Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Follicular, Indolent and Mantle-Cell Non-Hodgkin Lymphomas — Brad S Kahl, MD

Select Publications

Advani RH et al. **Two doses of polatuzumab vedotin (PoV, anti-CD79b antibody-drug conjugate) in patients (pts) with relapsed/refractory (RR) follicular lymphoma (FL): Durable responses at lower dose level.** *Proc ASCO* 2015;**Abstract 8503**.

Dreyling M et al. **Phase 2A study of copanlisib, a novel PI3K inhibitor, in patients with indolent lymphoma.** *Proc ASH* 2014;**Abstract 1701**.

Le Gouill S et al. **Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: First interim analysis of the Phase III prospective Lyma trial, a Lysa study.** *Proc ASH* 2014;**Abstract 146**.

Leonard JP et al. **Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance).** *J Clin Oncol* 2015;33(31):3635-40.

Robak T et al. **Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma.** *N Engl J Med* 2015;372(10):944-53.

Salles GA et al. **Idelalisib efficacy and safety in follicular lymphoma patients from a phase 2 study.** *Proc ASCO* 2015;**Abstract 8529**.

Sehn LH et al. **GADOLIN: Primary results from a phase III study of obinutuzumab plus bendamustine compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma.** *Proc ASCO* 2015;**Abstract LBA8502**.

Follicular, Indolent and Mantle-Cell Non-Hodgkin Lymphomas

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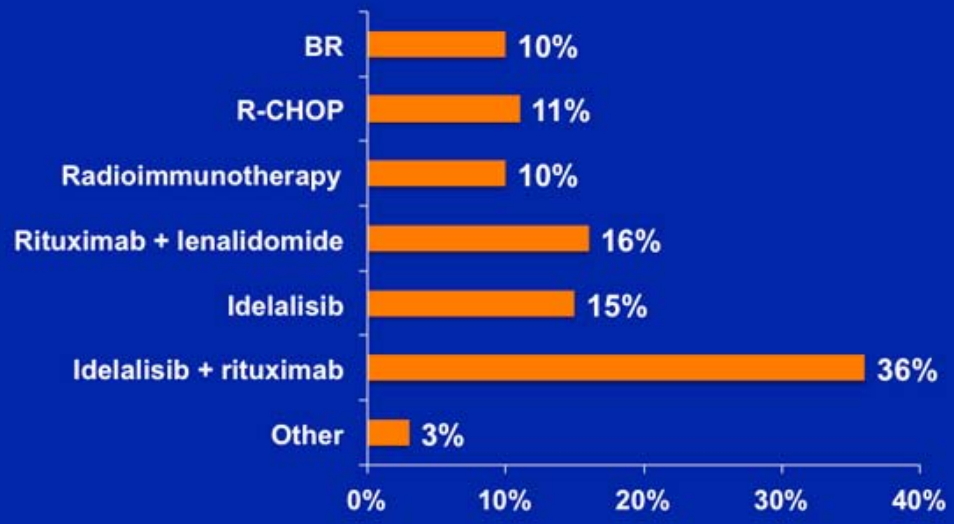
Disclosures

Consulting Agreements	Celgene Corporation, Genentech BioOncology, Takeda Oncology

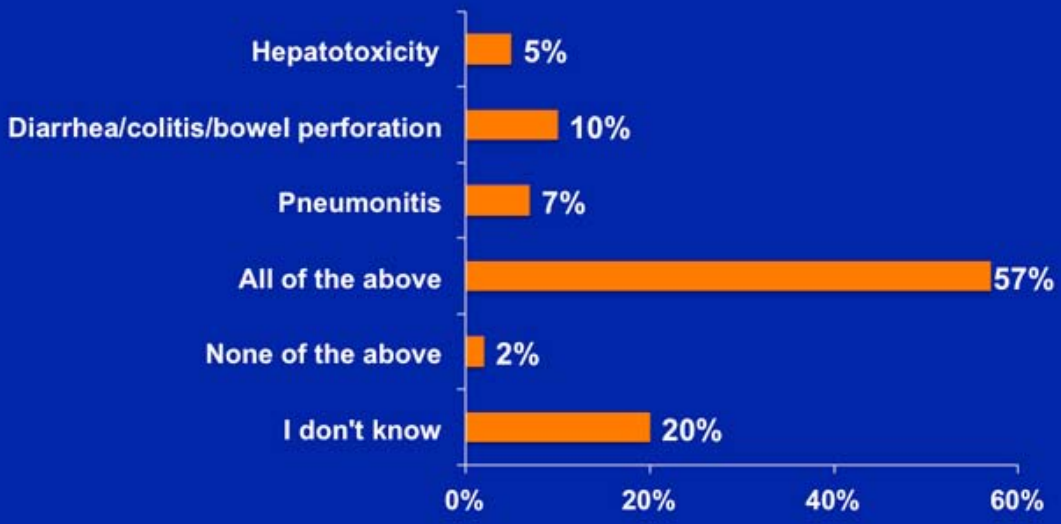
AUDIENCE POLL

A 76-year-old otherwise healthy patient with follicular lymphoma receives BR followed by 2 years of rituximab maintenance but 2 years later develops disease progression. Which treatment would you most likely recommend at this point?



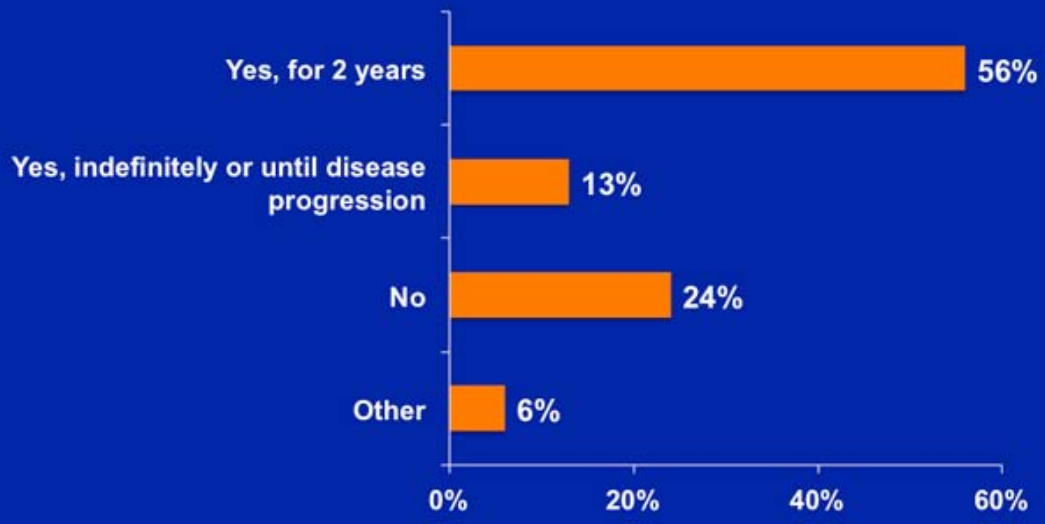
AUDIENCE POLL

Which of the following serious side effects is associated with idelalisib?



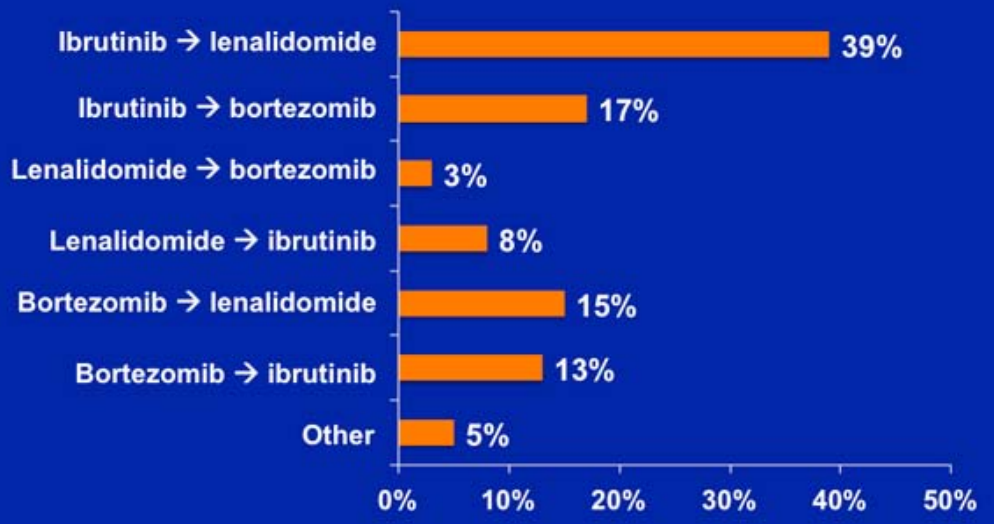
AUDIENCE POLL

In general, do you recommend maintenance rituximab for younger patients with mantle-cell lymphoma (MCL) who have received rituximab/chemotherapy followed by transplant?



AUDIENCE POLL

A 75-year-old patient with MCL responds to BR but after 18 months develops moderately symptomatic disease progression. The patient is not a candidate for transplant. In general, what would be your next 2 systemic treatments for this patient?



Idelalisib Efficacy and Safety in Follicular Lymphoma Patients from a Phase 2 Study

Salles GA et al.

Proc ASCO 2015;Abstract 8529.

Oral Idelalisib in Refractory FL

- Indolent NHL refractory to rituximab and alkylating agent
  - Median (range) prior treatments: 4 (2-12)
  - N = 72 FL (Grade 1, 2 or 3a)
- **ORR: 56%**
- Median PFS: 11 mo
- Median OS: Not reached
- KM-estimated OS
  - 1 year: 87%
  - 1.5 years: 74%
  - 2 years: 68%
- **Most common AEs (any/Grade ≥3)**
  - Diarrhea: 51%/14%
  - Cough: 32%/0%
  - Pyrexia: 29%/4%
  - Fatigue: 28 %/0%

Salles GA et al. *Proc ASCO* 2015;Abstract 8529.

Conclusions

Critical finding(s): Idelalisib has substantial clinical activity in double-refractory FL, with an ORR of 56% and a median response duration of 11 months.

The toxicity profile is modest, and idelalisib is generally well tolerated.

Clinical implication(s): Patients with relapsed or refractory FL can be treated effectively with idelalisib, an oral targeted agent.

Monitoring for transaminitis, colitis and pneumonitis is essential.

This agent represents an important new therapeutic option in FL.

Conclusions

Research relevance: Idelalisib is being combined with conventional cytotoxics (both front line and in the relapsed/refractory setting).

Idelalisib plus rituximab will be compared to R-CHOP in patients who relapse within 2 years of BR therapy in a planned US Intergroup trial.

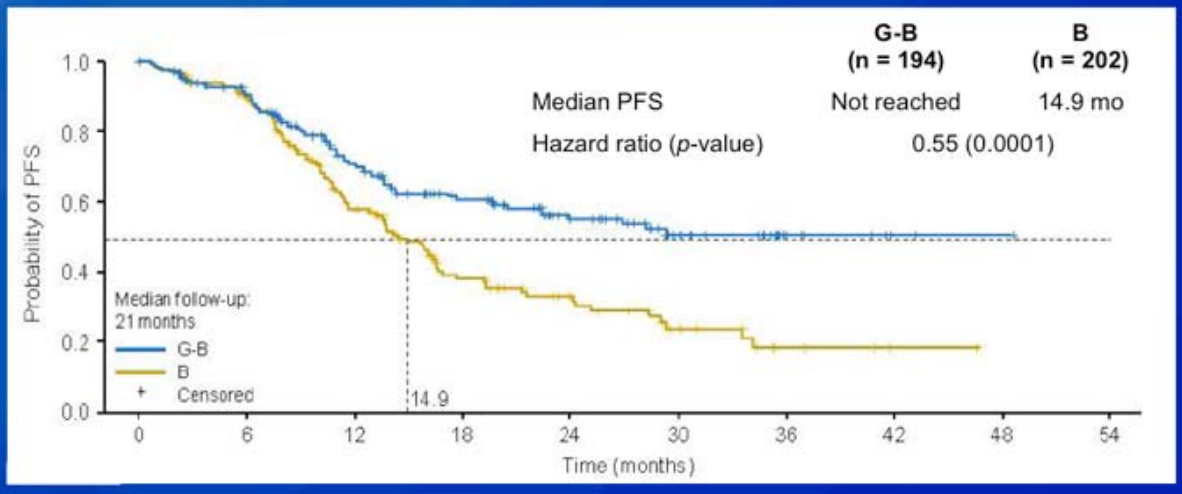
Idelalisib should be combined with other targeted agents in clinical trials.

GADOLIN: Primary Results from a Phase III Study of Obinutuzumab plus Bendamustine Compared with Bendamustine Alone in Patients with Rituximab-Refractory Indolent Non-Hodgkin Lymphoma

Sehn LH et al.

Proc ASCO 2015;Abstract LBA8502.

GADOLIN: PFS by Independent Radiology Facility Review



Sehn LH et al. *Proc ASCO* 2015;Abstract LBA8502.

Conclusions

Critical finding(s): The combination of obinutuzumab and bendamustine with obinutuzumab maintenance generated significantly longer PFS compared to bendamustine alone (29 vs 14 months by investigator assessment).

Clinical implication(s): The bendamustine/obinutuzumab combination is a clinically available option for patients with rituximab-refractory indolent lymphoma. The ORR and CR were similar between the two arms, suggesting maintenance therapy with obinutuzumab was predominantly responsible for the clinical benefit.

Conclusions

Research relevance: These data suggest that obinutuzumab (an anti-CD20 moAb) has activity in rituximab-refractory indolent lymphoma. Further study is needed to confirm or refute this. Such trials are under way.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance)

John P. Leonard, Sin-Ho Jung, Jeffrey Johnson, Brandelyn N. Pitcher, Nancy L. Bartlett, Kristie A. Blum, Myron Czuczman, Jeffrey K. Giguere, and Bruce D. Cheson

Epub ahead of print August 24, 2015

Response and Progression-Free Survival

Outcome	L Arm (n = 45)	LR Arm (n = 46)
Overall response		
No. of patients	24	35
%	53.3	76.1
95% CI*	37.9 to 68.3	61.2 to 87.4
Complete response		
No. of patients	9	18
%	20.0	39.1
95% CI	9.6 to 34.6	25.1 to 54.6
Partial response rate, %	33.3	37.0
Median TTP, years	1.1	2.0
2-Year TTP, %	27	52

Leonard JP et al. *J Clin Oncol* 2015;[Epub ahead of print].

Conclusions

Critical finding(s): The combination of rituximab and lenalidomide was substantially more active than lenalidomide alone in patients with recurrent follicular lymphoma. Median TTP was approximately doubled for the R^2 arm. Toxicity was not substantially different between the two arms.

Clinical implication(s): Given the likely synergy with the combination of rituximab and lenalidomide, there is little reason to give lenalidomide as a single agent in lymphoma. The synergy has been demonstrated in FL, MCL and CLL.

Conclusions

Research relevance: The R^2 combination is being compared head to head to R-chemo in the front-line setting in FL. The RELEVANCE trial is fully accrued and results are pending.

The R^2 combination is currently being compared to R alone as a maintenance strategy in E2408 (front-line FL) and E1411 (front-line MCL).

Two Doses of Polatuzumab Vedotin (PoV, Anti-CD79b Antibody-Drug Conjugate) in Patients (pts) with Relapsed/Refractory (RR) Follicular Lymphoma (FL): Durable Responses at Lower Dose Level

Advani RH et al.

Proc ASCO 2015;Abstract 8503.

- N = 45 relapsed/refractory FL received PoV at 1.8 or 2.4 mg/kg + rituximab 375 mg/m^2
- Objective response rate
  - 2.4 mg/kg: 19/25 (76%) CR: 44% PFS: 15 mo
    1.8 mg/kg: 15/20 (75%) CR: 10% PFS: Not reached

Conclusions

Critical finding(s): 1.8 mg/kg of PoV may be as effective as the 2.4-mg/kg dose with less peripheral neuropathy.

In addition, limiting the treatment duration to 8 cycles, at either dose level, appeared to lessen the risk of peripheral neuropathy.

Clinical implication(s): This agent is not commercially available at this time.

Research relevance: A lower dose and/or shorter duration of treatment may be a better partner for combination studies.

PoV could be tested as a substitute for vincristine in CHOP-based regimens.

Phase 2A Study of Copanlisib, a Novel PI3K Inhibitor, in Patients with Indolent Lymphoma

Dreyling M et al.
Proc ASH 2014;Abstract 1701.

PI3K Inhibitor Copanlisib in R/R Indolent NHL/CLL: Efficacy and Adverse Events

- N = 33 (FL = 16, CLL = 13, MZL = 3, SLL = 1)
- Relapsed or refractory to ≥2 prior lines of treatment (median = 4)

- Independent radiologic review ORR = 47% (1 CR, 1 uCR, 13 PR)
  - ORR for FL = 47%
  - ORR for CLL = 38%
- Median duration of response: 287 days
- Median PFS: 240 days

- Grade 3/4 AEs
  - Hypertension: 49% (Grade 3)
  - Neutropenia: 30%
  - Hyperglycemia: 30% (Grade 3)
  - Anemia: 15%

Dreyling M et al. *Proc ASH* 2014;Abstract 1701.

Conclusions

Critical finding(s): Good single-agent activity for this novel PI3K inhibitor

Notable for IV administration (days 1, 8 and 15 q28d)

Grade 3 hypertension in 49%, Grade 3 hyperglycemia in 30%

Clinical implication(s): This agent is not commercially available at this time.

Research relevance: A drug that certainly can be developed as a single agent or in combination.

Toxicity profile may limit development.

Rituximab Maintenance versus Wait and Watch After Four Courses of R-DHAP Followed by Autologous Stem Cell Transplantation in Previously Untreated Young Patients with Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective Lyma Trial, a Lysa Study

Le Gouill S et al.

Proc ASH 2014;Abstract 146.

Survival Outcomes from Randomization (Median Follow-Up 29.7 Months)

Survival	Rituximab (n = 119)	Watch and wait (n = 119)	Hazard ratio	*p*-value
Two-year EFS	93.2%	81.5%	2.1	0.015
Two-year OS	93.4%	93.9%	NR	NS

NR = not reported; NS = not significant

- PFS was statistically different between the 2 study arms ($p = 0.015$).

Le Gouill S et al. *Proc ASH* 2014;Abstract 146 (Abstract only).

Conclusions

Critical finding(s): Maintenance rituximab after autoSCT for MCL significantly improved PFS.

No OS benefit has been observed to date.

Clinical implication(s): Many centers have adopted this strategy, signifying a change in the standard of care.

Research relevance: This represents a new "control arm" that must form the basis for comparison in any randomized, controlled trial.

Would be interesting to compare rituximab maintenance to "as-needed" rituximab based on molecular relapse as was done in the Nordic trial.

The NEW ENGLAND JOURNAL of MEDICINE

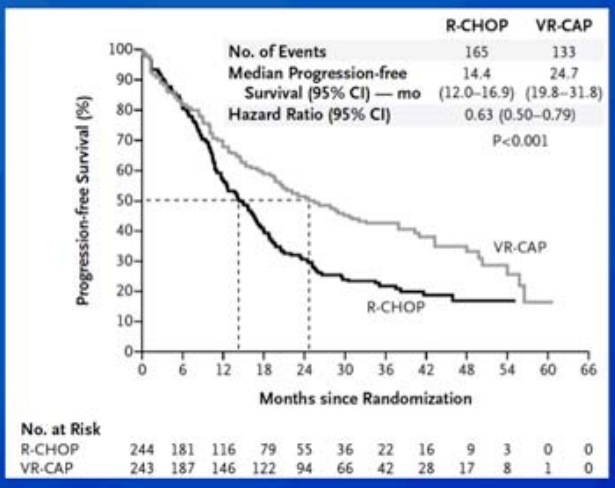
ORIGINAL ARTICLE

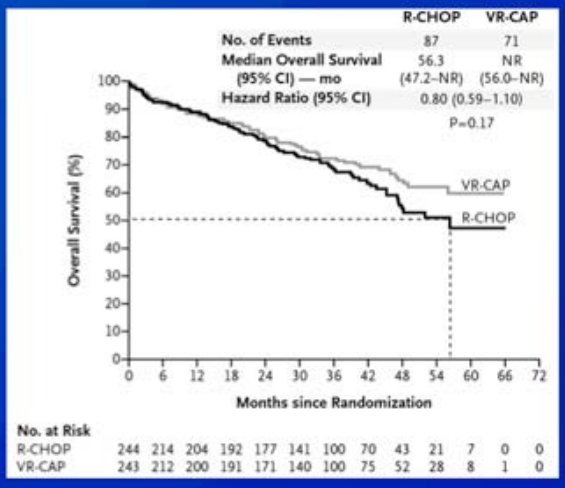
Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma

Tadeusz Robak, M.D., Huiqiang Huang, M.D., Jie Jin, M.D., Jun Zhu, M.D., Ting Liu, M.D., Olga Samoilova, M.D., Halyna Pylypenko, M.D., Gregor Verhoef, M.D., Ph.D., Noppadol Siritanaratkul, M.D., Evgenii Osmanov, M.D., Ph.D., Julia Alexeeva, M.D., Ph.D., Juliana Pereira, Ph.D., Johannes Drach, M.D., Jiri Mayer, M.D., Xiaonan Hong, M.D., Rumiko Okamoto, M.D., Lixia Pei, Ph.D., Brendan Rooney, Ph.D., Helgi van de Velde, M.D., Ph.D., and Franco Cavalli, M.D., for the LYM-3002 Investigators*

N Engl J Med 2015;372:944-53

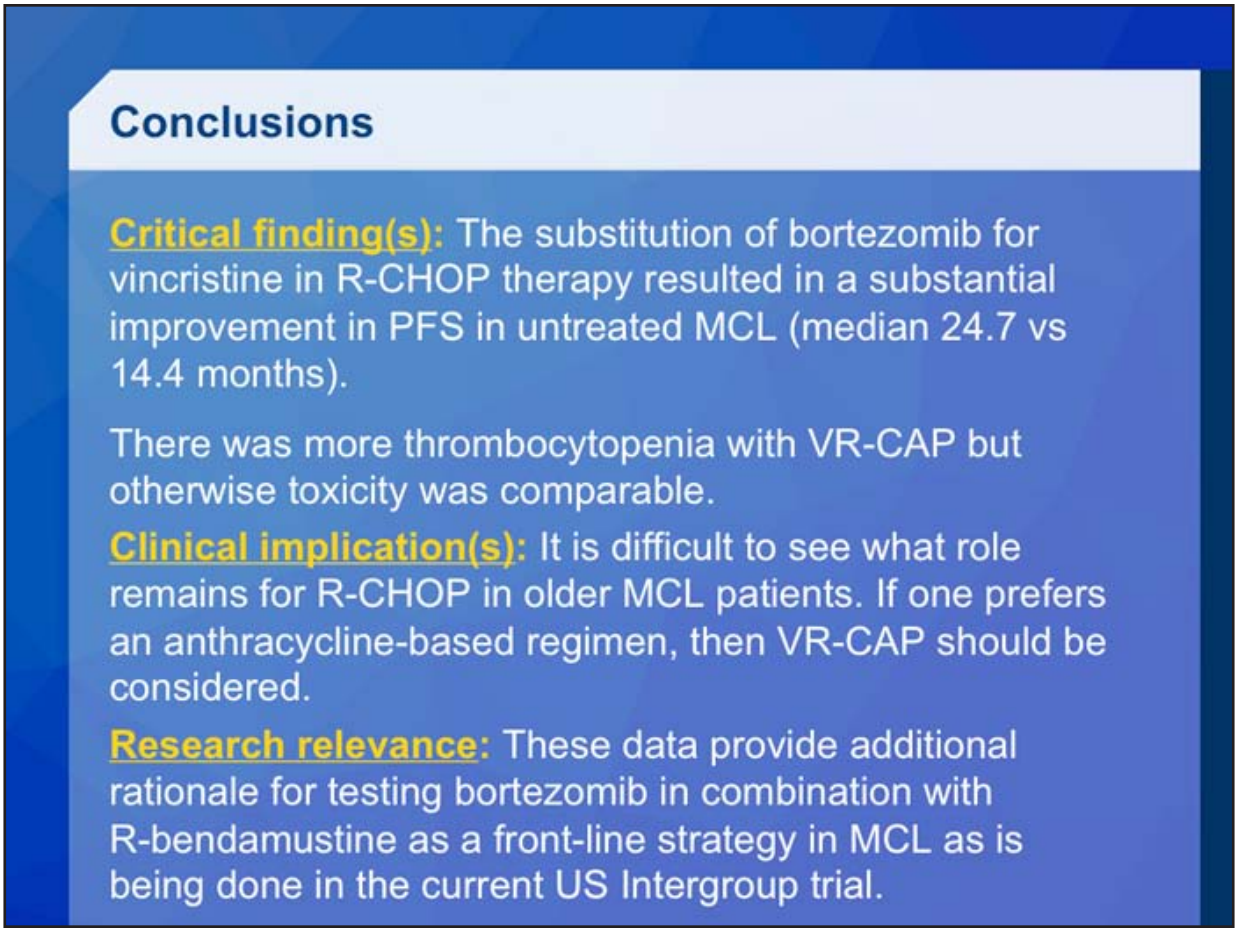
Survival Analyses: Intention-to-Treat





NR = not reached

Robak T et al. *N Engl J Med* 2015;372(10):944-53.


Conclusions
Critical finding(s): The substitution of bortezomib for vincristine in R-CHOP therapy resulted in a substantial improvement in PFS in untreated MCL (median 24.7 vs 14.4 months).
There was more thrombocytopenia with VR-CAP but otherwise toxicity was comparable.
Clinical implication(s): It is difficult to see what role remains for R-CHOP in older MCL patients. If one prefers an anthracycline-based regimen, then VR-CAP should be considered.
Research relevance: These data provide additional rationale for testing bortezomib in combination with R-bendamustine as a front-line strategy in MCL as is being done in the current US Intergroup trial.