agenda and abstracts of satellite symposia

Tuesday, June 14, 2011 13:00 – 15:00 *(room B I)*

PFIZER

OPEN TOPICS IN MANTLE CELL LYMPHOMA: CASE DISCUSSION AND STATE OF THE ART

Chair: M. Ghielmini, Bellinzona (Switzerland)

SHOULD EVERYBODY RECEIVE TRANSPLANT IN FIRST LINE?

C. Geisler, Copenhagen (Denmark)

IS THERE A ROLE FOR MAINTENANCE IN MCL?

M. Dreyling, Munich (Germany)

HOW SHOULD WE TREAT LOCALIZED MCL?

M. Ghielmini, Bellinzona (Switzerland)

WHAT ARE THE NEW THERAPEUTIC OPTIONS?

G. Hess, Mainz (Germany)

Tuesday, June 14, 2011, 13:00 – 15:00 *(room B II)*

MUNDIPHARMA / GLAXOSMITHKLINE

CHEMOIMMUNOTHERAPY: SHAPING THE FUTURE OF NHL MANAGEMENT

Co-chairs: J. Friedberg, Rochester NY (USA) and M. Rummel, Giessen (Germany)

CO-CHAIR'S INTRODUCTION

J. Friedberg, Rochester NY (USA)

TOWARDS A MOLECULAR UNDERSTANDING OF RESISTANCE IN INHL

R. Gascoyne, Vancouver B.C. (Canada)

FIRST-LINE TREATMENT OF INHL: AN EVOLVING PARADIGM

M. Rummel, Giessen (Germany)

Q & A

Faculty moderated

CHEMOIMMUNOTHERAPY: IMPROVING OUTCOMES IN RELAPSED/REFRACTORY INHL

M. van Oers, Amsterdam (The Netherlands)

Q & A

Faculty moderated

THE GREAT DEBATE: *CLINICAL DILEMMAS - HOW DO WE TREAT PATIENTS REFRACTORY TO CHEMOIMMUNOTHERAPY?*

J. Friedberg, Rochester NY (USA) and M. van Oers, Amsterdam (The Netherlands)

FUTURE DEVELOPMENTS IN THE TREATMENT OF NHL

M. Czuczman, New York NY (USA)

CO-CHAIR'S SUMMARY AND MEETING CLOSE

M. Rummel, Giessen (Germany)

Tuesday, June 14, 2011, 16:00 – 18:00 *(room A)*

prIME Oncology

HOW I TREAT HEMATOLOGIC MALIGNANCY IN 2011: EXPERT GUIDANCE FOR THE CLINICIAN

Chair : J. O. Armitage, Omaha NE (United States)

16:00 **WELCOME AND INTRODUCTION**
J. O. Armitage, Omaha NE (United States)

16:05 **HOW I TREAT CHRONIC LYMPHOCYTIC LEUKEMIA**
S. Stilgenbauer, Ulm (Germany)

16:30 **HOW I TREAT WALDENSTRÖM MACROGLOBULINEMIA**
S. Treon, Boston MA (United States)

16:55 **HOW I TREAT FOLLICULAR LYMPHOMA**
J. O. Armitage, Omaha NE (United States)

17:30 **HOW I TREAT MANTLE CELL LYMPHOMA**
B. D. Cheson, Washington, D.C. (United States)

17:55 **SYMPOSIUM "PEARLS"**
J. O. Armitage, Omaha NE (United States)

Tuesday, June 14, 2011, 16:00 – 18:00 *(room B II)*

JANSSEN

RECENT ADVANCES IN THE MANAGEMENT OF FOLLICULAR LYMPHOMA AND OTHER HEMATOLOGICAL MALIGNANCIES *(part 1)*

Chair: P.L. Zinzani, Bologna (Italy)

WELCOME AND INTRODUCTION

J. Clare, London (UK) and P.L. Zinzani, Bologna (Italy)

PAST, PRESENT AND FUTURE IN FOLLICULAR LYMPHOMA: PROGNOSTIC FACTORS AND TREATMENT OUTCOMES IN FOLLICULAR LYMPHOMA

E. Kimby, Stockholm (Sweden)

INDIVIDUALIZING TREATMENT OPTIONS IN NON HODGKINS LYMPHOMA

F. Offner, Gent (Belgium)

INDIVIDUALIZING TREATMENT OPTIONS IN MULTIPLE MYELOMA: BALANCING EFFICACY AND TOLERABILITY OF TREATMENTS IN MULTIPLE MYELOMA

P. Moreau, Paris (France)

PANEL DISCUSSION AND INTERACTIVE QUESTIONS

J. Clare, London (UK), P.L. Zinzani, Bologna (Italy) and all faculty

Refreshments

'RECENT ADVANCES IN THE MANAGEMENT OF FOLLICULAR LYMPHOMA AND OTHER HEMATOLOGICAL MALIGNANCIES'

During the Janssen-sponsored satellite symposium at ICML a distinguished and experienced international faculty will review current best practice and the latest developments with novel agents which are changing the treatment of Non-Hodgkins Lymphoma and improving outcomes for patients.

The presentations will provide an opportunity to discuss the important open questions in treatment of follicular lymphoma and look at how we best assess patient prognosis and response to treatment. Factors to consider when individualising therapy and the role of rituximab maintenance in treatment regimens will also be discussed.

In addition, treatment of follicular lymphoma in the relapsed/refractory setting will be reviewed, and patient cases will be presented to provide examples of the latest clinical insights on how to choose the right therapy for different patient groups. The role of proteasome inhibition in treatment of NHL will be reviewed. Finally, strategies for management of toxicities in both current and novel agents will also be discussed.

Throughout the symposium program discussion and Q&A sessions are included to encourage clinicians to interact, ask questions and to share experiences relevant to everyday clinical practice.

Tuesday, June 14, 2011, 19:00 – 21:00 *(room A)*

F. HOFFMANN–LA ROCHE LIMITED
MANAGEMENT OF B-CELL MALIGNANCIES TODAY: A LONG-TERM PERSPECTIVE
Chair: F. Cavalli, Bellinzona (Switzerland)

CHAIR'S WELCOME
F. Cavalli, Bellinzona (Switzerland)

FOLLICULAR LYMPHOMA: SCIENTIFIC RATIONALE FOR LONG-TERM DISEASE CONTROL WITH RITUXIMAB MAINTENANCE
G. Salles, Pierre Bénite (France)

MANAGING RELAPSE IN FOLLICULAR LYMPHOMA
M. van Oers, Amsterdam (Netherlands)

CLINICAL EXPERIENCE WITH RITUXIMAB MAINTENANCE THERAPY
M. Dreyling, Munich (Germany)

PANEL DISCUSSION AND Q&A
All faculty

MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA: THE IMPORTANCE OF FRONTLINE TREATMENT
M. Hallek, Cologne (Germany)

PANEL DISCUSSION AND Q&A
All faculty

Tuesday, June 14, 2011, 19:00 – 21:00 *(room BI)*

NOVARTIS

ADDRESSING THE UNMET CLINICAL NEED IN MALIGNANT LYMPHOMA THROUGH NOVEL AGENTS

Chair: I. Ghobrial, Boston MA (USA)

WELCOME AND INTRODUCTION

I. Ghobrial, Boston, MA (USA)

INHIBITION OF mTOR AS NOVEL TREATMENT STRATEGY IN MALIGNANT LYMPHOMA

P.B. Johnston, Rochester, MN (USA)

Q&A

P.B. Johnston, Rochester, MN (USA)

NOVEL TREATMENT OPTIONS FOR PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA.

I. Ghobrial, Boston, MA (USA)

Q&A

I. Ghobrial, Boston, MA (USA)

TARGETING OF CD40 IN THE TREATMENT OF NON-HODGKIN AND HODGKIN LYMPHOMA

M.A. Fanale, Houston, TX (USA)

Q & A

M.A. Fanale, Houston, TX (USA)

PANEL DISCUSSION

All faculty

SUMMARY: FUTURE DIRECTIONS IN THE TREATMENT OF LYMPHOMA

I. Ghobrial, Boston, MA (USA)

Tuesday, June 14, 2011, 18:30 – 20:30 *(room B II)*

JANSSEN

RECENT ADVANCES IN THE MANAGEMENT OF FOLLICULAR LYMPHOMA AND OTHER HEMATOLOGICAL MALIGNANCIES (part 2)

Chair: P.L. Zinzani, Bologna (Italy)

PROTEASOME INHIBITION IN LYMPHOMA

O. O'Connor, New York, NY (USA)

TREATMENT OPTIONS IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

P.L. Zinzani, Bologna (Italy)

SELECTING PATIENTS FOR CURRENT AND NEW TREATMENT OPTIONS (PATIENT CASES)

P.L. Zinzani, Bologna (Italy) and Faculty

PANEL DISCUSSION

J. Clare, London (UK), P.L. Zinzani, Bologna (Italy) and all faculty

CLOSING REMARKS

P.L. Zinzani, Bologna (Italy)

Wednesday, June 15, 2011, 19:00 – 21:00 (room BI)

MILLENNIUM: THE TAKEDA ONCOLOGY COMPANY
EMERGING TREATMENT STRATEGIES IN CD30-EXPRESSING LYMPHOMAS
Chair: A. Engert, Cologne (Germany)

WELCOME AND INTRODUCTION
A. Engert, Cologne (Germany)

OVERVIEW OF TREATMENT OPTIONS FOR PATIENTS WITH CD30-EXPRESSING LYMPHOMAS: FOCUS ON HODGKIN LYMPHOMA
A. Engert, Cologne (Germany)

EMERGING TREATMENT STRATEGIES IN CD30-EXPRESSING RELAPSED/REFRACTORY HODGKIN LYMPHOMA: EVIDENCE FROM CLINICAL STUDIES
A. Engert, Cologne (Germany)

OVERVIEW OF TREATMENT OPTIONS FOR PATIENTS WITH CD30-EXPRESSING LYMPHOMAS : FOCUS ON ALCL
T. Illidge, Manchester (UK)

TREATMENT OPTIONS FOR CD30 TARGETING IN ALCL: INITIAL CLINICAL EXPERIENCE
T. Illidge, Manchester (UK)

FUTURE DEVELOPMENT OF CD30-TARGETED TREATMENT
P.L. Zinzani, Bologna (Italy)

Q&A
All Faculty

SUMMARY AND CLOSE
A. Engert, Cologne (Germany)

OVERVIEW OF TREATMENT OPTIONS FOR PATIENTS WITH CD30-EXPRESSING LYMPHOMAS: FOCUS ON HODGKIN LYMPHOMA

A. Engert
Klinik I für Innere Medizin, Universität zu Köln, Cologne (Germany)

CD30 is a transmembrane protein that belongs to the tumour necrosis factor receptor family. CD30 is expressed on the surface of Reed–Sternberg cells in Hodgkin lymphoma (HL), in addition to cells from other lymphocytic malignancies such as anaplastic large cell lymphoma (ALCL). In contrast, CD30 expression is restricted to activated B and T lymphocytes and eosinophils in healthy individuals.[1] This expression profile means that CD30 is an attractive target for therapeutic intervention in HL and ALCL. Currently, two main therapeutic strategies that target the CD30 antigen are being evaluated: monoclonal antibodies and antibody–drug conjugates (ADCs).

Although monoclonal antibodies against CD30, such as MDX-060 and SGN-30, showed promise in preclinical studies, the results from initial clinical studies have been disappointing.[2,3] Thus, ADCs are under investigation to try to enhance the antitumour activity of monoclonal antibodies. For example, the investigational ADC brentuximab vedotin (SGN-35) contains the potent antitubulin agent monomethyl auristatin E (MMAE) attached to a CD30-specific monoclonal antibody. This ADC binds to CD30-positive malignant cells and, after internalisation, releases MMAE inside the cell via lysosomal degradation. MMAE then disrupts the microtubule network inducing cell cycle arrest and subsequent apoptosis.[4] Brentuximab vedotin is currently under clinical investigation as a new treatment for CD30-expressing lymphomas, such as HL and ALCL.

References

1. Al Shamkhani A. Curr Opin Pharmacol 2004;4:355–9.
2. Bartlett NL et al. Blood 2008;111:1848–54.
3. Ansell SM et al. J Clin Oncol 2007;25:2764–9.
4. Ansell SM. Expert Opin Investig Drugs 2011;20: 99–105.

EMERGING TREATMENT STRATEGIES IN CD30-EXPRESSING RELAPSED/REFRACTORY HODGKIN LYMPHOMA: EVIDENCE FROM CLINICAL STUDIES

A. Engert
Klinik I für Innere Medizin, Universität zu Köln, Cologne (Germany)

Approximately 20–30% of patients with Hodgkin lymphoma (HL) either relapse after or are refractory to first-line treatment, and these patients

currently have a poor prognosis.[1] Given that the few available treatment options for patients with relapsed or refractory (R/R) HL have limited efficacy and may be associated with substantial toxicity, novel effective therapies for such patients are urgently required.
Brentuximab vedotin (SGN-35) is an investigational antibody–drug conjugate which contains an antimitotic drug (monomethyl auristatin E) linked to an anti-CD30 monoclonal antibody. Clinical evidence to date has indicated that brentuximab vedotin has significant activity in patients with R/R HL. The results of a pivotal Phase II study in 102 patients with R/R HL showed that brentuximab vedotin (1.8 mg/kg of body weight IV every 3 weeks) was associated with an objective response rate of 75% (as determined by an independent review committee) and tumour shrinkage was observed in 94% of patients. Adverse events with brentuximab vedotin were manageable and mainly Grade 1 or 2 in intensity.[2]

Following on from these promising results, brentuximab vedotin is currently being investigated in the AETHERA study: a randomised, placebo-controlled Phase III clinical trial in high-risk HL patients following autologous stem cell transplantation.[3] In addition, brentuximab vedotin is also being investigated in combination with doxorubicin, bleomycin, vinblastine and dacarbazine as first-line therapy in patients with advanced-stage HL.[4] The results of these ongoing studies are awaited.

References

1. Gerber HP. Biochem Pharmacol 2010;79:1544–52.
2. Chen R et al. Presentation at American Society of Hematology 2010: Abstract 283.
3. AETHERA study. Available at www.clinicaltrials.gov. Last accessed 4 March 2011.
4. NCT01060904. Available at www.clinicaltrials.gov. Last accessed 4 March 2011.

OVERVIEW OF TREATMENT OPTIONS FOR PATIENTS WITH CD30-EXPRESSING LYMPHOMAS: FOCUS ON ALCL

T. Illidge
School of Cancer and Imaging Sciences, University of Manchester, Manchester (UK)

Anaplastic large cell lymphoma (ALCL) is a rare and aggressive neoplasm. In recent years, it has emerged that the primary cutaneous and systemic forms of ALCL are clinically and immunophenotypically distinct, and ALCL pathogenesis has been linked to phosphorylation of anaplastic lymphoma kinase (ALK). Lymphomas that aberrantly express ALK (ALK-positive ALCL) have a better prognosis than those that are ALK negative. All types of ALCL strongly and uniformly express CD30.[1]
CHOP chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine, prednisone) are the established standard of care for ALCL, though patients with ALK-negative disease tend to have poor outcomes.[2,3]
For patients with relapsed or chemotherapy-refractory disease, salvage chemotherapy and high-dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT) is the standard of care. However, many patients – particularly those with ALK-negative disease – are sufficiently responsive to chemotherapy to reach autologous or allogenic stem cell transplantation therapy.[4] Those patients who relapse after HDCT and ASCT have very few further options.[4]
Therapies under investigation for ALCL treatment include novel chemotherapy combinations (e.g. gemcitabine, pralatrexate, CHOP plus targeted therapies), therapies targeting ALK signalling, histone deacetylase inhibitors, and therapies targeting CD30 such as the antibody–drug conjugate brentuximab vedotin (SGN-35).

References

1. Stein H et al. Blood 2000;96:3681-95.
2. Jacobsen E. Oncologist 2006;11: 831–40.
3. Savage KJ et al. Blood 2008;111: 5496–504.
4. Ansell SM. Expert Opin Investig Drugs 2011;20: 99–105.

TREATMENT OPTIONS FOR CD30 TARGETING IN ALCL: INITIAL CLINICAL EXPERIENCE

T. Illidge
School of Cancer and Imaging Sciences, University of Manchester, Manchester (UK)

Proof of principle studies showed that monoclonal antibodies targeting CD30 have *in vitro* and clinical activity in anaplastic large cell lymphoma (ALCL). Brentuximab vedotin (SGN-35) is an investigational antibody–drug conjugate containing the antitubulin agent monomethyl auristatin E (MMAE) linked to an anti-CD30 monoclonal antibody, and is designed to selectively target CD30-expressing neoplasms. Preclinical studies revealed antitumour activity from brentuximab vedotin in cultured CD30-positive cell lines.[1] The binding, internalisation and clinicopathological activity of this antibody–drug conjugate have also been demonstrated in tissue derived from patients with anaplastic lymphoma kinase (ALK)-negative ALCL.
Following Phase I studies in patients with CD30-positive haematological malignancies (including ALCL), a Phase II multicentre study of brentuximab vedotin (1.8 mg/kg of body weight by IV every 3 weeks) was performed in 58 patients with relapsed or refractory systemic ALCL.[2] The primary endpoint (overall objective response) was achieved in 87% (57% complete remission, 30% partial remission, median duration of response not met). Complete remission rate was 57% in this group of patients with both ALK-positive and ALK-negative disease. Adverse events were limited and manageable.[2]
Ongoing studies with brentuximab vedotin in patients with ALCL include a Phase II retreatment study and a study of CHOP chemotherapy combination as initial therapy in patients with unfavourable prognostic features.

References

1. Fromm J et al. Presented at ASH annual meeting, Orlando, FL, 2010.
2. Shustov A et al. Presented at ASH annual meeting, Orlando, FL, 2010.

FUTURE DEVELOPMENT OF CD30-TARGETED TREATMENT

P.L. Zinzani
Institute of Haematology and Medical Oncology 'L & A Seragnoli', University of Bologna, Bologna (Italy)

Novel lymphoma therapies that target CD30 are being investigated in patients with relapsed/refractory disease. The development of antibodies to specific epitopes on membrane-associated CD30, rather than soluble CD30,[1] and a wave of second-generation antibodies that claim increased cytotoxic and phagocytotic effects over first-generation antibodies,[2] are some of the refinements in CD30 targeting that are currently being explored.
Radioimmunotherapy is reported to be an effective option for Hodgkin's lymphoma. Pilot studies of a radioimmunoconjugate comprising an anti-CD30 antibody and ^{131}I-Ki-4 suggest that, while this treatment may control tumour burden, it was associated with severe haematological toxicity.[3]
Preclinical studies suggest a conjugate of the anti-CD30 antibody HeFi-1 and ^{90}Y may have antitumour activity in CD30-positive lymphomas.[4]
Another development is use of diabodies, rather than antibodies, in conjugates.[5] Diabody–drug conjugates employ antibody fragments, rather than whole antibodies, to target CD30-positive cells, and these smaller molecules should be internalised by the tumour cell more readily, improving the delivery of the cytotoxic conjugate.
Continued research into the molecular mechanisms involved in CD30 signalling will help to refine therapeutic targets. Clinical studies are needed to assess the long-term effects of anti-CD30 therapies and their use in combination with chemotherapy.

References

1. Nagata S et al. Proc Natl Acad Sci USA 2005;102:7946–51.
2. Younes A et al. Blood 2008;112 (Abstract 5012).
3. Schnell R et al. J Clin Oncol 2005;23:4669–78.
4. Zhang M et al. Proc Natl Acad Sci USA 2007;104:8444–8.
5. Kim K M et al. Mol Cancer Ther 2008;7:2486–97.

Thursday, June 16, 2011, 19:00 – 21:00 *(room B I)*

SEATTLE GENETICS and MILLENNIUM: THE TAKEDA ONCOLOGY COMPANY
EVOLUTION OF MAb TECHNOLOGY IN LYMPHOMAS
Chair: F. Cavalli, Bellinzona (Switzerland)

WELCOME AND INTRODUCTION
F. Cavalli, Bellinzona (Switzerland)

COMBINING ANTI-CD20 ANTIBODIES WITH CHEMOTHERAPY
P.L. Zinzani, Bologna (Italy)

LIFE AFTER RITUXIMAB THE NEXT GENERATION OF MONOCLONAL ANTIBODIES IN LYMPHOMA
A. Younes, Houston, TX (USA)

MODIFIED TARGETING TECHNOLOGIES: IMMUNOCONJUGATES, RIT, BISPECIFIC AbS
A. Goy, Hackensack NJ (USA)

ADCS: AURISTATINS AND OTHER PAYLOADS
P. Hamlin, New York NY (USA)

Thursday, June 16, 2011, 19:00 – 21:00 *(room B II)*

CELGENE

EXTENDING RESPONSE DURATION IN LYMPHOMAS: THE ROLE OF EMERGING NEW TREATMENTS

Chairs: B. Coiffier, Lyon (France) and M. Czuczman, New York NY (USA)

WELCOME AND INTRODUCTION

B. Coiffier, Lyon (France)

NEW EVIDENCE FOR MECHANISM OF ACTION OF IMIDS® IN LYMPHOMAS, FOCUS ON MCL

J. Gribben, London (UK)

NOVEL AGENTS IN MANTLE CELL LYMPHOMA, PRECLINICAL & CLINICAL EVIDENCE

M. Trněný, Prague (Czech Republic)

RATIONALE FOR MAINTENANCE IN LYMPHOMA – CAN THE CURRENT STANDARD OF CARE BE IMPROVED?

G. Salles, Lyon Sud (France)

HOW CAN WE BEST COMBINE IMMUNOTHERAPIES WITH CHEMOTHERAPY IN LYMPHOMAS?

B.D. Cheson, Washington D.C. (USA)

HDAC INHIBITORS IN T-CELL LYMPHOMAS

B. Coiffier, Lyon (France)

CONCLUSION

M. Czuczman, New York NY (USA)

NEW EVIDENCE FOR MECHANISM OF ACTION OF IMIDS® IN LYMPHOMAS, FOCUS ON MCL

J. Gribben, MD, DSc, FRCP, FRCPath, FMedSci
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Lenalidomide is an orally available drug that belongs to the group of IMiDs® compounds. Several recent studies have provided data on the mechanisms of action (MOA) of lenalidomide in the treatment of lymphomas.

The current hypothesis is that lenalidomide has a dual MOA, which includes direct tumoricidal and antiproliferative effects as well as immunomodulatory effects. The tumoricidal and antiproliferative effects of lenalidomide were shown to correlate with baseline levels of Cyclin D1, which is associated with cell cycle G1/S transition in mantle cell lymphoma (MCL) cells. Additionally, lenalidomide results in the upregulation of tumour suppressor genes including SPARC, p21, and p27, resulting in cell cycle arrest.[1,2] The immunomodulatory effects of lenalidomide result in an "indirect" reduction of the tumour cell burden through enhancement of the adaptive, innate, and humoral immune system. Lenalidomide activation of T, NK, and NKT cells via restoration of substandard immunological synapse formation, may lead to enhanced immune-mediated tumour-cell killing, [3–5]

as well as downregulation of expression of inhibitory ligands on the surface of lymphoma cells, including PDL-1 and CD200.[6] Enhanced immunological synapse formation is associated with redistribution or "capping" of membrane proteins, including CD20 and CD19, towards the immunological synapse, accompanied by redistribution of essential cytoskeleton-signalling molecules (e.g. Rac1 and Vav1), which are required for immune synapse formation, F-actin polymerization, and lipid raft aggregation.[7]

The enhanced formation of immunological synapses and the resulting capping of membrane proteins (e.g. CD20) might promote the binding of CD20-specific monoclonal antibodies and improve antibody-dependent cell-mediated cytotoxicity, thus providing a rationale for a lenalidomide and rituximab combination regimen. Indeed, preliminary clinical data have shown synergistic effects of this regimen in vivo.[8–10]

An early DLBCL study with lenalidomide has shown that the immunohistochemically defined GCB-like and non-GCB sub-groups exhibit distinctive clinical responses to lenalidomide.[11] It is not clear if this difference is to due to direct or indirect activity of lenalidomide.

The dual MOA of lenalidomide provides the preclinical rationale which, with early clinical evidence of its combination with Rituximab, supports the investigation of lenalidomide combination regimens within ongoing clinical trials. Thus, its effects on the adaptive, innate, and humoral immune systems offer rational possibilities for inclusion of lenalidomide in studies of maintenance strategies and combination therapies, including immunotherapy regimens. Several of these regimens are currently under clinical investigation. These trials include provision to carry out ex vivo work designed to validate the MOA hypothesis derived from pre-clinical work.

References
1. Zhang L, et al. Blood. 2008;112:[abstract 2612].
2. Zhang L, et al. J Clin Oncol. 2010;28:[abstract 8090].
3. Gaidarova S, et al. Blood. 2009;114:[abstract 1687].
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5. Ramsay AG, et al. Blood. 2009;114:4713-20.
6. Ramsay AG, et al. Blood. 2010;116:[abstract 696].
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10. Fowler NH, et al. J Clin Oncol. 2010;28:[abstract 8036].
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NOVEL AGENTS IN MANTLE CELL LYMPHOMA, PRECLINICAL & CLINICAL EVIDENCE

M. Trněný, MD, PhD
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Mantle cell lymphoma (MCL) represents around 6% of all non-Hodgkin lymphomas.[1] The introduction of rituximab, high-dose therapy, and cytarabine has improved outcomes, especially in young patients, but the majority of patients will relapse.[2] Following relapse median life expectancy declines to 1–2 years.[3] The management of relapsed MCL remains a great challenge and bortezomib and temsirolimus are currently the only drugs approved by the FDA and EMEA, respectively, for the treatment of relapsed/refractory MCL.

Bortezomib was shown to result in an overall response rate (ORR) of 33% (8% complete response [CR]), with a median response duration of 9 months.[4,5] Temsirolimus given at a dose of 250 mg/week on a 4 weekly cycle resulted in an ORR of 38%, a CR rate of 2.9%, and in patients responding a median response duration of 6.9 months.[6] In a subsequent 3-arm study, the ORR in the temsirolimus 175/75 mg and 175/25 mg groups were 22% and 6%, respectively, with median PFS durations of 4.8 and 3.7 months. In the third arm, physicians choice, the ORR was 2% and the median PFS was 1.9 months.[7] Novel compounds and treatment combinations are under investigation aiming to further improve patient outcomes.

Lenalidomide is an immunomodulatory agent with cytotoxic properties that correlate with baseline levels of cyclin D1[8] and anti-proliferative activity in MCL cells. These effects were shown to be synergistically enhanced by the addition of rituximab.[9] Clinically, single-agent lenalidomide was shown to have activity in patients with relapsed/refractory MCL resulting in an ORR of 42–53% (20% CR), and a median response duration of 13.7 months.[3,10] The prospective randomized study MCL-002 (SPRINT®) is currently underway to determine the efficacy and safety of lenalidomide compared with investigator's choice in relapsed or refractory MCL. In the ongoing MCL-001 (EMERGE®; NCT00737529) single-arm phase 2 trial, lenalidomide is being investigated in patients who have relapsed after or are refractory to bortezomib. The latest results from an ongoing study combining lenalidomide and dexamethasone in relapsed/refractory MCL, showed an ORR of 52%, including a CR rate of 24%, and a median response duration of 18 months.[11] The authors concluded that the addition of dexamethasone did not appear to add to the clinical efficacy of lenalidomide when compared to earlier data and may have contributed additional toxicity.[8,10] Preliminary clinical data support the synergy observed in vitro with lenalidomide plus rituximab and suggest that lenalidomide combination regimens may have a role in the future.[12]

References
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2. Goy A, Kahl B. Crit Rev Oncol Hematol. [Epub ahead of print 2010 Dec 16].
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11. Zaja F, et al. Blood. 2010;116:[abstract 966].
12. Wang L, et al. Blood. 2009;114:2719.

RATIONALE FOR MAINTENANCE IN LYMPHOMA – CAN THE CURRENT STANDARD OF CARE BE IMPROVED?

G. Salles
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Monoclonal antibodies such as the anti-CD20 antibody rituximab have revolutionized the treatment of non-Hodgkin lymphoma (NHL). In aggressive lymphomas, the combined modality immunochemotherapy has shown significant improvements in overall survival (OS) and event-free survival (EFS) compared with chemotherapy alone.[1] However, rituximab maintenance strategies have proven to be ineffective in diffuse large B-cell lymphoma (DLBCL).[2] A recent update of the long-term follow-up of the Intergroup E2294/C9793 trial, which investigated rituximab maintenance in patients with DLBCL following R-CHOP or CHOP, showed that the long-term failure rate in R-CHOP responders was 58% at 9 years.[3] Similarly, the 10-year follow-up of the LNH 98.5 study revealed that the 10-year OS in R-CHOP treated patients was 44%, with 40% of all R-CHOP treated patients relapsing within 10 years.[4]

As we accrue evidence that DLBCL patients have an important risk of late relapse, there is a need for improved treatment regimens. Maintenance therapy with the immunomodulatory agent lenalidomide has improved progression-free survival (PFS) for multiple myeloma patients.[5,6] The single-agent activity of lenalidomide in B-NHL,[7,8] together with its dual mode of action via tumoricidal and immunomodulatory effects, have prompted the investigation of lenalidomide maintenance in the treatment of DLBCL patients. The actively enrolling phase 3 REMARC study is investigating the efficacy of lenalidomide maintenance in patients with DLBCL in first remission after R-CHOP induction.[9]

In indolent lymphomas, rituximab has proven its efficacy in both induction immunochemotherapy regimens and maintenance treatment. Recently, the PRIMA trial has shown a significant improvement in 3-year PFS in patients with follicular lymphoma (FL) when treated with rituximab maintenance (75%), compared with no maintenance (58%; $p < 0.0001$) in first remission after an immunochemotherapy-based induction regimen. Additionally, 2 years after randomization, patients receiving rituximab maintenance showed higher complete responses compared with no maintenance (72% vs 52%; $p = 0.0001$).[10]

However, questions remain about how to eventually avoid relapses in FL patients and how to further improve remission-free living in these patients. Fowler et al. evaluated the efficacy and safety of a front-line lenalidomide and rituximab combination therapy in patients with untreated stage III/IV indolent NHL. Their phase 2 trial showed an overall response rate of 89%, including a complete response rate of 73% and nearly all of the FL patients (16/17 [94%]) in the study attained a CR with this "chemotherapy-free" regimen.[11] This provided the rationale for designing a phase 3 randomized trial comparing the efficacy of frontline rituximab and lenalidomide therapy with an immunochemotherapy-based regimen followed by rituximab maintenance.

The use of lenalidomide in maintenance regimens in lymphoma clinical trials will be discussed, including a review of recent safety data from multiple myeloma and on-going lymphoma studies.

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HOW CAN WE BEST COMBINE IMMUNOTHERAPIES WITH CHEMOTHERAPY IN LYMPHOMAS?

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The availability of agents directed against specific cell receptors or intracellular pathways has revolutionized treatment approaches for patients with lymphomas. Rituximab was the first antibody to demonstrate safety and efficacy not only as a single agent, but also as an integrated part of chemoimmunotherapy regimens, and it has provided the first evidence of prolongation of survival in diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and even chronic lymphocytic leukaemia (CLL).[1–3] The success of this antibody led to the development of a series of further human and humanized anti-CD20 antibodies, as well as antibodies targeting other surface receptors.[4] Combinations of antibodies in the relapsed setting as well as initial treatment also show enhanced efficacy.[5,6] Other available active antibody-related constructs include radioimmunotherapy, bi-specific antibodies, small modular immunopharmaceuticals, and drug-antibody conjugates.[7–9]

A number of agents under investigation target signalling pathways within the lymphoma cell. B-cell receptor (BCR) activation initiates a series of downstream events that enhance the survival of the lymphoma cell. These involve the spleen tyrosine kinase (SyK) and Bruton's tyrosine kinase. Targeting the former with fostamatinib[10] and the latter with PCI32765[11] has yielded promising results in a number of lymphoma histologies. Other important pathways include PI3-kinase, which can be targeted with CAL-101,[12] and the mTOR pathway, against which everolimus and temsirolimus are directed.[13,14]

It has also become apparent that the lymphoma microenvironment plays an important role in lymphoma survival. Lenalidomide, an immunomodulatory compound, exhibits a number of effects on the microenvironment and is active against many lymphoma subtypes, most notably with an approximately 50% response rate in relapsed and refractory mantle cell lymphoma.[15–17] Response rates of 86% have been reported when combined with rituximab in patients with follicular and low-grade NHL, and ongoing studies are evaluating this agent in combination with bendamustine and other drugs.[18]

The future direction of anti-cancer clinical research is away from toxic, non-specific chemotherapy and towards drugs that target specific lymphoma-related pathways. The eventual goal is to deliver personalized therapy based on a better understanding of the biology of each patient's lymphoma.

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HDAC INHIBITORS IN T-CELL LYMPHOMAS

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Histone deacetylase (HDAC) inhibitors have proven to be effective in various haematological malignancies, in particular cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL). HDACs catalyze the removal of acetyl moieties from lysine residues of histone and non-histone proteins, thus regulating their structure and function.[1] As a result, HDAC inhibitors exhibit a variety of biological effects, which include regulation of gene transcription, induction of autophagy and apoptosis, and inhibition of angiogenesis. It is unclear to date which of these effects are responsible for the clinical effects seen in the treatment of T-cell lymphomas.

For patients with T cell lymphoma, CHOP(-like) regimens remain the standard of care but while many patients initially respond, most experience rapid relapse or disease recurrence,[2,3] thus new treatment options are warranted to treat patients with this dismal prognosis.

Belinostat and vorinostat are relatively non-selective inhibitors of HDACs, predominantly acting on HDAC 1, 2, 3, and 6.[4] In patients with relapsed or refractory PTCL or CTCL, single-agent belinostat was shown to be well tolerated with durable overall response rates (ORR) of 25% and 14% respectively.[5] Oral vorinostat resulted in an ORR of 29.7%, including 1% complete response (CR), in 74 patients with relapsed or refractory CTCL.[6]

The recent final results of two phase II trials of romidepsin, an inhibitor of HDACs 1, 2, and 3,[4,7] have reported ORRs of 38%[8] and 26%[9] in PTCL and 34%[10] in CTCL patients who had received at least one prior treatment. In the larger PTCL trial,[9] the CR/CRu rate was 13% with overall median response duration of 12 months. Median duration of response was not reached in CR patients. Grade ≥ 3 or higher adverse events (AE) were reported in 66% of patients and included pneumonia (5%), pyrexia (5%), sepsis (5%), and vomiting (5%).[9] Among the 45 evaluable PTCL patients in a second trial,[8] the median response duration was 9 months and CR rate was 18%. Grade ≥ 3 AEs included nausea (9%), fatigue (20%), thrombocytopenia (35%), and decreased granulocytes (43%).[8] Most patients experienced a short prolongation of QTc but ECG values returned to baseline within 24 hours and were not associated with functional cardiovascular changes or clinical symptoms.[8,9] Other commonly observed AEs were gastrointestinal disturbances and asthenic conditions.[10] This AE profile is in line with that observed in other HDAC inhibitors.

The pleiotropic mechanisms of action of HDAC inhibitors and the activity seen in the PTCL monotherapy studies conducted so far are the rationales for ongoing and planned combination therapy clinical trials.

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Friday, June 17, 2011, 18:30 – 20:30 *(room B I)*

MUNDIPHARMA

OPTIMISING THERAPY IN THE ELDERLY MULTIPLE MYELOMA PATIENT
Co-chairs: H. Ludwig, Wien (Austria) and A. Palumbo, Turin (Italy)

OPTIMISING THERAPY IN THE ELDERLY MULTIPLE MYELOMA PATIENT
H. Ludwig, Wien (Austria)

WELCOME AND INTRODUCTION
H. Ludwig, Wien (Austria)

THE ELDERLY PATIENT - RELEVANCE OF CO-MORBIDITIES IN TREATMENT PLANNING
H. Ludwig, Wien (Austria)

TREATMENT STRATEGIES IN THE TRANSPLANT INELIGIBLE PATIENT
M.V. Mateos, Salamanca (Spain)

MANAGEMENT OF ADVERSE EVENTS IN MYELOMA
A. Palumbo, Turin (Italy)

COMBINATIONS IN RELAPSED MYELOMA
P. Moreau, Nantes (France)

CONCLUSION AND WRAP UP
H. Ludwig, Wien (Austria)