

MABTHERA IN AGGRESSIVE NHL

RITUXIMAB COMBINED WITH DEXABEAM
SALVAGE THERAPY FOLLOWED BY HIGH
DOSE THERAPY (HDT) IN PATIENTS WITH
RELAPSED OR REFRACTORY B-NHL: FIRST
RESULTS OF A PHASE II MULTICENTRE
STUDY

Abstract 308

Hess G et al. Poster presentation

Friday 1745-1900

RITUXIMAB WITH DEXABEAM SALVAGE THERAPY AND HIGH DOSE THERAPY (HDT) IN RELAPSED OR REFRACTORY B-NHL

This study demonstrates that MabThera is active in salvage regimens even in those patients who have received MabThera in earlier lines of therapy

RITUXIMAB WITH DEXABEAM SALVAGE THERAPY AND HIGH DOSE THERAPY (HDT) IN RELAPSED OR REFRACTORY B-NHL

Aims:

- To examine the safety and efficacy of MabThera combined with Dexa-BEAM

Methods:

- Prospective Phase II data for R-Dexa-BEAM plus HDT in relapsing aggressive or indolent lymphoma
- Prior R was not an exclusion criterion
- Addition of R to salvage therapy (R-BEAM or R-TBI/CY) gave high response rates and improved remission
- Success of therapy was not affected by prior R

RITUXIMAB WITH DEXABEAM SALVAGE THERAPY AND HIGH DOSE THERAPY (HDT) IN RELAPSED OR REFRACTORY B-NHL

Results:

Median follow-up 2.2 years post-HDT

- 103 evaluable patients, median 1 previous line of therapy
- 67 aNHL (DLCL 55, MCL 7, FL grade 3: 5)
- 36 iNHL (FL grade 1-2: 29, MZL 6, IC 1)

- PFS (63%) and OS (83%) in aNHL
- PFS (63%) and OS (100%) in iNHL

72% of patients proceeded to HDT

- HDT was predominantly R-BEAM
- Recovery occurred after a median of 11 days (8-27)

Patients re-staged at day 60

- ORR 80% (aNHL) and 90% (iNHL)

RITUXIMAB WITH DEXABEAM SALVAGE THERAPY AND HIGH DOSE THERAPY (HDT) IN RELAPSED OR REFRACTORY B-NHL

Conclusions:

- MabThera containing previous therapy was not associated with inferior outcomes,
- HDT is improved with the addition of R
- R-Dexa-BEAM followed by SCT can be considered as the established salvage therapy for NHL

LONG-TERM RESULTS OF THE GELA
STUDY COMPARING R-CHOP AND CHOP
CHEMOTHERAPY IN OLDER PATIENTS
WITH DIFFUSE LARGE B-CELL LYMPHOMA
SHOW A LONG TERM BENEFIT FOR THE
ADJUNCTION OF RITUXIMAB TO CHOP

Abstract 407

Coiffier B et al. Oral presentation

Saturday 1045-1100

LONG-TERM RESULTS OF THE GELA STUDY

Landmark study in aNHL showing long term survival and cure with 8 cycles of MabThera added to CHOP

Median follow-up now >7 years

- OS >50%, EFS 42% with R-CHOP
- OS 35%, EFS 24% with CHOP alone

Cures were achieved even in elderly patients at high risk

LONG-TERM RESULTS OF THE GELA STUDY

Results:

399 patients with untreated DLBCL

- Median age 69 years (60-80) at diagnosis
- 60% had poor risk lymphoma (aaIPI 2 or 3)
- Patients randomised to 8 cycles of CHOP (n=197) or R-CHOP (n=202)

LONG-TERM RESULTS OF THE GELA STUDY

Median follow-up 7.1 years at this analysis

	CHOP	R-CHOP	
Events	76%	58%	P=0.0002
Alive	35%	53%	
lymphoma/toxicity	80%	71%	
other cancer	5%	5%	
other whilst CR	15%	22%	

Death during CR was associated with high aalPI and comorbidity before lymphoma diagnosis

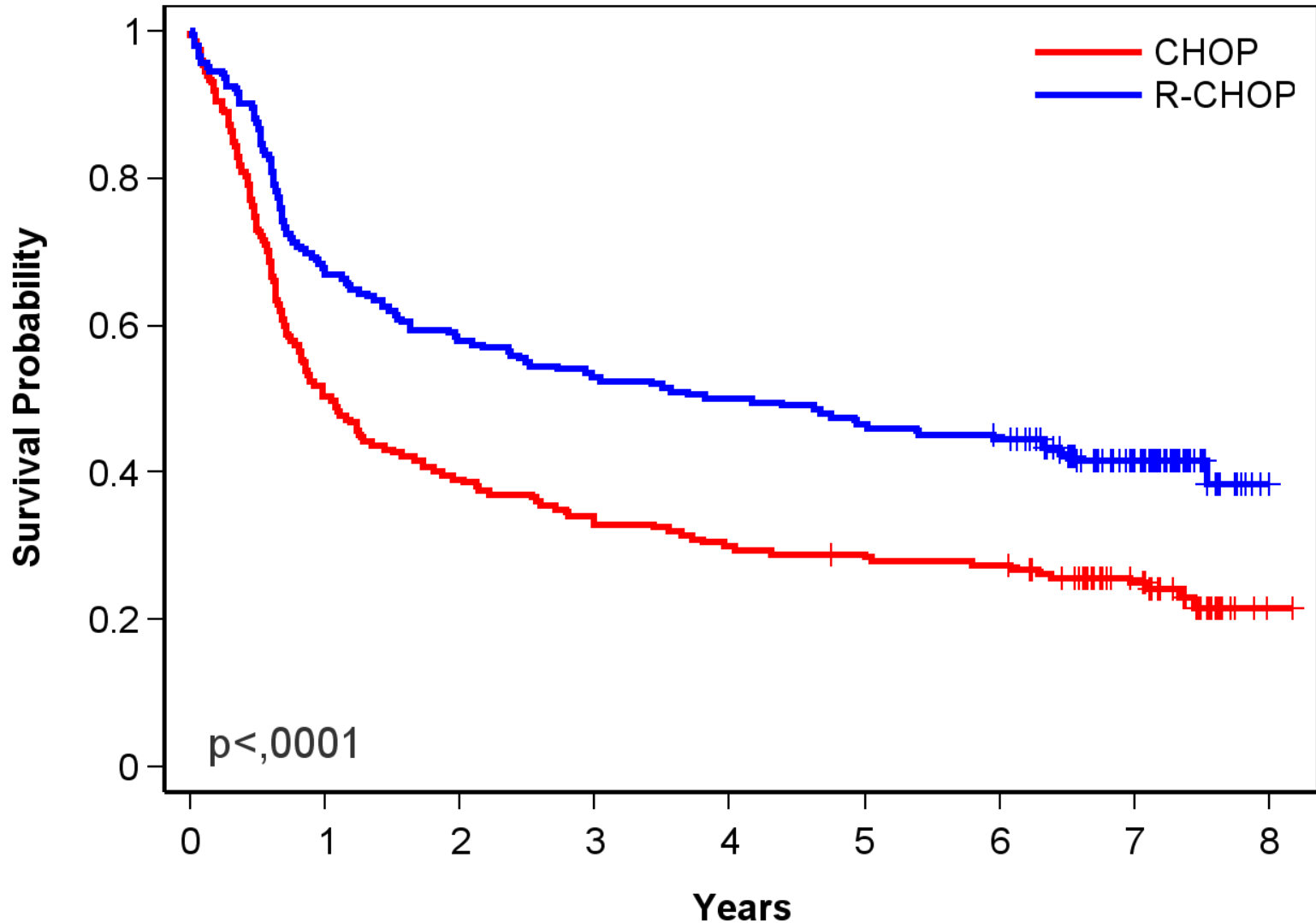
LONG-TERM RESULTS OF THE GELA STUDY

bcl-2-negative patients receiving R-CHOP experienced a statistically significant improvement in PFS but not OS compared with patients receiving CHOP because of an improved response to salvage therapy

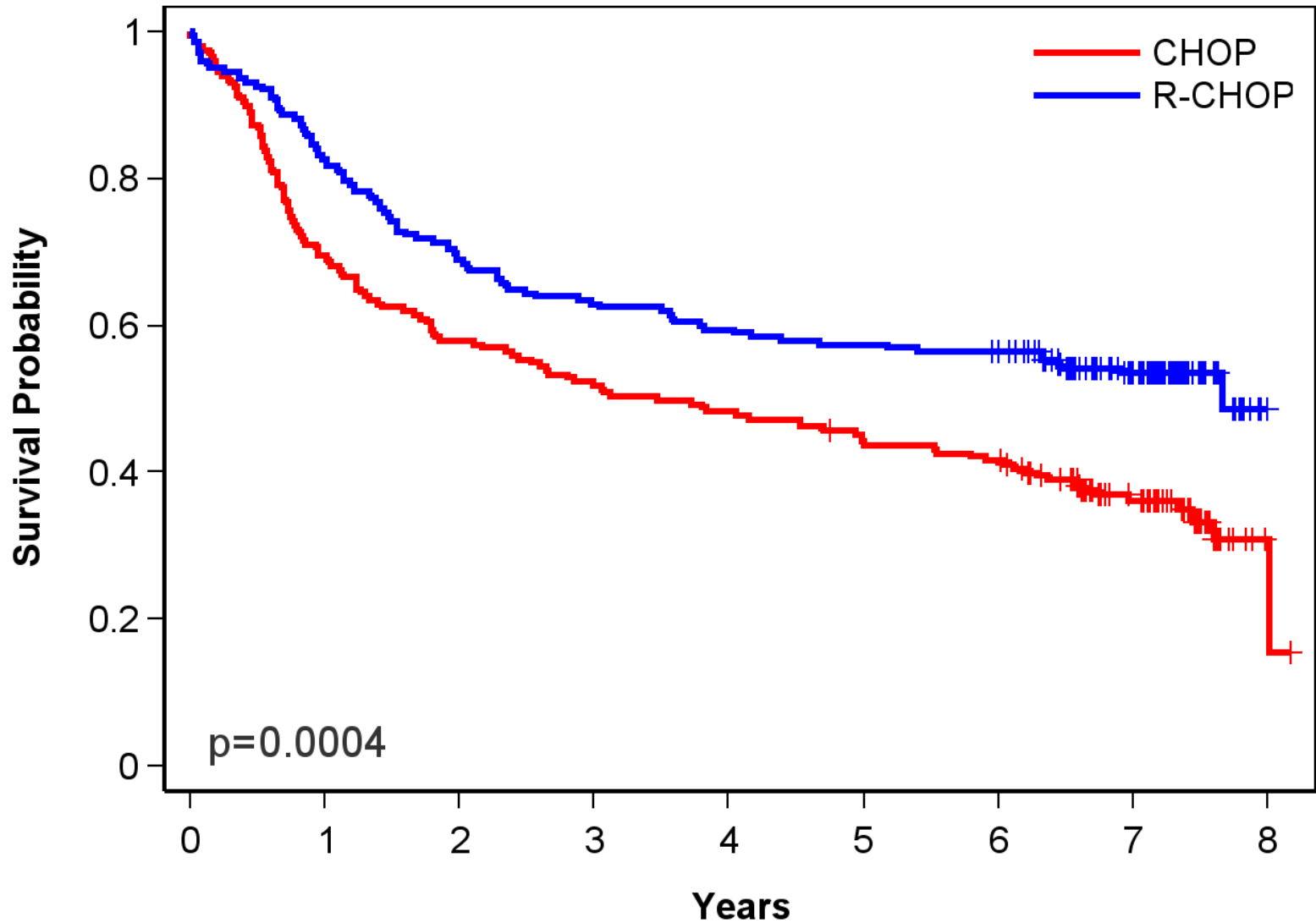
Survival with R-CHOP treatment was good even in the presence of poor risk parameters;

Parameter	R-CHOP
Age >75 years	43%
PS=2	38%
B symptoms	54%
Stage IV	47%
High LDH level	45%
Hb <10 g/dl	54%
High aaIPI	42%

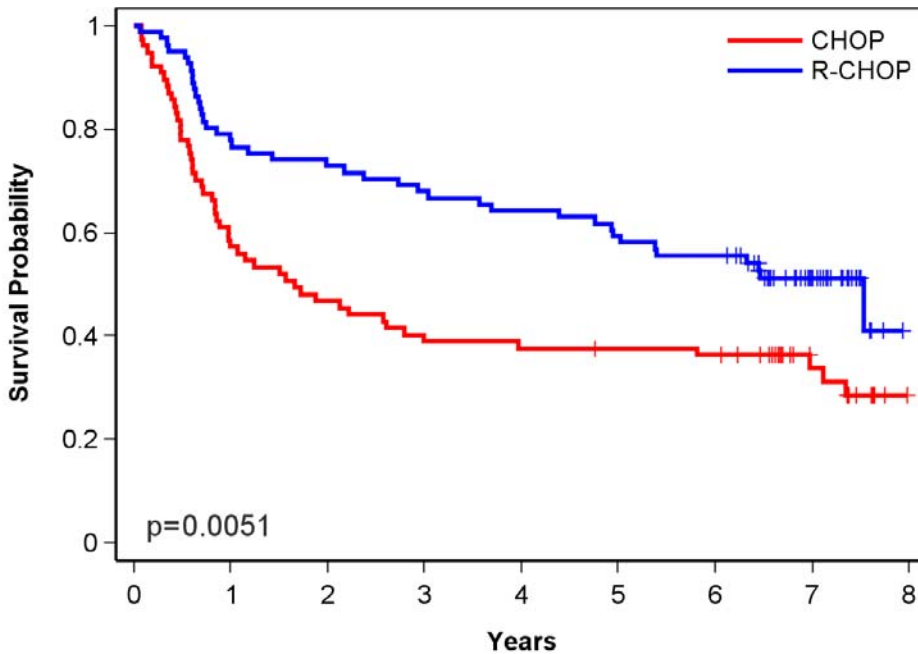
EFS – Median follow-up 7 y



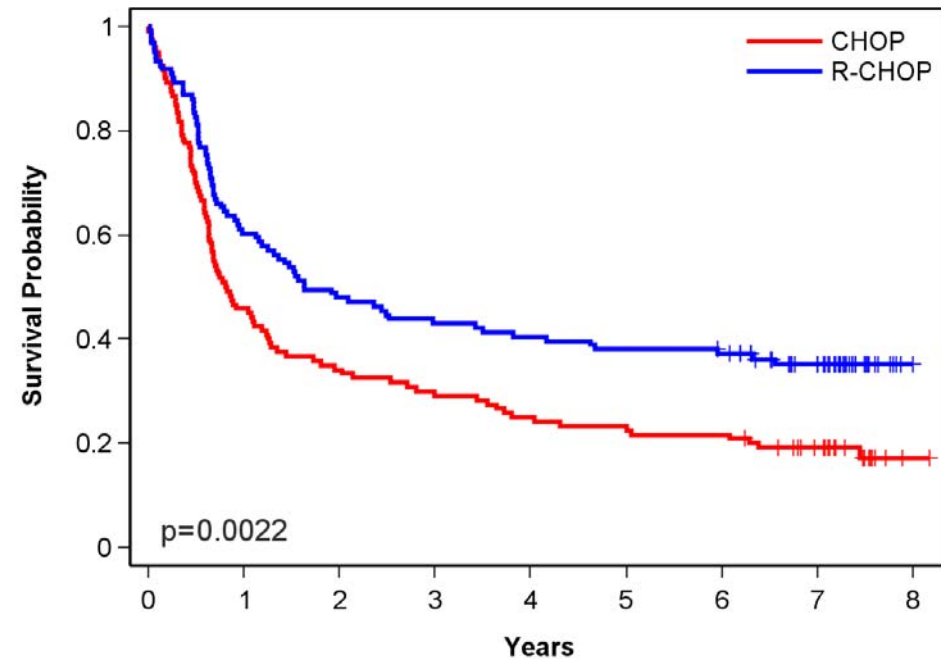
OS – Median follow-up 7 y



Progression-free survival according to aalPI

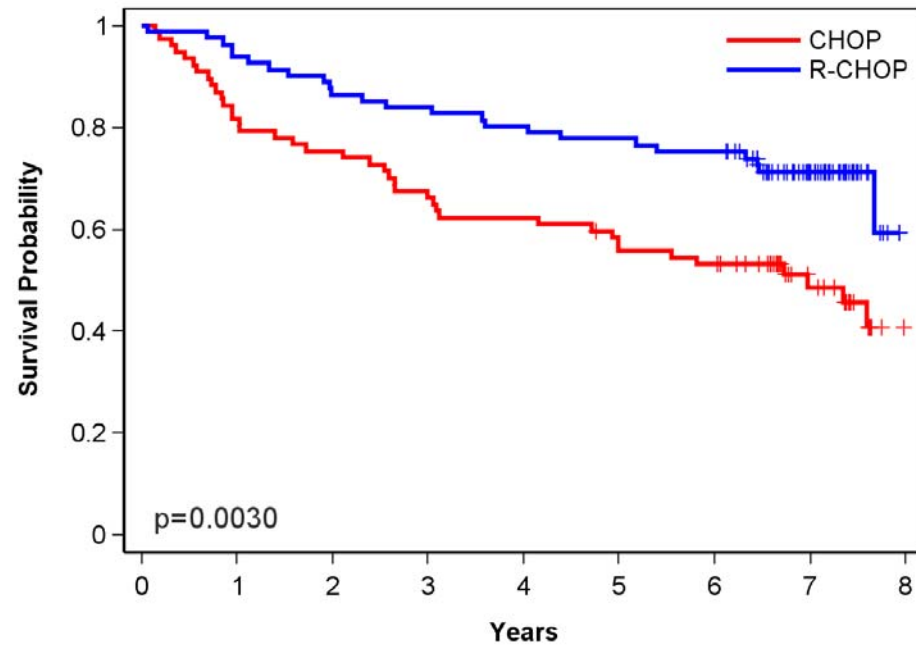


Low risk patients

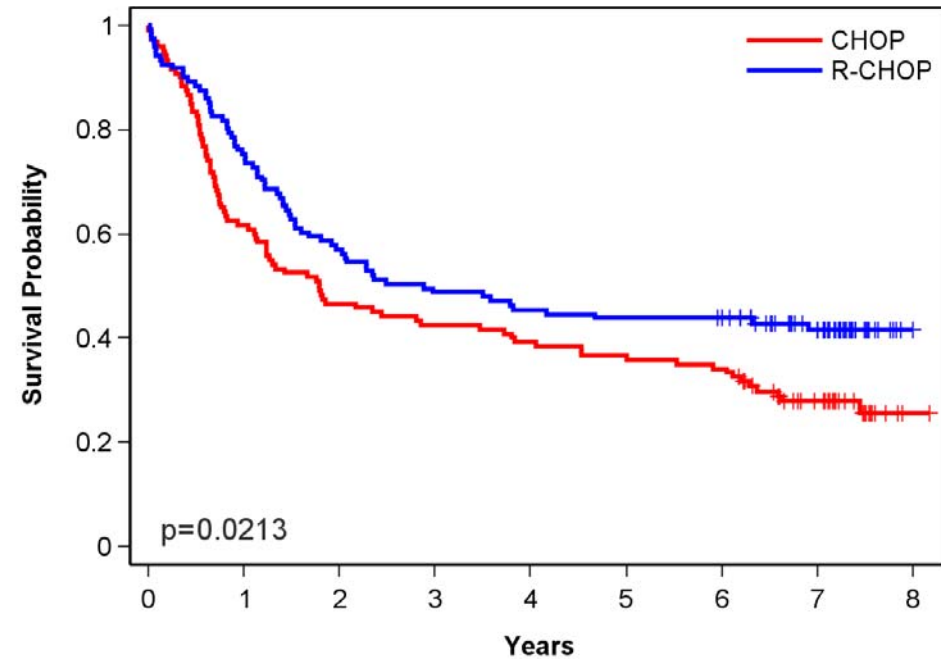


High risk patients

Overall survival according to aalPI

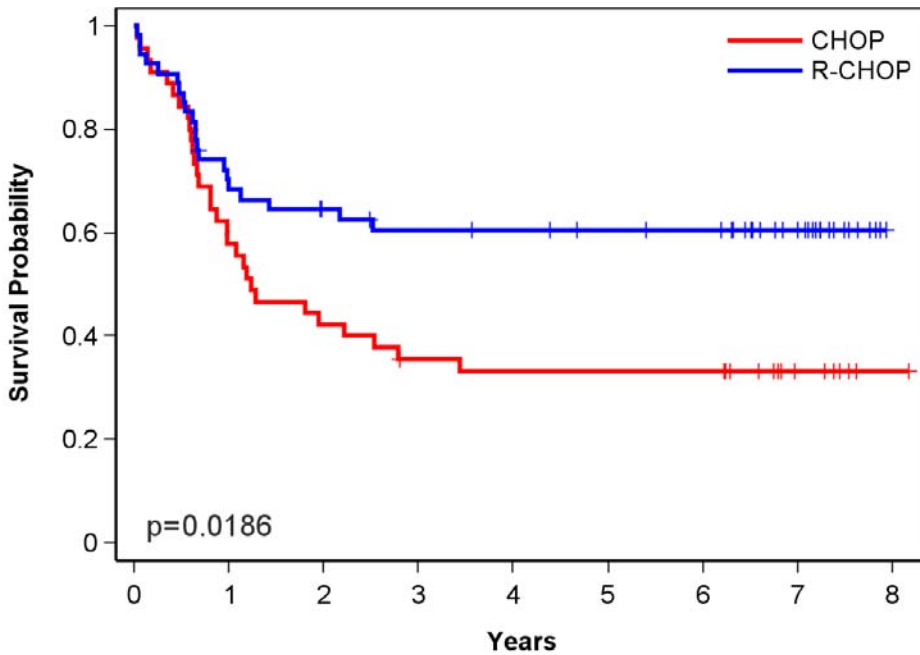


Low risk patients

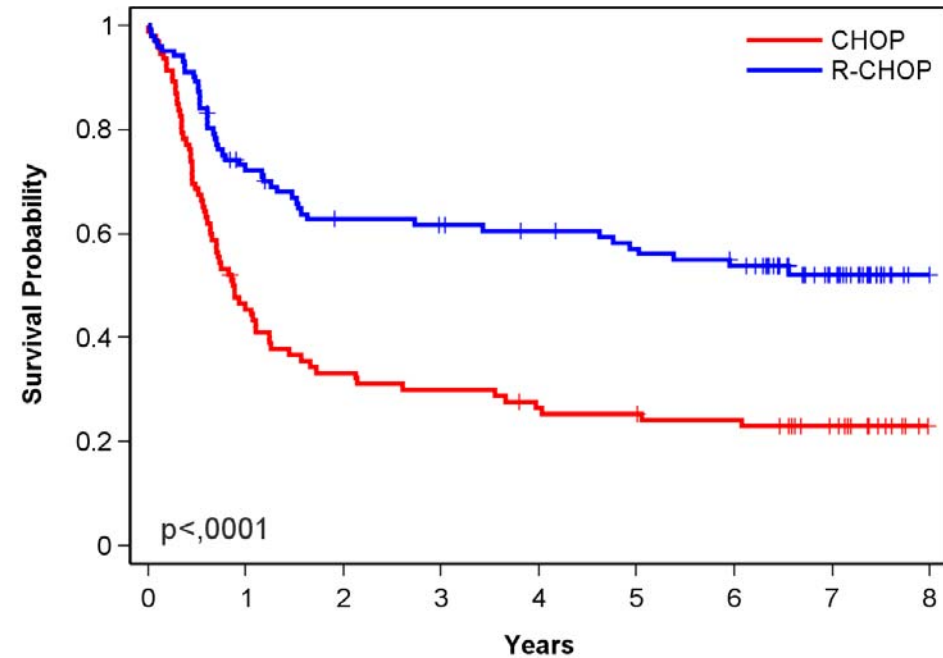


High risk patients

GELA study: Progression-free survival

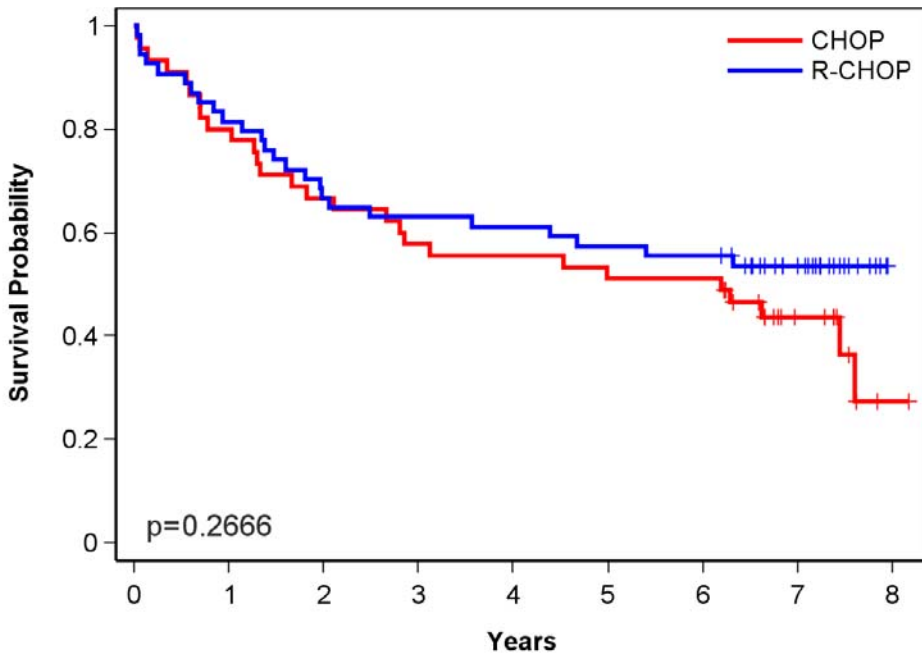


Bcl-2 protein expression –
P = 0.0186

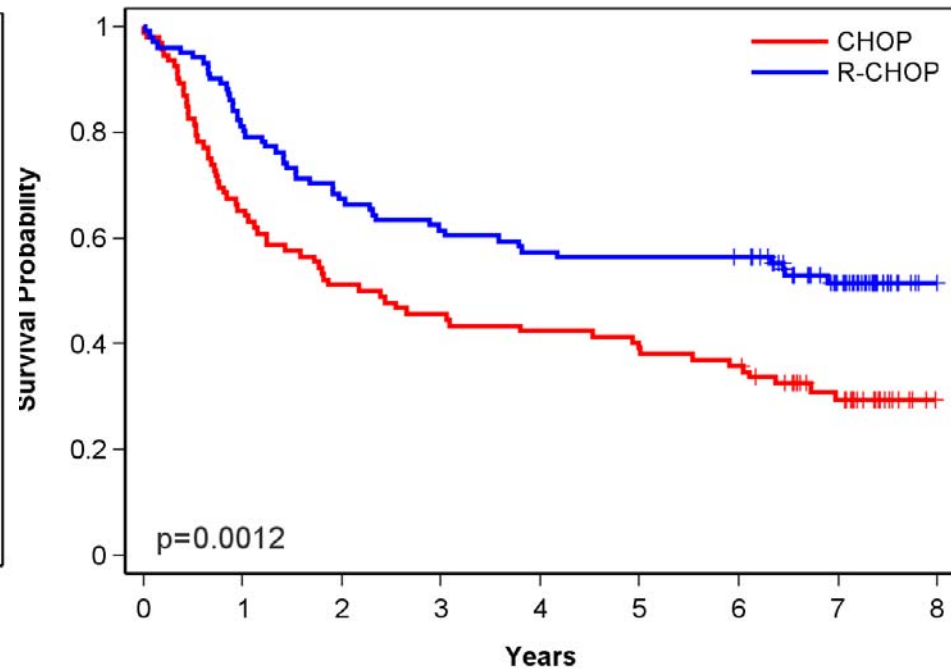


Bcl-2 protein expression +
P < 0.0001

GELA study: Overall survival



Bcl-2 protein expression -
P = 0.27



Bcl-2 protein expression +
P = 0.0012

LONG-TERM RESULTS OF THE GELA STUDY

- These data confirm the long-term benefits associated with adding R to CHOP
- All age groups (60-80) benefit from the addition of R to CHOP, irrespective of other risk factors and concomitant diseases

ADDITION OF RITUXIMAB TO DOSE-DENSE
AND HIGH DOSE CHEMOTHERAPY (HDC)
WITH AUTOLOGOUS TRANSPLANTATION
(ASCT) IN UNTREATED POOR-PROGNOSIS
DIFFUSE LARGE B-CELL LYMPHOMA
(DLBCL): RESULTS OF PHASE II TRIAL

Abstract 408

Vitolo U et al. Oral presentation

Saturday 1100-1115

R PLUS HDC WITH ASCT IN UNTREATED POOR PROGNOSIS DLBCL

8 cycles of MabThera added to chemotherapy is standard treatment for DLBCL

This Phase II study of R plus HDC followed by BEAM conditioning and ASCT shows a high CR and improved OS and FFS when compared to historical controls.

R PLUS HDC WITH ASCT IN UNTREATED POOR PROGNOSIS DLBCL

Methods:

- Stage III-IV DLBCL with intermediate high or high aalPI
- Induction: 4 courses R-MegaCEOP every 14 days with GCSF support
- 2 courses intensified R-MAD including PBSC harvest
- ASCT conditioned by BEAM

- Control group from previous Phase II study treated with up-front HDC and ACST but without R:
 - 8-week MACOPB
 - MAD and ASCT/BEAM as above

R PLUS HDC WITH ASCT IN UNTREATED POOR PROGNOSIS DLBCL

Results at median follow-up 41 months:

- 94 patients, median age 47 years (19-60)
- CR in 77 patients (82%)
- PR in 1 patient (1%)
- No response in 11 patients (12%)
- 5 patients (5%) died due to toxicity, although few severe early toxicities were reported and late toxicity was minimal (no MDS, ANLL or solid tumour)

	R-HDC (n=94)	Control (n=47)	HR R vs Control (95% CI)	p
4-year FFS	73%	44%	0.46 (0.25-0.85)	0.01
4-year OS	80%	54%	0.46 (0.23-0.93)	0.03

R PLUS HDC WITH ASCT IN UNTREATED POOR PROGNOSIS DLBCL

- These data suggest that MabThera in combination with dose-dense and high-density chemotherapy may further improve the outcome of DLBCL treatment in poor prognosis patients
- This hypothesis is being tested by comparing R plus DDC/HDC with R plus DDC by Intergruppo Italiano Linfomi

COST-EFFECTIVENESS OF CHOP-LIKE
CHEMOTHERAPY PLUS RITUXIMAB
VERSUS CHOP-LIKE CHEMOTHERAPY
ALONE IN YOUNG PATIENTS WITH GOOD-
PROGNOSIS DIFFUSE LARGE-B-CELL
LYMPHOMA

Abstract 600

Ferrara F et al. Poster presentation

Saturday 1800-1915

COST EFFECTIVENESS OF MABTHERA IN YOUNG PATIENTS WITH GOOD-PROGNOSIS DLBCL

MabThera has been shown to be highly cost effective in its indications

This 3-year model assessed the cost impact of adding R to CHOP (like) therapy on the Italian National Health Service demonstrating that it is highly cost-effective in DLBCL and in fact dominant (i.e. cost saving)

COST EFFECTIVENESS OF MABTHERA IN YOUNG PATIENTS WITH GOOD-PROGNOSIS DLBCL

The model simulated a complete or non-complete response to initial R-CHOP (like) therapy or CHOP (like) therapy alone at 5 months and 3 Years

Efficacy data were taken from the MabThera International Trial MInT Group study and direct medical costs on Italian treatment patterns

It was assumed that lack of efficacy would be followed by rescue therapy of a debulking phase followed by autologous transplant

COST EFFECTIVENESS OF MABTHERA IN YOUNG PATIENTS WITH GOOD-PROGNOSIS DLBCL

Results:

- In terms of OS, the addition of R to CHOP (like) chemotherapy added 1.91 Life Years (LY; 19.69 for R-CHOP vs 17.78 for CHOP)
- Expected costs per patient were € 23,617.57 for R-CHOP (like) therapy and € 25,370.08 for CHOP (like) chemotherapy alone
- 3-years CR ICER was calculated at € 661.43 for R-CHOP (like) chemotherapy vs CHOP (like) chemotherapy alone

Conclusions:

- R-CHOP (like) chemotherapy is therefore the dominant strategy for young patients with good prognosis DLBCL
- R-CHOP (like) chemotherapy is highly cost-effective even in the worst-case scenario

COMPREHENSIVE GERIATRIC
ASSESSMENT-ADAPTED CHEMOTHERAPY
IN 100 ELDERLY PATIENTS (≥ 70 YEARS)
WITH DIFFUSE LARGE B-CELL NON-
HODGKIN'S LYMPHOMA (DLBCL)

Abstract 867

Spina M et al. Oral presentation

Sunday 0900-0915

COMPREHENSIVE GERIATRIC ASSESSMENT- ADAPTED CHEMOTHERAPY IN DLBCL

An 8-cycle CHOP-like regimen is regarded as the best partner for MabThera in patients with DLBCL

Some components of CHOP are often contra-indicated in older patients

Individually selecting chemotherapy to partner MabThera leads to potentially enables curative treatment to be given to elderly patients with co-morbidities

COMPREHENSIVE GERIATRIC ASSESSMENT- ADAPTED CHEMOTHERAPY IN DLBCL

Methods:

- CHOP or R-CHOP was given to patients with no comorbidity
- patients with mild cardiopathy received CEOP or R-CEOP (epirubicin was substituted for doxorubicin)
- patients with moderate or severe cardiopathy received CVP or R-CVP (anthracyclines were omitted)
- patients with diabetes received CHO, CEO, R-CHO or R-CEO (prednisone was omitted)
- patients with neuropathy received CHP, R-CHP, CEP or R-CEP (vincristine was omitted)
- Dose of chemotherapy was based on CGA score (ADL and IADL)
- All patients received prophylactic filgrastim

COMPREHENSIVE GERIATRIC ASSESSMENT- ADAPTED CHEMOTHERAPY IN DLBCL

Results:

- 100 patients were treated (41 male, 59 female; median age 75 years)

Administered regimens

- Full-dose chemotherapy: R-CHOP 22%, CHOP 16%, R-CEOP 4%, CEOP 8%
- 75%-dose chemotherapy: R-CHOP 10%, CHOP 8%, R-CEOP 9%, CEOP 6%
- 50%-dose chemotherapy: CVP 5%, R-CVP 9%

Toxicity was acceptable

- 4 deaths (2 septic shock, 1 acute respiratory failure and 1 acute MI)
- 29% of patients experienced grade 3-4 neutropenia
- 13% experienced mucositis
- 13% experienced febrile neutropenia
- 9% experienced peripheral neuropathy
- 3% experienced cardiac toxicity
- 1% experienced skin toxicity

COMPREHENSIVE GERIATRIC ASSESSMENT- ADAPTED CHEMOTHERAPY IN DLBCL

Results ctd:

- 76% of patients achieved CR
- At a median follow-up of 24 months
 - only 16% of CR patients have relapsed
 - 73 patients are alive
 - 63 patients are alive and in CR

Conclusions:

- Adapting chemotherapy by comprehensive geriatric assessment is a successful approach in elderly patients with DLBCL
- This approach extends the possibility of a cure to elderly patients with aNHL by avoiding the under-treatment of otherwise healthy patients and the over-treatment of patients with comorbidities

THE GEMOX-R (GEMCITABINE, OXALIPLATIN, RITUXIMAB) REGIMEN IS A HIGHLY EFFECTIVE SALVAGE REGIMEN IN ELDERLY PATIENTS WITH REFRACTORY-RELAPSING DIFFUSE LARGE B-CELL LYMPHOMA (DLCL) NOT CANDIDATES TO AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT). A PHASE II STUDY

Abstract 1177

Rodriguez J et al. Publication only

R-GEMOX SALVAGE IN ELDERLY DLBCL PATIENTS WHO ARE NOT ASCT CANDIDATES

MabThera based chemotherapy is a useful treatment alternative for some elderly or poor-prognosis patients with relapsed aggressive lymphoma not suitable for ASCT

MabThera + GEMOX is an active alternative in elderly patients not suitable for ASCT, even after receiving MabThera in prior lines of therapy

R-GEMOX SALVAGE IN ELDERLY DLBCL PATIENTS WHO ARE NOT ASCT CANDIDATES

Background:

- An alternative consolidation therapy to ASCT is required for patients with refractory or relapsing DLBCL who are chemosensitive to standard salvage therapy

Results:

- 33 elderly DLCL patients (median 69 years [32-85]) not suitable for ASCT were included
- 36% primary refractory, 42% received R-GEMOX at first relapse
- First-line therapies
 - CHOP-R (61%), CHOP (21%), EPOCH-R (12%), CNOP (3%)
 - 1 patient first line with severe cardiac disease
- 73% Ann Arbor stage III-IV, 55 high LDH, 52% ECOG>1, 67% a-IPI>1

R-GEMOX SALVAGE IN ELDERLY DLCL PATIENTS WHO ARE NOT ASCT CANDIDATES

Results ctd:

- Median of 4 R-GEMOX cycles given
- OS 41%, PFS 31% at 12 months
- For living patients
 - median follow-up 11 months: ORR 47%, CR 36%
 - median survival 10.8 months
 - Survival of 26+ months in one patient with HIV
- Toxicity
 - 39% neutropenia grade III-IV
 - 36% thrombocytopenia grade III-IV
 - 6% neurotoxicity grade III-IV

R-GEMOX SALVAGE IN ELDERLY DLCL PATIENTS WHO ARE NOT ASCT CANDIDATES

Conclusions:

- R-GEMOX is a viable salvage treatment for elderly patients with DLCL who are not candidates for ASCT
- R-GEMOX shows high activity and reasonable tolerability

BORTEZOMIB, RITUXIMAB, AND
DEXAMETHASONE (BORID) INDUCES HIGH
RESPONSE RATES AND DURABLE
COMPLETE REMISSIONS IN PATIENTS WITH
RELAPSED/REFRACTORY MANTLE CELL
LYMPHOMA

Abstract 1188

Drach et al. Publication only.

BORID IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

The addition of MabThera to chemotherapy improves survival in patients with Mantle Cell Lymphoma (MCL)

This study demonstrates that the addition of bortezomib and dexamethasone to MabThera is associated with high response rates and durable responses in relapsed refractory patients with MCL

- 88% of patients had received prior MabThera

BORID IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

Aims:

- To evaluate the activity and safety of the proteasome inhibitor bortezomib to added to dexamethasone and MabThera

Methods:

- Patients with progressive MCL after at least one prior therapy were eligible to receive BORID:
 - Bortezomib was given 1.3 mg/m² days 1, 4, 8, 11
 - Dexamethasone 40 mg orally on days 1-4
 - MabThera 375 mg/m² day 1

BORID IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

Results:

- 16 patients were enrolled
- Median age 67 years (48-75)
- Median line of prior therapy 3 (1-6)
 - MabThera included in 88%
 - Thalidomide 50%
 - HDT 31%
 - FLudarabine based 31%
- Median time from previous line to relapse 42 months (11-98)

BORID IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

Results ctd:

- 11/15 pts (evaluable) achieved a response
 - 5 CR (4 had PET and were negative for disease)
 - 6 PR
 - In addition 2 had SD
- Skin infiltrates preceded achievement of CR in 2 patients
- Remission status was associated with duration of response
 - CR PFS (22+, 17+, 12+, 12 and 4+ months)
 - PR PFS (15, 11, 6+ 6 and 6 months)

BORID IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

Results ctd:

- Severe adverse events (> grade II) included
 - infections (herpes zoster in 2 pts, bacterial pneumonia, mucosal candidiasis)
 - peripheral neuropathy (3 pts)
 - fatigue (2 pts)
 - vasculitic skin infiltrates (3 pts)
 - Thrombopenia (< 50 G/L) (2 pts)
- All adverse events were manageable

BORID IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

Conclusions:

- The MabThera containing regimen BORID has high activity in this heavily pretreated MCL population
 - 88% had received prior MabThera
- Quality of response is associated with duration of PFS
- An early vasculitic rash may be an indicator of favourable response

POST ASCT RITUXIMAB CONSOLIDATION
THERAPY ELIMINATES PERSISTING FDG PET
POSITIVITY IN DIFFUSE LARGE B CELL
LYMPHOMA (DLBCL) PATIENTS

Abstract 1261

Remenvi P et al. Publication only

POST ASCT RITUXIMAB CONSOLIDATION THERAPY IN DLBCL

This study demonstrates the efficacy of MabThera containing consolidation on patients with minimal residual disease following MabThera containing salvage therapy for DLBCL

The majority of patients had received MabThera in previous lines of therapy and shows that MabThera containing salvage therapy is effective even in patients who have received prior MabThera

POST ASCT RITUXIMAB CONSOLIDATION THERAPY IN DLBCL

Methods:

- MabThera containing salvage therapy followed by ASCT with MabThera consolidation was investigated in patients with DLBCL
- Minimal residual disease following ASCT was assessed by PET

Results:

- 16 patients (median age 50 years [19-60]) underwent ASCT
- 14 had relapsed on R-CHOP
- Salvage therapies were R-DHAP, RIME and R-GEMP
- 12/16 achieved CR (assessed by CT scan)
- conditioning therapy was BEAM (containing median 5.62×10^6 [3.77-11.41] CD34 positive cells)
- FDG PET scan was performed two months after SCT

POST ASCT RITUXIMAB CONSOLIDATION THERAPY IN DLBCL

Results ctd:

- 13/16 (81%) patients are in CR at a median of 12 months (6-20) follow-up
- 3/13 patients had positive PET scans with low tumor burden indicating minimal residual disease
 - these patients were all PET-negative 3 months after R

Conclusions:

- MabThera may control low tumor burden without additive toxicity in DLBCL patients following SCT

MABTHERA MAINTENANCE THERAPY

RITUXIMAB MAINTENANCE THERAPY IN CD20+ B-CELL NON-HODGKIN-LYMPHOMA – FIRST RESULTS OF A MULTICENTER PROSPECTIVE RANDOMISED PHASE II STUDY

Abstract 298 (and 297 – QoL)

Witzens-Harig M et al. Poster presentation

Friday, 1745-1900

Page 4 and 6

RITUXIMAB MAINTENANCE THERAPY IN CD20+ B-CELL NON-HODGKIN-LYMPHOMA

MabThera maintenance therapy in relapsed / refractory follicular lymphoma improves (EORTC 20981)

- Overall survival
- Progression Free Survival by ~ 3 years

This study demonstrates that MabThera maintenance therapy has benefit in a broader B-cell population

- Large % of patients have aggressive NHL
- Results of NHL-13 study eagerly awaited

RITUXIMAB MAINTENANCE THERAPY IN CD20+ B-CELL NON-HODGKIN-LYMPHOMA

Methods:

- 172 patients (pts) with CD20+ NHL randomised (after “standard induction”) if PR or CR for indolent and CR in aggressive CR to
 - MabThera Maintenance Therapy Q3M vs. Observation
- Histological subtypes included
 - DLBCL - 69 pts
 - Follicular lymphoma - 41 pts
 - Mantle cell lymphoma - 18 pts
 - Primary mediastinal lymphoma - 15 pts
 - Marginal zone lymphoma - 9 pts
 - Burkitt’s lymphoma - 3 pts
 - Immunocytoma - 2 pts
 - Primary intestinal lymphoma - 1 pt
 - Hairy cell leukemia - 1 pt
 - CLL - 1 pt
 - Unclassified B-cell lymphoma - 2 pts

RITUXIMAB MAINTENANCE THERAPY IN CD20+ B-CELL NON-HODGKIN-LYMPHOMA

Results:

Interim Analysis on 162 patients

- Event Free Survival significantly greater in MabThera maintenance therapy vs Observation ($P < 0.05$)
- Overall survival no difference at this stage
- 2 pts experienced grade III events (1 x leucopenia, 1 x infection)

QoL during MabThera maintenance therapy assessed in separate study (106 pts Abstract 297)

- No negative effect on QoL during maintenance

RITUXIMAB MAINTENANCE THERAPY FOR PATIENTS WITH FOLLICULAR LYMPHOMA. A COST-EFFECTIVE STRATEGY?

Abstract 303

Francisco J et al. Poster presentation

Friday, 1745-1900

Page 8

RITUXIMAB MAINTENANCE THERAPY FOR PATIENTS WITH FOLLICULAR LYMPHOMA. A COST-EFFECTIVE STRATEGY?

MabThera therapy has been shown to be highly cost effective

- Aggressive lymphoma (NICE)
- 1st Line induction + CVP (NICE, Lewis et al ASH 2006)
- Maintenance therapy in relapsed FL in Canadian setting (Maturi et al ASH 2006)

This abstract demonstrates that MabThera maintenance therapy is highly cost-effective in Spanish Health System

RITUXIMAB MAINTENANCE THERAPY FOR PATIENTS WITH FOLLICULAR LYMPHOMA. A COST-EFFECTIVE STRATEGY?

Aims:

- To determine cost effectiveness of MabThera maintenance therapy from Spanish perspective vs current clinical practice

Methods:

- Taking data from EORTC 20981 study (Van oers et al *Blood* 2006)
- Deterministic, 3 health state transition model

RITUXIMAB MAINTENANCE THERAPY FOR PATIENTS WITH FOLLICULAR LYMPHOMA. A COST-EFFECTIVE STRATEGY?

Results:

- Total cost for MabThera maintenance +8,026€ > than observation
- Incremental cost per quality-adjusted life year (QALY) gained was 9,358€
- Cost per LY gained of 8,493€
- Cost per PFS year gained of 5,485€
- Sensitivity analyses demonstrate results remains cost-effective for all variable tested

RITUXIMAB MAINTENANCE THERAPY FOR PATIENTS WITH FOLLICULAR LYMPHOMA. A COST-EFFECTIVE STRATEGY?

Conclusions:

- Rituximab maintenance therapy, when compared to observation alone
 - improves overall survival and progression free survival [3 years]
 - is a cost effective strategy in patients with relapsed or refractory follicular lymphoma who attain a response with further therapy

PROSPECTIVE, MULTICENTER
RANDOMIZED GITMO/IIL TRIAL COMPARING
INTENSIVE (R-HDS) VERSUS
CONVENTIONAL CHEMOIMMUNOTHERAPY
(CHOP-R) IN HIGH-RISK FOLLICULAR
LYMPHOMA AT DIAGNOSIS: THE SUPERIOR
MOLECULAR REMISSION (MR) RATE OF R-
HDS EXPLAINS ITS BETTER CLINICAL
PERFORMANCE

Abstract 406

Ladetto M et al. Oral Presentation,
Saturday, 1030-1045, Mozart III

R-HDS VS. R-CHOP IN HIGH-RISK FOLLICULAR LYMPHOMA AT DIAGNOSIS: MR AND OUTCOME

MabThera + chemotherapy improves overall survival in 1st line FL
(Schulz et al, JNCI 2007 – Cochrane meta-analysis, + 4 studies)

MabThera maintenance therapy improves overall survival and PFS in relapsed refractory FL

Ongoing PRIMA study evaluates the role of MabThera maintenance after 1st line induction

This study shows R-HDS better than R-CHOP in “high-risk” FL but unknown role once PRIMA results reported

R-HDS VS. R-CHOP IN HIGH-RISK FOLLICULAR LYMPHOMA AT DIAGNOSIS: MR AND OUTCOME

Objectives:

- Compare EFS of R-CHOP to R-HDS (crossover from R-CHOP to R-HDS allowed)

Methods:

- Planned sample size 240 (stopped at 136)
- High risk FL (aa IPI >1 or IIL >2, 18-60 years)
- Primary endpoint EFS
- Secondary endpoint PFS, DFS, OS
- Molecular remission (MR) based on BM PCR

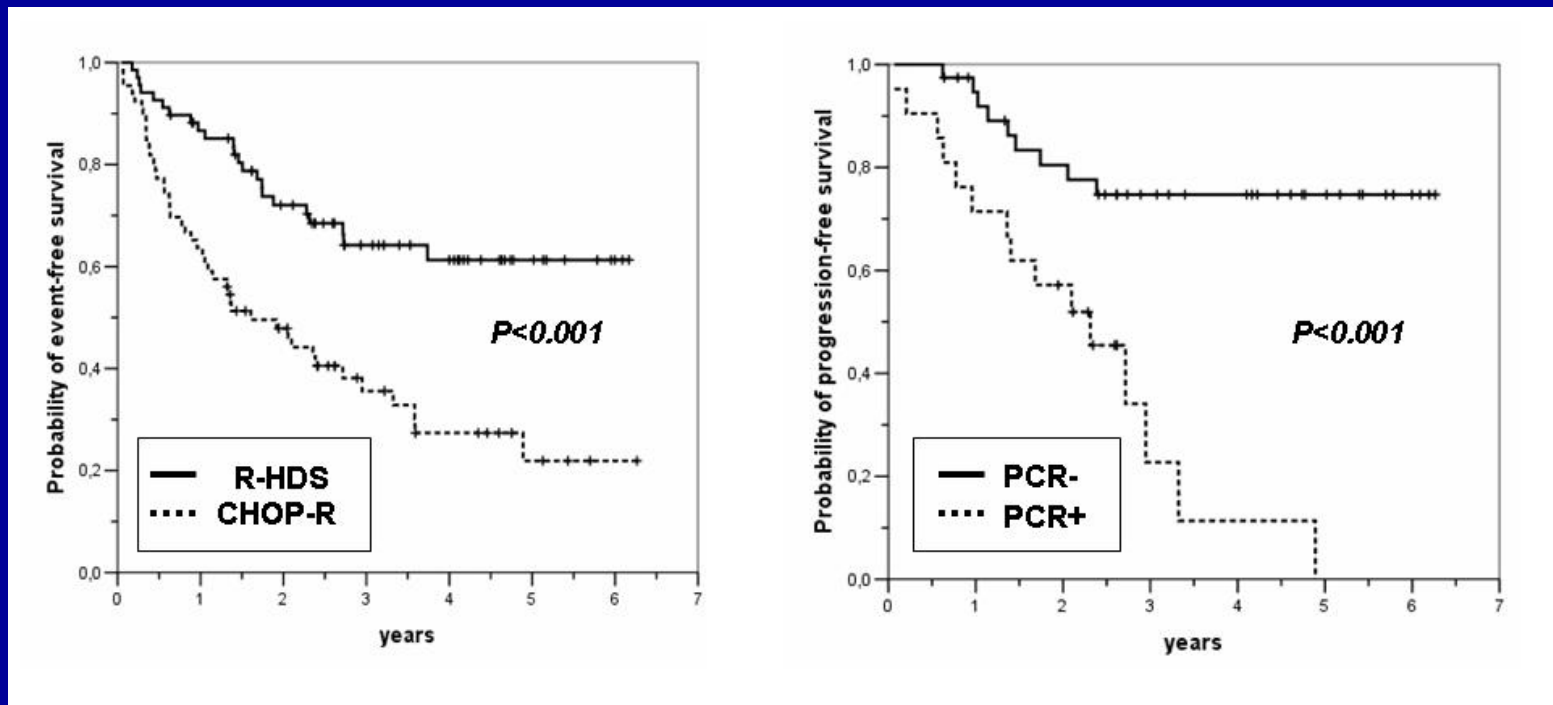
R-HDS VS. R-CHOP IN HIGH-RISK FOLLICULAR LYMPHOMA AT DIAGNOSIS: MR AND OUTCOME

Results at median f/u of 39 months:

- Patients well matched for risk factors
- EFS 62% vs 33% (R-HDS vs R-CHOP)
- PFS 70% vs 36%
- OS 81% in both arms
- MR rate of 80% vs 44% ($p < 0.001$)
- MR associated with better PFS ($p < 0.001$)
- Patients with or without MR had similar PFS irrespective of therapy
- MR was strongest prognostic factor for PFS, EFS, DFS

R-HDS VS. R-CHOP IN HIGH-RISK FOLLICULAR LYMPHOMA AT DIAGNOSIS: MR AND OUTCOME

PFS by i) Induction therapy ii) by MR status



R-HDS VS. R-CHOP IN HIGH-RISK FOLLICULAR LYMPHOMA AT DIAGNOSIS: MR AND OUTCOME

Conclusions

- R-HDS better than R-CHOP for EFS and PFS in high risk FL
- MR is the strongest predictor of outcome
- Superiority of R-HDS is due to superior MR rate

RITUXIMAB MAINTENANCE THERAPY: AN
EFFECTIVE AND TOLERABLE STRATEGY
TO IMPROVE AND PROLONG RESPONSE IN
CD20+ B-CELL LYMPHOPROLIFERATIVE
DISORDERS

Abstract 1508

Marin-Nielba et al. Publication.

MABTHERA MAINTENANCE THERAPY: IN CD20+ B-CELL DISORDERS INCLUDING MABTHERA PREVIOUSLY TREATED

MabThera maintenance therapy has shown improved outcomes

- In 1st line FL
- In relapsed / refractory FL
- After Chemo +/- MabThera
- After MabThera monotherapy
- After CR and PR to induction therapy

This study shows that MabThera maintenance therapy is effective

- In a mixed group of B-Cell malignancies
- In patients previously treated with MabThera

MABTHERA MAINTENANCE THERAPY: IN CD20+ B-CELL DISORDERS INCLUDING MABTHERA PREVIOUSLY TREATED

Aims:

- To evaluate the safety and efficacy of MabThera maintenance therapy

Methods:

- Patients with CD20 +ve NHL with CR or CR (MRD positive)
- First line or relapse
- Prior MabThera allowed
- Induction +/- MabThera
- MRD negative → Q3M MabThera maintenance for 2 years
- MRD positive → 4 doses Q6M maintenance for 2 years

MABTHERA MAINTENANCE THERAPY: IN CD20+ B-CELL DISORDERS INCLUDING MABTHERA PREVIOUSLY TREATED

Efficacy Results at median follow-up of 12 months:

- 49 patients (FL 28, MZL 11, WM 3, MCL 2, DLBCL 3, CLL 2)
- Stage III/IV 42 (89.3%)
- 33/49 (67%) had received MabThera previously **(Note to Roche as discussed this is not clear if it was in prior lines of therapy or in induction)**

MABTHERA MAINTENANCE THERAPY: IN CD20+ B-CELL DISORDERS INCLUDING MABTHERA PREVIOUSLY TREATED

Efficacy Results at median follow-up of 12 months:

- 40 pts achieved MRD negative CR
 - 95% (38) are still in CR with MabThera maintenance
 - 1 pt not evaluable (< 3 months follow-up)
- 9 pts achieved with MRD positive CR
 - 55% (5) became MRD negative
 - 2 remain in CR with MRD positive
- No differences in efficacy were seen in patients previously treated with MabThera compared to those who were not

MABTHERA MAINTENANCE THERAPY: IN CD20+ B-CELL DISORDERS INCLUDING MABTHERA PREVIOUSLY TREATED

Safety Results at median follow-up of 12 months:

- 4 episodes of neutropenia grade 3/4 (all with previous myelotoxicity during induction)
- 4 fever
- 2 diarrhoea
- 5 lymphopenia with hypogammaglobulinaemia (not associated infections)
- 1 anaemia grade 3
- 1 hypertransaminasaemia in HCV+ pt were recorded.

→ All episodes were manageable

→ Only the HCV + patient required interruption of MabThera maintenance

MABTHERA MAINTENANCE THERAPY: IN CD20+ B-CELL DISORDERS INCLUDING MABTHERA PREVIOUSLY TREATED

Conclusions:

MabThera maintenance therapy

- Is effective improving CR (eradicating MRD) and prolonging TTF in first-line and relapsed patients
- Is effective in patients who have received MabThera in prior lines of therapy
- Is safe and manageable. Cases with neutropenia are probable due to myelotoxicity from induction therapy
- No differences were seen between both schedules regarding efficacy or associated toxicity

MABTHERA IN THE TREATMENT OF CHRONIC LYMPHOCYtic LEUKAEMIA

MAINTENANCE IMMUNOTHERAPY WITH
LOW-DOSE RITUXIMAB IMPROVES
OUTCOME IN “HIGH RISK” CHRONIC
LYMPHOCYTIC LEUKEMIA

Abstract 361

Del Poeta G et al. Oral Presentation

Saturday 0800-0815, Mozart III

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

MabThera maintenance therapy has proven benefits in patients with relapsed follicular lymphoma (Van oers et al Blood 2006) improving

- Overall survival
- Progression Free Survival by ~ 3 years

In Phase II studies MabThera 500 mg/m² in induction (first dose 375 mg/m² has shown high rates of and durable responses (Keating et al JCO 2005) with

- Overall response (OR) rates > 90%
- Complete response (CR) rates > 70%

This study shows that MabThera maintenance therapy may also improve outcomes in CLL

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Background:

Phase II studies of MabThera in combination with chemotherapy in CLL to produce

- High OR and CR rates
- Durable responses
- Low dose MabThera given over a longer duration of time may help prevent CD20 shaving reaction

Aims:

To assess the efficacy of MabThera maintenance therapy in CLL patients

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Methods:

- Patients with symptomatic untreated CLL received 6 x monthly doses of MabThera in combination with Fludarabine
- Remission status decided by flow cytometry of CD19+/5+/79b-
- Also assessed prior to therapy
 - VH mutation status
 - CD 38
 - ZAP-70 (>20%)
 - Unfavourable cytogenetics (trisomy 12, del 11q, del 17p)
- Patients in MRD positive CR/PR received
 - 4 x monthly cycles of MabThera consolidation
 - 12 x monthly cycles of “low-dose” MabThera 150 mg/m²

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Results Induction:

- 79 patients enrolled
- Median age 60 years (37-74)
- Modified RAI
 - 9 patients low
 - 67 intermediate
 - 3 high
- Based on NCI criteria
 - 63/79 (80%) CR
 - 12/79 (15%) PR
 - 4/79 (5%) Stable Disease

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Results maintenance median follow-up of 38 months:

- 35 patients with MRD positivity within 1 year of induction therapy received consolidation and maintenance
- 13 patients MRD positive did not receive further MabThera
- Overall PFS (all 79 patients) was 69% at 6 years from induction
- Maintenance MRD positive patients had
 - Longer duration of response (80% vs 20% for non-maintenance MRD positive patients)
 - Similar duration of response to MRD negative patients who did not receive maintenance

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Results maintenance median follow-up of 38 months ctd:

- Significantly shorter PFS was noted in
 - CD 38 positive patients (43% vs 79% at 5 years, $p = 0.005$)
 - Unmutated VH patients (45% vs 94% at 2.5 years, $p = 0.001$)
 - ZAP-70 positive patients (39% vs 88% at 5 years, $p = 0.00004$)
- In the “high risk” subset PFS was
 - 64% in maintenance vs 13% no maintenance

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Conclusions:

- MabThera maintenance therapy has the potential to prolong PFS
 - In patients who are MRD positive after MabThera – fludarabine induction
 - In patients with “high risk” CLL

POST-REMISSIONAL RITUXIMAB
ADMINISTRATION FOR THE TREATMENT OF
OLDER CHRONIC LYMPHOCYTIC LEUKEMIA
(CLL) PATIENTS RESPONSIVE TO FIRST-
LINE THERAPY WITH CHLORAMBUCIL AND
PREDNISONE

Abstract 124

Mauro F et al, Poster presentation

Friday 1745-1900

RITUXIMAB IN OLDER CLL PATIENTS RESPONSIVE TO FIRST-LINE CHLORAMBUCIL

The low toxicity and high efficacy of MabThera make it an ideal treatment for patients with CLL

Many patients with CLL are elderly and may have co-morbidities and so are unable to tolerate aggressive fludarabine based chemotherapy

Chlorambucil followed by MabThera shows high efficacy in this study

- The combination of MabThera and chlorambucil is an attractive one in this patient population and is the subject of a new study

RITUXIMAB IN OLDER CLL PATIENTS RESPONSIVE TO FIRST-LINE CHLORAMBUCIL

Aims:

- MabThera was given post chlorambucil remission to try and improve responses in patients over 60 years with CLL

Methods:

- Patients were treated with
 - 6 x monthly courses of chlorambucil 10 mg/m²/day (d 1-5) + prednisone 25 mg/m²/day (d 1-5)
 - Consolidation with 4 weekly doses of MabThera

RITUXIMAB IN OLDER CLL PATIENTS RESPONSIVE TO FIRST-LINE CHLORAMBUCIL

Results pre-MabThera:

- 19 patients with PR enrolled
- Median age 65 years (61-81)
- 5 patients IgVH unmutated at baseline

Results post-MabThera:

- Reduction in residual disease
- 13/19 (68%) converted from PR to CR
 - 2/13 (15%) had MRD < 1% CD5/CD19+
- Median follow-up 65 months all patients now relapsed
- Median time to new treatment 29.5 months
- MabThera was well-tolerated (mild infusion reactions in 3 patients)

RITUXIMAB IN OLDER CLL PATIENTS RESPONSIVE TO FIRST-LINE CHLORAMBUCIL

Conclusions:

- Consolidation of chlorambucil with MabThera shows efficacy in this patient population
 - Time to new CLL treatment 29.5 months
 - Conversion of 68% of PR's to CR's
- This is a well tolerated and is a suitable treatment combination for elderly patients with CLL

THE COMBINATION OF LUMILIXIMAB AND
FCR (FCRL) PRODUCES HIGH RATES OF
COMPLETE RESPONSE AND HAS
COMPARABLE TOLERABILITY TO FCR IN
PATIENTS WITH RELAPSED CLL: RESULTS
OF A PHASE I/II STUDY

Abstract 123

Byrd J et al. Poster presentation

Friday 1745-1900

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

MabThera will become the backbone of CLL therapy in the future

- 2 ongoing phase III studies
 - CLL8 R-FC vs FC in 1st line CLL
 - REACH R-FC vs FC in relapsed CLL

New compounds are likely to be added to MabThera based therapy

Lumiliximab shows activity in this heavily pretreated population when added to R-FC

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Aims:

- To investigate the safety and efficacy of the anti CD23 antibody, Lumiliximab added to R-FC in CLL

Methods:

- 31 patients with relapsed CLL (non-refractory to R-FC)
- Treated with 375 mg/m² (n=3) or 500 mg/m² lumiliximab in combination with R-FC up to 6 cycles

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Results:

- 22/31 (71%) of patients responded to FCRL
- 51% CR
- 75% (6/8) ORR in del 11q patients with 63% (5/8) CR
- 25% (1/4) PR in del 17p

- Grade 3 or 4 AE's were reported in 65% of patients
 - Nausea 77%
 - Pyrexia 61%
 - Neutropenia 58%
 - Chills 55%
 - Fatigue 48%

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Retrospective comparison with R-FC alone (Wierda W, et al. *JCO* 2050)

	R-FC	FCRL
% patients R naïve	15	60
Rai stage I/II	47	74
ORR	73	71
CR	25	52

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Conclusions:

Lumiliximab

- may have added activity to R-FC
- may be an add on therapy to MabThera based CLL treatment in the future

CLINICAL EFFICACY OF OXALIPLATIN,
FLUDARABINE, CYTARABINE, AND
RITUXIMAB (OFAR) COMBINATION
THERAPY IN PATIENTS WITH RICHTER'S
SYNDROME OR FLUDARABINE-
REFRACTORY CHRONIC LYMPHOCYTIC
LEUKEMIA: RESULTS OF A PHASE I-II
CLINICAL TRIAL

Abstract 364

Tsimberidou A-M et al. Oral presentation

Saturday 0845-0900

CLINICAL EFFICACY OF OFAR IN PATIENTS WITH RICHTER'S SYNDROME OR FLUDARABINE-REFRACTORY CLL

MabThera based therapy will be the treatment of the future for CLL as it is in NHL

Richters Syndrome (RS) and fludarabine refractory CLL have limited treatment options

This study shows the addition of oxaliplatin and cytarabine (A) to RF has activity and could be a potential treatment of the future

CLINICAL EFFICACY OF OFAR IN PATIENTS WITH RICHTER'S SYNDROME OR FLUDARABINE-REFRACTORY CLL

Aims:

- To identify a safe tolerated dose, dose limiting toxicity (DLT) and activity of oxaliplatin in combination with MabThera and F and A

Methods:

- Increasing doses of oxaliplatin (17.5, 20, or 25 mg/m²/d) were given on days 1-4 of the treatment cycles

Results:

- 64 patients (26 RS, 38 F refractory CLL)
- Highest tolerated oxaliplatin dose was 25 mg/m² with no DLT

CLINICAL EFFICACY OF OFAR IN PATIENTS WITH RICHTER'S SYNDROME OR FLUDARABINE-REFRACTORY CLL

	RS	F Refractory CLL
Age (median) years	66 (41-78)	62 (34-78)
No. prior therapies median	3 (0-10)	4 (1-11)
Rai stage III/IV	n/a	63%
ORR % (n) (CR/PR)	44% (11/25) (3 CR, 7 PR)	43% (15/35) (1CR, 2 nCR, 12 PR)

CLINICAL EFFICACY OF OFAR IN PATIENTS WITH RICHTER'S SYNDROME OR FLUDARABINE-REFRACTORY CLL

Results ctd:

- by cytogenetics
 - 41% (9/22) del 17p
 - 56% (5/9) del 11q
 - 100% (5/5) trisomy 12
 - 40% (2/5) del 13q
 - 33% (4/12) no genomic aberrations
- Grade 3 / 4 toxicity occurred in 14 patients

Conclusions

- The addition of oxaliplatin to a MabThera based regimen is active

RAPID INFUSION OF MABTHERA

RITUXIMAB RAPID INFUSION

Rapid infusion of MabThera can help efficiency and capacity of centres delivering cancer therapy, saving valuable time resource

Increasing application of MabThera as in maintenance therapy will lead to more infusions for more patients

These studies show confirm earlier studies that show rapid infusion of MabThera is safe and feasible and

- Is as effective as normal infusion rates in DLBCL (abstract 708)
- Is a cost effective way of administration even in elderly patients across a range of B-cell disorders (abstract 605)

RITUXIMAB RAPID INFUSION (90 MINUTES)
IS FEASIBLE AFTER THE FIRST DOSE IN AN
OUT-PATIENT SETTING, A SINGLE CENTER
PROSPECTIVE STUDY OF 80 COURSES

Abstract 605

Brice P et al. Poster presentation

Saturday 1800-1915

Page 30

RITUXIMAB RAPID INFUSION IS FEASIBLE AFTER FIRST DOSE

Aims:

- To prospectively evaluate a 90 minute infusion time of MabThera

Methods:

- If 1st dose tolerated, 2nd dose given at 400 mg/hr
- Patients with reaction to first dose given oral antihistamine to take the night before
- All patients received premedication 30 mins prior
 - methylprednisolone 120 mg
 - paracetamol 1g
 - dexchlorpheniramine 4 mg

RITUXIMAB RAPID INFUSION IS FEASIBLE AFTER FIRST DOSE

Results:

- 100 doses were given to 62 patients (20 not analysed)
- Median age 59 years (29-87)
- Diagnoses
 - FL 29 patients
 - DLBCL 14 patients
 - MZL 7 patients
 - CLL 7 patients
 - MCL 4 patients
 - NLPHL 1 patient
- Therapy
 - MabThera monotherapy 15 patients
 - R-CHOP 21 patients
 - R-CVP 13 patients
 - R-Fludarabine 11 patients
 - Other 2 patients

RITUXIMAB RAPID INFUSION IS FEASIBLE AFTER FIRST DOSE

Results:

- Median duration of infusion was 90 minutes
- Only 10 courses exceeded this time
- 2 patients required dose interruption for infusion related symptoms
- No other AE's were reported
 - BP's and temps remained in normal ranges
 - No patients required overnight admission

Conclusions:

- Rapid infusion of MabThera after IV premedication is a cost effective way of administration
- It can be safely given in an out-patient setting even in the elderly

RAPID INFUSION RITUXIMAB IS AS
EFFECTIVE AND SAFE AS CONVENTIONAL
INFUSION REGIMES IN THE TREATMENT OF
DIFFUSE LARGE B CELL LYMPHOMA: A 2
YEAR PROSPECTIVE STUDY

Abstract 708

Gibbs S et al. Poster presentation

Saturday 1800-1915

RAPID INFUSION RITUXIMAB IS AS EFFECTIVE AND SAFE AS CONVENTIONAL INFUSION IN DLBCL

Aims:

- To assess whether rapid infusion regimens are as effective and safe as conventional administration in DLBCL

Methods:

- Patients with DLBCL were treated with CHOP in combination with MabThera
- All received premedication 1 hour before infusion
 - 1g paracetamol
 - 8 mg chlorphenamine
 - 100 mg prednisolone
 - 5 mg tropisetron
- First infusion given at standard rate and if tolerated:
- Second infusion onwards given over 90 mins

RAPID INFUSION RITUXIMAB IS AS EFFECTIVE AND SAFE AS CONVENTIONAL INFUSION IN DLBCL

Results:

- 61 patients received 250 rapid infusions
- 93% patients received 3 weekly R-CHOP

- At a median follow-up of 16 months
 - CR 69%
 - OS 77%

- In patients 60-80 years
 - CR 79% (GELA 75% at 2 years)
 - OS 79% (GELA 70% at 2 years)

- In patients 18-60 years (IPI 0-1)
 - CR 92% (MInT 86% at 15 months)
 - OS 92% (MInT)

- No adverse events reported

RAPID INFUSION RITUXIMAB IS AS EFFECTIVE AND SAFE AS CONVENTIONAL INFUSION IN DLBCL

Conclusions:

- Rapid infusion is as effective as conventional rate infusion
- Should be the standard of care and is well tolerated

MABTHERA IN OTHER B- CELL DISORDERS

HIGH CURE RATE OF ADULT BURKITT'S AND OTHER HIGH GRADE NHL BY THE COMBINATION OF SHORT INTENSIVE CHEMOTHERAPY CYCLES WITH RITUXIMAB

Abstract 410

Hoelzer D et al. Oral presentation

Saturday 1130-1145, Mozart III

HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

The addition of MabThera to short intensive chemotherapy regimens has produced high cure rates in adult patients with Burkitt's lymphoma

The addition of MabThera allows chemotherapy doses to be reduced

HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

Background:

- Further intensification of chemotherapy has failed to improve on current results in adults with Burkitt's NHL and B-ALL

Aims:

- To assess the efficacy of the addition of MabThera to chemotherapy in patients with Burkitt's lymphoma and other high grade NHL

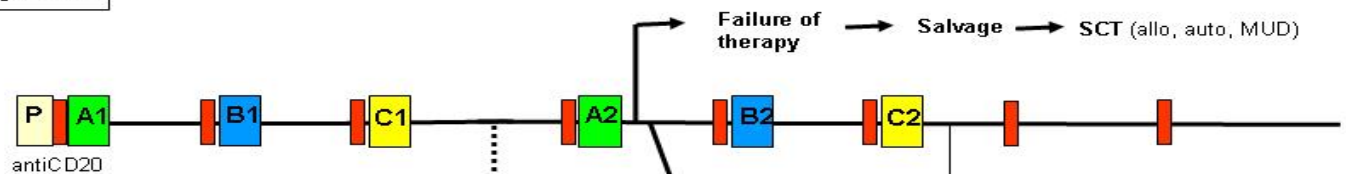
Methods:

- MabThera 375 mg/m² was given before each chemo cycle
- MabThera maintenance (2 cycles) was given after chemo
- High dose Ara-C (HDAC) was also included 2 g/m²
- High dose methotrexate (HDMTX) was reduced from 3 to 1.5 g/m²
- In elderly patients (>55yrs) no HDAC was given and HDMTX was 500 mg/m²

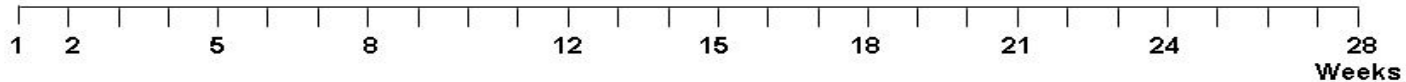
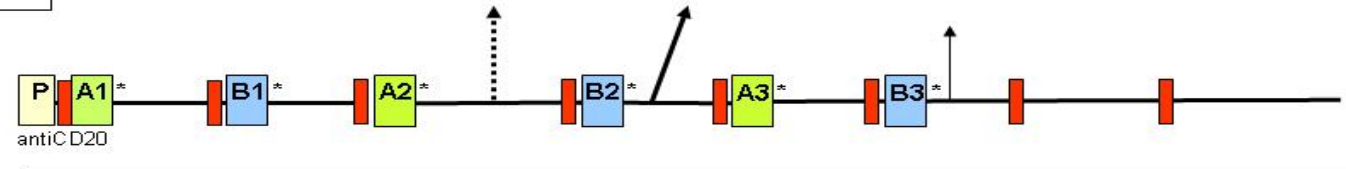
HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

Multicentre Study to Optimize Therapy of B-ALL, Burkitt's NHL and Other High-grade Non-Hodgkin's Lymphoma in Adults (GMALL-B-ALL/NHL 2002)

15-55 years



> 55 yrs



HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

Results:

- 376 patients with high grade B-NHL were enrolled
- 272 were evaluable after the first 2 cycles
- Median age – 38 years (16-78)
- Histological sub-types
 - 115 patients Burkitt's NHL (Stage III-IV, 52%, extranodal involvement 78%, aaIPI >1 47%)
 - 70 patients Mature B-ALL
 - 62 patients DLBCL (42 mediastinal, stage III-IV 63%, extranodal inv. 77%, aaIPI >1 63%)
 - 14 patients Burkitt's like lymphoma
 - 11 patients LACL

HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

Results continued:

- The Complete Response (CR) rate after two cycles was
 - 90% in Burkitt's NHL
 - 81% in B-ALL
 - 74% in DLBCL;
- Death during therapy occurred in 3%, 11% and 2% respectively
- The OS at 3 yrs (15-55 years)
 - 91% for Burkitt's NHL
 - 79% for B-ALL
 - 91% for DLBCL
- The OS at 3 yrs (>55 years)
 - 84% for Burkitt's NHL
 - 39% for B-ALL
 - 67% for DLBCL
- No CNS relapses were seen in young patients
- Some CNS relapses were seen in older patients

HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

Results continued:

- No difference in OS was seen Burkitt (92%) vs Burkitt-like NHL (86%)
- Major grade III/IV toxicity was
 - Haematological (28-37%)
 - Mucositis (36%, 37%, 28% in cycles A1, B1, C1 respectively)
- Compared to the trial B-NHL90 with 270 pts the OS at 3 yrs improved significantly from
 - 54% to 80% ($p < .0001$) overall
 - 56% to 85% ($p < .0001$) in younger patients
 - 39% to 65% ($p = .01$) in older patients

HIGH CURE RATE OF ADULT BURKITT'S AND HIGH GRADE NHL BY THE COMBINATION OF CHEMOTHERAPY WITH RITUXIMAB

Conclusions:

- The addition of MabThera in adult Burkitt's and other high grade NHL
 - Is feasible
 - Has high overall survival rates in both elderly and young patients
- Future studies will look at reducing toxicity
 - And will include HDAC for elderly patients to prevent CNS relapse

PHARMACEUTICAL DEVELOPMENT OF
HIGH DOSE RADIOLABELLED RITUXIMAB
AS CONSOLIDATION TREATMENT FOR
PATIENTS WITH RELAPSED OR
REFRACTORY CD20 POSITIVE B-CELL NON-
HODGKIN'S LYMPHOMA

Abstract 741

Tran et al. Poster presentation

Saturday 1800-1915

HOT MABTHERA

“Hot” MabThera has been proposed as an alternative to commercially available radio-labelled antibodies

The efficacy of radio-labelled antibodies has been questioned and there are no good randomised controlled studies

“Hot” MabThera would potentially compete against full-course MabThera

This study shows that it is possible to radio-label MabThera with ^{131}I and still preserve the reactivity of MabThera. No clinical data is presented.

COMPETITORS

FEASIBILITY STUDY OF RITUXIMAB
FOLLOWED BY ANTI-IDIOTYPE
IMMUNOTHERAPY WITH TUMOR-SPECIFIC
IDIOTYPE-KLH (FAVID®) AND GM-CSF IN
INDOLENT B-CELL LYMPHOMAS

Abstract 418

Zucca et al. Oral presentation.

Saturday 1100-115, Strauss III

FEASIBILITY STUDY OF RITUXIMAB WITH FAVID[®] AND GM-CSF IN INDOLENT NHL

Vaccines remain experimental therapy in NHL

MabThera maintenance therapy has been shown to improve overall survival and progression free survival

The PFS in this study were disappointing although the authors suggest further evaluation in disseminated marginal zone lymphoma is warranted

FEASIBILITY STUDY OF RITUXIMAB WITH FAVID[®] AND GM-CSF IN INDOLENT NHL

Aims:

- To assess the feasibility of using idiotype-KLH vaccine (FavId)

Methods:

- Patients with pretreated (1 naïve) indolent B-cell NHL received 4 x weekly MabThera
- ~ 8 weeks later by 6 monthly s/c injections of FavId and GM-CSF
- Patients without progression could receive
 - FavId every 2 months for 6 months and then
 - FavId every 3 months until disease progression

FEASIBILITY STUDY OF RITUXIMAB WITH FAVID[®] AND GM-CSF IN INDOLENT NHL

Methods (Note to ROCHE we have made this deliberately lengthy to show complexity!):

- FavId was prepared by
 - Taking tumour biopsy
 - Preparing frozen tumour cell suspension
 - Within 2 hours shipping to the US
 - Manufacturing patient specific vaccine in the US
 - Shipping under controlled conditions back to Switzerland

FEASIBILITY STUDY OF RITUXIMAB WITH FAVID® AND GM-CSF IN INDOLENT NHL

Results:

- 9 patients received vaccine therapy
- Main side effect was transient erythema / itching

#	NHL type	Biopsy Site	Successful Favid® production	Response after Rituximab	Vaccine Therapy	Outcome (from start of Favid®)
02	FL	LN	yes	complete response (CR)	completed (6 cycles)	PD at 9 months
03	MZL	BM	yes	CR	ongoing (12 cycles)	CR at 18 months
04	FL	LN	yes	partial response (PR)	ongoing (6 cycles)	PR at 6 months
05	CLL	LN	yes	no change (NC)	discontinued (progression after 4 cycles)	dead (septic shock)
06	MCL	LN	yes	NC	ongoing (7 cycles)	stable disease at 8 months
07	MZL	BM	yes	CR	ongoing (6 cycles)	CR at 6 months
08	FL	LN	yes	PR	discontinued (progression after 4 cycles)	alive, with disease at 7 months
09	FL	LN	yes	CR	ongoing (6 cycles)	CR at 6 months
10	MZL	soft tissue	yes	PR	ongoing (1 cycle)	not assessed
11	FL	LN	ongoing	PR	planned	not assessed
12	MZL	BM	yes	PR	planned	not assessed

FEASIBILITY STUDY OF RITUXIMAB WITH FAVID[®] AND GM-CSF IN INDOLENT NHL

Conclusions:

- Limited efficacy was seen with this complicated therapy compared to the results seen in similar patient populations with treatments such as MabThera maintenance therapy

LENALIDOMIDE (REVLIMID) IS AN ACTIVE AGENT IN RELAPSED AND TREATMENT- REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Abstract 314

Ferrajoli et al. Oral presentation

Saturday 0830-0845, Mozart III

LENALIDOMIDE IN TREATMENT-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

MabThera will be the backbone of therapy for CLL in the future with its high response rates and durable responses

Lenalidomide is an immunomodulatory agent that has a number of modes of action and is shown in this study to have activity in this study

Lenalidomide is likely to be partnered with MabThera in future Phase III studies

LENALIDOMIDE IN TREATMENT-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Methods:

- Lenalidomide given orally to patients
 - 10 mg/day for first 4 weeks
 - Escalated by 5 mg every 28 days to a max of 25 mg/day

Results:

- 45 patients enrolled
- Data for the first 35 patients - median follow-up 9 months
- Median follow-up < 3 months for remaining 10 patients
- All patients had at least 1 prior purine containing regimen
- Median age 64 (49-86)
- Median prior treatments 4 (1-15)

LENALIDOMIDE IN TREATMENT-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Results:

- 13 patients responded (3 CR, 1 nPR, 9 PR)
- Median response duration 11+ months
- 2/3 CR were MRD negative
- Most common toxicity Grade \geq 3 neutropenia and thrombocytopenia
- 12 x serious infections
- VEGF and b-FGF levels were greatly reduced at 3 months

Conclusions:

- Lenalidomide is active in this heavily pre-treated population

FRACTIONATED RADIOIMMUNOTHERAPY
IN NHL WITH DOTA-CONJUGATED,
HUMANIZED ANTI-CD22 EPRATUZUMAB AT
HIGH CUMULATIVE 90Y DOSES

Abstract 409

Morschhauser F et al. Oral presentation

Saturday 1115-1130, Mozart III

FRACTIONATED RADIOIMMUNOTHERAPY IN NHL WITH ANTI-CD22 EPRATUZUMAB

Radiolabelled antibodies have been relatively unsuccessful in NHL because of

- Safety concerns
- Lack of good controlled data
- Practicality of administration

This study describes radio-labelled epratuzumab in a mixed group of B cell NHL, potentially competing with MabThera induction and maintenance

FRACTIONATED RADIOIMMUNOTHERAPY IN NHL WITH ANTI-CD22 EPRATUZUMAB

Aims:

- To determine the maximum tolerated dose of 90Y-epratuzumab

Methods:

- Patients with relapsed NHL with < 25% BM involvement
- Escalated 90Y doses

Results:

- 55 patients with a median of 3 prior therapies
- No SAE's other than haematological DLT in previous BMT patients
- 53% Objective Response
- 30% (17/55) CR

FRACTIONATED RADIOIMMUNOTHERAPY IN NHL WITH ANTI-CD22 EPRATUZUMAB

Conclusions:

- Authors conclude it is feasible and safe
- Potential benefit after patients have become refractory to MabThera maintenance therapy

ALEMTUZUMAB

Zenz et al. Abstract 118

Hillmen et al. Abstract 127

Robak et al. Abstract 128

Poster presentations, Friday 1745-1900

ALEMTUZUMAB

MabThera will become the agent of choice in first-line CLL in combination with FC

Alemtuzumab causes both T and B cell depletion and as such is associated with high rates of infection, particularly CMV

It is also ineffective in patients with bulky lymph nodes

These studies look at the use of Alemtuzumab in

- p53 mutated patients who are fludarabine refractory
- 1st line CLL compared to chlorambucil

ALEMTUZUMAB

Zenz et al shows

- An incidence of 33% p53 deletions in F refractory patients with CLL
- That the ORR after alemtuzumab is similar in patients with and without p53 mutations
 - 31% vs 34% respectively
 - There was similar OS between the groups

Hillmen demonstrates PFS from the previously presented CAM 307 Study:

- 23.3 months for alemtuzumab vs 14.7 months chlorambucil (R-FC 5 year TTP = 70%, Tam et al ASCO 2007)
- At 2 years f/u there were 24 deaths in both arms
- 53% became CMV PCR positive with symptomatic CMV infection in 16%

ALEMTUZUMAB

Robak analysed the same study looking at the effect of cytogenetics abnormalities in the study and showed the following frequencies:

- 13q (49%)
- sole 13q (24%)
- 11q (19%)
- 17p (7 %)
- 6q (4 %)
- trisomies 12 (14%) and 8q (5%)

- PFS was 3x higher for alemtuzumab than chlorambucil in 17p patients but there was no difference in the 11q patients

ALEMTUZUMAB AS CONSOLIDATION
THERAPY AFTER FLUDARABINE,
CYCLOPHOSPHAMIDE AND RITUXIMAB
REGIMEN (FC-R) FOR THE TREATMENT OF
YOUNG PATIENTS WITH CHRONIC
LYMPHOCYtic LEUKEMIA

Abstract 113

Gonnella F et al. Poster presentaton

Friday 1745-1900

ALEMTUZUMAB AS CONSOLIDATION THERAPY AFTER REGIMEN R-FC FOR YOUNG PATIENTS WITH CLL

A study has demonstrated the potential benefits of MabThera maintenance therapy for patients who are minimal residual disease (MRD) positive post-induction in CLL (Del Poeta et al, EHA 2007)

Alemtuzumab is a potential competitor for MabThera in this indication

- It is currently indicated for fludarabine refractory CLL

This study shows that alemtuzumab may be used as consolidation in patients after MabThera containing induction therapy

- However, it is associated with a high (>80%) CMV infection

ALEMTUZUMAB AS CONSOLIDATION THERAPY AFTER REGIMEN R-FC FOR YOUNG PATIENTS WITH CLL

Aims:

- To assess whether alemtuzumab consolidation can improve the quality of response to MabThera based induction therapy

Methods:

- Young, untreated CLL patients
- Treated with 6 cycles of MabThera added to FC
- BM tested for MRD 1 month after last cycle
- All patients treated with alemtuzumab for 12 weeks

ALEMTUZUMAB AS CONSOLIDATION THERAPY AFTER REGIMEN R-FC FOR YOUNG PATIENTS WITH CLL

Results:

- 12 patients treated (median age 45 years)
- 100% clinical CR
- 9/12 patients MRD positive 1 month after last cycle
- Patients received alemtuzumab
- At 12 months follow-up, all patients remain in MRD negative CR

Safety:

10/12 patients (83%) had CMV reactivation after alemtuzumab therapy

MULTICENTER PHASE II CLINICAL TRIAL OF
90Y-IBRITUMOMAB TIUXETAN WITH HIGH-
DOSE CHEMOTHERAPY FOLLOWED BY
AUTOLOGOUS STEM CELL
TRANSPLANTATION IN RELAPSED,
REFRACTORY, OR HIGH-RISK B-CELL NON-
HODGKIN'S LYMPHOMA, PRELIMINARY
REPORT

Abstract 719

Kang et al. Poster Presentation

Saturday 1800-1915

ZEVALIN + ASCT IN HIGH RISK B-CELL NHL

8 cycles of R-CHOP are the gold standard to achieve a cure in DLBCL and there is growing evidence for the use of MabThera in conditioning and post ASCT regimens, including use in patients who received MabThera in the first-line setting

The use of Zevalin in this setting is experimental

ZEVALIN + ASCT IN HIGH RISK B-CELL NHL

Aims:

- To evaluate the safety and efficacy of Zevalin in combination with HDC followed by ASCT

Methods:

- Patients were given 2 doses of MabThera and then a single dose of Zevalin followed by HDC followed by ASCT

Results:

- 13 patients entered the study (10/13 DLBCL)
- Pre ASCT
 - Continued CR 38.5% (5/13), induced CR 23.1% (3/13)
 - Continued or induced PR 15.4% (2/13)
 - At 6 months f/u median PFS / OS had not been reached

Conclusions:

- Long-term outcomes from this small study are awaited. The use of Zevalin in this setting would compete with MabThera retreatment

GENERAL INTEREST

ANGIOGENESIS IS A PREREQUISITE FOR
SOLID TUMOUR GROWTH AND
DISSEMINATION BUT THERE IS
RELATIVELY FEW DATA RELATED TO ITS
SIGNIFICANCE IN HODGKIN LYMPHOMA.

Abstract 182

Passam F et al. Poster presentation

Friday 1745-1900

ANGIOGENESIS IN HODGKIN LYMPHOMA

Angiogenesis has been shown to be important for growth of many solid tumours and NHL

The RA-CHOP study looks at the use of Avastin in DLBCL

This study shows high levels of VEGF expression, particularly in early disease of Hodgkin Lymphoma

ANGIOGENESIS IN HODGKIN LYMPHOMA

Angiogenesis has been shown to be important for growth of many solid tumours and NHL

The RA-CHOP study looks at the use of Avastin in DLBCL

This study shows high levels of VEGF expression, particularly in early disease of Hodgkin Lymphoma

ANGIOGENESIS IN HODGKIN LYMPHOMA

Methods and results:

- Slides from lymph nodes for patients with HL were examined for markers of angiogenesis
- VEGF
 - was negative in the neoplastic population in 53%
 - 30% of cases showed strong staining
 - the reactive lymph node population was positive in >50%
- HIF1a was positive in the neoplastic compartment in 31%
- PDGFRa positive in 95%

ANGIOGENESIS IN HODGKIN LYMPHOMA

- Micro Vessel Density had a median of 2.6 which was not different from reactive lymph nodes
- VEGF in the non-neoplastic compartment correlated significantly with Ann Arbor stage with increased staining in I-II versus stages III and IV (spearman rho: -0.329, p:0.017)
- Also higher VEGF score in reactive cells correlated with increased incidence of complete response (p:0.03). Increased MVD was associated with the presence of necrotic lesions in the material (p:0.05)

Conclusions:

- Microvessel formation is not increased in HL in comparison to reactive lymph nodes although there is expression of angiogenic molecules by neoplastic and surrounding cells
- VEGF shows a higher level of expression in earlier stages of disease

MABTHERA IN THE TREATMENT OF CLL

MAINTENANCE IMMUNOTHERAPY WITH
LOW-DOSE RITUXIMAB IMPROVES
OUTCOME IN “HIGH RISK” CHRONIC
LYMPHOCYTIC LEUKEMIA

Abstract 361

Del Poeta G et al. Oral Presentation

Saturday 08:00-08:15, Mozart III

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Methods:

- symptomatic untreated CLL
- 6 x monthly doses of MabThera in combination with Fludarabine
- Remission status decided by flow cytometry
- Patients in MRD positive CR/PR received
 - 4 x monthly cycles of MabThera consolidation
 - 12 x monthly cycles of “low-dose” MabThera 150 mg/m²

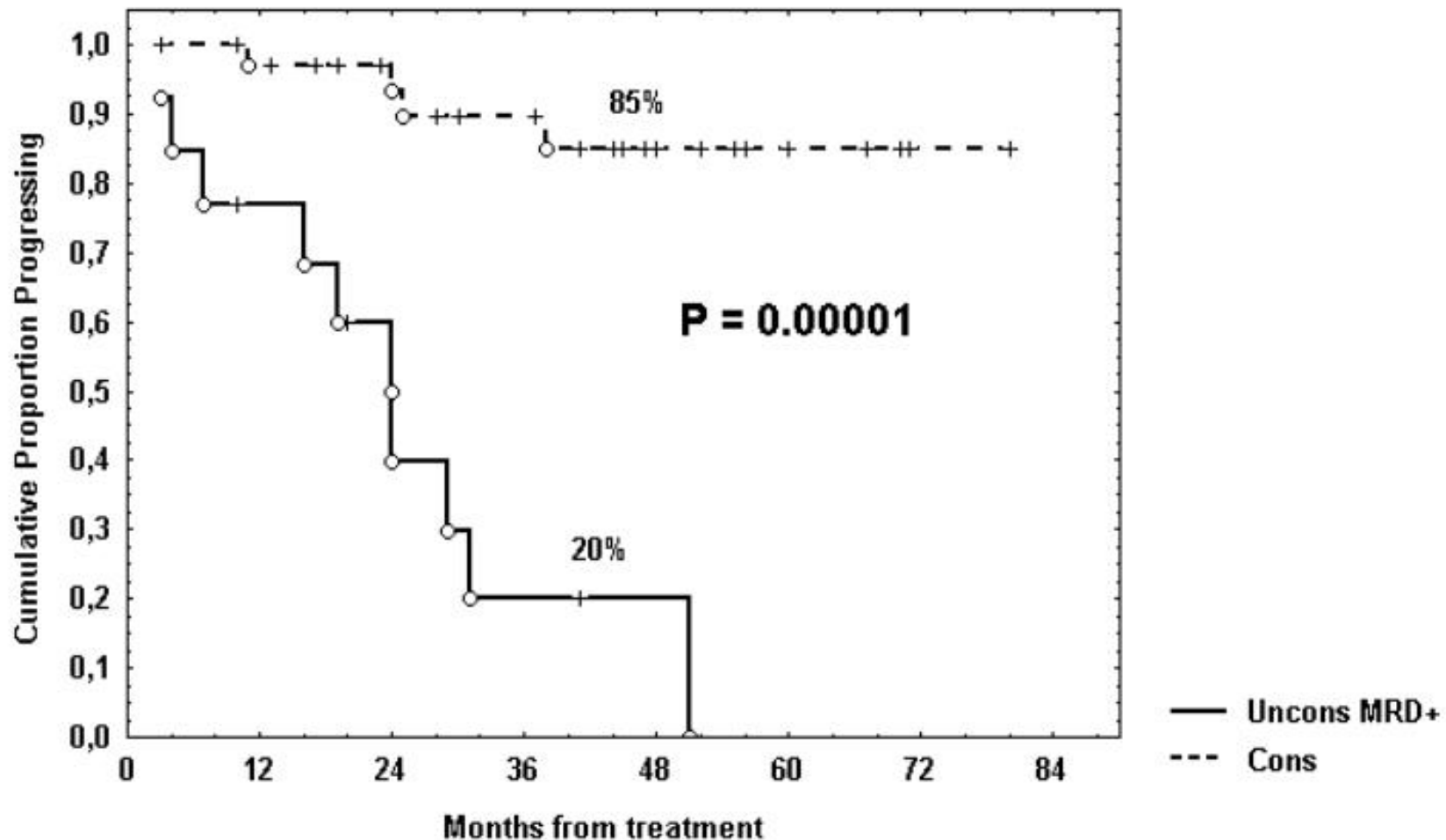
MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Results Induction:

- 79 pts Median age 60 years (37-74)
- Modified RAI
 - 9 pts low 67 pts intermediate 3 high
- Based on NCI criteria
 - 63/79 (80%) CR
 - 12/79 (15%) PR
 - 4/79 (5%) Stable Disease

} = 95% ORR

Duration of response in consolidated versus non-consolidated MRD+ patients



MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

Results maintenance : median follow-up of 38 months

- 35 pts MRD+ received consolidation and maintenance
- 13 patients MRD+ did not receive further MabThera

Overall PFS was 69% at 6 years from induction (all 79 pts)

(Tam, ASCO 2007 : 70% at 5 yr)

Maintenance MRD+ patients had

- Longer duration of response (80% vs 20% for non-maintenance MRD+ patients)
- Similar duration of response to MRD negative patients who did not receive maintenance

MAINTENANCE IMMUNOTHERAPY WITH LOW-DOSE RITUXIMAB IMPROVES OUTCOME IN “HIGH RISK” CLL

- Significantly shorter PFS was noted in
 - CD 38 positive patients (43% vs 79% at 5 years, $p = 0.005$)
 - Unmutated VH patients (45% vs 94% at 2.5 years, $p = 0.001$)
 - ZAP-70 positive patients (39% vs 88% at 5 years, $p = 0.00004$)
- In the “high risk” subset PFS was 64% in maintenance vs 13% no maintenance

Ongoing Roche supported trials for maintenance in CLL are using the 375 or 500 mg/m² regimen

Post-alkylating agent consolidation with MabThera

POST-REMISSIONAL RITUXIMAB
ADMINISTRATION FOR THE TREATMENT OF
OLDER CLL PATIENTS RESPONSIVE TO
FIRST-LINE THERAPY WITH
CHLORAMBUCIL AND PREDNISONE

Abstract 124

Mauro F et al, Poster presentation

Friday 1745-1900

COMPETITORS

LENALIDOMIDE (REVLIMID) IS AN ACTIVE AGENT IN RELAPSED AND TREATMENT- REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Abstract 314

Ferrajoli et al. Oral presentation

Saturday 0830-0845, Mozart III

LENALIDOMIDE IN TREATMENT-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Methods:

- Lenalidomide given orally to patients
 - 10 mg/day for first 4 weeks
 - Escalated by 5 mg every 28 days to a max of 25 mg/day

Results:

- 45 pts, median age 64 (49-86)
- data for the first 35 patients
- median follow-up 9 months
(Median follow-up < 3 months for remaining 10 patients)
- Median prior treatments 4 (1-15), including at least 1 purine containing regimen

LENALIDOMIDE IN TREATMENT-REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

Results:

- 13 patients responded (3 CR, 1 nPR, 9 PR)
 - Median response duration 11+ months
 - 2/3 CR were MRD negative
 - Most common toxicity Grade ≥ 3 = neutropenia and thrombocytopenia
 - 12 serious infections
- Lenalidomide is active in this heavily pre-treated population

Lenalidomide is likely to be partnered with MabThera in future studies

ALEMTUZUMAB – CAM 307 updates (abstracts 118-127-128)

Hillmen demonstrates PFS from the previously presented **CAM 307** study:

- PFS = 23.3 months vs 14.7 months for CLB
(R-FC 5yr TTP = 70%, Tam et al ASCO 2007)
- 53% CMV PCR + with 16% symptomatic infection
- 24 deaths in both arms at 2 years f/u

Robak looked at the effect of cytogenetics abnormalities :

- PFS was 3x higher for alemtuzumab than chlorambucil in 17p patients (7% of pts)
- but no difference in the 11q patients (11% of pts)

ALERT
THU

Use data from MDACC ++++
Wierda, ASH 2006, abstract 31

Friday 1745-1900

THE COMBINATION OF LUMILIXIMAB AND
FCR (FCRL) PRODUCES HIGH RATES OF
COMPLETE RESPONSE AND HAS
COMPARABLE TOLERABILITY TO FCR IN
PATIENTS WITH RELAPSED CLL: RESULTS
OF A PHASE I/II STUDY

Abstract 123

Byrd J et al. Poster presentation

Friday 1745-1900

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Aims:

- To investigate the safety and efficacy of the anti CD23 antibody, Lumiliximab added to R-FC in CLL

Methods:

- 31 patients with relapsed CLL (non-refractory to R-FC)
- Treated with 375 mg/m² (n=3) or 500 mg/m² lumiliximab in combination with R-FC up to 6 cycles

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Results:

- ORR = 22/31 (71%), including CR =51%
- 75% (6/8) ORR in del 11q patients with 63% (5/8) CR
- 25% (1/4) PR in del 17p

- Grade 3 or 4 AE's were reported in 65% of patients
 - Nausea 77%
 - Neutropenia 58%
 - Fatigue 48%
 - Pyrexia 61%
 - Chills 55%

LUMILIXIMAB ADDED TO FCR IN PATIENTS WITH RELAPSED CLL

Retrospective comparison with R-FC alone (Wierda W, et al. *JCO* 2005)

	R-FC	FCR-L
% patients R naïve	15	60
Rai stage I/II	47	74
ORR	73	71
CR	25	52