
Updates in the Treatment of Non-Hodgkin Lymphoma: ASH 2008

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Topics

- Mantle Cell Lymphoma
 - What is the standard of care for younger patients? (abstracts 581, 769, 833, 3050)
 - Other regimens
- New Agents
 - Do vaccines work in FL? (236)
 - Lenalidomide (262, 268)

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Active questions in MCL

- Younger patients
 - Are intensive therapies the way to go?
 - If yes, which intensive therapy approach?
 - Conventional R-hyperCVAD with alternating R-MTX/Ara-C?
 - Aggressive cytoreduction followed by ASCT?
 - If yes, does the method of cytoreduction matter?
- Older patients
 - Not addressed today

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Conventional R-hyperCVAD update

- Abstract 833: MD Anderson (Romaguera et al)
 - 6 – 8 cycles of R-hyperCVAD alternating with R-MTXAraC
 - 97 pts (65 under \leq 65y), median follow-up : 84 mo
 - Patients \leq 65 y
 - 7y FFS : 52%, 7y OS : 68%
- Abstract 3050: Multicenter trial from GISL (Merli et al)
 - N = 32, median age 54
 - 7 patients unable to complete therapy due to toxicity
 - 2 toxic deaths
 - 2 yr FFS 75%
 - Results are similar to SWOG report at ASH 07
 - Efficacious but some issues with tolerability

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**Early consolidation with
myeloablative radiochemotherapy
followed by
autologous stem cell transplantation
in first remission of mantle cell lymphoma**

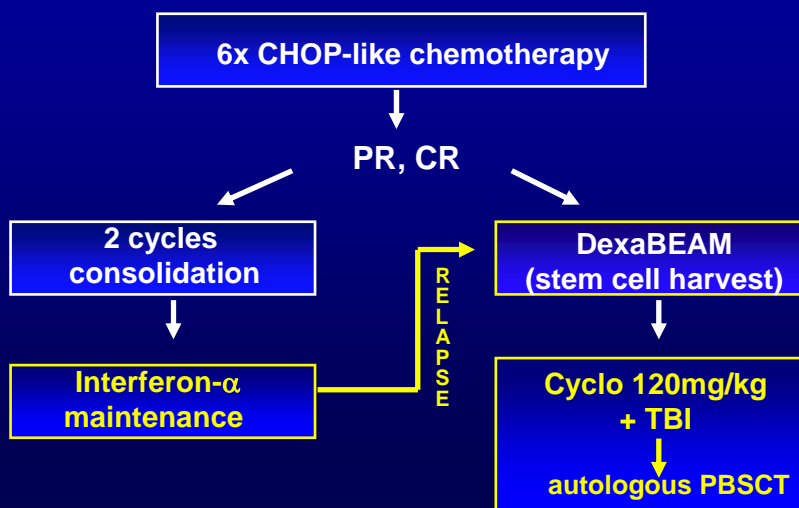
**Long term follow-up of a randomized trial
of the *European MCL Network***



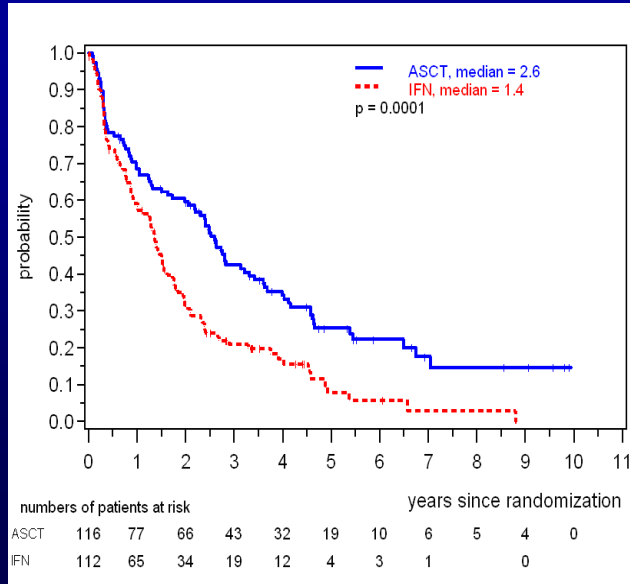
M. Dreyling, E. Hoster, A. van Hoof, B. Metzner,
C. Gisselbrecht, M. Reiser, M. Pfreundschuh,
L. Trümper, H. Steinhauer, J. Boiron, M. Boogaerts, A. Aldaoud, V. Silingardi, H. Kluin-Nelemans,
M. Unterhalt, W. Hiddemann



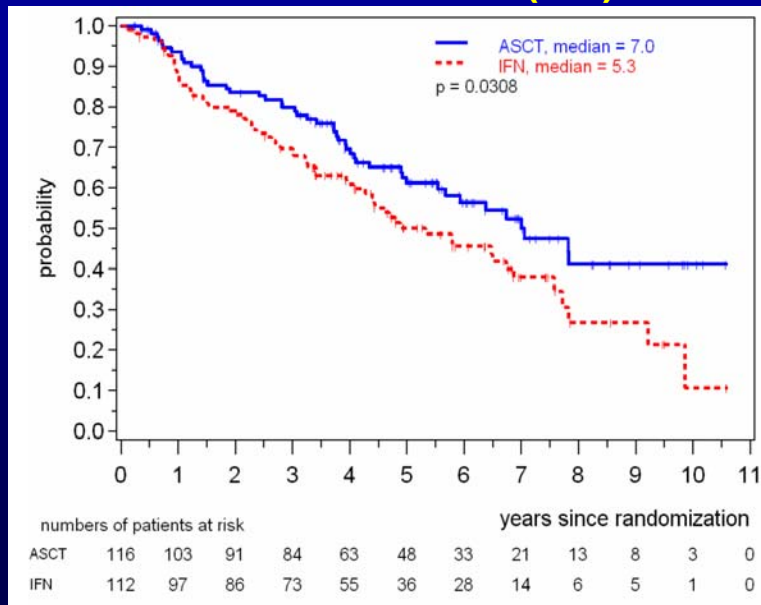
European MCL Network: ASCT vs. IFN



European MCL Network: ASCT vs. IFN Time to treatment failure (ITT)



European MCL Network: ASCT vs. IFN Overall Survival (ITT)



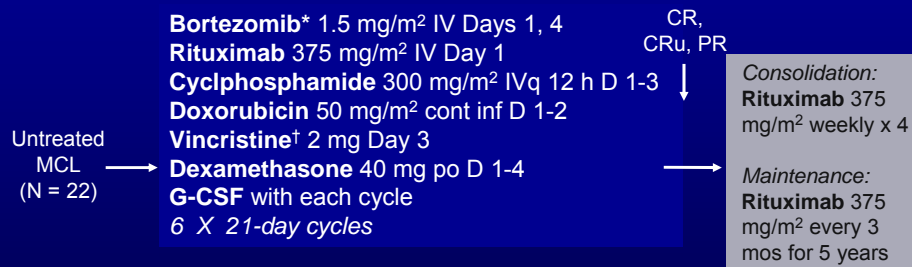
Conclusions

- ASCT applied in first remission
 - Prolongs the remission durability
 - Appears to favorably impact OS
- Note the “control” arm median OS
 - 5+ yrs despite 1st remission of only 1.5 yrs
- What would happen if a better cytoreduction was used?

MCL Conclusions: younger patients

- Several trials demonstrating median remissions of greater than 5 years with intensive strategies in younger patients
- Conventional hyperCVAD excellent results at MD Anderson
 - Appears unlikely similar results will be realized in 2 multicenter trials
- AutoSCT consolidation prolongs remission and survival in one small RCT from the European MCL consortium
- 2 trials demonstrate outstanding long term outcomes with high dose cytarabine incorporated into induction followed by autoSCT
 - Nordic and GELA
 - Multicenter and ITT
- Ongoing European RCT of R-CHOP vs. R-CHOP/R-DHAP followed by ASCT

VcR-hyperCVAD in First-line MCL: Phase II Study Schema



* Dose adjusted to 1.3 mg/m² for pts 8-22

† Dose adjusted to 1 mg for pts 15-22

Kahl B, et al. ASH 2008. Abstract 265.

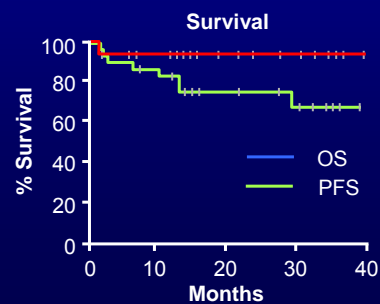
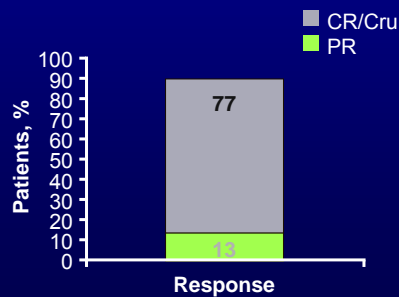
VcR-hyperCVAD in First-line MCL: Response and Survival

- Overall response rate 90%

2-yr PFS: 75%

2-yr OS: 97%

Median follow-up 23 months



Kahl B, et al. ASH 2008. Abstract 265.

VcR-hyperCVAD in First-line MCL: Toxicity

- 2 dose modifications made due to painful peripheral neuropathy
 - 1/16 pts at final dose level experienced neuropathy
- Thrombocytopenia and neutropenia most frequent hematologic toxicities

Grade 3/4 Non-Hematologic Adverse Events,* n	Patients (N = 30)
Neuropathy	10
Elevated glucose	4
Low sodium	4
Dehydration	2
Pain	2
Fatigue	2

Grade 3/4 Hematologic/Infection Adverse Events,* n	Patients (N = 30)
Thrombocytopenia	23
Neutropenia	20
Lymphopenia	12
Anemia	8
Febrile neutropenia	5
Infection without neutropenia	4

*Occurring in > 1 patient.

Kahl B, et al. ASH 2008. Abstract 265.

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 - Other regimens
- New Agents
 - Do vaccines work in FL? (236)
 - Lenalidomide (262, 268, 3060)

Lenalidomide for Relapsed MCL

- Abstract 262: Zinzani et al.
 - 25 mg/day 1-21 q 28
 - N = 39, median of 3 prior therapies
 - ORR 41% (16/39), SD 26%
 - Median PFS 7.1 months, median RD not reached
 - Grade 3-4 neutropenia 50%, thrombocytopenia 25%
- Abstract 1560: Reeder et al.
 - 14 patients with prior bortezomib
 - ORR 57% (8/14)

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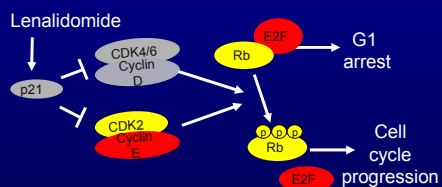
Lenalidomide for Relapsed MCL and DLBCL

- Abstract 268: Czuczman et al.
 - N = 73, median 3 prior treatments
 - ORR 29% (21/73), CR 4%
 - Median RD ~ 3-4 months
 - Grade 3-4 neutropenia 32%, thrombocytopenia 15%
 - 2 cases of acute renal failure, 2 acute confusional states
- Lenalidomide has promising activity in recurrent MCL
 - Efficacy more modest in recurrent DLBCL
 - Dose and schedule issues remain

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NHL-003: Single Agent Lenalidomide in R/R MCL (Rationale)

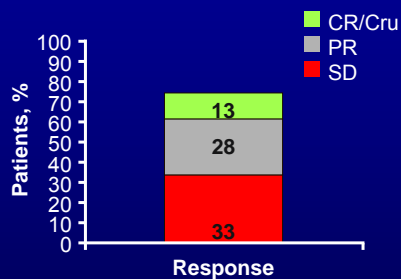
- MCL is an aggressive B-cell non-Hodgkin's lymphoma (NHL) with suboptimal responses to conventional chemotherapy
 - Short DOR and limited PFS
- Lenalidomide induces *p21* tumor suppressor expression, leading to cell cycle arrest
 - *Cyclin D1* overexpression common in MCL
 - *Cyclin D1* overexpression relative to *p21* predisposes to lenalidomide-induced cell cycle arrest



Zinzani PL, et al. ASH 2008. Abstract 262.

NHL-003: Single Agent Lenalidomide in R/R MCL (Interim Response Results)

- Patient Population (N = 53)^[1]
 - 39 pts evaluable for response
 - ≥ 1 previous treatment
 - ECOG PS ≤ 2
- Study endpoints by International Workshop Lymphoma Response Criteria^[2]
 - Primary endpoint
 - ORR
 - Secondary endpoints
 - DOR, PFS, Safety



Median PFS: 216 days (95% confidence interval: 75-344)

- Median DOR not reached

1. Zinzani PL, et al. ASH 2008. Abstract 262; 2. Cheson BD et al. J Clin Oncol 1999;17:2454

NHL-003: Single Agent Lenalidomide in R/R MCL (Interim Safety Results)

- Cytopenias most frequent grade 3/4 adverse events
- Dose reductions required in 15 patients (38%)
 - Median time to first dose reduction: 1.8 months (range: 0.4-8.4)
 - Most frequently due to neutropenia (52%) and thrombocytopenia (23%)
- Led to treatment discontinuation in 6 patients (15%)

Adverse Event, %	Patients (n = 39)	
	Grade 3	Grade 4
Hematologic		
▪ Neutropenia	31	21
▪ Thrombocytopenia	13	13
▪ Anemia	10	3
▪ Febrile neutropenia	3	8
▪ Leukopenia	8	0
Nonhematologic		
▪ Fatigue	10	0
▪ Pain	5	0
▪ Pleural effusion	5	0
▪ Dyspnea	3	5
▪ General deterioration in physical health	3	3

Zinzani PL, et al. ASH 2008. Abstract 262.

R2: Preliminary Results of a Phase II Study of Lenalidomide and Rituximab in Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma (NHL)

Treatment

- Lenalidomide was initiated at a dose of 25 mg administered orally once daily, on days 1–21 of a 28-day cycle, and continued until disease progression.
- Following the development of tumor lysis syndrome (TLS) in the first 2 patients enrolled, the protocol was amended to reduce the starting dose of lenalidomide to 20 mg and TLS prophylaxis was provided.
- Rituximab 375 mg/m² was infused starting on day 15 of cycle 1 and repeated weekly for a total of 4 doses. If after cycle 2 a patient had less than a CR, 4 additional doses could be administered at the discretion of the treating physician

DeRoock I et al. ASH 2008. Abstract 3060.

R² for Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma (NHL)

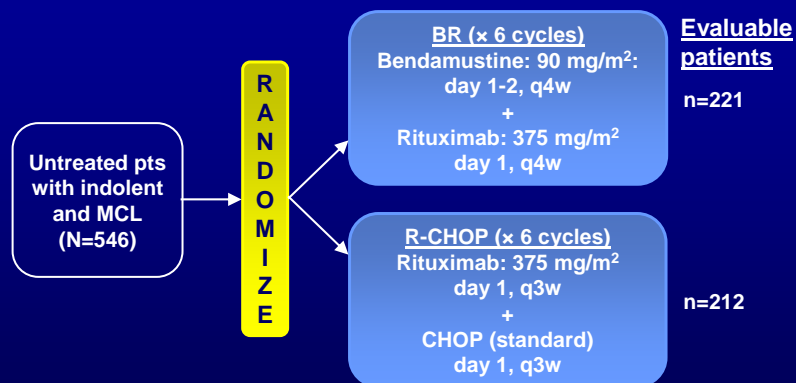
Table 2. Patient response to lenalidomide plus rituximab therapy (N = 8).

Response	Evaluable patients, n (%)
Complete response unconfirmed	3 (38)
Partial response	4 (50)
Stable disease	1 (13)

Median PFS is currently ongoing and > 168 days

DeRoock I et al. ASH 2008. Abstract 3060.

Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas



- Primary end point: To prove a noninferiority of BR vs R-CHOP in EFS (defined as a difference of less than 10% in EFS after 3 years)

Rummel et al. ASH, 2008. Abstract 2596.

Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas: Response



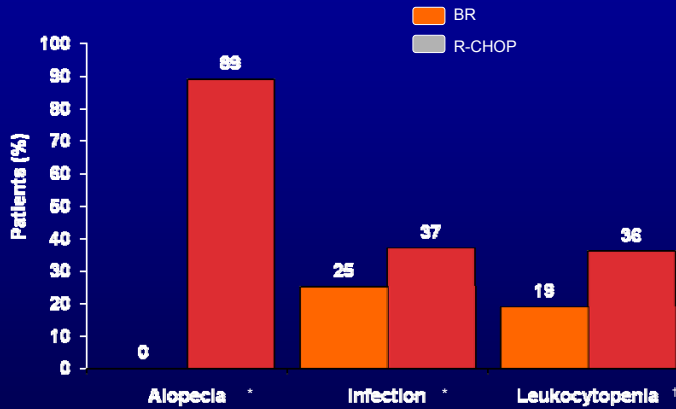
Median follow-up of 28 months.
Rummel et al. ASH, 2008. Abstract 2596.

Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas: Survival

Regimen	BR	R-CHOP	P-value
End point			
EFS (months)	Not reached	39	Not significant
Death (n)	25	25	N/A

Rummel et al. ASH, 2008. Abstract 2596.

Phase 3 Trial of Bendamustine + Rituximab vs R-CHOP in First-Line Indolent and Mantle Cell Lymphomas: Safety



*All grades; †Grade 3/4
Rummel et al. ASH, 2008. Abstract 2596.

A Placebo-Controlled Phase III Trial of Patient-Specific Immunotherapy with Mitumprotimut-T (Id-KLH) and GM-CSF Following Rituximab in Patients with CD20+ Follicular Lymphoma

A. Freedman, S. Neelapu, C. Nichols,
M.J. Robertson, B. Djulbegovic, J. Winter,
D.P. Gold, J.F. Bender,
M. Stewart, R.G. Ghalie, and P. Hamlin

Paul A. Hamlin, MD

Presenting for the FavId-06 Trial Investigators

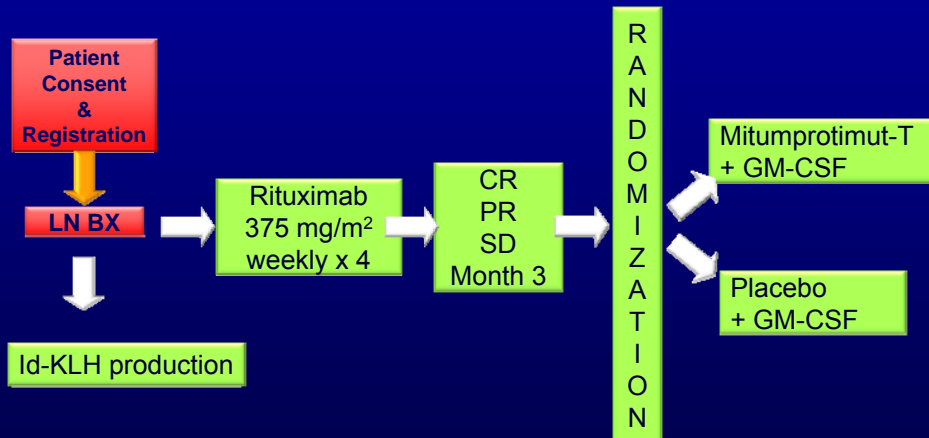
Background

- Mitumprotimut-T is a patient-specific Id-KLH vaccine in which the Id protein is produced by proprietary recombinant technology (Specifid[®], Favril, San Diego, CA)
- A Phase II trial of mitumprotimut-T + GM-CSF in treatment-naïve and relapsed/refractory follicular B-cell lymphoma patients achieving SD/PR/CR to rituximab has resulted in:
 - late conversions to CR
 - an event-free survival plateau at 4 years, suggesting a vaccine activity¹⁻²
- This Phase III trial was conducted to confirm these results

1. O Koc, et al. Blood 2007;110(11):abstr 3427
2. O Koc et al. Blood 2007;110(11):abstr 2567

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Phase III Trial Schema



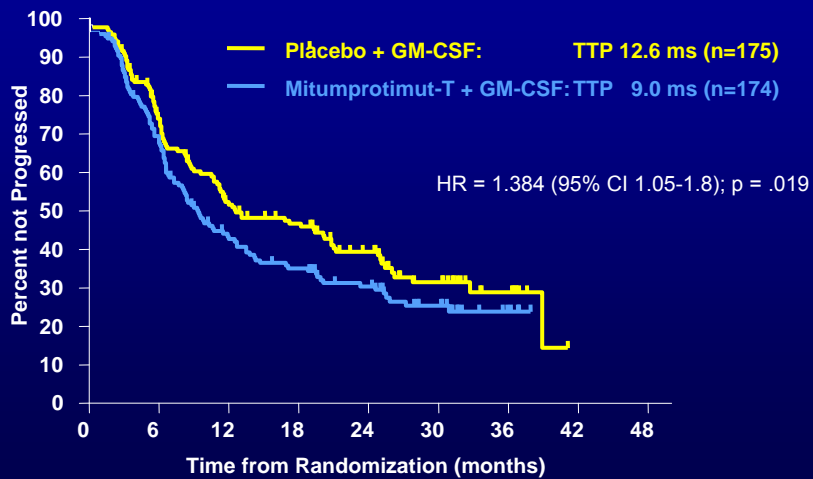
* Each vaccination consists of 1 mL mitumprotimut-T 1 mg or placebo, SQ, Day 1 and Leukine[®] (GM-CSF) 250 mcg, SQ, Days 1-4, monthly x6, Q 2 months x6, then Q 3 months until PD or unacceptable toxicity

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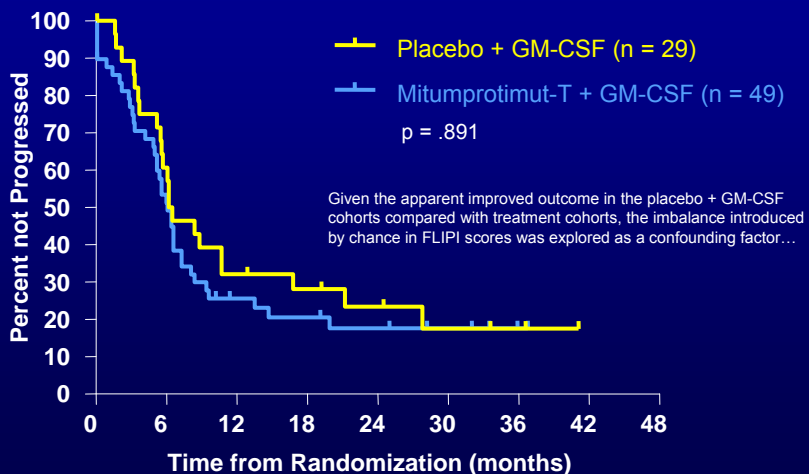
Patient Characteristics

		No. of Patients	
		Mitumprotimut-T (n = 174)	Placebo (n = 175)
Age (years)	Median (range)	56 (22 - 86)	53 (21- 81)
ECOG PS	0	146 (84%)	152 (87%)
	1	28 (16%)	22 (13%)
Stage	I-II	17 (10%)	28 (16%)
	III-IV	155 (89%)	146 (83%)
	B Symptoms Present	12 (7%)	23 (13%)
Prior therapy	Treatment-naive	137 (79%)	138 (79%)
	Relapsed/refractory	37 (21%)	37 (21%)
FLIPI Risk Group	Low	51 (29%)	78 (47%)
	Intermediate	71 (41%)	66 (38%)
	High	49 (28%)	29 (17%)
	Unknown	3 (2%)	2 (1%)

Time to Progression: Intent-to-Treat (N = 349)



Time to Progression: FLIPI High Risk Group (N = 78)



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Conclusions

- Patient-specific Id-KLH and GM-CSF therapy does not improve TTP, objective response rate, or duration of response in patients with CD20+ follicular lymphoma who achieve SD or an objective response following rituximab
- Results consistent with another randomized Phase 3 trial in treatment-naïve patients with CD20+ follicular lymphoma who achieve CR/PR following CVP chemotherapy¹
- Possible reasons for failure
 - Immunosuppressive effect of rituximab
 - Id is a weak immunogen
 - Id irrelevant target

1. R Levy, et al. Proc AACR, 2008 (abstr LB-204)

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