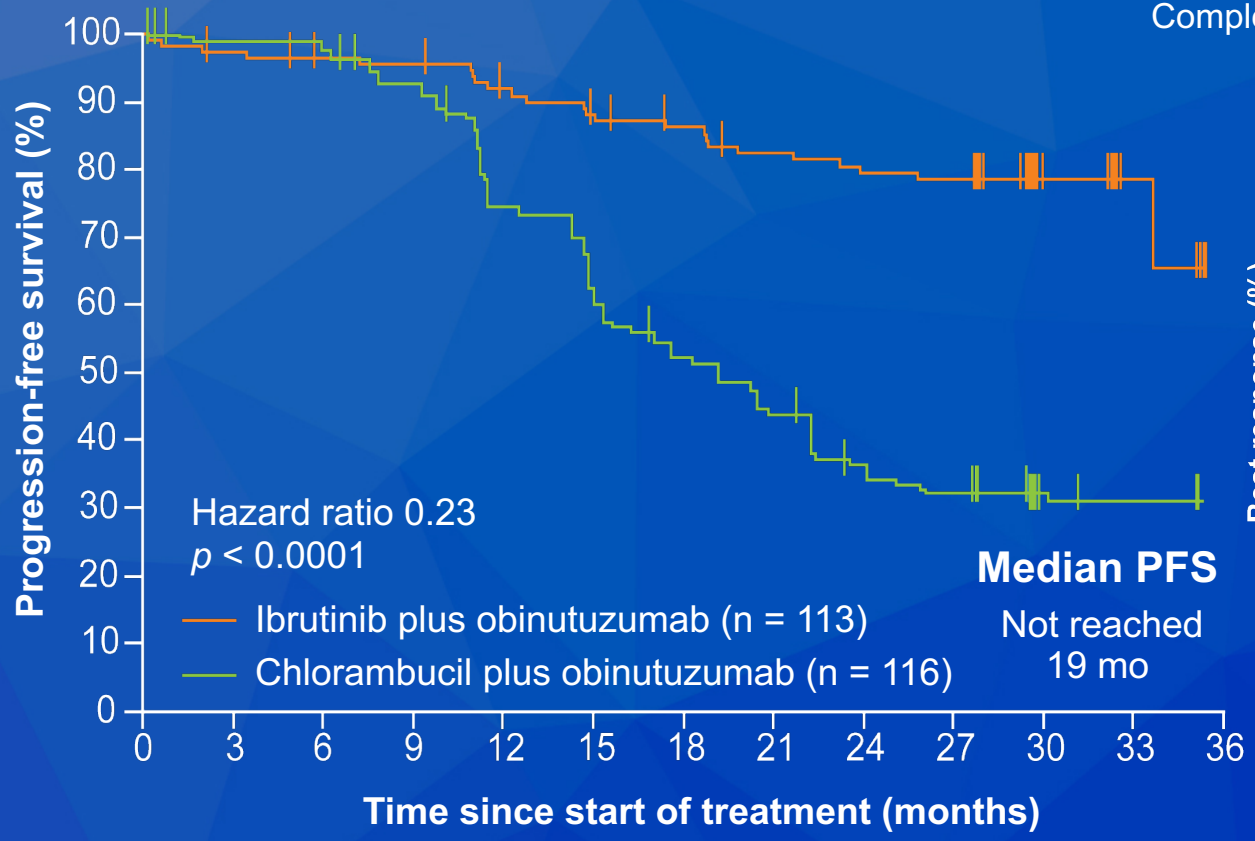
Shanafelt TD et al. ASH 2019;Abstract 33.

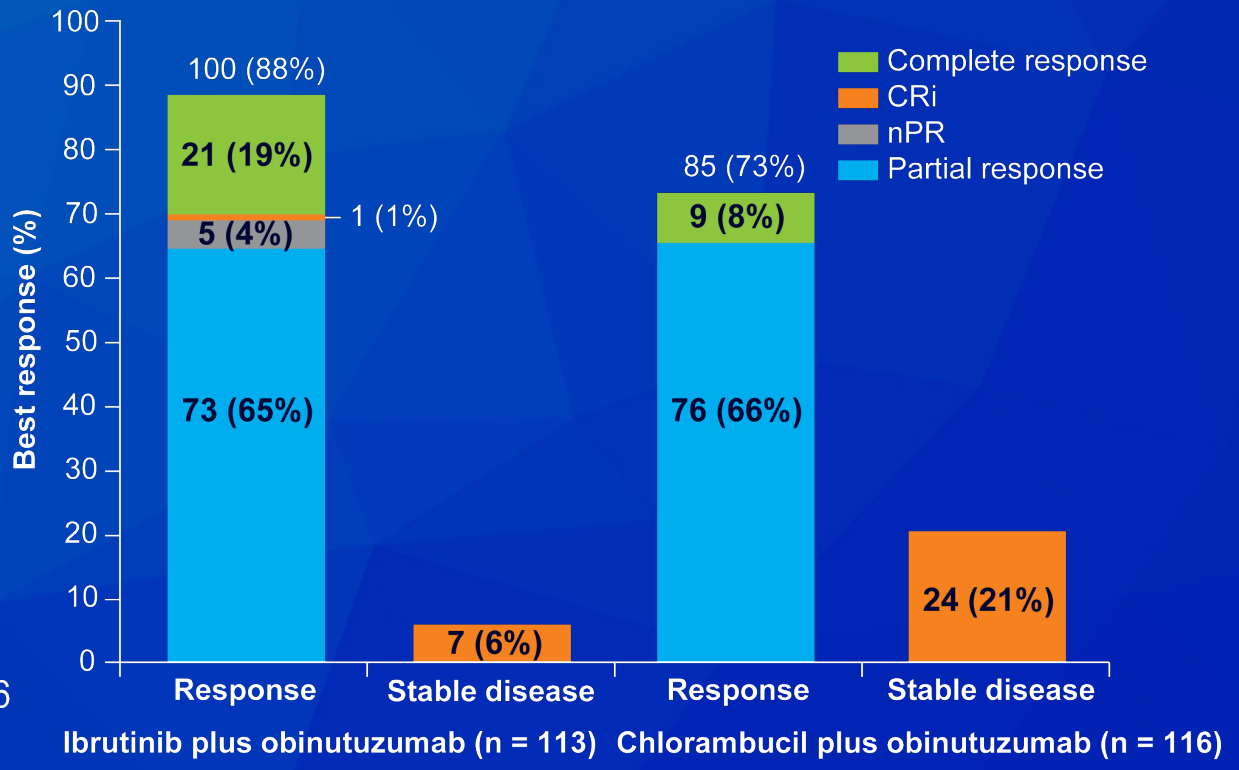
Ibrutinib plus Obinutuzumab versus Chlorambucil plus Obinutuzumab in First-Line Treatment of Chronic Lymphocytic Leukaemia (iLLUMINATE): A Multicentre, Randomised, Open-Label, Phase III Trial

Moreno C et al.
Lancet Oncol 2019;20(1):43-56.

iLLUMINATE: A Phase III Trial of Ibrutinib and Obinutuzumab as First-Line Therapy for CLL

Best response	Ibrutinib + obinutuzumab	Chlorambucil + obinutuzumab	Rate ratio	*p*-value
Overall response	88%	73%	1.21	0.0035
Complete response or CRi	19%	8%	2.51	0.0096





- The most common Grade 3 or 4 adverse events in both groups were neutropenia and thrombocytopenia.
- Serious adverse events occurred in 65 (58%) of 113 patients who received ibrutinib/obinutuzumab and 40 (35%) of 115 patients who received chlorambucil/obinutuzumab.

Moreno C et al. *Lancet Oncol* 2019;20(1):43-56.

Editorial – Dr LaCasce

More than 5 years ago, the FDA approved ibrutinib in relapsed/refractory CLL. Now, the results of multiple ibrutinib trials in the treatment-naïve setting are emerging. In the Alliance study, patients over the age of 65 were assigned to ibrutinib (I), ibrutinib plus rituximab (IR) or bendamustine plus rituximab (BR). The ibrutinib-containing arms were associated with significantly higher 2-year PFS compared with BR, and there was no difference between I and IR. Hematologic toxicity was higher with BR, and non-hematologic toxicity was more common in the ibrutinib arms, including 12%-13% grade 5 events compared with 9% with BR. In the ECOG-ACRIN study, patients 70 or younger without 17p deletion were assigned in a 2:1 randomization to ibrutinib plus rituximab (IR) versus fludarabine, cyclophosphamide and rituximab (FCR). PFS and OS were both superior in the IR arm. In a planned subgroup analysis, IR was superior in patients with unmutated but not mutated IGHV.

Editorial – Dr LaCasce (continued)

In the iLLUMINATE study, patients were randomized to obinutuzumab plus ibrutinib vs obinutuzumab plus chlorambucil, which resulted, not surprisingly, in a dramatic benefit in the ibrutinib-containing arm. Based on these results, the FDA approved the combination of obinutuzumab plus ibrutinib for treatment-naïve patients with CLL.

Although these studies clearly demonstrate the superiority of ibrutinib with or without anti-CD20 antibody therapy compared to chemoimmunotherapy, time-limited chemoimmunotherapy for patients with mutated IGHV without other high-risk features may still be favored by some. Until longer follow-up is reported, FCR may remain the standard approach in younger patients with mutated IGHV given data demonstrating the possibility of long-term remission. Lastly, the added contribution of rituximab or obinutuzumab in ibrutinib-containing regimens remains an open question.

FDA Approval of Venetoclax for CLL and SLL

Press Release – May 15, 2019

"The US Food and Drug Administration approved venetoclax for adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Approval was based on CLL14 (NCT02242942), a randomized (1:1), multicenter, open label, actively controlled trial of venetoclax in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) in 432 patients with previously untreated CLL with coexisting medical conditions."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-venetoclax-cll-and-sll

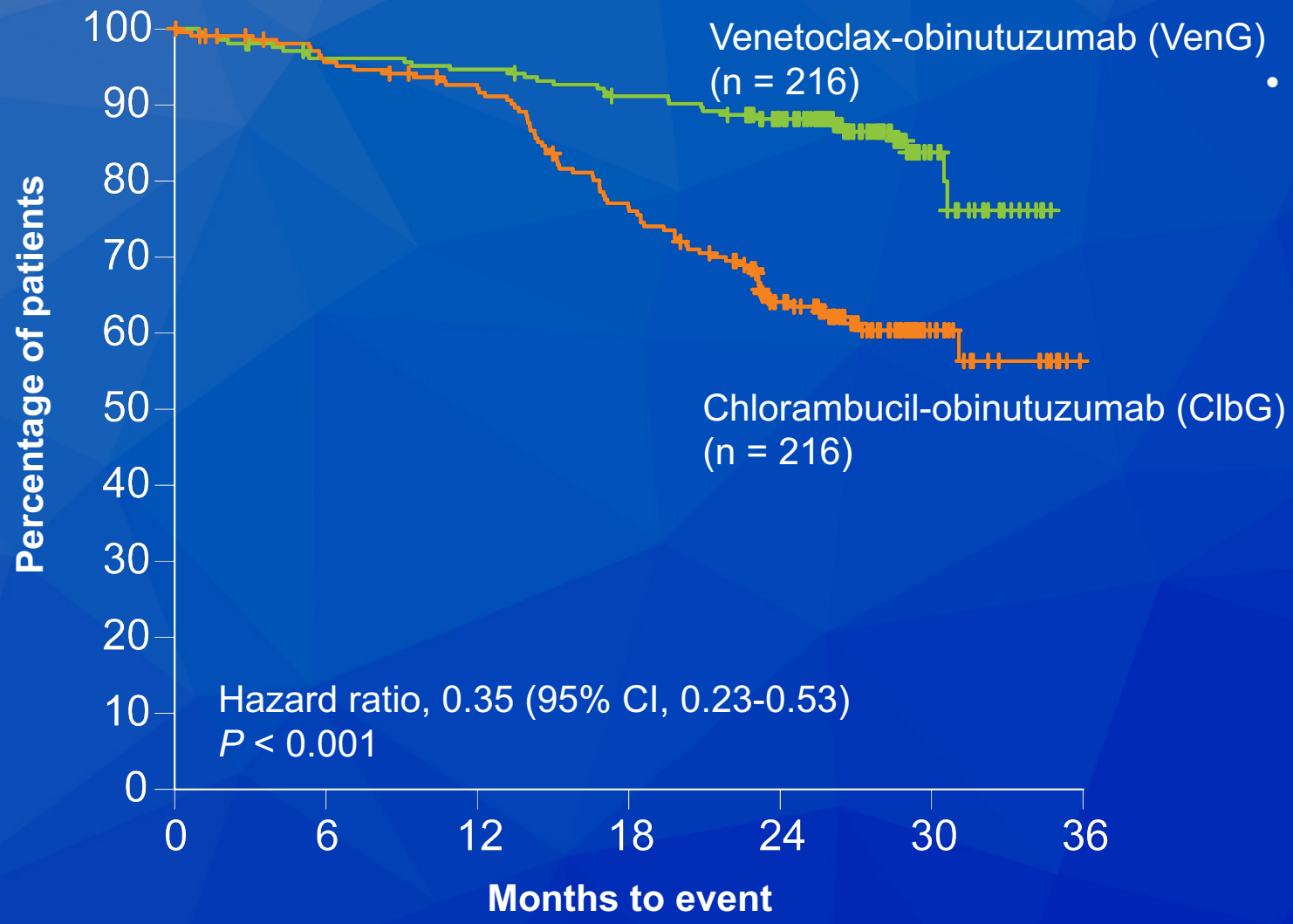
Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions[1]

Effect of Fixed-Duration Venetoclax plus Obinutuzumab (VenG) on Progression-Free Survival (PFS), and Rates and Duration of Minimal Residual Disease Negativity (MRD-) in Previously Untreated Patients with Chronic Lymphocytic Leukemia (CLL) and Comorbidities[2]

[1] Fischer K et al.
N Engl J Med 2019;380(23):2225-36.

[2] Fischer K et al.
Proc ASCO 2019;Abstract 7502.

CLL14: Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Medical Conditions – Investigator Assessed PFS



- Fixed duration of venetoclax/obinutuzumab: Superior outcome in all relevant subgroups including patients with no IGHV mutation and those with del(17p) or TP53 mutations

Fischer K et al. *N Engl J Med* 2019;380(23):2225-36; Fischer K et al. *Proc ASCO* 2019;Abstract 7502.

Quantitative Analysis of Minimal Residual Disease (MRD) Shows High Rates of Undetectable MRD After Fixed-Duration Chemotherapy-Free Treatment and Serves as Surrogate Marker for Progression-Free Survival: A Prospective Analysis of the Randomized CLL14 Trial

Fischer K et al.
ASH 2019;Abstract 36.

CLL14: Prospective, Quantitative Analysis of MRD

- VenG achieved higher rates of undetectable MRD at end of treatment (EOT) compared with ClbG.
- Landmark analysis from EOT revealed that undetectable MRD correlated with favorable PFS rates at 24 months as compared with detectable MRD:
  - VenG: 89.1% vs 61.9%
  - ClbG: 93.9% vs 32.6%
- Further landmark analysis of PFS by MRD status demonstrated that undetectable MRD translated into improved PFS regardless of the clinical response status at EOT.
- Fixed-duration treatment with VenG achieves unprecedentedly high and sustainable rates of undetectable MRD in patients with previously untreated CLL and coexisting conditions.
- Findings confirm the prognostic value of MRD assessment at EOT for this chemotherapy-free treatment regimen.
- Due to high concordance of undetectable MRD in peripheral blood and bone marrow (BM) in the context of VenG, BM assessments may not be required for these patients.

Fischer K et al. ASH 2019;Abstract 36.

Editorial – Dr LaCasce

In the German CLL-14 study, patients with comorbidities (score of greater than 6 on the Cumulative Illness Rating Scale or a creatinine clearance of less than 70 mL/min) were randomized to 12 cycles of venetoclax plus obinutuzumab (VO) versus chlorambucil plus obinutuzumab. Response rates and PFS were significantly higher in the venetoclax arm. Toxicity rates were similar in both arms and there was no significant tumor lysis in the venetoclax arm using standard dosing ramp-up. VO was also associated with higher MRD negativity rates. Based on the results of this study, the FDA approved VO as initial therapy in patients with CLL without restriction based on age or comorbidities.

Given time-limited therapy and the favorable toxicity profile, this regimen is a very appealing front-line choice in patients with CLL. Longer-term follow-up is necessary, however, to assess the outcome of patients who relapse after venetoclax, specifically regarding response to BTK inhibitors and other subsequent therapeutic options.

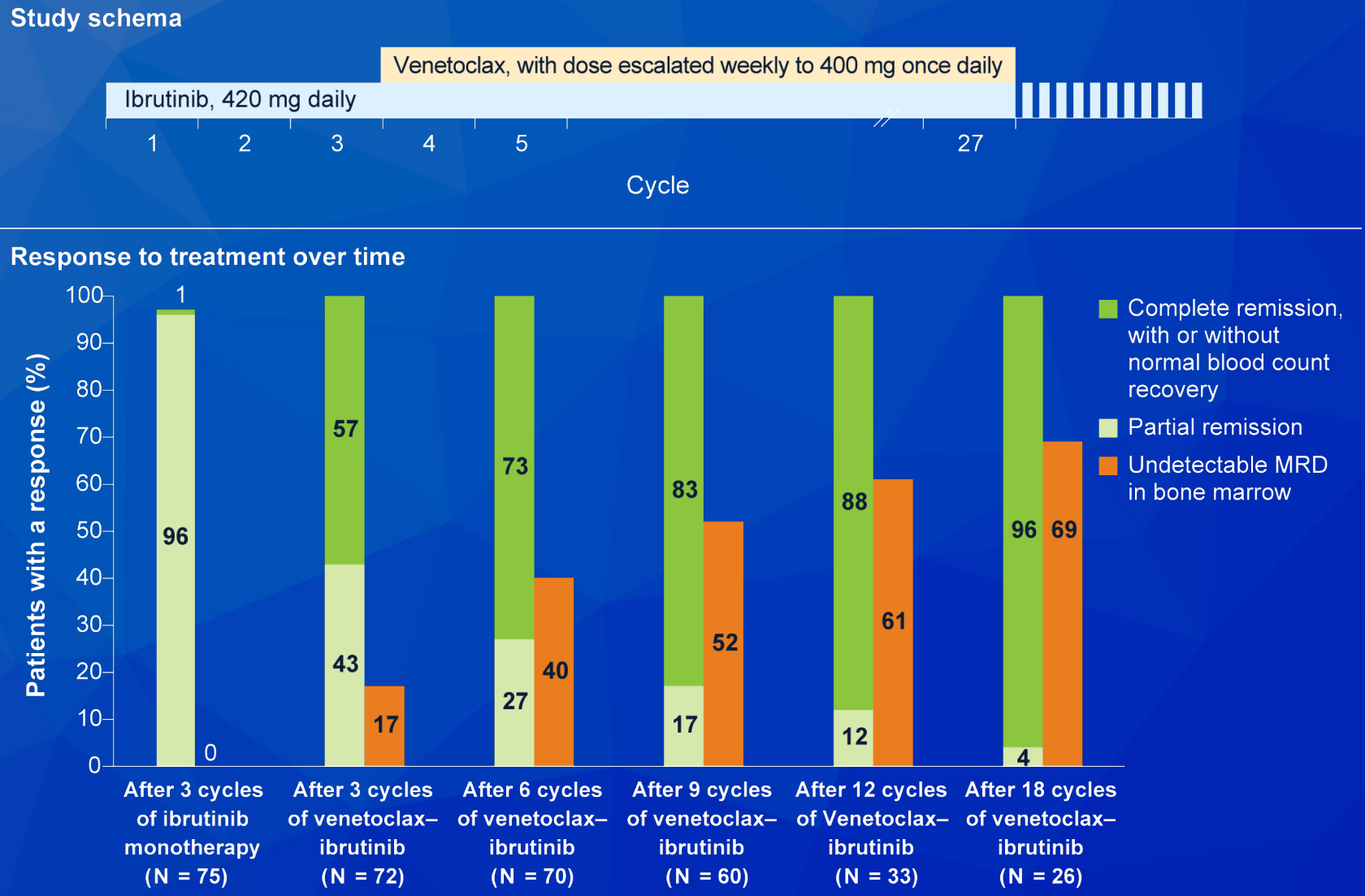
Editorial – Dr LaCasce (continued)

In addition, given that the study enrolled only patients with medical comorbidities, additional data is needed to assess the outcomes in a broader group of patients, particularly in young patients, where the optimal sequencing of therapies may be most important. Lastly, for patients with 17p deletion/P53 mutation, it is unclear whether discontinuation of therapy will result in favorable disease control. With this and the iLLUMINATE study, no future trials should include a chlorambucil-containing arm.

Ibrutinib and Venetoclax for First-Line Treatment of CLL

Jain N et al.
N Engl J Med 2019;380(22):2095-103.

Ibrutinib and Venetoclax for Untreated, High-Risk and Older Patients with CLL

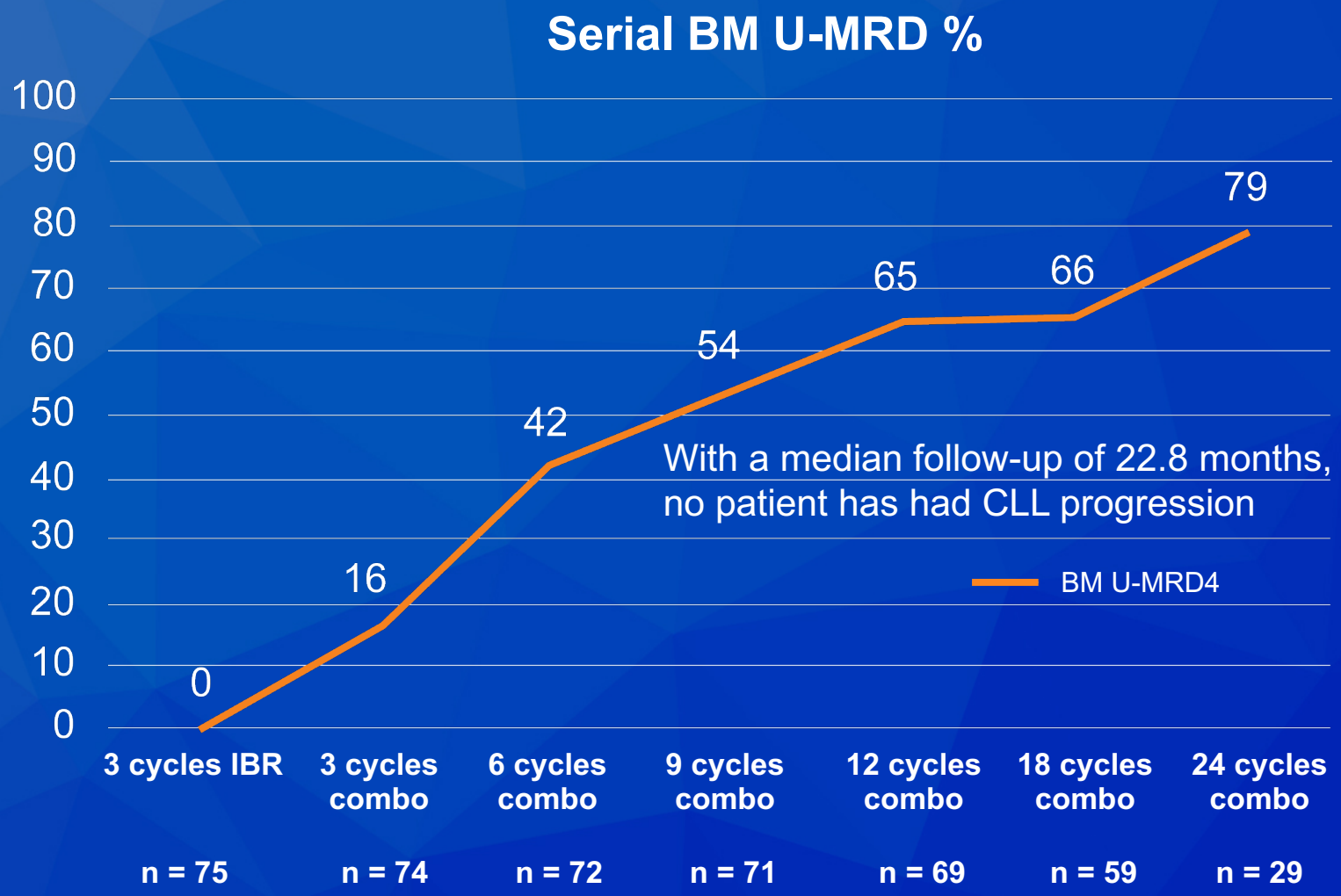


Jain N et al. *N Engl J Med* 2019;380(22):2095-103.

Combined Ibrutinib and Venetoclax for First-Line Treatment for Patients with Chronic Lymphocytic Leukemia (CLL)

Jain N et al.
ASH 2019;Abstract 34.

Ibrutinib and Venetoclax for Untreated, High-Risk and Older Patients with CLL: Serial Bone Marrow MRD Responses



Jain N et al. ASH 2019;Abstract 34.

Editorial — Dr Abramson

Another novel approach in the initial management of CLL would be combining a BTK inhibitor with venetoclax. Unlike BTK inhibitors, venetoclax is capable of inducing undetectable minimal residual disease (MRD), and can be given as time-limited as opposed to continuous therapy. The combination of these two classes of targeted drugs may further augment that efficacy. Jain and colleagues conducted a single center phase II trial of ibrutinib and venetoclax as initial therapy in older adults or in younger adults with high risk features.

Treatment was continued for 2 years and then discontinued for patients with undetectable MRD. Nearly 805 patients achieved undetectable MRD at the two-year timepoint, and the PFS and OS were superb. This is an extremely promising approach that is currently under investigation in randomized clinical trials and may well become a standard of care option in the future.

Project Orbis: FDA Approves Acalabrutinib for CLL and SLL

Press Release – November 21, 2019

"On November 21, 2019, the Food and Drug Administration approved acalabrutinib for adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. The FDA, the Australian Therapeutic Goods Administration, and Health Canada collaborated on this review. Approval was based on two randomized, actively controlled trials in patients with CLL: ELEVATE-TN (NCT02475681) and ASCEND (NCT02970318). Efficacy in both trials was based on progression-free survival (PFS) as assessed by independent review.

ELEVATE-TN randomized 535 patients with previously untreated CLL to one of three arms: acalabrutinib monotherapy, acalabrutinib plus obinutuzumab, or obinutuzumab plus chlorambucil. With a median follow-up of 28.3 months, PFS was significantly improved in both acalabrutinib arms. Compared to the obinutuzumab plus chlorambucil arm, the hazard ratio (HR) for PFS was 0.10 ($p < 0.0001$) with acalabrutinib plus obinutuzumab and 0.20 ($p < 0.0001$) with single agent acalabrutinib.

ASCEND randomized 310 patients with relapsed or refractory CLL after at least one prior systemic therapy to receive either acalabrutinib or investigator's choice (either idelalisib plus a rituximab product, or bendamustine plus a rituximab product). With a median follow-up of 16.1 months, PFS was significantly longer in the acalabrutinib arm compared to the investigator's choice arm (HR 0.31; $p < 0.0001$).

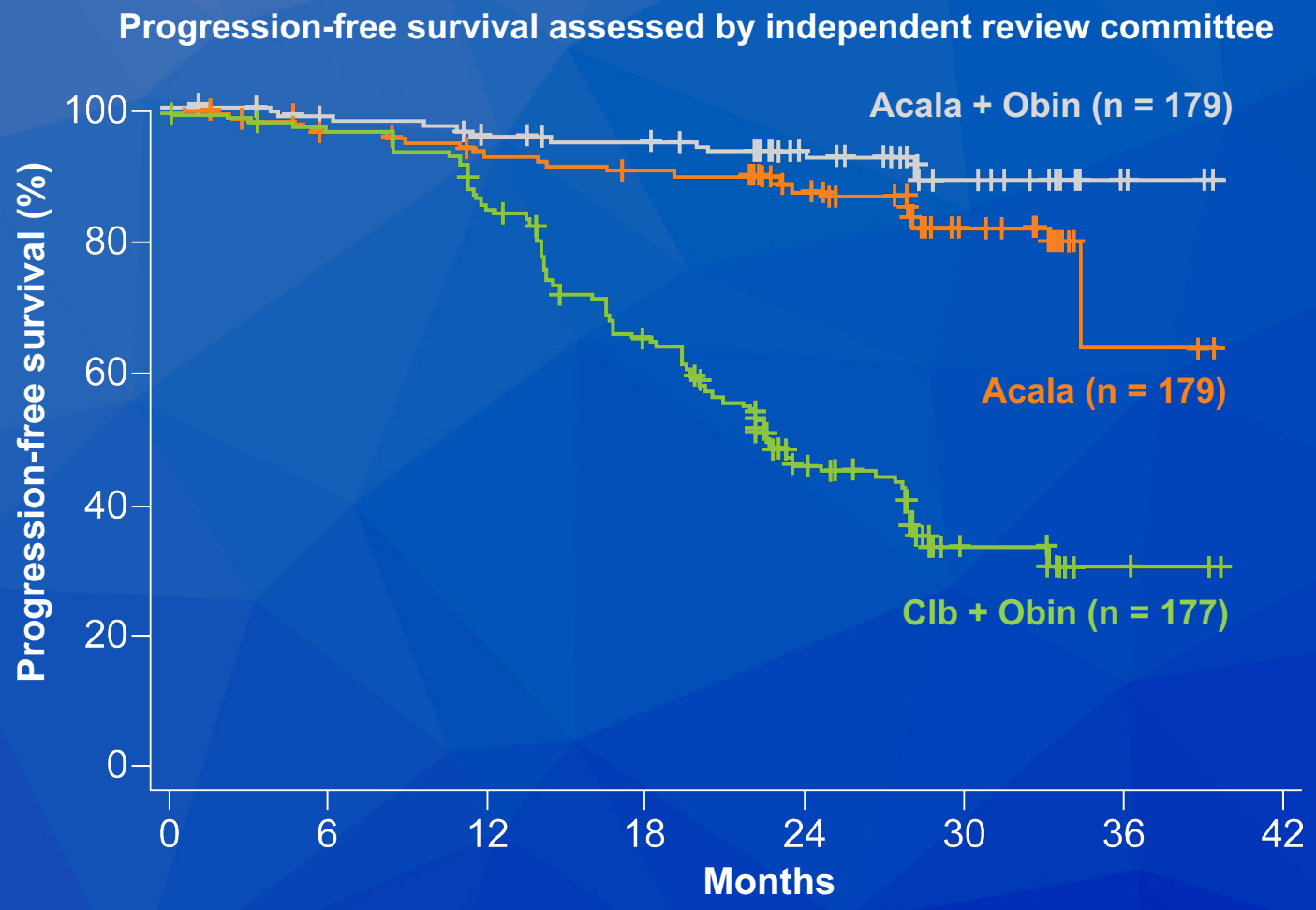
In both trials, median PFS had not been reached in the acalabrutinib arms. In addition, median overall survival had not been reached in any arm for either trial, with fewer than 15% of patients experiencing an event."

https://www.fda.gov/drugs/resources-information-approved-drugs/project-orbis-fda-approves-acalabrutinib-cll-and-sll

ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone vs O plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naïve Chronic Lymphocytic Leukemia (CLL)

Sharman JP et al.
ASH 2019;Abstract 31.

ELEVATE-TN: Interim Results After a Median Follow-Up of 28 Months



Outcome	Acala + Obin	Clb + Obin	Acala
Median PFS	NR	22.6 mo	NR
HR (p-value)	0.10 ($p < 0.0001$)		—
	—	0.20 ($p < 0.0001$)	
30-mo PFS	90%	34%	82%
30-mo OS	95%	90%	94%
ORR	94%	79%	85%
Select AEs	**n = 178**	**n = 169**	**n = 179**
Atrial fibrillation (All grades)	3%	1%	4%
Bleeding (All grades)	43%	12%	39%
Hypertension (Grade ≥3)	3%	3%	2%

- Median OS was not reached in any arm

Sharman JP et al. ASH 2019;Abstract 31.

Editorial — Dr Abramson

Non-chemotherapy-based targeted therapies have largely eclipsed traditional chemoimmunotherapy regimens in the initial management of CLL with either ibrutinib (+/- obinutuzumab) or venetoclax + obinutuzumab considered appropriate up-front treatment options based on randomized clinical trials. The ELEVATE TN trial adds a second BTK inhibitor to the up-front treatment armamentarium with acalabrutinib (+/- obinutuzumab), which was superior to chlorambucil-obinutuzumab in terms of progression-free survival. This three-arm study also found a modest PFS benefit for the addition of obinutuzumab to acalabrutinib compared to acalabrutinib alone, but either combination or monotherapy should be considered reasonable options based on excellent outcomes in both arms relative to the chemoimmunotherapy arm.

Editorial — Dr Abramson (continued)

The safety profile for acalabrutinib appears somewhat more favorable than that of ibrutinib, with lower incidence of serious bleeding, atrial fibrillation, and arthralgias, though notably bruising and bleeding still occur with acalabrutinib, and so caution is still advised, particularly in patients on anticoagulants or anti-platelet therapies. Headache is a unique toxicity of acalabrutinib, but is typically caffeine sensitive.

Efficacy and Safety of Zanubrutinib in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with Del(17p): Initial Results from Arm C of the Sequoia (BGB-3111-304) Trial

Tam CS et al.
ASH 2019;Abstract 499.

SEQUOIA: Efficacy and Safety of Zanubrutinib in Untreated CLL/SLL with Del(17p)

Best response	Treatment naïve with del(17p) (n = 90)
ORR	83 (92.2%)
PR	68 (75.6%)
PR with lymphocytosis	15 (16.7%)
Select AEs	**n = 109**
Any AE	93 (85.3%)
Infections	39.4%
Bruising	24.8%
Minor bleeding	18.3%
Neutropenia	13.8%
Arthralgia/myalgia	8.3%

- With median follow-up of 7 months:
  - Grade ≥3 = 33 (30.3%)
  - Treatment discontinuation due to AEs = 1 (0.9%)
- One patient died due to Grade 5 pneumonia that occurred 8 days after the last dose of zanubrutinib

Tam CS et al. ASH 2019;Abstract 499.

FDA Approval of Zanubrutinib for MCL

Press Release – November 14, 2019

"The Food and Drug Administration granted accelerated approval to zanubrutinib for adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Efficacy was evaluated in BGB-3111-206 (NCT03206970), a phase 2 open-label, multicenter, single-arm trial of 86 patients with MCL who received at least one prior therapy. Zanubrutinib was given orally at 160 mg twice daily until disease progression or unacceptable toxicity. Efficacy was also assessed in BGB-3111-AU-003 (NCT02343120), a phase 1/2, open-label, dose-escalation, global, multicenter, single-arm trial of B-cell malignancies, including 32 previously treated MCL patients treated with zanubrutinib administered orally at 160 mg twice daily or 320 mg once daily."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanubrutinib-mantle-cell-lymphoma

Editorial – Dr Cheson

With ibrutinib and acalabrutinib already on the market, the question remains: Is there space for another BTK inhibitor? Zanubrutinib is the third agent in the class to be approved for relapsed and refractory MCL based on a high overall response rate, with good tolerability. Where and when it will be used in this patient population remains to be determined. Zanubrutinib has also demonstrated activity in CLL in the SEQUOIA trial. The present report details the outcome of Arm-C of that trial, which includes high-risk patients on the basis of the 17p-deletion. A response rate of over 90% was achieved with good tolerability, but with follow-up too short for meaningful interpretation. As above, where does this BTK inhibitor fit in relative to the other two that are approved? The results of a randomized trial against ibrutinib are eagerly awaited in CLL.

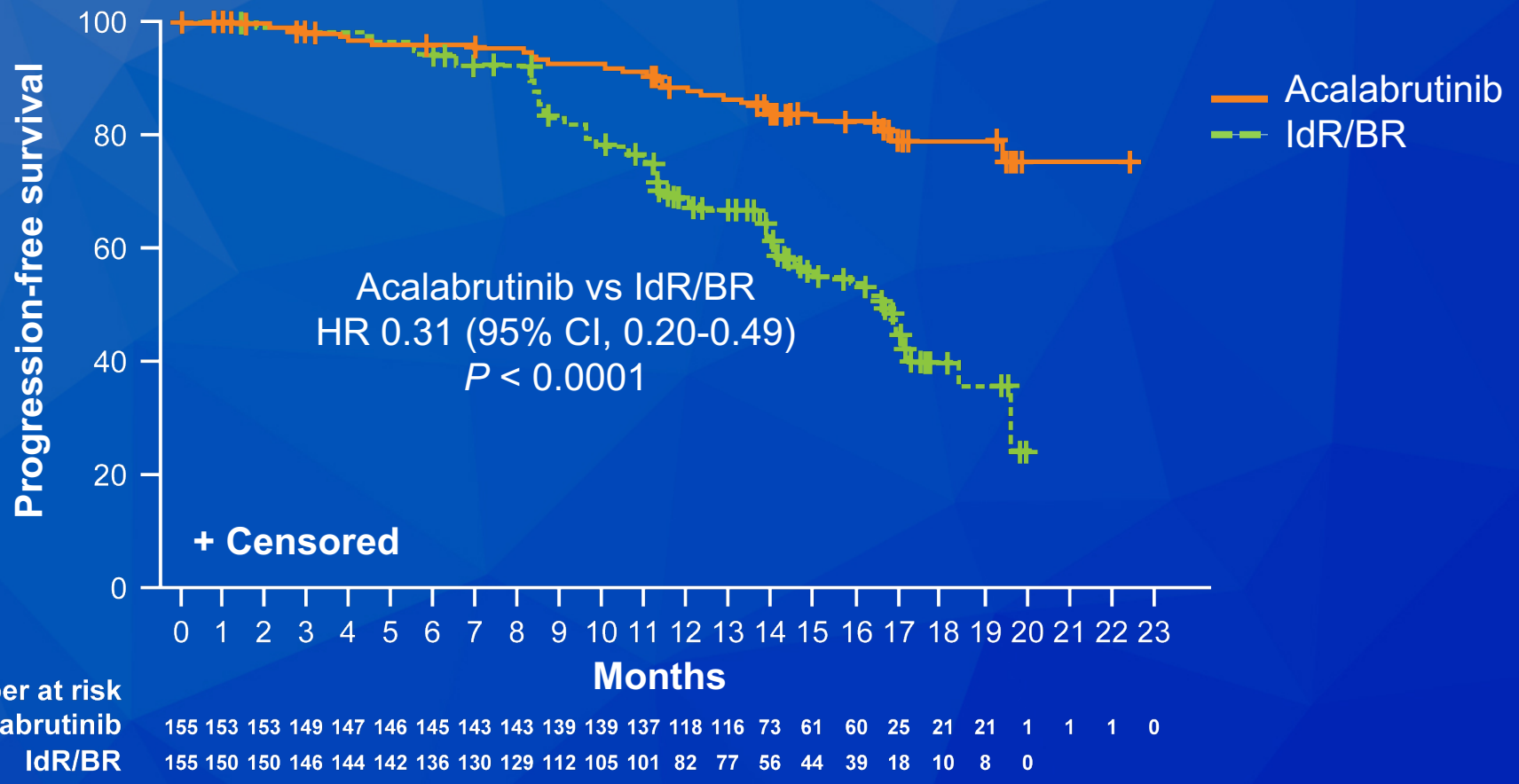
Editorial – Dr Cheson

However, optimism is tempered a bit by the recent availability of the data from a head to head comparison in patients with Waldenström Macroglobulinemia, where zanubrutinib was found not to be superior to ibrutinib. Such studies are clearly needed before adopting a drug just because it is the newest one available, has exciting clinical data, and certainly before extrapolating among diseases.

ASCEND Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab plus Idelalisib (IdR) or Bendamustine (BR) in Patients with Relapsed/ Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

Ghia P et al.
Proc EHA 2019;Abstract LB2606.

ASCEND: Acalabrutinib versus Idelalisib/Rituximab or Bendamustine/Rituximab for Relapsed/Refractory CLL



- **Grade ≥3 AEs** - **Acalabrutinib**: neutropenia (16%), anemia (12%) and pneumonia (5%); **IdR:** neutropenia (40%) and diarrhea (24%); **BR**: neutropenia (31%), anemia (9%) and constipation (6%)
- **AEs of special interest:** atrial fibrillation (5.2% of pts on acalabrutinib vs 3.3% on IdR/BR), bleeding AEs (26% vs 7.2%; including major hemorrhage [1.9% vs 2.6%]), Grade ≥3 infections (15% vs 24%), and 2nd primary malignancies (excluding NMSC; 6.5% vs 2.6%)

Ghia P et al. *Proc EHA* 2019;Abstract LB2606.

ELEVATE-RR (NCT02477696): A Randomized, Multicenter, Open-Label, Non-Inferiority, Phase III Study of Acalabrutinib (ACP-196) versus Ibrutinib in Previously Treated Subjects with High Risk Chronic Lymphocytic Leukemia

Editorial – Dr LaCasce

The ASCEND study in relapsed/refractory CLL randomized patients to acalabrutinib versus investigator choice of rituximab plus idelalisib (IR) or rituximab plus bendamustine (BR). At interim assessment, the study met its primary endpoint of improvement in PFS in the acalabrutinib arm. Overall response rates were similar in both arms and there was no difference in overall survival with crossover to acalabrutinib allowed. Interestingly, atrial fibrillation was seen in 5% of patients receiving acalabrutinib versus 3% in the IR and BR arms. Bleeding events were more common in patients receiving acalabrutinib, with very low rates of major hemorrhage.

Based on the results of multiple trials, the efficacy of both ibrutinib and acalabrutinib in relapsed/refractory and previously untreated patients with CLL is clear. The ELEVATE-RR study will compare the activity of the two agents head to head in a non-inferiority design.

Editorial – Dr LaCasce

Perhaps even more interesting will be the comparison of toxicity, particularly with regard to atrial fibrillation and risk of bleeding. Remaining questions include, with the approval of venetoclax plus obinutuzumab in previously untreated patients, what is the optimal sequencing of agents, particularly in patients with high-risk features, including 17p deletion/P53 mutation and complex cytogenetics? In addition, multiple studies of time-limited 3-drug combinations, including venetoclax, BTK inhibitors and obinutuzumab, are under way to enhance MRD rates. How these studies will impact outcomes in the relapsed/refractory setting will be critically important.

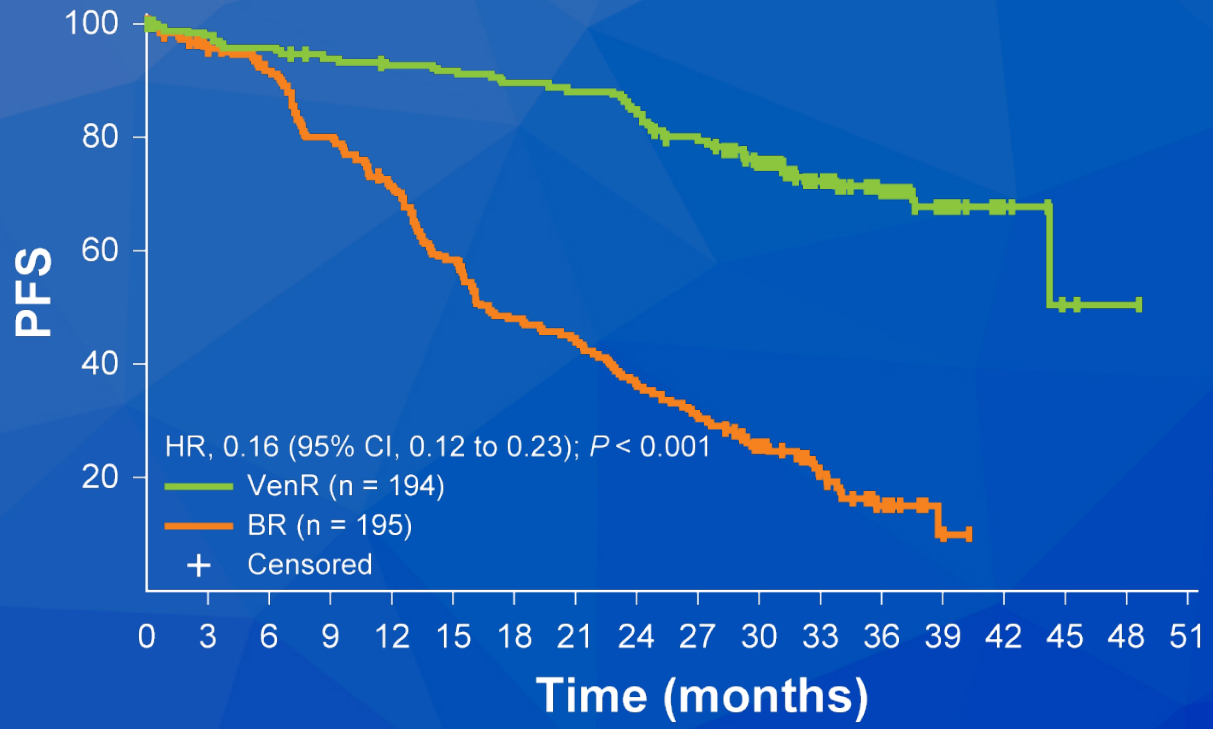
Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study[1]

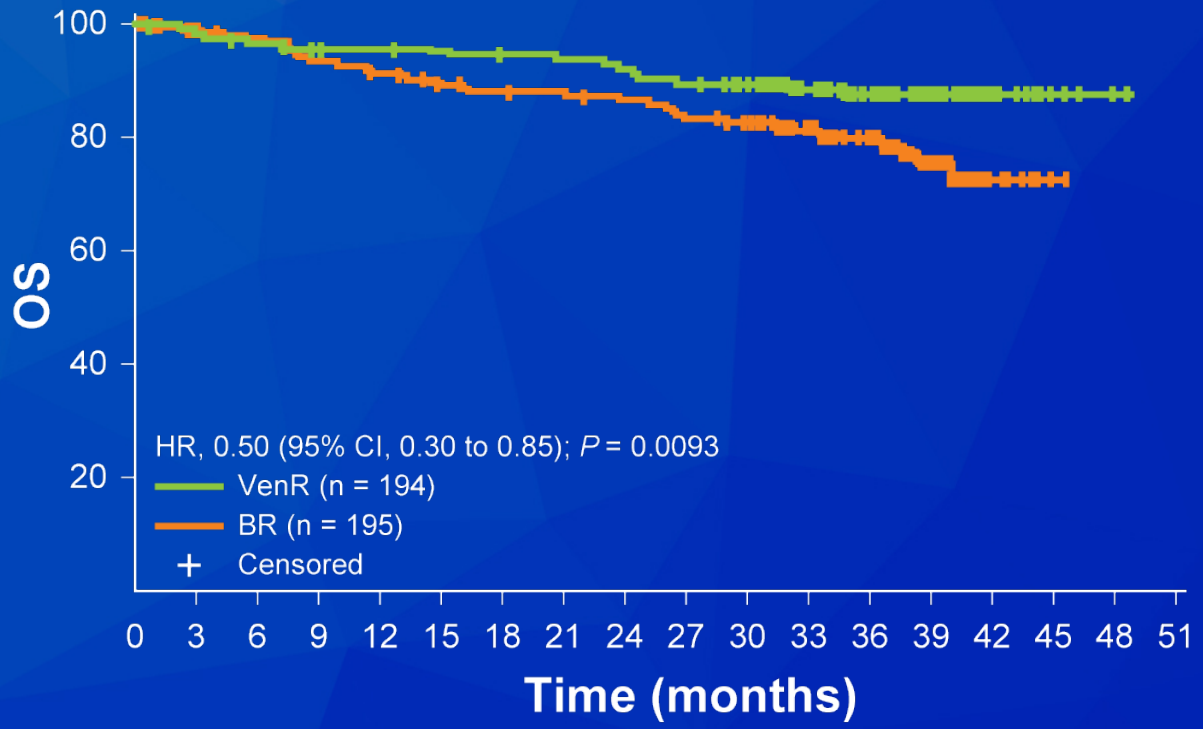
Four-Year Analysis of MURANO Study Confirms Sustained Benefit of Time-Limited Venetoclax-Rituximab (VenR) in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)[2]

[1] Kater AP et al.
J Clin Oncol 2019;37(4):269-77.

[2] Seymour JF et al.
ASH 2019;Abstract 355.

MURANO: Progression-Free Survival, Overall Survival and Safety with Venetoclax-Rituximab in R/R CLL





No. at risk:

VenR	194	190	185	179	176	174	170	167	161	150	135	99	61	21	6	2	1
BR	195	178	164	142	128	103	84	79	65	55	41	26	10	2			

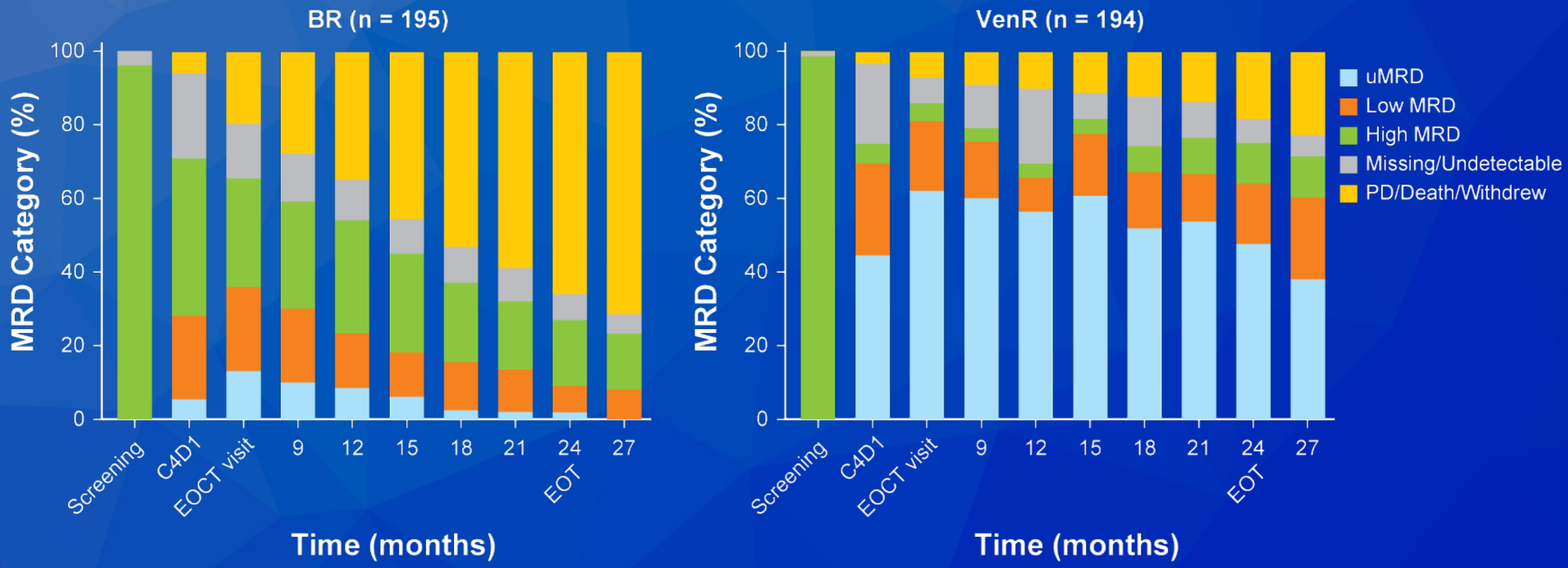
No. at risk:

VenR	194	190	185	183	182	179	178	176	173	168	163	128	87	39	13	4	2
BR	195	181	175	167	162	155	152	150	147	141	136	111	76	34	9	1	

Grade 3-4 AEs occurred in 59/171 pts (35%); the most frequent were neutropenia (20 pts, 12%), anemia (5 pts, 3%), and thrombocytopenia (3 pts, 2%).

Kater AP et al. *J Clin Oncol* 2019;37(4):269-77.

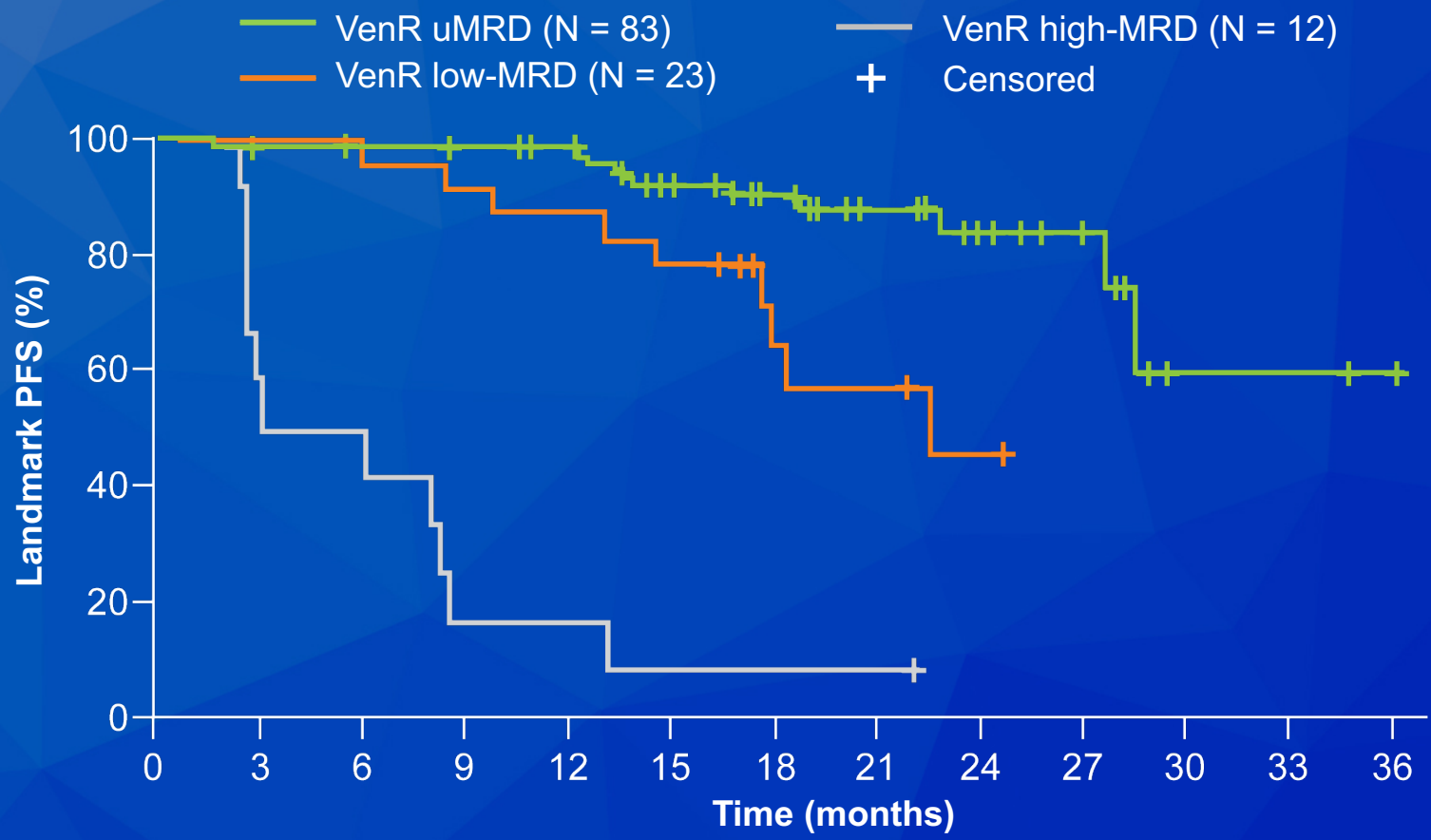
MURANO: Peripheral Blood MRD Status for Venetoclax + Rituximab (VenR) Compared to BR at Various Timepoints



- VenR achieved a higher rate of peripheral blood-undetectable MRD (uMRD) at end of combination therapy (EOCT), which was sustained through month 24 (end of therapy).
- Overall, uMRD status predicted longer PFS.

Kater AP et al. *J Clin Oncol* 2019;37(4):269-77.

MURANO: Landmark Analysis of PFS Based on MRD Status at End of Treatment



No. of patients at risk:

VenR uMRD	83	78	77	76	74	63	42	33	13	9	2	2	1
VenR low-MRD	23	23	23	21	20	17	9	7	1				
VenR high-MRD	12	8	6	2	2	1	1	1					

Seymour JF et al. ASH 2019;Abstract 355.

Editorial – Dr LaCasce

Perhaps even more interesting will be the comparison of toxicity, particularly with regard to atrial fibrillation and risk of bleeding. Remaining questions include, with the approval of venetoclax plus obinutuzumab in previously untreated patients, what is the optimal sequencing of agents, particularly in patients with high-risk features, including 17p deletion/P53 mutation and complex cytogenetics? In addition, multiple studies of time-limited 3-drug combinations, including venetoclax, BTK inhibitors and obinutuzumab, are under way to enhance MRD rates. How these studies will impact outcomes in the relapsed/refractory setting will be critically important. The VR regimen is a very appealing option for patients with relapsed/refractory CLL given the fixed duration of therapy and favorable toxicity profile. Longer follow-up will be critical to assess relapses after the 2-year mark with the discontinuation of venetoclax, particularly in high-risk patients. In addition, for relapsed patients who are BTK inhibitor naïve, further studies are needed to determine the optimal second-line therapy.

Rapid Undetectable MRD (uMRD) Responses in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Treated with Lisocabtagene Maraleucel (liso-cel), a CD19-Directed CAR T Cell Product: Updated Results from Transcend CLL 004, a Phase 1/2 Study Including Patients with High-Risk Disease Previously Treated with Ibrutinib

Siddiqi T et al.
ASH 2019;Abstract 503.

TRANSCEND CLL 004: Undetectable MRD Responses in R/R CLL/SLL Treated with Lisocabtagene Maraleucel

Best response at median follow-up of 9 months	All evaluable patients (n = 22)
ORR	18 (82%)
CR/CRi	10 (45.5%)
PR/nodular PR	8 (36%)
Undetectable MRD (10^{-4}) at any time	**n = 20**
Blood (by flow cytometry)	15 (75%)
Bone marrow (by NGS)	13 (65%)
Pharmacokinetics	
Median time to peak expansion of CAR+ T cells	15 days

- Liso-cel toxicities, including CRS and NE, were manageable at both dose levels tested.

Siddiqi T et al. ASH 2019;Abstract 503.

Editorial — Dr Abramson

Patients who progress on ibrutinib have historically had a grave prognosis in CLL, though the availability of venetoclax has provided a highly effective option for these patients. Patients who progress after both BTK inhibitors and venetoclax, however, continue to constitute an unmet medical need. The interim analysis of the first 23 patients enrolled on the ongoing TRANSCEND CLL study offers hope for this patient population. TRANSCEND CLL evaluates the anti-CD19 CAR T-cell lisocabtagene maraleucel in relapsed/refractory CLL patients who have failed a BTK inhibitor. These were heavily pre-treated patients with a median of 5 prior lines of therapy. 91% of patients were ibrutinib refractory and more than half had failed both ibrutinib and venetoclax. Liso-cel was remarkably effective with 3/4 of patients attaining undetectable MRD in the blood and 2/3 undetectable MRD in the bone marrow. Expected toxicities of cytokine release syndrome and neurotoxicity were manageable and reversible.

Editorial — Dr Abramson (continued)

More data is needed in a greater number of patients and longer follow up to assess durability of response, but these early data suggest that this CAR T cell will become a valuable addition to the treatment armamentarium for CLL patients refractory to both BTK and Bcl-2 inhibition.

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Patients (Pts) with Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL): Results of the Phase 2 ZUMA-2 Study

Wang ML et al.
ASH 2019;Abstract 754.

ZUMA-2: Interim Efficacy and Safety of KTE-X19 in R/R MCL

Investigator-assessed response	n = 28
ORR	86%
CR	57%
12-mo duration of response	83%
12-mo PFS	71%
12-mo OS	86%

- The most common Grade ≥3 AEs (≥20% of pts) were anemia (54%), decreased platelet count (39%), neutropenia (36%), decreased neutrophil count (32%), decreased white blood cell count (29%), encephalopathy (25%), and hypertension (21%).
- No Grade 5 CRS or neurologic events occurred.
- All CRS events and most neurologic events (15/17 pts) were reversible.
- There was 1 Grade 5 AE of organizing pneumonia that was considered related to conditioning chemotherapy.
- Peak CAR T-cell expansion was observed between days 8 and 15 and declined over time.

Wang ML et al. ASH 2019;Abstract 754.

Editorial – Dr S Smith

The 2017 approval for CAR-T therapy for r/r DLBCL has substantially changed the options for patients, with approximately 40% of patients achieving durable remissions. It is well established that patients in need of third-line therapy for DLBCL have a life expectancy of 6-12 months, and CAR-T offers a meaningful option in the third-line setting, albeit with significant cost and potential toxicity. There are now two commercially available products (axi-cel and tisa-cel) with one additional product expected to be approved in 2020 (liso-cel). The excitement and promise of CAR-T is that other diseases may also benefit from this type of cellular therapy. The ZUMA-2 trial evaluated axi-cel in 28 patients with r/r MCL with at least one year of follow-up (total 60 patients enrolled). The key aspects of the trial include a heavily pretreated patient population with a median of 4 prior therapies, 57% being refractory to the most recent line of treatment, and 21% having blastoid morphology.

Editorial – Dr S Smith

In addition, all patients had prior BTK inhibitors. In this population, the ORR is 86% (CR 57%) with 12-month duration of response over 80% and 12-month OS being 86%. The expected survival after progression on a BTK inhibitor is dismal and is approximately 2-6 months. Of note, the median age on this trial was 65 years. Toxicity was not significantly different from other CAR-T trials in DLBCL, and there were no grade 5 events. Overall, this is an extremely difficult disease to manage after first or second relapse, and these numbers are tremendously exciting. The trial by Siddiqi et al, TRANSCEND CLL 004, tests liso-cel in r/r CLL/SLL. Patients had either standard-risk or high-risk (del 17p, TP53 mutation, unmutated IGHV, or complex karyotype) disease. This is a smaller trial (23 patients) with median age 66 years and most patients (83%) having high-risk disease with median 5 prior therapies. The authors do not report how many patients received prior chemotherapy (presumably very low).

Editorial – Dr S Smith

Consistent with other trials of CAR-T, there is a high ORR of 82% with a CR rate of 45%. Follow-up is quite short, but patients with response at 9 months remain progression free, and responses deepened over time. Achieving BM uMRD (undetectable MRD) at 30 days seems to be an important early marker and occurred in 65% of evaluable patients. Toxicity was similar to prior reports.

In my opinion, the use of a costly and potentially toxic regimen such as CAR-T is most easily rationalized in diseases such as MCL and DLBCL, where multiple relapses are associated with high disease-related mortality. There is more controversy on the timing of using CAR-T in patients with CLL. The lymphodepleting regimen used is fludarabine-cyclophosphamide in this trial, and given the declining use of chemotherapy in general, there is at least a possibility that some of the early MRD negativity and responses are related to chemotherapy effect. Nevertheless, these early results are promising.

Lymphomas and CLL — Drs Abramson, LaCasce and Smith

Chronic Lymphocytic Leukemia

Diffuse Large B-Cell Lymphoma

Hodgkin Lymphoma

Peripheral T-Cell Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

FDA Approval of Polatuzumab Vedotin-Piiq for DLBCL

Press Release – June 10, 2019

"The US Food and Drug Administration granted accelerated approval to polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate indicated in combination with bendamustine and a rituximab product for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies.

Approval was based on Study GO29365 (NCT02257567), an open-label, multicenter clinical trial that included a cohort of 80 patients with relapsed or refractory DLBCL after at least one prior regimen."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-polatuzumab-vedotin-piiq-diffuse-large-b-cell-lymphoma

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma[1]

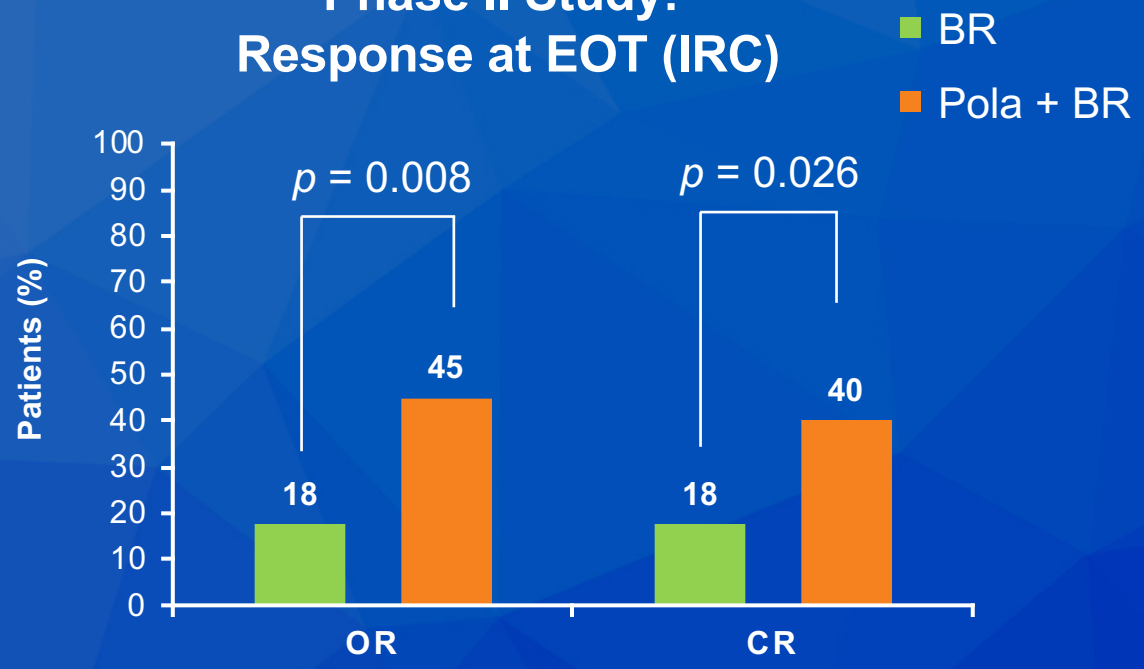
Randomized Phase 2 Trial of Polatuzumab Vedotin (Pola) with Bendamustine and Rituximab (BR) in Relapsed/Refractory (R/R) FL and DLBCL[2]

[1] Sehn LH et al.
J Clin Oncol 2020;38(2):155-65.

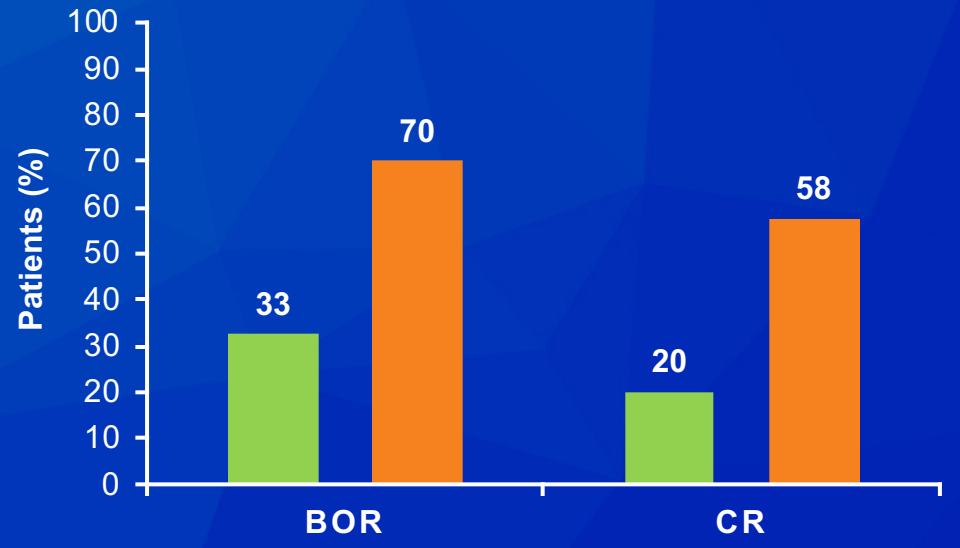
[2] Sehn LH et al.
Proc ASCO 2018;Abstract 7507.

GO29365 Study Primary Endpoint: PET CR Rate at End of Treatment

Phase II Study: Response at EOT (IRC)

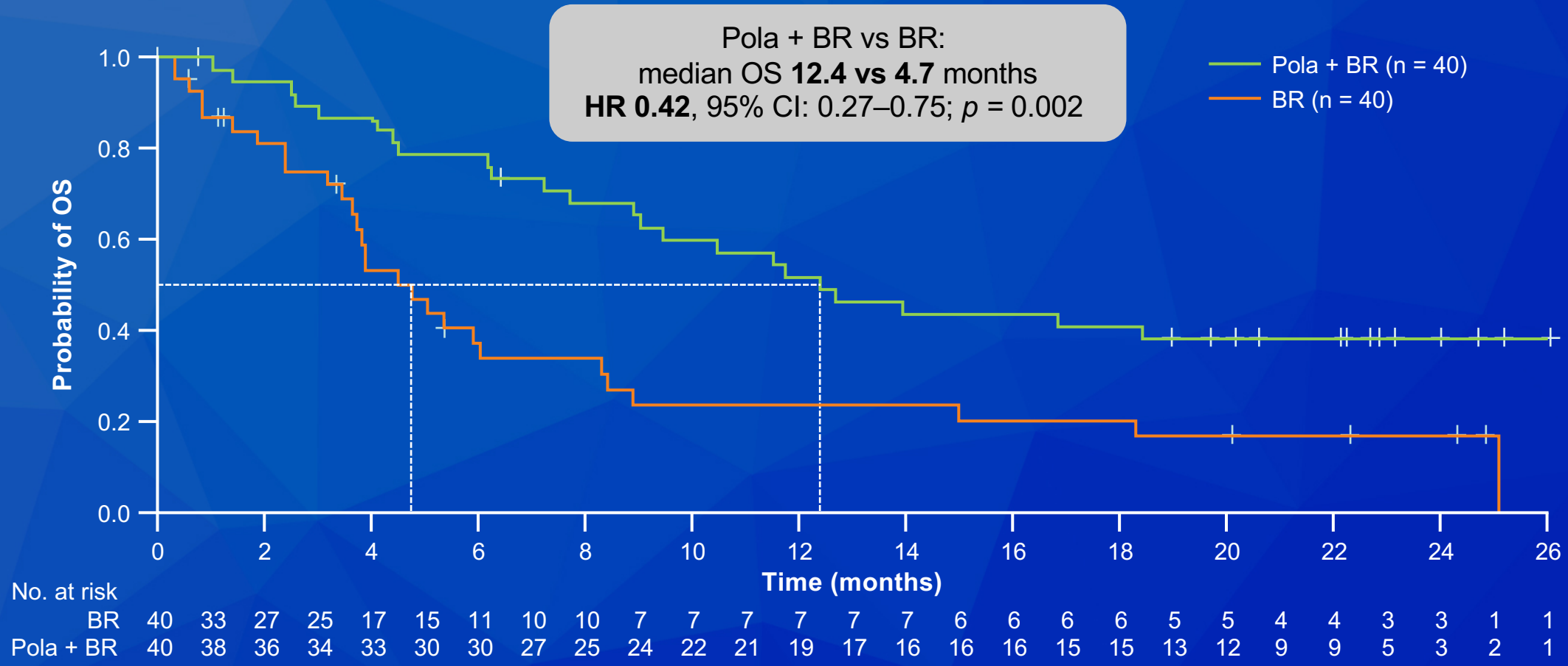


Phase II Study: Best overall response and CR (INV)



Sehn LH et al. *J Clin Oncol* 2020;38(2):155-65; Sehn LH et al. *Proc ASCO* 2018;Abstract 7507.

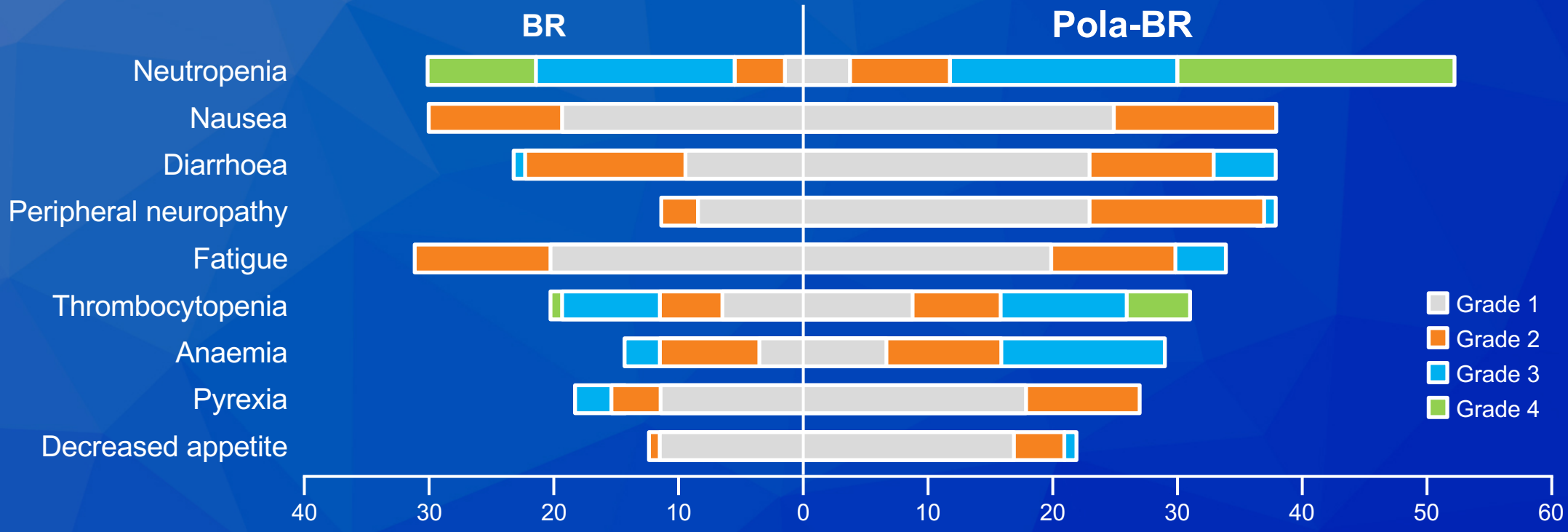
GO29365 Study: Overall Survival Significantly Longer with Pola-BR versus BR



Median follow-up: 22.3 months

Sehn LH et al. *J Clin Oncol* 2020;38(2):155-65.

GO29365 Study: All-Grade AEs in ≥20% Patients



Median number of completed cycles: 3 (range, 1-6) with BR; 5 (range, 1-6) with pola + BR

Sehn LH et al. *J Clin Oncol* 2020;38(2):155-65; Sehn LH et al. *Proc ASCO* 2018;Abstract 7507.

Polatuzumab Vedotin in Combination with Immunochemotherapy in Patients with Previously Untreated Diffuse Large B-cell Lymphoma: An Open-Label, Non-Randomised, Phase 1b-2 Study

Tilly H et al.
Lancet Oncol 2019;20(7):998-1010.

Phase Ib-II Study of Polatuzumab Vedotin plus Immunochemotherapy in Patients with Previously Untreated DLBCL

Efficacy of polatuzumab vedotin at the recommended Phase II dose (1.8 mg/kg)

	Polatuzumab vedotin (1.8 mg/kg) plus R-CHP or G-CHP group (n = 66)
Overall response	59 (89%)
Complete response	51 (77%)
Partial response	8 (12%)

The most common Grade ≥3 AEs were neutropenia (20 [30%]), febrile neutropenia (12 [18%]), and thrombocytopenia (6 [9%]).
4 deaths were reported during follow-up: 2 treatment-related (1 complication of atrial fibrillation, 1 septic shock); 2 due to disease progression.

Tilly H et al. *Lancet Oncol* 2019;20(7):998-1010.

POLARIX: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination with Rituximab and CHP (R-CHP) versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma (NCT03274492)

Editorial – Dr Moskowitz

- ADC to CD79b had impressive single-agent activity with neuropathy as the dose-limiting side effect.
- Approved in combination with BR (which is too bad) for relapsed and refractory DLBCL — more than a doubling of the CR rate, longer DOR, PFS and most importantly OS. There was a 1-year improvement in OS for the ABC subtype.
- CHP + Pola — phase 1B study, majority of pts have DLBCL
- Toxicity profile not really different from R-CHOP, nor is the CR rate
- The PFS curves are excellent
- Missing from the data is time from diagnosis to treatment which can determine favorability of the cohort
- I agree that the data did warrant a phase III study vs R-CHOP that is nearly done with enrollment

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Schuster SJ et al.
NEJM 2019;380(1):45-56.

JULIET: Updated Efficacy and Safety Data

- Efficacy results reported for patients with ≥3-mo follow-up or earlier discontinuation

Clinical endpoint	N = 93
Best ORR	52%
CR	40%
PR	12%
Median duration of response	Not reached

- Safety is reported for all infused patients

Grade 3/4 AEs of special interest	
Cytopenias lasting >28 days	32%
Cytokine release syndrome (CRS)*	22%
Infections	20%
Febrile neutropenia	15%
Neurologic AEs	12%

* 14% Grade 3 and 8% Grade 4 by Penn grading scale

- Response rates were consistent across prognostic subgroups
- Median OS among all infused patients was 12 mo
  - 12-mo OS = 49%
- 12-month relapse-free survival among responders: 65%

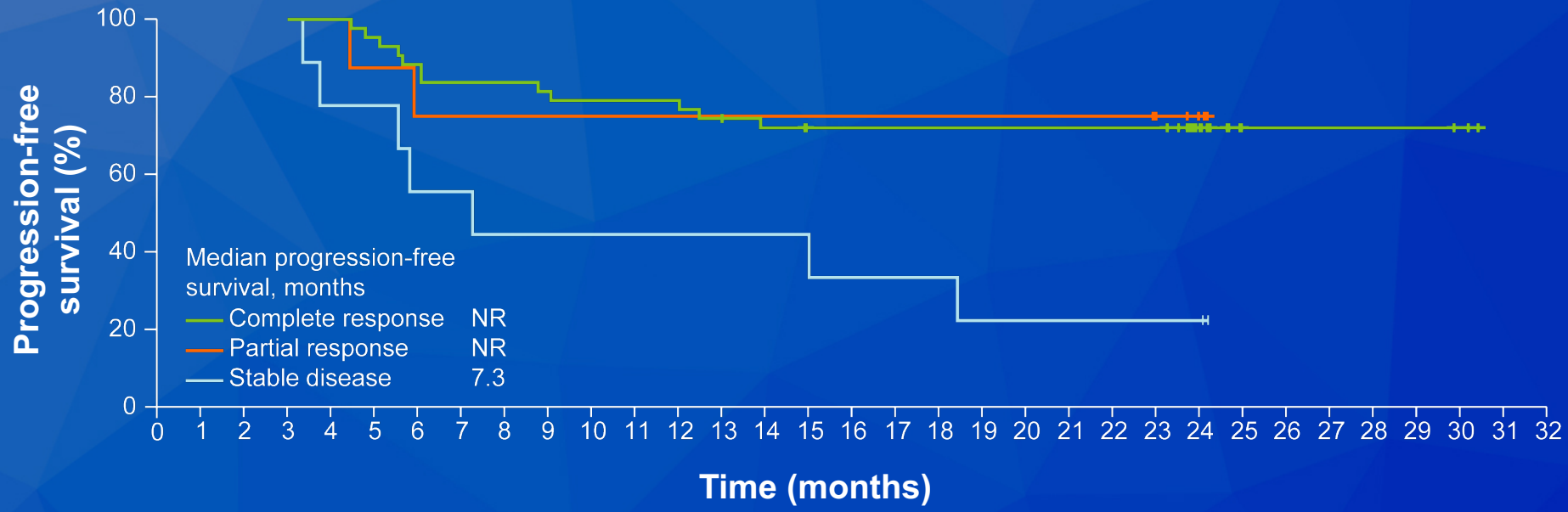
- 14% of patients received tocilizumab for management of CRS
- No deaths were attributed to tisagenlecleucel

Schuster SJ et al. *NEJM* 2019;380(1):45-56.

Long-Term Safety and Activity of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma (ZUMA-1): A Single-Arm, Multicenter, Phase 1-2 Trial

Locke FL et al.
Lancet Oncol 2019;20(1):31-42.

ZUMA-1: Two-Year Follow-Up on Safety and Activity of Axicabtagene Ciloleucel in Refractory Large B-Cell Lymphoma



	Investigator assessed (n = 101)
Objective response rate	83%
Complete response	58%
Partial response	25%
Median duration of response	11.1 mo
Median PFS	5.9 mo
Median OS	NR

Select AEs	Safety assessed (n = 108)
Grade ≥3 AEs	98%
Cytokine release syndrome	11%
Neurological events	32%
Neutropenia	39%
Encephalopathy	23%
Thrombocytopenia	24%

Locke FL et al. *Lancet Oncol* 2019;20(1):31-42.

Pivotal Safety and Efficacy Results from TRANSCEND NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel (liso-cel) in Relapsed/Refractory (R/R) Large B Cell Lymphomas

Abramson JS et al.
ASH 2019;Abstract 241.

TRANSCEND NHL 001: Safety and Efficacy of Lisocabtagene Maraleucel in Patients with R/R Large B-Cell Lymphomas

Response	ORR	CR
DLBCL cohort, all patients (n = 255)	73%	53%
Age ≥65 years (n = 107)	78%	61%
SPD ≥50 cm^3 (n = 69)	62%	33%
LDH ≥500 U/L (n = 57)	63%	40%
Chemorefractory (n = 170)	71%	52%

Select treatment-emergent adverse events	All patients receiving Liso-cel (n = 268)	
	Any grade	Grade ≥3
Cytokine release syndrome	42%	2%
Neurologic events	30%	10%
Prolonged Grade ≥3 cytopenia	—	37%

SPD = sum of the product of the greatest diameters

- Median PFS = 6.8 months
- Median OS = 19.9 months

Abramson JS et al. ASH 2019;Abstract 241.

Ongoing Phase III Studies of CAR T-Cell Therapies versus Standard of Care in R/R DLBCL

Trial	No. of patients	Arms
BELINDA (NCT03570892)	318	Tisagenlecleucel Standard therapy
ZUMA-7 (NCT03391466)	350	Axicabtagene ciloleucel Standard therapy
TRANSFORM (NCT03575351)	182	Lisocabtagene maraleucel Standard therapy

Standard therapy: Platinum-based chemotherapy followed by high-dose therapy and autologous stem cell transplant

www.clinicaltrials.gov. Accessed January 2020.

Editorial – Dr Moskowitz

- Designer treatment
- Will be restricted to transplant centers
- Each center is convinced that their CAR T cell is the “best”
- Now industry is heavily involved and each industry partner believes their drug is superior
- Toxicity is significantly under reported, but is more manageable
- Efficacy is inflated
- Data is not analyzed by intent to treat
- The patients on the clinical trials were a favorable cohort; remember, heavily pretreated patients are favorable; the poor-risk patients have already passed away

Editorial – Dr Moskowitz

- Cost is an issue
- There are so many companies that it is easy to give this therapy for free for now on a clinical trial
- However, about 25% of patients can be cured; is this any better than newer agents that target CD19?

Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant to or Relapsing After Chimeric Antigen Receptor T-Cell (CAR-T) Therapies, and Is Active in Treatment through Multiple Lines

Schuster SJ et al.
ASH 2019;Abstract 6.

GO29781: Results of the Phase I/Ib Trial of Mosunetuzumab

Best response	Evaluable patients (n = 16)
ORR	7 (43.8%)
CR	4 (25%)
DLBCL	2 (12.5%)
FL	2 (12.5%)

ORR and CR rates among efficacy-evaluable patients across all dose levels:

- iNHL: 64.1% (41/64) and 42.2% (27/64)
- aNHL: 34.7% (41/119) and 18.6% (22/119)
- CRs appeared durable
- 3 responses (1 CR, 2 PR) with re-treatment with M were observed allowed in CR patients who relapsed.

Adverse events

- Neurological AEs were reported in 44% of patients (Gr 1, 28.0%; Gr 2, 12.8%; Gr 3, 3.2%).
  - Common neurologic AEs were headache (14.7%), insomnia (10.1%) and dizziness (9.2%).

Schuster SJ et al. ASH 2019;Abstract 6.

Editorial – Dr S Smith

The recent approvals for CAR-T in relapsed and refractory DLBCLs has positively impacted the outlook for patients, with an estimated 40% of eligible patients achieving durable remission. Unfortunately, there are many challenges to widespread adoption of CAR-T as third line (or earlier lines) of treatment, including availability, cost, and toxicity. In addition, more than half of patients undergoing CAR-T will not respond or benefit from the procedure. With this backdrop, the activity of mosunetuzumab in r/r NHL, including post-CAR-T failures, is very promising.

Mosunetuzumab is a bispecific antibody with advantages over agents such as blinatumomab, because of its structure. Blinatumomab, currently approved for ALL, has activity in DLBCL/NHL, but its use is limited by the inconvenient 4- or 8-week continuous infusion along with significant toxicity, such as fevers, CRS, and neurotoxicity.

Editorial – Dr S Smith

Mosunetuzumab overcomes these problems by being a full-length bispecific antibody (thereby allowing weekly dosing) and by testing a “step-up” approach, which appears to mitigate the CRS and neurotoxicity.

In this plenary abstract, 218 patients with heavily pre-treated, r/r NHL (including 23 patients relapsing after CAR-T), the ORR and CR rates were 64.1% (41/64) and 42.2% (27/64) in iNHL patients and 34.7% (41/119) and 18.6% (22/119) in aNHL pts, respectively. Of note, responses appear durable (with short follow-up) and the “step-up” dosing was associated with only 1.4% grade 3 CRS and 3.2% grade 3 NT. Approximately 25% of patients post-CAR-T responded. Overall, this is promising and exciting and may effectively offer a salvage option.

Lymphomas and CLL — Drs Abramson, LaCasce and Smith

Chronic Lymphocytic Leukemia

Diffuse Large B-Cell Lymphoma

Hodgkin Lymphoma

Peripheral T-Cell Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

Brentuximab Vedotin with Chemotherapy for Stage 3/4 Classical Hodgkin Lymphoma (cHL): 4-Year Update of the ECHELON-1 Study

Bartlett NL et al.
ASH 2019;Abstract 4026.

ECHELON-1: Brentuximab Vedotin with Chemotherapy for Stage 3 or Stage 4 Classical HL (4-Year Update)

Summary of 42-month PFS by PET2 status

	A + AVD n = 664	ABVD n = 670	
All patients (ITT)	82.4%	76.2%	0.697 (0.547-0.890)
PET2-	85.0%	79.6%	0.695 (0.526-0.919)
PET2+	68.3%	51.5%	0.552 (0.308-0.989)

- Upon continued follow-up, 81% of patients with peripheral neuropathy (PN) in the A+AVD arm had either complete resolution (64%) or improvement (17%) of their PN events compared with 83% with either complete resolution (74%) or improvement (8%) in the ABVD arm.
- Among patients with ongoing PN after continued follow-up, the majority were Grade 1/2 events, with 89% (59% Grade 1) and 95% (65% Grade 1) on the A+AVD and ABVD arms, respectively.
- Overall survival data are not yet mature.

CI = confidence interval

Bartlett NL et al. ASH 2019;Abstract 4026.

Editorial – Dr Moskowitz

- BV-AVD vs ABVD
- Primary endpoint was modified PFS; in retrospect the results are identical to PFS in this data set
- 3-year data is holding with nearly a 6%-7% improvement in mPFS
- For pts interim PET2 negative, 87% vs 81%, but more interesting, for PET2+ we now have results if one continues ABVD (which should not be done!) — only 54.7% of pts are progression-free at 3 years
- Should 100 patients with AS HL receive BV + AVD if only 6-7 need it?
- There is no difference between ABVD and BV + AVD for Stage III patients
- More delays in therapy and toxic deaths in the non-US treated patients; G-CSF is required

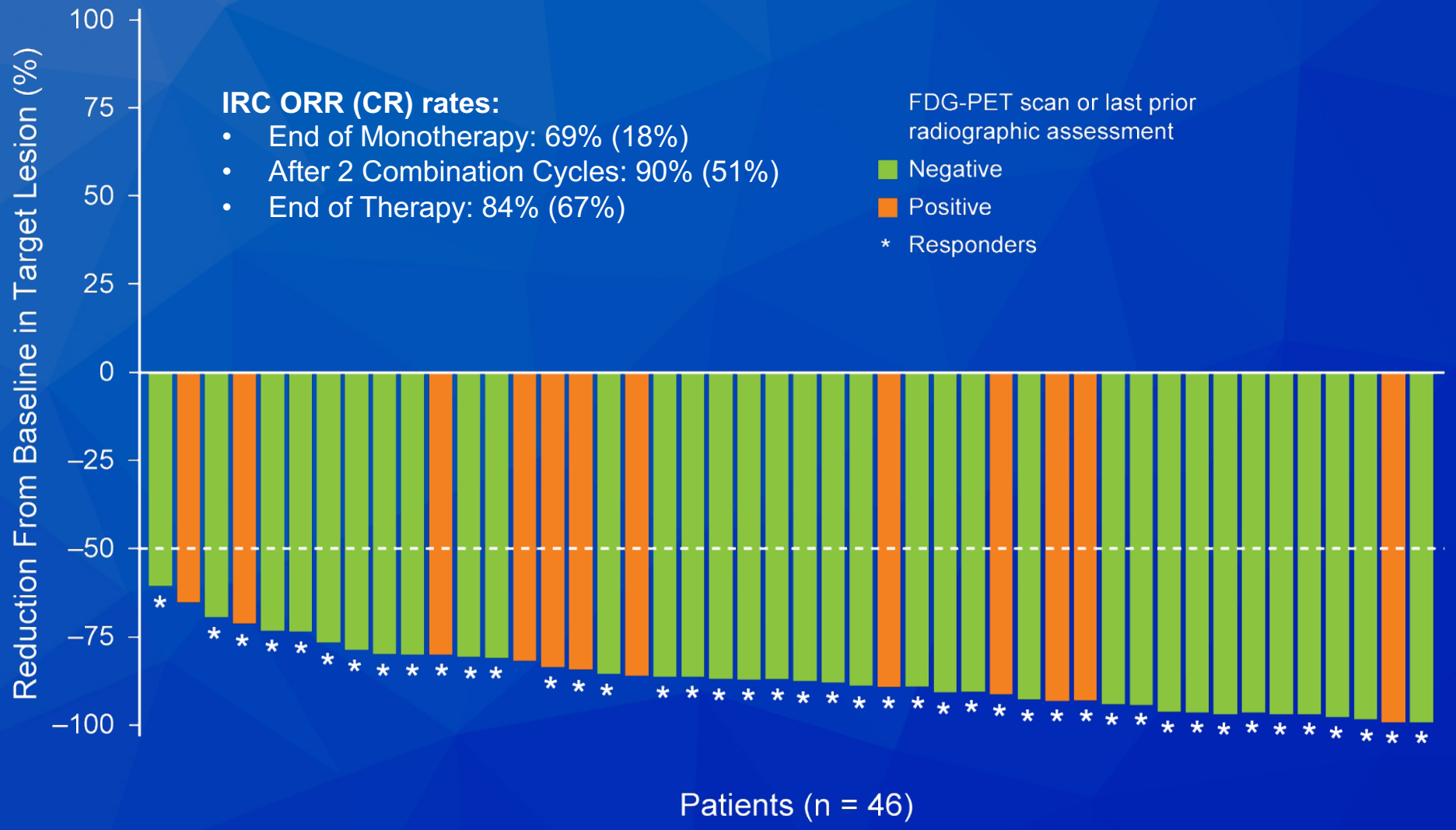
Editorial – Dr Moskowitz

- Remember that PET-adapted therapy is standard in US; if one looks at a comparison between BV + AVD and PET-adapted treatment, very unlikely that we will see a PFS difference
- Cost — 250K vs almost free
- I currently give for pts with Stage IV disease

Nivolumab for Newly Diagnosed Advanced-Stage Classic Hodgkin Lymphoma: Safety and Efficacy in the Phase II CheckMate 205 Study

Ramchandren R et al.
J Clin Oncol 2019;37(23):1997-2007.

CheckMate 205 (Cohort D): Change in Target Lesion and Response Across Treatment



Ramchandren R et al. *J Clin Oncol* 2019;37(23):1997-2007.

Editorial – Dr Moskowitz

- Update at Lugano
- Induction therapy with nivolumab, reimage, then 6 cycles of N-AVD
- Intergroup study dropped induction
- Remember, PET imaging is difficult with CPI because of false-positive results
- 51 pts, well balanced
- CR rate to induction only 18%-25% — poor
- Interim restaging PET-negative rate is suspect 20% — disparity between IRC and INV
- End of study PET-neg rate 69%-80%
- Unfortunately, PFS at 21 months is 83%, which has dropped since publication
- Intergroup study BV-AVD vs N-AVD a compromise, but please participate

Lymphomas and CLL — Drs Abramson, LaCasce and Smith

Chronic Lymphocytic Leukemia

Diffuse Large B-Cell Lymphoma

Hodgkin Lymphoma

Peripheral T-Cell Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

FDA Approval of BV in Combination with Chemotherapy for Adults with Previously Untreated Systemic Anaplastic Large Cell Lymphoma (sALCL) and CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Press Release – November 16, 2018

"The FDA has approved BV in combination with CHP chemotherapy (cyclophosphamide/doxorubicin/prednisone) for previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified. This is the first FDA approval for previously untreated PTCL including sALCL.

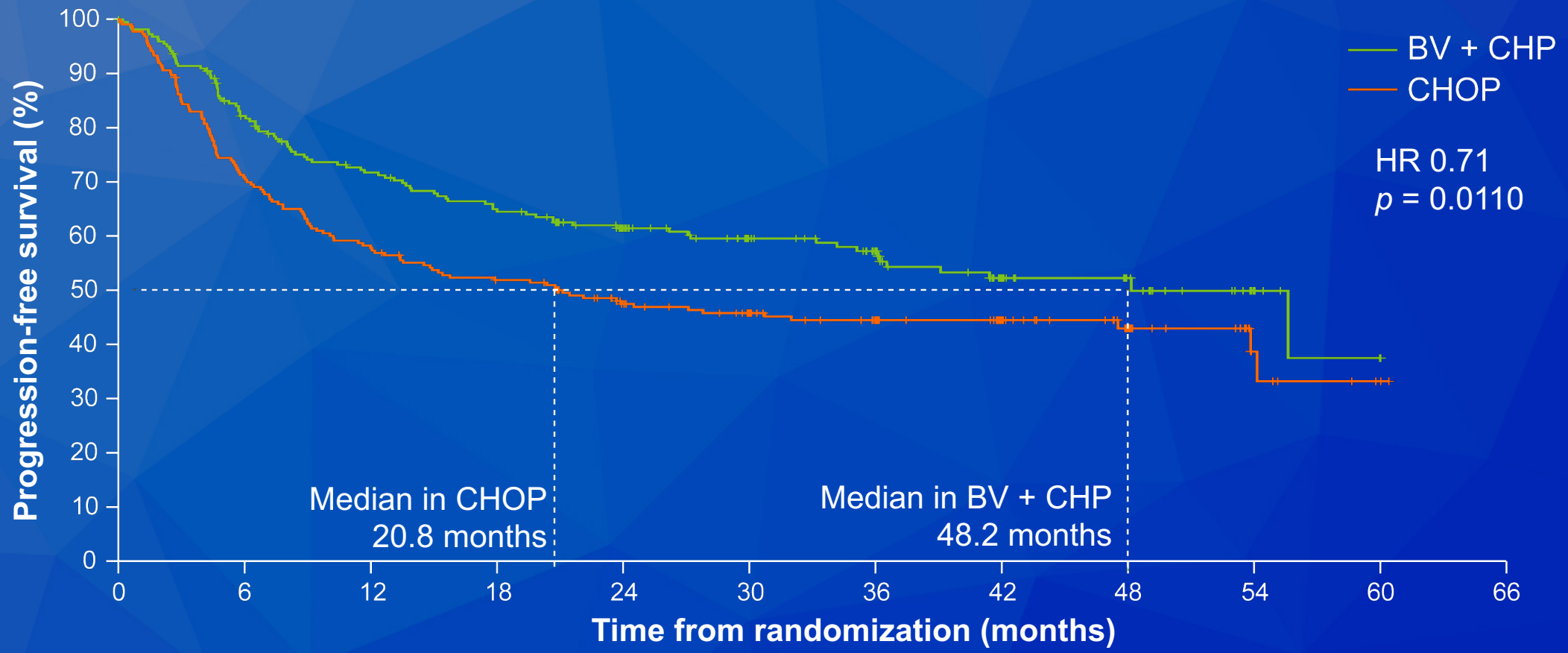
Approval was based on ECHELON-2 (NCT01777152), a double-blind, multicenter trial that randomized 226 patients to brentuximab vedotin plus CHP and 226 patients to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)."

https://www.fda.gov/drugs/fda-approves-brentuximab-vedotin-previously-untreated-salcl-and-cd30-expressing-ptcl

Brentuximab Vedotin (BV) with Chemotherapy for CD30-Positive Peripheral T-Cell Lymphoma (ECHELON-2): A Global, Double-Blind, Randomised, Phase III Trial

Horwitz S et al.
Lancet 2019;393(10168):229-40.

ECHELON-2: Efficacy and Safety Summary



- Median OS was not reached in either subgroup ($p = 0.0244$, HR 0.66), though it was numerically in favor of BV + CHP for key patient subgroups analyzed.
- Adverse events, including incidence and severity of febrile neutropenia (BV + CHP = 18%; CHOP = 15%) and peripheral neuropathy (BV + CHP = 52%; CHOP = 55%) were similar between groups.
  - Fatal adverse events: BV + CHP = 7 (3%); CHOP = 9 (4%)

Horwitz S et al. *Lancet* 2019;393(10168):229-40.

Editorial – Dr Moskowitz

- BV-CHP vs CHOP
- ALCL, PTCL, AILT
- HOME RUN
- This could be the first aggressive lymphoma study where there is an OS advantage between the 2 study arms
- At 4 years 2.5x improvement in PFS and a 12% improvement in OS
- Somewhat shocking, FDA approved the regimen for ALCL as well as PTCL
- Remember that there were patients on both arms that received an ASCT in first CR
- We do not know if BV-AVD is superior to CHOPE, and there are no results of BV-CHEP

Lymphomas and CLL — Drs Abramson, LaCasce and Smith

Chronic Lymphocytic Leukemia

Diffuse Large B-Cell Lymphoma

Hodgkin Lymphoma

Peripheral T-Cell Lymphoma

Follicular Lymphoma

Mantle Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

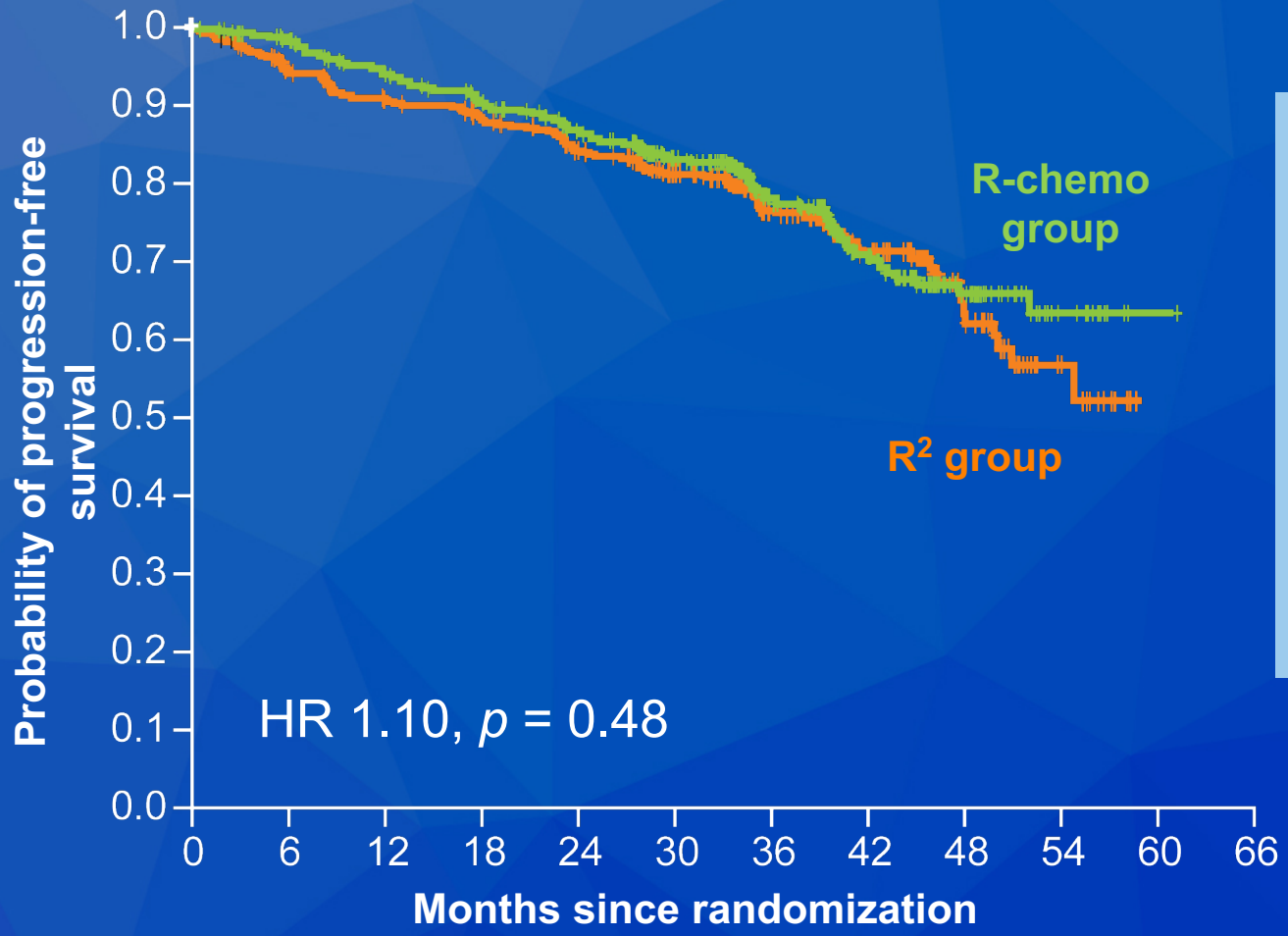
ORIGINAL ARTICLE

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

F. Morschhauser, N.H. Fowler, P. Feugier, R. Bouabdallah, H. Tilly, M.L. Palomba, C. Fruchart, E.N. Libby, R.-O. Casasnovas, I.W. Flinn, C. Haioun, H. Maisonneuve, L. Ysebaert, N.L. Bartlett, K. Bouabdallah, P. Brice, V. Ribrag, N. Daguindau, S. Le Gouill, G.M. Pica, A. Martin Garcia-Sancho, A. López-Guillermo, J.-F. Larouche, K. Ando, M. Gomes da Silva, M. André, P. Zachée, L.H. Sehn, K. Tobinai, G. Cartron, D. Liu, J. Wang, L. Xerri, and G.A. Salles, for the RELEVANCE Trial Investigators*

N Engl J Med 2018;379(10):934-47.

RELEVANCE: Rituximab + Lenalidomide (R^2) versus Rituximab + Chemotherapy (R-chemo) in Untreated, Advanced FL



Grade 3-4 adverse events	R^2 (n = 507)	R-chemo (n = 503)
Neutropenia	32%	50%
Febrile neutropenia	2%	7%
Cutaneous reactions	7%	1%
Diarrhea	2%	1%
Tumor lysis syndrome	1%	<1%

- Efficacy results were similar between R^2 and R-chemo in advanced, untreated follicular lymphoma.
- The safety profile differed between the 2 groups.

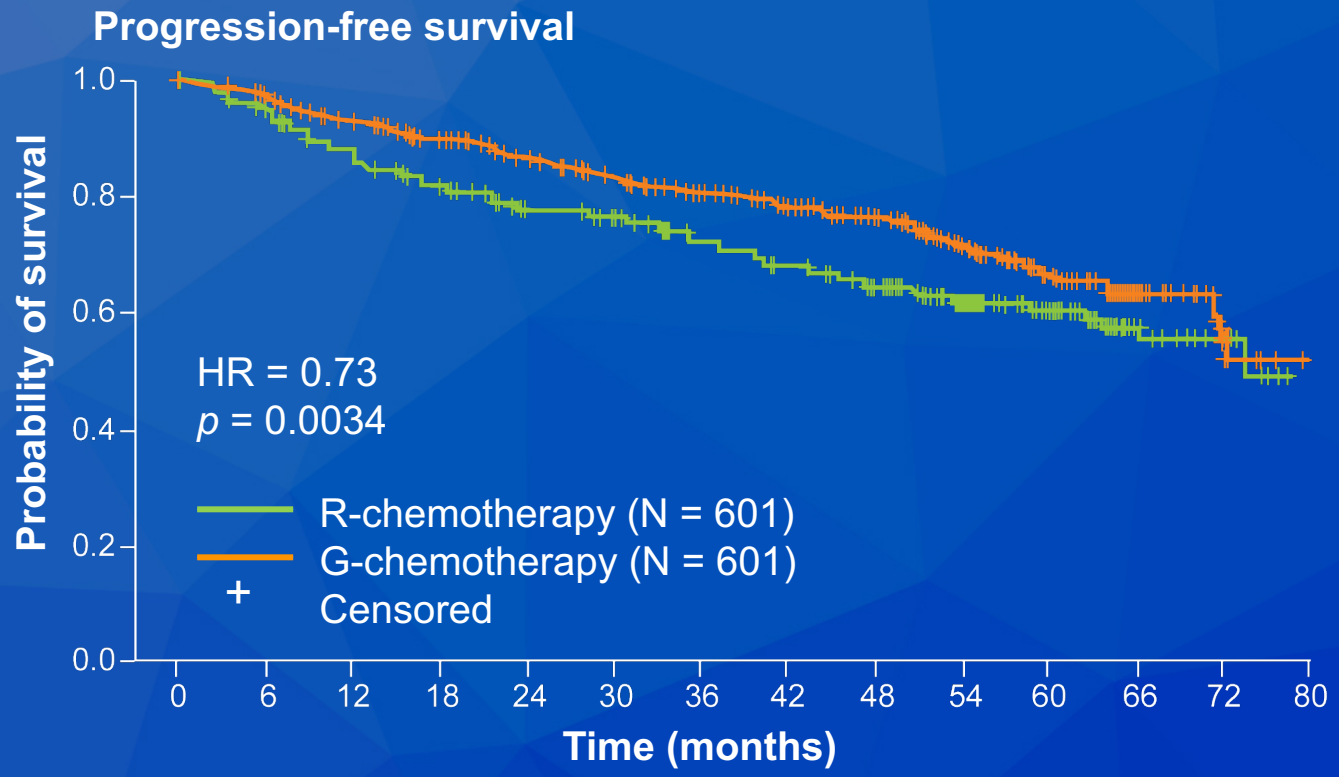
Morschhauser F et al. *N Engl J Med* 2018;379(10):934-47.

Obinutuzumab-Based Immunochemotherapy Prolongs Progression-Free Survival and Time to Next Anti-Lymphoma Treatment in Patients with Previously Untreated Follicular Lymphoma: Four-Year Results from the Phase III GALLIUM Study

Townsend W et al.

Proc ASH 2018;Abstract 1597.

GALLIUM: Four-Year Safety and Efficacy Results with Obinutuzumab-Based Immunochemotherapy for Previously Untreated Follicular Lymphoma



	G-chemo (n = 601)	R-chemo (n = 601)
Any adverse event (AE)	99.8%	99.5%
Grade 3-5 AEs	79.2%	71.2%
Infections	22.2%	18.6%
Neutropenia	48.4%	41.4%
Second cancer	6.9%	4.4%

G = obinutuzumab; R = rituximab

- G-chemo continues to demonstrate clinically meaningful improvements in outcomes relative to rituximab (R)-chemo for patients with previously untreated FL
- OS data remain immature, with additional follow-up needed to draw conclusions
- Safety data are consistent with those reported in the primary analysis

Townsend W et al. *Proc ASH* 2018;Abstract 1597.

Editorial – Dr M Smith

Given that rituximab, the first therapeutic anti-cancer monoclonal antibody, was approved more than 20 years ago, it is surprising how little we know about optimal dose and schedule and even the precise mechanisms of action. Over those 20 years, many attempts have been made to create engineered monoclonal anti-CD20 antibodies with characteristics superior to rituximab. Currently, only two of these have been approved for use, ofatumumab, which is not used widely, and obinutuzumab. The GALLIUM trial compared rituximab and obinutuzumab, in combination with chemotherapy (CHOP, CVP or bendamustine) as induction, followed by antibody-alone maintenance as therapy for previously untreated FL. The original publication and more recent 4.5-year follow-up continue to demonstrate prolonged PFS (4-yr PFS 78% vs 67%) and time to next lymphoma treatment (4-yr TTNT 84% vs 77%) in the obinutuzumab cohort, with no difference in OS (91% vs 90%).

Editorial – Dr M Smith

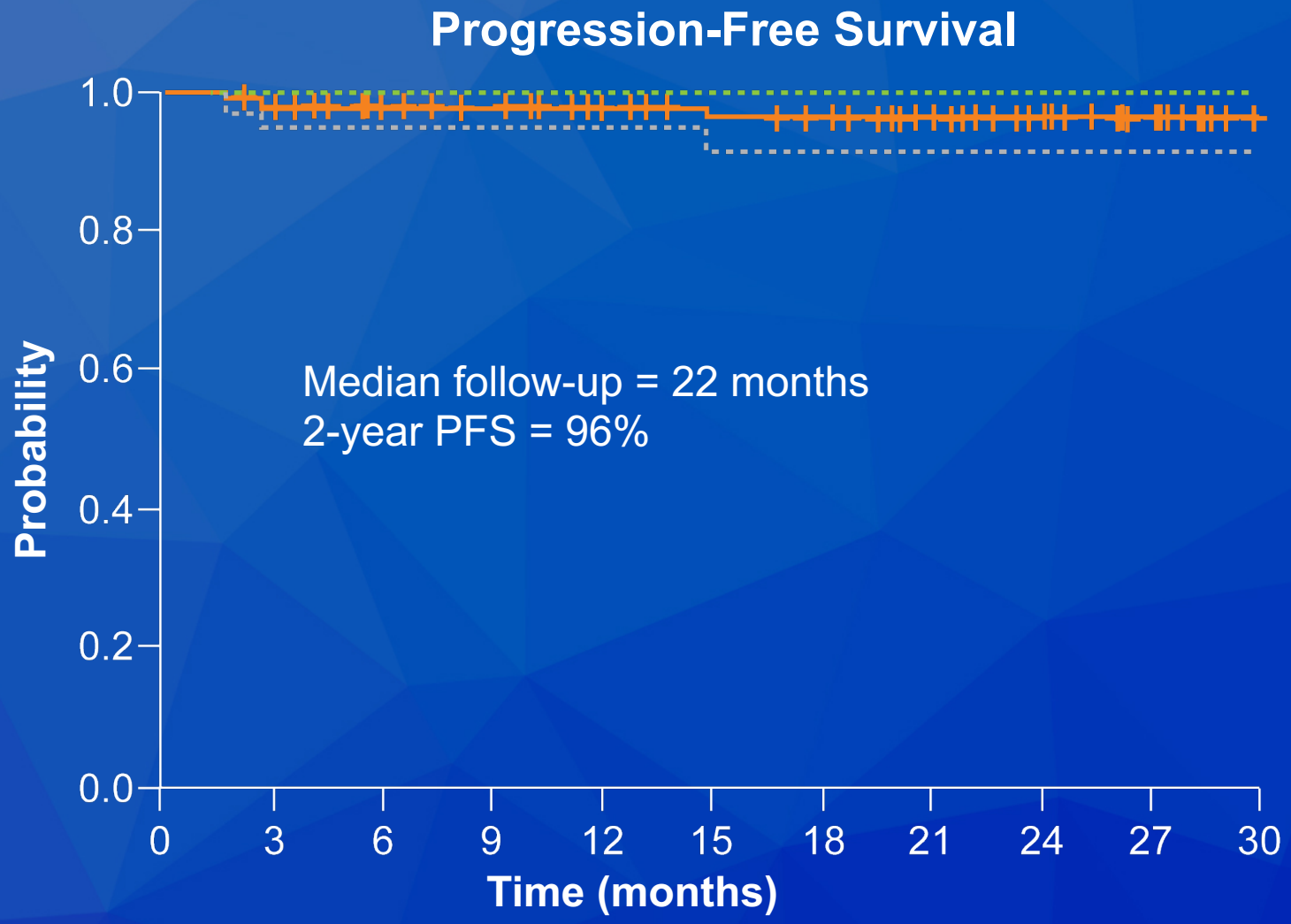
Before one concludes that obinutuzumab is better than rituximab, one needs to realize that obinutuzumab was given at a higher dose more frequently, achieving higher levels early on in the chemotherapy course. Thus, the conclusion is that obinutuzumab as given results in slightly better PFS and TTNT than rituximab as given. Nonetheless, it does show the benefit of this dosing schedule, which adds little to toxicity and does yield prolonged benefit.

The theoretic rationale for combining anti-CD20 antibody with lenalidomide, and clinical data for the R^2 combination, led to combination trials of obinutuzumab with lenalidomide. In the multicenter, single-arm phase 2 GALEN study of obinutuzumab + lenalidomide for refractory follicular lymphoma, this combination was active. In GALEN, the antibody was given once every four weeks rather than with the weekly loading schedule. This would permit a direct comparison with R^2, although it is not clear to me this would be optimal use of limited patient and investigator resources.

Results of a Phase II Study of Obinutuzumab in Combination with Lenalidomide in Previously Untreated, High Tumor Burden Follicular Lymphoma (FL)

Nastoupil LJ et al.
ASH 2019;Abstract 125.

Results of a Phase II Trial of Obinutuzumab in Combination with Lenalidomide in Untreated High Burden FL



- ORR = 98% (85 CR, 1 PR)
  - CR at first response assessment = 92%
- No deaths have been observed to date.
- 11 patients discontinued therapy due to AEs.
  - Most common reason = upper respiratory tract infection (n = 5)
  - Other reasons include bradycardia with sick sinus syndrome, urinary tract infection, constipation and abdominal pain.
- Most common Grade ≥3 AEs: neutropenia, rash, lung infection and neutropenic fever

Nastoupil LJ et al. ASH 2019;Abstract 125.

Editorial – Dr Nastoupil

I presented the results of a single-center, open-label Phase II study exploring the safety and efficacy of obinutuzumab in combination with lenalidomide in previously untreated, high tumor burden (defined by GELF criteria) follicular lymphoma (FL). The GALLIUM study demonstrated obinutuzumab was associated with improved PFS when combined with chemotherapy in previously untreated, high tumor burden FL when compared to rituximab combinations. The RELEVANCE study demonstrated that lenalidomide in combination with rituximab was not superior to R-chemotherapy combinations in high tumor burden FL. However, lenalidomide and rituximab resulted in high response rates, robust PFS and a favorable toxicity profile. Our hypothesis was this immune therapy approach could be further enhanced with replacement of rituximab with obinutuzumab. We enrolled 90 subjects, and with a median follow-up of 24 months, only 3 progression events had been observed, with a 2-year PFS estimate of 96%.

Editorial – Dr Nastoupil

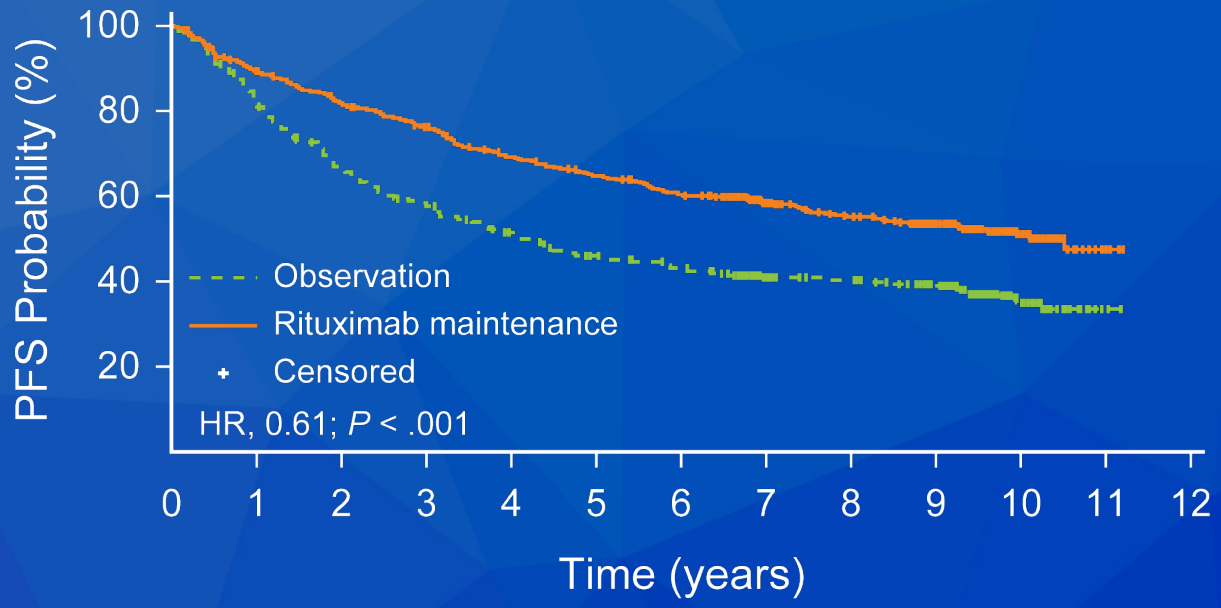
Response rates were also very high, with nearly 90% of patients achieving a complete response after 3 cycles of therapy. The safety profile was also favorable, with no grade 5 events and grade 3 or higher adverse events being primarily hematologic (17% neutropenia) and manageable. This single-center experience should be further explored in a multicenter study, as the results are very promising.

Sustained Progression-Free Survival Benefit of Rituximab Maintenance in Patients with Follicular Lymphoma: Long-Term Results of the PRIMA Study

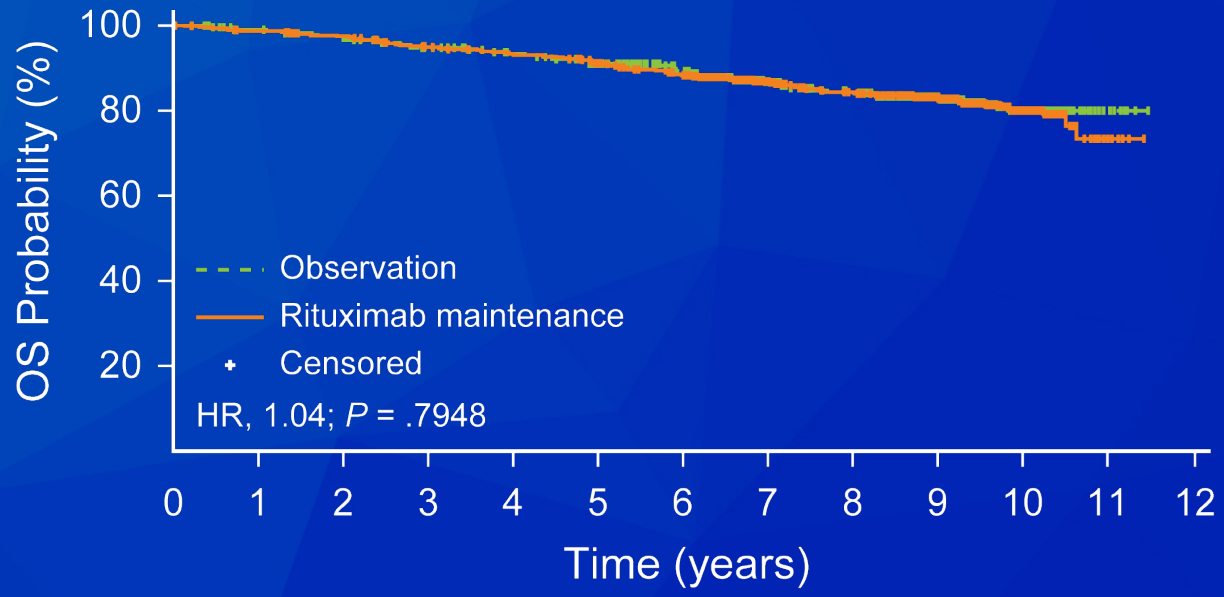
Bachy E et al.
J Clin Oncol 2019;37(31):2815-24.

PRIMA: Survival Analyses After 9 Years of Follow-Up

Median PFS: 10.5 yrs vs 4.1 yrs



Median OS: Not reached; Estimated 10-year OS = 80% both arms



Bachy E et al. *J Clin Oncol* 2019;37(31):2815-24.

FDA Approves Lenalidomide for Follicular and Marginal Zone Lymphoma

Press Release – May 28, 2019

"On May 28, 2019, the Food and Drug Administration approved lenalidomide in combination with a rituximab product for previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL).

Approval was based on two clinical trials: AUGMENT (NCT01938001) and MAGNIFY (NCT01996865). In AUGMENT, 358 patients with relapsed or refractory FL or MZL were randomized (1:1) to receive lenalidomide and rituximab or rituximab and placebo. In the single-arm component of MAGNIFY, 232 patients with relapsed or refractory FL, MZL, or mantle cell lymphoma received 12 induction cycles of lenalidomide and rituximab.

In AUGMENT, the primary endpoint was progression-free survival (PFS) in the intent-to-treat population, as determined by an independent review committee (IRC)."

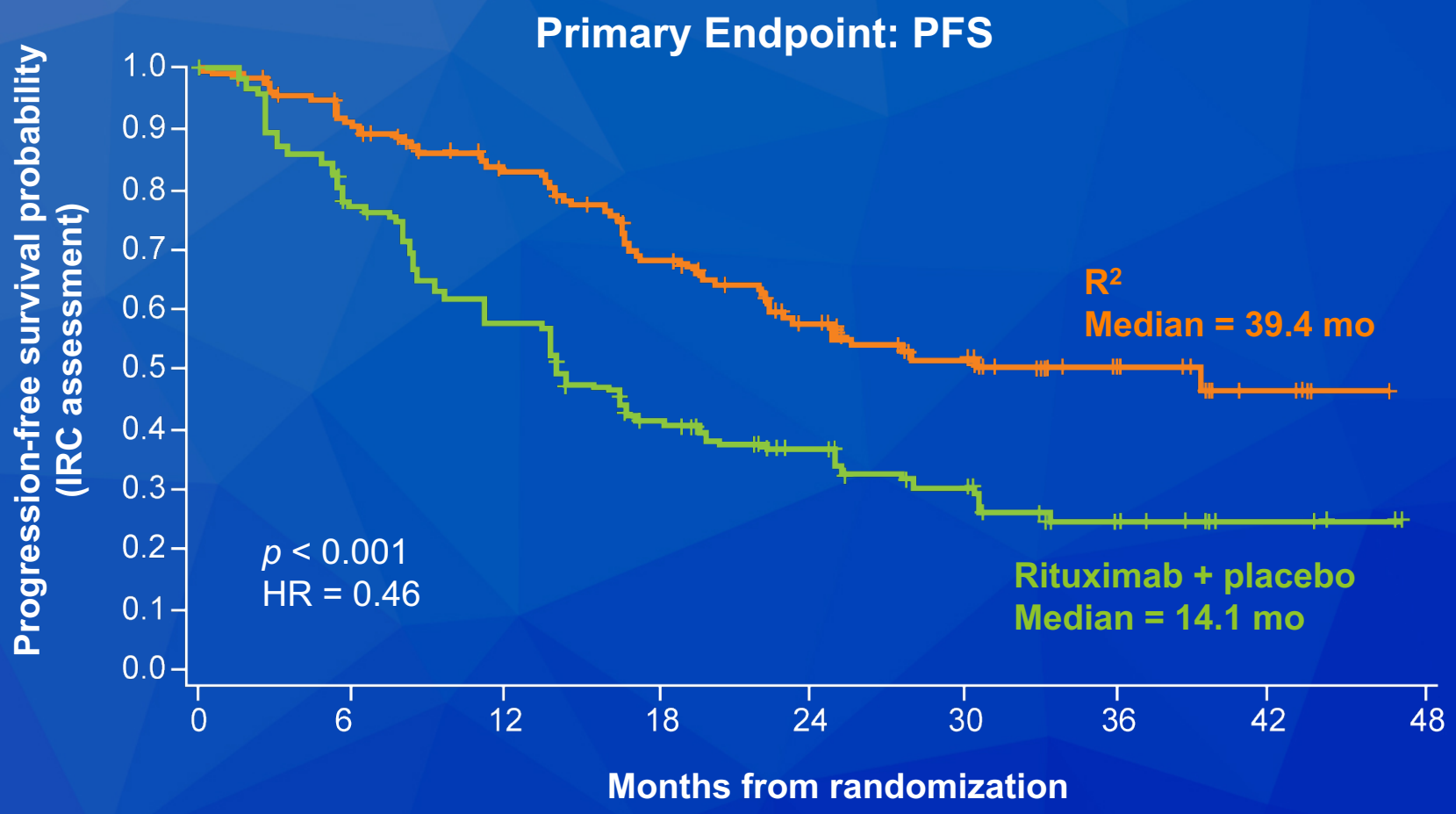
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenalidomide-follicular-and-marginal-zone-lymphoma

AUGMENT: A Phase III Study of Lenalidomide plus Rituximab versus Placebo plus Rituximab in Relapsed or Refractory Indolent Lymphoma

Leonard JP et al.

J Clin Oncol 2019;37(14):1188-99.

AUGMENT: R² versus Rituximab/Placebo in R/R FL or Marginal Zone Lymphoma



	R² (n = 178)	R/placebo (n = 180)
ORR	78%	53%
CR	34%	18%
Median DOR	36.6 mo	21.7 mo

Leonard JP et al. *J Clin Oncol* 2019;37(14):1188-99.

Editorial – Dr M Smith

Indolent non-Hodgkin lymphoma (iNHL) is still incurable and in need of novel therapies. Lenalidomide has long been known to be active not only against myeloma but also in CLL and mantle cell lymphoma. Preclinical and clinical data suggest that the addition of rituximab, so called R2 [rituximab-lenalidomide], improves outcomes compared with lenalidomide alone. Thus, a series of trials have investigated the efficacy of R2 in iNHL. AUGMENT is a randomized trial of R2 versus rituximab-placebo in relapsed/refractory iNHL (follicular lymphoma [FL] grades 1-3A, marginal zone lymphoma). Virtually all patients have received prior rituximab, usually with chemotherapy, at least once. It is not surprising, therefore, that the combination regimen prolonged the primary endpoint of PFS compared with rituximab alone (median 39 vs 14 months). Note lenalidomide was given for up to 12 cycles, rituximab weekly x 4 in cycle 1 followed by 4 more doses each on day 1 of cycles 2-5. Median time to next lymphoma therapy was “not reached” vs 32 months.

Editorial – Dr M Smith

FL patients whose disease progresses in less than 24 months (POD24) have poor outcomes and represent a population that requires improved therapies. Post-hoc analysis of the AUGMENT data indicates that the expected poor outcomes in patients with POD24 were not observed in the R2 cohort, suggesting that the different mechanism of action of lenalidomide compared with standard immunochemotherapy may obviate POD24 as a prognostic indicator. Additional preliminary analysis, with relatively small numbers, suggests that rate and depth response to subsequent therapy may be higher following R2. The MAGNIFY trial also included relapsed/refractory FL grades 1-3A and marginal zone lymphoma. All patients received R2 for up to 12 cycles, then were randomized to receive additional R2 or rituximab maintenance alone.

Editorial – Dr M Smith

While data on the maintenance question are not yet mature, R2 yielded an ORR of 73% (CR 45%) and, even in “rituximab-refractory” patients, an ORR of 63% (CR 40%). Based on these two large trials, the FDA has approved lenalidomide, in combination with rituximab, for previously treated follicular and marginal zone lymphoma patients.

Treatment Emergent Adverse Events Vary with Different PI3K Inhibitors

Awan F et al.
Proc EHA 2019;Abstract PF378.

Select Grade 3/4 Treatment Emergent Adverse Events by PI3K Inhibitor

TEAE	Idelalisib (N = 163)	Copanlisib (N = 142 or 168)	*p*-value
Diarrhea	13.5%	4.8%	0.0068
Hyperglycemia	1.2%	39.3%	<0.0001
Hypertension	1.2%	27.4%	<0.0001
Increased ALT	17.8%	1.4%	<0.0001
Increased AST	12.9%	1.4%	0.0001

TEAE	Idelalisib (N = 261)	Duvelisib (N = 442)	*p*-value
Anemia	5%	14.9%	<0.0001
Diarrhea or colitis	11.5%	22.9%	0.0002
Neutropenia	28.4%	41.6%	0.0005
Rash	3.1%	9.3%	0.0019
Increased ALT	15.7%	7.7%	0.0014
Increased AST	12.3%	5.4%	0.0022

Awan F et al. *Proc EHA* 2019;Abstract PF378.

Editorial – Dr M Smith

- PI3K is involved in cell signaling. It has 4 isoforms. The α and β isoforms are expressed in a wide variety of cells, while γ and δ isoforms are limited to hematopoietic cells. PI3K δ is involved in signaling downstream of the BCR complex in B cells and so was a logical target for small molecule inhibitors. Idelalisib, a PI3K δ inhibitor developed based on this concept, was the first PI3K inhibitor approved for use in CLL and lymphoma. The drug is effective but has some unique toxicities (hepatitis, colitis), reflecting immune activation related at least in part to decreased T-reg function, which have limited its use. PI3K inhibitors that target additional isoforms have been developed. Duvelisib — an oral agent, as is idelalisib — is a dual γ/δ inhibitor with activity against CLL and indolent B-cell lymphoma. Toxicity is similar to idelalisib as expected. Another recently approved PI3K inhibitor copanlisib, administered via IV, primarily inhibits α and δ PI3K isoforms.

Editorial – Dr M Smith

- With the α isoform being ubiquitously expressed and involved in cellular energetic signaling, copanlisib has unique toxicities including hyperglycemia and hypertension. These are often fairly acute but transient. Additional agents targeting the PI3K pathway are also under study, including umbralisib, a PI3Kδ inhibitor that also inhibits casein kinase 1 and may have an improved toxicity profile.
- Duvelisib was compared with ofatumomab in relapsed/refractory CLL and demonstrated improved PFS. Cross-trial comparison, with all those caveats, suggests to me similar efficacy as idelalisib in a similar study design. The Phase 2 DYNAMO evaluated duvelisib in relapsed/refractory iNHL with an ORR 47% and median PFS ~10 months, perhaps a bit less promising than idelalisib data in a similar population.

Editorial – Dr M Smith

- The phase 2 CHRONOS-1 trial of copanlisib administered weekly days 1, 8 and 15 q28 days in relapsed/refractory iNHL revealed an ORR 60% (17% CR). Ongoing trials are investigating combinations with rituximab or R-chemo.

Polatuzumab Vedotin plus Obinutuzumab and Lenalidomide in Patients with Relapsed/Refractory Follicular Lymphoma: Primary Analysis of the Full Efficacy Population in a Phase Ib/II Trial

Diefenbach C et al.
ASH 2019;Abstract 126.

GO29834: Activity and Safety of Polatuzumab Vedotin in Combination with Obinutuzumab and Lenalidomide in R/R FL

Responses at the end of induction (n = 46)				
Best overall response	Modified Lugano 2014[1]		Lugano 2014	
	By INV	By IRC	By INV	By IRC
Objective response	38 (83%)	35 (76%)	38 (83%)	35 (76%)
CR	28 (61%)	30 (65%)	34 (74%)	33 (72%)
PR	10 (22%)	5 (11%)	4 (9%)	2 (4%)

[1] Requires a negative bone marrow biopsy to confirm PET-CR, and PET-PR must also meet CT-PR criteria

- With a median follow-up of 11.27 months, median PFS was not reached.
- A subgroup analysis showed that 71% (15/21) of patients who were refractory to their last treatment achieved a CR.
- In total, 5 patients experienced PD: 3 in C1 or C2 and 2 at the month 12 response assessment.

Diefenbach C et al. ASH 2019;Abstract 126.

Editorial – Dr Nastoupil

Polatuzumab is an antibody-drug conjugate targeting CD79b and is FDA approved for R/R DLBCL in combination with bendamustine and rituximab. However, polatuzumab is not approved for the treatment of FL. Lenalidomide and obinutuzumab have a promising efficacy and safety profile in relapsed FL, as does obinutuzumab in combination with polatuzumab. Therefore, a triplet combination was pursued, exploring the safety and efficacy of polatuzumab, obinutuzumab and lenalidomide in R/R FL. Fifty-six patients were enrolled in the phase I and phase IB study. The primary efficacy endpoint was the CR rate, and it was 65% in this study. With a median follow-up of nearly 12 months, the median PFS had not been reached and only 5 subjects had experienced a progression event, which is promising in this setting given the PI3K inhibitors are associated with a median PFS of about 12 months. Lenalidomide and rituximab was associated with a median PFS of approximately 40 months in R/R FL. With no new safety concerns, this combination should be further explored in a randomized trial to discern whether a triplet is necessary over lenalidomide + rituximab/obinutuzumab.

Lymphomas and CLL — Drs Abramson, LaCasce and Smith

Chronic Lymphocytic Leukemia

Diffuse Large B-Cell Lymphoma

Hodgkin Lymphoma

Peripheral T-Cell Lymphoma

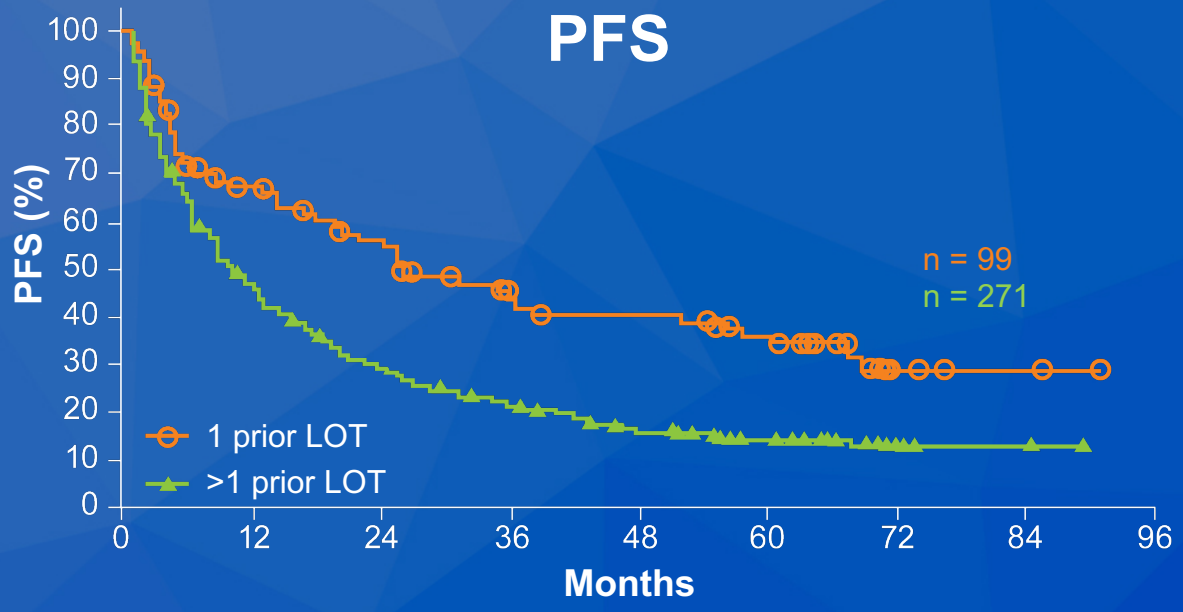
Follicular Lymphoma

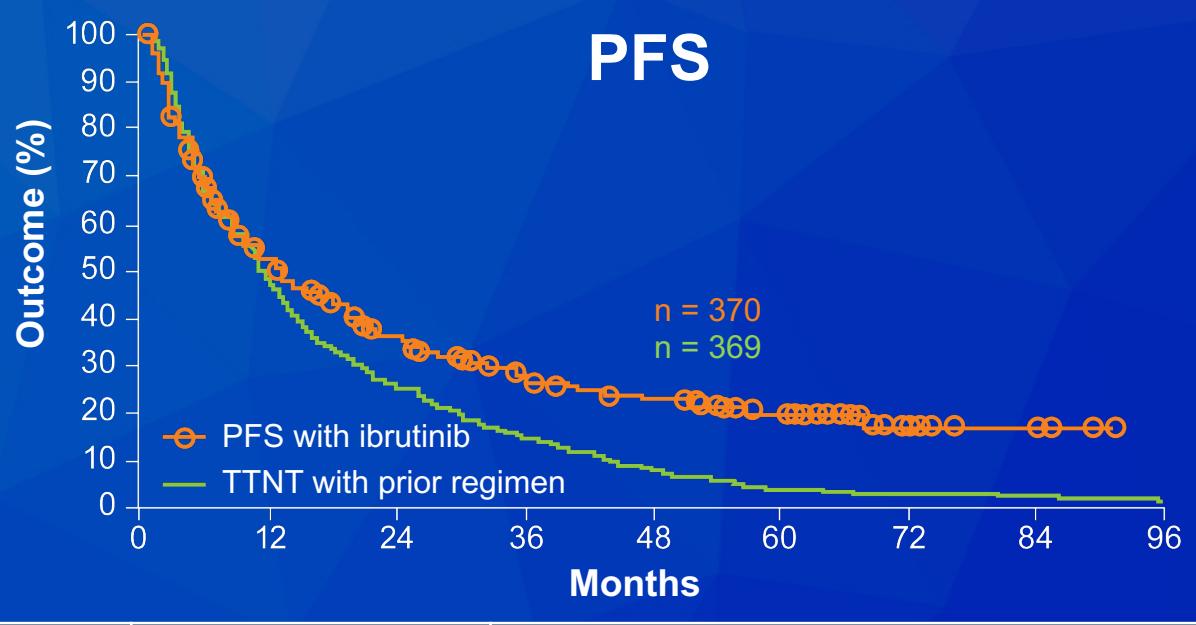
Mantle Cell Lymphoma

Long-Term Outcomes with Ibrutinib versus the Prior Regimen: A Pooled Analysis in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) with Up to 7.5 Years of Extended Follow-Up

Rule S et al.
ASH 2019;Abstract 1538.

Pooled Analysis in R/R MCL with Up to 7.5 Years of Extended Follow-Up





LOT = line of therapy;
TTNT = time to next therapy

Endpoint	Overall (N = 370)	Prior lines of therapy	
		1 (n = 99)	>1 (n = 271)
Overall response rate, n (%)	**258 (69.7)**	**77 (77.8)**	**181 (66.8)**
CR	102 (27.6)	37 (37.4)	65 (24.0)
PR	156 (42.2)	40 (40.4)	116 (42.8)
PFS[a] median (95% CI), mo	**12.5 (9.8-16.6)**	**25.4 (17.5-51.8)**	**10.3 (8.1-12.5)**
Patients with CR (n = 102)	67.6 (51.7-NE)	68.5 (38.0-NE)	67.7 (41.7-NE)
Patients with PR (n = 156)	12.6 (10.3-16.6)	24.2 (13.9-36.5)	10.5 (8.3-12.9)
OS[a] median (95% CI), mo	**26.7 (22.5-38.4)**	**61.6 (36.0-NE)**	**22.5 (16.2-26.7)**
Patients with CR (n = 102)	NR (NE-NE)	NR (NE-NE)	NR (71.4-NE)
Patients with PR (n = 156)	23.6 (20.6-32.2)	36.0 (21.8-55.6)	22.6 (17.2-26.9)

Rule S et al. ASH 2019;Abstract 1538.

[a] Kaplan-Meier estimate

Editorial – Dr Cheson

While initial therapy for patients with mantle cell lymphoma (MCL) may be a bit controversial, it is quite clear that BTK inhibitors are currently the standard in the relapsed/refractory setting. Whereas there are 3 BTK inhibitors approved by the FDA for MCL (ibrutinib, acalabrutinib, zanubrutinib), the longest follow-up is with ibrutinib. The present study that involved a large pooled analysis with up to 7.5 years of follow-up produced some interesting observations. First, not unexpectedly, there was a good correlation between the extent of prior therapy and duration of response, with those who had a single line of therapy achieving a PFS of over 2 years. Second, unlike what is usually experienced with chemotherapy, the duration of response with ibrutinib is often longer than with the prior regimen. Third is that not only did a substantial proportion of patients remain in remission longer than 5 years, but there is a suggestion of a late plateau on the PFS curve. Importantly, there were no late toxicities noted.

Editorial – Dr Cheson

One next step will be to combine ibrutinib with other active drugs to further improve on its efficacy (see the next abstract). However, why wait for patients to relapse after chemoimmunotherapy? We should be moving our most effective drugs into the front-line setting, as is being tested with ibrutinib. Once that happens, however, novel effective agents will need to be rapidly developed for patients who subsequently relapse.

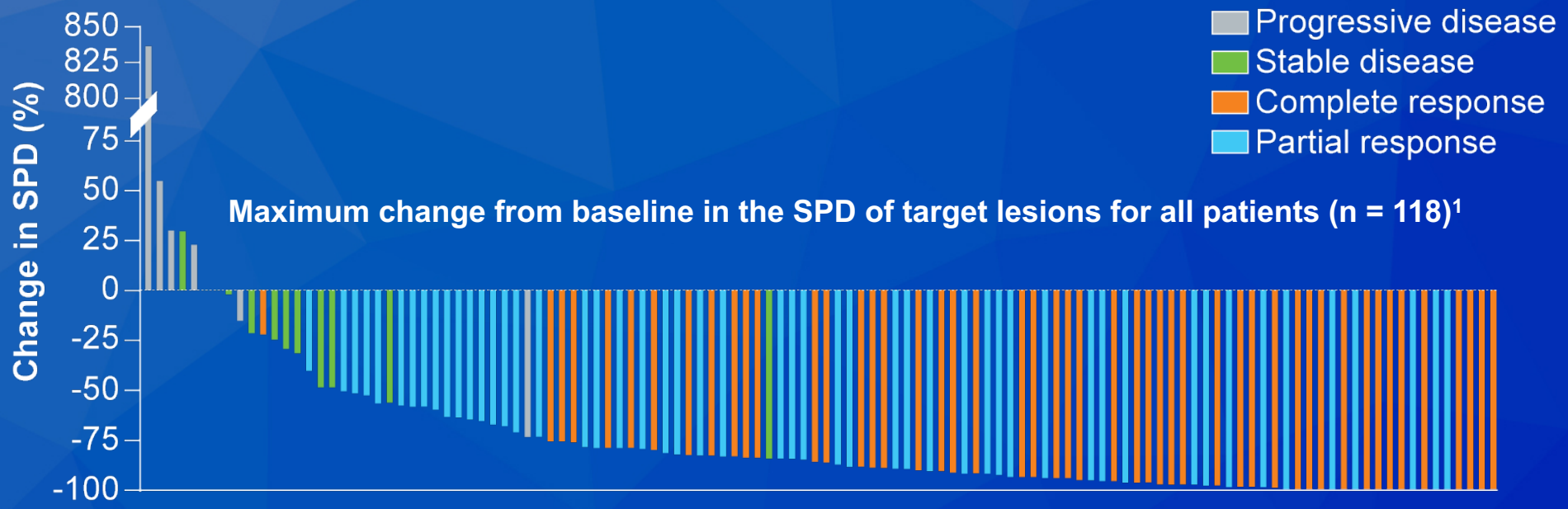
Acalabrutinib in Relapsed or Refractory Mantle Cell Lymphoma (ACE-LY-004): A Single-Arm, Multicentre, Phase 2 Trial[1]

Long-Term Follow-Up of Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Mantle Cell Lymphoma[2]

[1] Wang M et al.
Lancet 2018;391(10121):659-67.

[2] Wang M et al.
Proc ASH 2018;Abstract 2876.

ACE-LY-004 Phase II Trial of Acalabrutinib: Response and Long-Term Follow-Up Results



Long-term follow-up >24 mo[2]	N = 124
Overall response rate	81%
Complete response	43%
Partial response	38%
Median PFS	19.5 mo

- The AE profile was largely similar to earlier reporting, with limited additional safety events observed in an additional year of follow-up.[2]

[1] Wang M et al. *Lancet* 2018;391(10121):659-67; [2] Wang M et al. *Proc ASH* 2018;Abstract 2876.

Editorial – Dr M Smith

Acalabrutinib has the same mechanism of action as ibrutinib. However, its kinome screen shows a more limited scope of inhibitory targets aside from BTK, which predicts it should have fewer off-target toxicities. Unfortunately, it requires twice-daily dosing and prohibition of PPI administration. Given the same BTK inhibition, it is expected to be equally efficacious, and the hope is that it will be better tolerated, at least in certain situations. While we await the head-to-head comparison in front-line CLL, there are data accumulating in mantle cell lymphoma (MCL). Two-year follow-up of one of the initial cohorts of relapsed/refractory MCL patients shows that acalabrutinib was well-tolerated and the ORR was ~80, with 40% CR. Median duration of response was ~2 years. Acalabrutinib has also been combined with BR, and initial safety and efficacy data indicate, as expected, high rates of ORR and CR in both treatment-naïve and previously treated patients, with no unexpected toxicity signals.

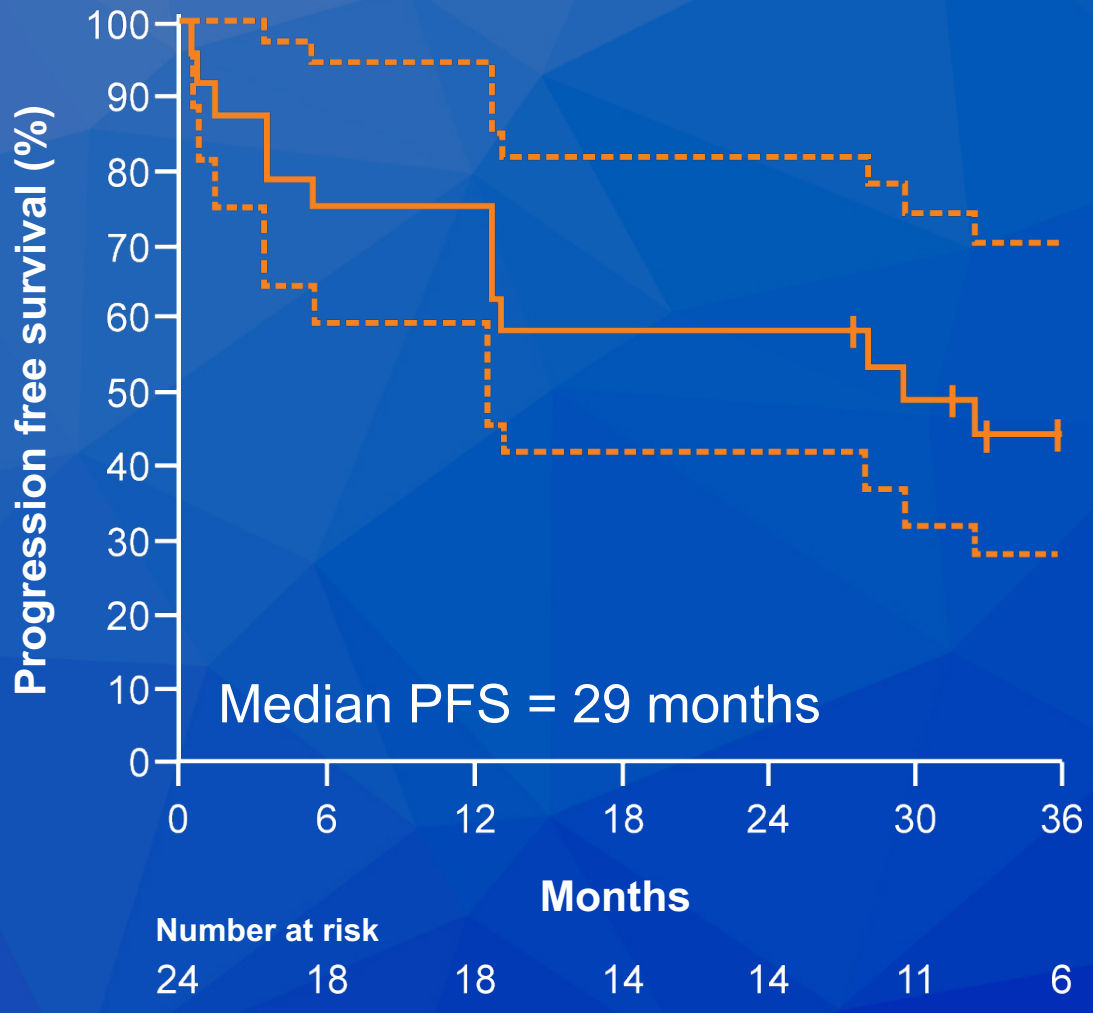
Editorial – Dr M Smith

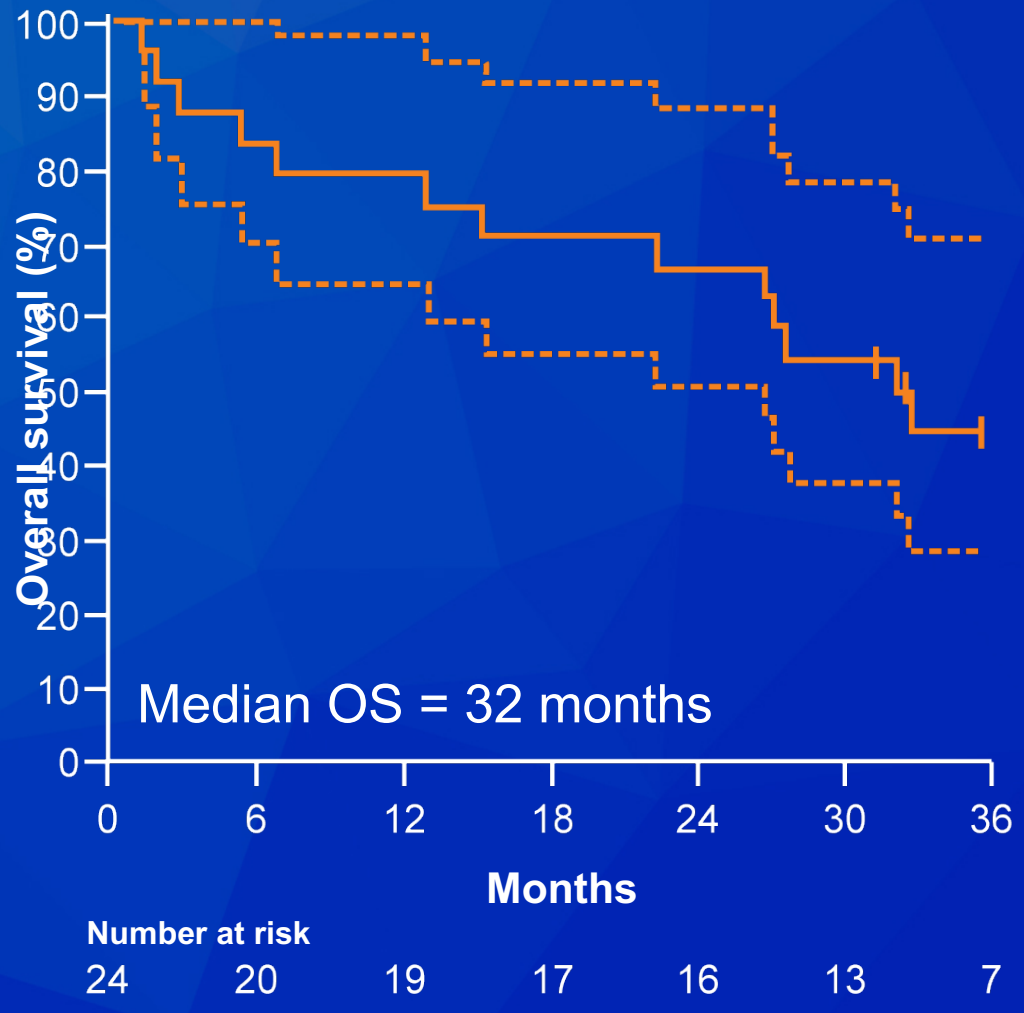
A randomized phase 3 of BR ± acalabrutinib is ongoing. We await these results, as we do the trial of BR ± ibrutinib. I expect that each of these trials will show that adding the BTK inhibitor provides benefit in terms of progression-free survival. Unfortunately, such trials will not answer the question of which BTKi, if either, is better and, importantly, also will not address the more pressing question of whether the best strategy is to add all agents together up-front or to use BTKi second line.

Three Year Update of the Phase II ABT-199 (Venetoclax) and Ibrutinib in Mantle Cell Lymphoma (AIM) Study

Handunnetti SM et al.
ASH 2019;Abstract 756.

Phase II Trial of Venetoclax and Ibrutinib in MCL: 3-Year Update





Dotted lines represent 95% CI

For pts with *TP53* aberrant MCL (n = 12), the ORR was 58% without PET and 50% with PET.

Handunnetti SM et al. ASH 2019;Abstract 756.

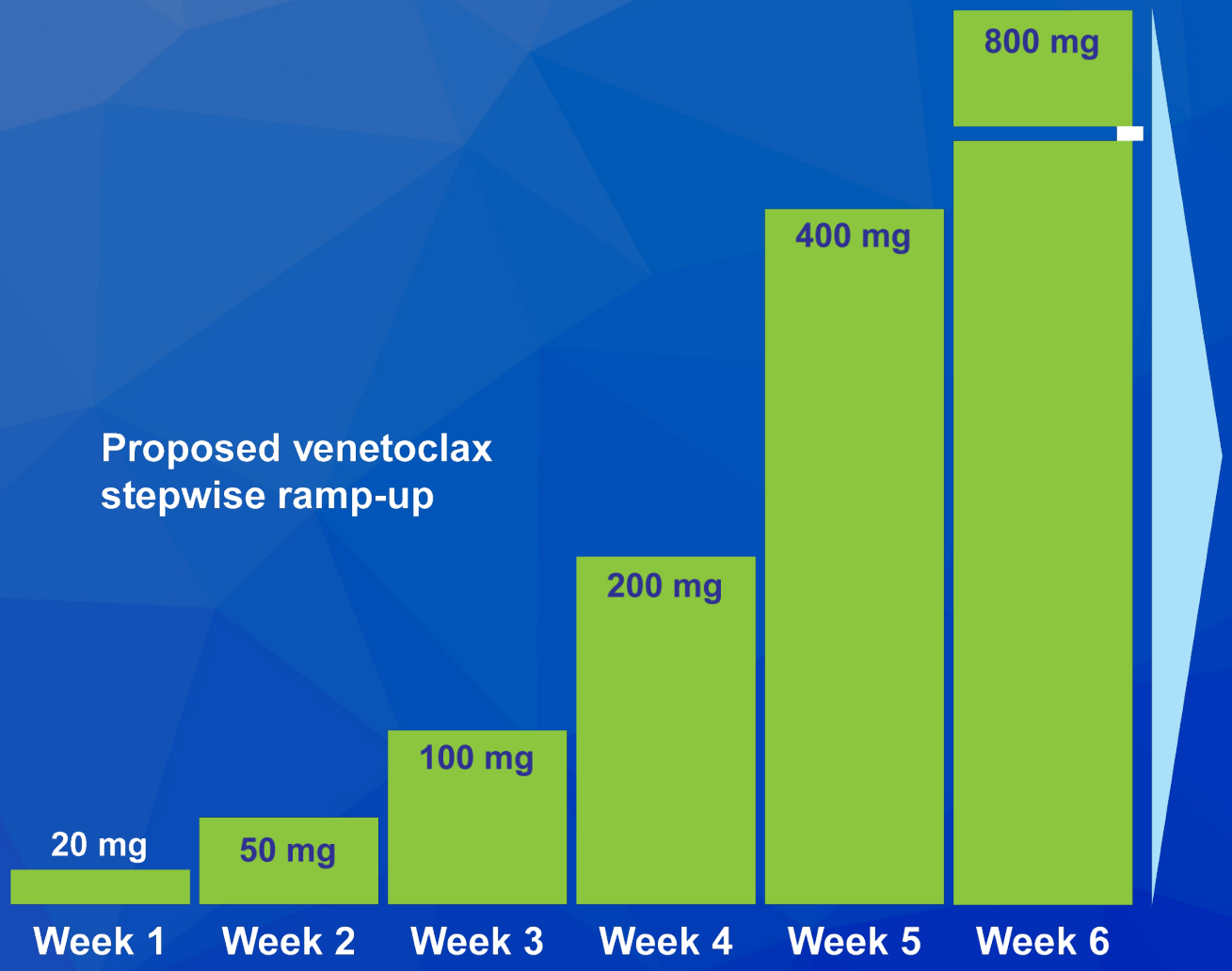
Editorial — Dr Abramson

The combination of BTK and Bcl-2 inhibition is also showing promise in mantle cell lymphoma, where both agents also have single agent efficacy. Handunnetti and colleagues report 3 year follow up of the AIM study of ibrutinib plus venetoclax in 23 patients with relapsed/refractory mantle cell lymphoma, and one previously untreated patient considered not to be a chemotherapy candidate. Extended follow up shows ongoing excellent efficacy of this regimen, previously reported by Tam et al in *The New England Journal of Medicine*. The median PFS was reached at 29 months, and the DOR has not been reached at 3 years. Responses were seen in half and 90% of patients with TP53 and ATM aberrations, respectively. This promising regimen warrants ongoing study in relapsed/refractory as well as previously untreated mantle cell lymphoma, including evaluation of treatment discontinuation in patients with MRD undetectable CR.

Revised Dose Ramp-Up to Mitigate the Risk of Tumor Lysis Syndrome When Initiating Venetoclax in Patients with Mantle Cell Lymphoma

Davids MS et al.
J Clin Oncol 2018;36(35):3525-7.

Proposed Stepwise Ramp-Up Dosing of Venetoclax for Patients with Mantle Cell Lymphoma



- To minimize tumor lysis syndrome risk, this dosing schedule has a venetoclax starting dose of 20 mg once daily for 7 days followed by a gradual stepwise weekly ramp-up to reach a dose of 400 mg daily by 5 weeks.
- For patients with MCL who receive venetoclax monotherapy, we suggest 1 additional ramp-up to 800 mg by 6 weeks, given the possibility of deeper responses observed at this dose compared to lower doses in the Phase I study.

Davids MS et al. *J Clin Oncol* 2018;36(35):3525-7.

Efficacy of Venetoclax Monotherapy in Patients with Relapsed, Refractory Mantle Cell Lymphoma Post BTK Inhibition Therapy

Eyre T et al.
Proc EHA 2018;Abstract S855.

Venetoclax Monotherapy in BTK Inhibitor-Resistant MCL: Results Summary

- N = 20 patients with relapsed/refractory MCL whose disease progressed on previous BTK inhibitor (BTKi) therapy

Clinical endpoint	Venetoclax (N = 20)
Overall response rate (ORR) Complete response rate	60% 20%
Median duration of response	Not reached
Median PFS	2.6 mo
Median OS	4.3 mo

- ORR among patients with responses to prior BTKi (n = 11) was higher than that among patients with primary resistance to BTKi (n = 9): 72.7% vs 44.4%
- No cases of clinical TLS were observed

Eyre T et al. *Proc EHA* 2018;Abstract S855.

Editorial – Dr M Smith

Venetoclax is a designer drug that promotes apoptosis by interfering with Bcl-2 function. Venetoclax is very active in CLL and is rapidly moving to earlier lines of CLL therapy, as will be discussed. Venetoclax also has activity in other disorders such as AML, where it has revolutionized the treatment approach to some elderly patients. While tumor lysis syndrome (TLS) was a clinical problem in this agent's development, this was primarily seen in CLL, requiring very careful dose escalation in the initial month of therapy. More rapid ramp-up without TLS has been possible in other diseases such as AML, FL and DLBCL. In MCL, TLS has been seen, and current recommendations, even though the drug is not yet approved to treat MCL, would be to adopt the CLL ramp-up parameters for MCL. As for clinical activity of venetoclax in mantle cell lymphoma (MCL), in the initial phase 1 experience, 21/28 (75%) patients with relapsed MCL responded to venetoclax therapy. In a "real-world" UK compassionate-use program, cohort ORR in 20 MCL patients with prior BTKi exposure was 12/20 (65%), with 20% CR.

Editorial – Dr M Smith

Unfortunately, in this latter data set, median PFS was <3 months, though median PFS in responders has not yet been reached, though with fairly short follow-up. A number of ongoing studies will begin to inform us where to best utilize this agent. It has been combined with bendamustine and anti-CD20 antibodies as front-line therapy. There is much excitement about combining it with ibrutinib or acalabrutinib, based on theoretical and preclinical data. This combination is further along in development in CLL. Venetoclax has also been combined with lenalidomide and other regimens such as R-BAC in MCL. A novel approach is a window study starting with ibrutinib-rituximab, allowing tumor reduction and correlative studies, followed by hyper-CVAD induction.

Editorial – Dr M Smith

Clearly this is an active new agent in MCL, but how best to use it is not clear. As with CLL and iNHL, we have to be careful about early interpretations of prolonged PFS as conferring overall benefit for combination therapy, i.e., synergy, when sequential use may be a better strategy. The concept of “time-limited” therapy currently being explored in CLL has not yet reached MCL trials.