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European Hematology Association

Selected Update on Lymphoma EHA 24 Congress

July 2019



This is a selection of lymphoma news, patient advocacy and/or policy related topics presented at the 24th annual EHA Congress in Amsterdam, from June 13 to June 16

The summaries are taken from the abstracts and materials available on the EHA website (EHA learning center) with additional commentary and notes from Natacha Bolaños



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INTRODUCTION



More than 12,600 haematology professionals from 123 countries (*41 countries Europe + 82 countries Outside Europe*) around the world met together in Amsterdam, for the 24th European Haematology Association (EHA) Congress. It is the largest EHA Congress ever recorded with a growth of more than a thousand participants from last year.

The 4-day program combined a broad range of topics from the rapidly evolving field of haematology. Updates on the diagnosis and management of patients with haematological disorders, as well as presentations on the cutting edge of basic, translational and clinical research formed part of the comprehensive yet easy-to-navigate congress program.

The extensive congress program included over 400 sessions of invited presentations, abstract presentations and sponsored sessions from EHA's industry partners. This report summarizes EHA's annual congress with the topics divided into the sections of the European Haematology Curriculum. Every section provides an introduction, video and links to webcasts and interviews with presenting authors and top experts.



Don't miss the **EHA24 Digital Congress Report** available in here:

- **General Report:**
<https://ehaweb.org/congress/reports/eha24-digital-congress-report/>
- **Lymphoid malignancies:**
<https://ehaweb.org/congress/reports/eha24-digital-congress-report/congress-topics/lymphoid-malignancies/>
- **SCT and special therapy & Topics-in-Focus Immunotherapy**
<https://ehaweb.org/congress/reports/eha24-digital-congress-report/congress-topics/stem-cell-transplantation-and-special-therapy/>
- **Patient Reported Outcomes and CAR-T expectations**
<https://ehaweb.org/congress/reports/eha24-digital-congress-report/congress-topics/general-skills/>

ADVOCACY TOPIC: EHA-PATIENT JOINT POLICY SYMPOSIUM

The EHA-Patient Joint Policy Symposium at EHA24 offered a day-long series of multi-stakeholder sessions on key policy and regulatory topics. In five sessions, mixed panels of haematologists, patient advocates, industry representatives and regulators treated an equally mixed audience to unfiltered views and lively debate.

INNOVATIVE THERAPIES: ACCESS, BENEFIT AND EXPECTATIONS

The question hanging over the introduction of novel gene and cell therapies – promising yet costly – is how access and benefit for patients can be optimized, given the complexity, budgetary burden and uncertainty about the long-term effectiveness of these treatments. Speakers in the morning sessions set out looking for answers, and did some expectation management along the way.

SESSION 1: ACCESS TO TREATMENT

Unsurprisingly, the panel members addressing the question at the heart of this session, ‘How to ensure patient access to innovation and affordability?’, did not come up with a unified answer. EMA’s Francesco Pignatti reminded the audience that neither innovation nor excellence are requirements for market authorization, which is based on safety and efficacy. Decisions on medical benefit and prescription are up to doctors and patients; the role of EMA is to make sure

No “excellence” required for marketing authorisation

- “Excellence” only foreseen in legislation in two specific situations
 - Conditional marketing authorisation (“major therapeutic advantage”)
 - Orphan designations (“significant benefit”)
- New “best” medicines may not be the favourite option for every patient
 - “Inferior” products according to some may still be the preferred option for others.
 - Approval of “better” medicines does not mean that authorisations for approved medicines are revoked.
- No single scale can capture the value of medicines from different perspectives.
- Focus on transparency and communication

they can make these decisions based on the best available information.

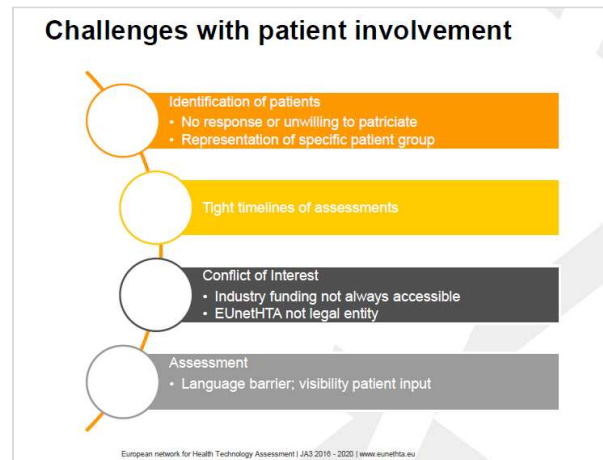
The fact that a mandate has its inherent limitations was also evident in the two contributions about HTA. Patient advocate Zack Pemberton-Whiteley stressed that patient involvement in HTA must be combined with real influence on decision-making.

A comparison of the different UK processes

	NICE	SMC	AWMSG
Scoping	✓	X	X
Technical Engagement	✓ (NEW)	X	X
Evidence Submission	✓	✓	✓
Patient Focused Meeting	X	✓ PACE (For rare and end of life medicines)	✓ CAPIG (For rare diseases only)
Committee Meetings	✓	✓	X (Public Gallery)
Opportunity to Appeal	✓ (ACD and FAD)	X	X
Publication	✓	✓	✓

NICE – National Institute for Health and Care Excellence; SMC – Scottish Medicines Consortium; AWMSG – All Wales Medicines Strategy Group

EUnetHTA, represented by Anne Willemssen, considers input from patients essential, especially in the scoping phase, however efforts to involve patients have so far met with limited success (patient advocates in the audience mention lack of resources, COI issues and skepticism about their influence as factors). Willemssen strongly defended the separation between joint clinical assessments, as piloted by EUnetHTA, and national-level appraisals; Pemberton-Whiteley argued for reimbursement decisions to be made at the European level.



Market access specialist Joao Carapinha discussed concepatients of ‘value-based’ versus ‘fair’ pricing. A believer in value-based pricing (VBP) – in his opinion, prices should not be fixed but always negotiable – he nonetheless warned policy makers against implementing VBP models, for lack of resources. ‘Who pays?’ remains the inevitable question.

Value-based Pricing & Fair Pricing are different approaches to improve market efficiency, but they are **not the only way ...**

- Fair Pricing Forum: November 2016 (Geneva) and April 2019 (Johannesburg)
- “Fair Price is one that is **affordable** for health systems and patients and that at the same time provides sufficient market incentive for industry to invest in innovation.”
 - “The time is ripe to rethink how medicines are priced ...” (p.1)
 - Transparency of R&D, production & marketing costs (p. 2)
 - Consumer vs. producer surplus (p.3)
- Value-based Pricing estimates the **value of the product** to a health-system.
 - Not linked to the cost of production or affordability.
 - Depends on the willingness-to-pay thresholds (based on QALYs or DALYs)
 - Linked to estimates of a person’s economic value (e.g. GDP per capita)



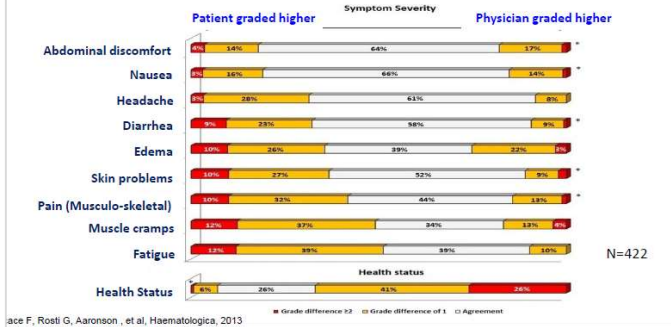
SESSION 2: PATIENT-REPORTED OUTCOMES (PRO)

Now that the importance of patient-reported outcomes is broadly recognized, the four speakers in this session focused on their implementation.

Patient advocate Giora Sharf discussed the use of PRO in clinical trials. The perception of the impact of PRO tends to differ between doctors and patients, but there is little doubt that they play a valuable role in stimulating discussion between the providers and the receivers of care.

Tom Coats (King’s College London) addressed the role of technology in hematology and cited “powerful studies” that suggest that PRO help make clinical decisions in cancer, with very good input even from computer-inexperienced patients.

Doctor/patient perception on impact on QoL differs



PROBE
Patient Reported Relevant Outcomes

Traditional Clinical Outcomes	Patient-Centric Outcomes
Lifespan (survival)	Educational pursuit
Factor levels (peaks & troughs)	Work / Career opportunities
Bleeding frequency (annualized bleed rate, target joints)	Family / Social life engagement
Joint outcomes (structure, range of motion)	Activity / Sports goals
Function and mobility	Decreased burden of illness

Enhancing the direct patient voice in healthcare decision-making.

Mark Skinner from the Institute for Policy Advancement in Washington, DC is equally convinced that “patients can influence the clinical pathway”, with the help of methodologically sound PRO tools, such as the one he presented, PROBE (PRO, Burdens & Experiences).

Another insightful contribution was provided by Sarah Liptrott of the Haematology Nurses & Health Care Professionals group (HNNHCP). Not only are nurses,

who play a prominent role in the interaction between physicians and patients, convinced that PRO are beneficial also for physicians – positively affecting satisfaction levels, efficiency and time; HNNHCP has also developed disease-specific PRO measures, such as for sickle cell disease.

SESSION 3: MANAGING THE HYPE ON CAR T

In front of an overflowing room – as befitted a session dedicated to a hype – Hermann Einsele (University of Würzburg) and Natacha Bolaños (Lymphoma Coalition) led a spirited discussion about CAR T-cell therapy. Patients, doctors, a nurse and an EU policymaker shared their optimism and concerns, in varying dosages, for the implementation of this revolutionary therapy.

To Brian Koffman, a doctor turned CLL patient who was one of the first 100 patients to participate in a CAR T trial, the balance is a positive one: while the side effects are tough and many patients get very ill, most recover fully. Ananda Plate of Myeloma Patients Europe agreed that CAR T is very promising, although in myeloma “it does not look like a miracle yet”. She called on all stakeholders to agree on a combined set of tools – communication, PRO/Quality of Life (QoL), health economics, protocol – that help achieve meaningful benefit for patients. Not knowing exactly what to expect from CAR T treatments causes uncertainty among both patients and nurses. As Mairead Ní Chonghaile of HNHCP asserted, “there is an awful lot of doubt and fear among healthcare professionals – all of them”.

Jan van de Loo, cancer expert of the European Commission, views health inequalities across Europe and pricing as the main issues. Acknowledging that Europe lags behind China and the US, yet faced with limited funding from Member States, the Commission is focusing its efforts on comprehensive uptake of CAR T in health systems, EU added value, partnerships and fostering innovation. The last round of Horizon 2020 calls will offer “lots of opportunities for cell therapy”, on top of the two specific CAR T topics in the most recent IMI2 call.

Do our expectations for CAR T cell therapy outweigh the facts? **YES Patient Perspectives on CAR-T gaps and challenges**

- There are only a handful of patients out more than 5 years
 - There is virtually no long term data
 - There is very little total data
 - The data that there is underwhelming
 - There is zero evidence that it is curative
- Much of why CAR-T works and doesn't and who gets severe AEs is still a subject of research.
- Patients are still dying from CRS and neuro events.
- CRS and neuro events often are dangerous, frightening and very painful
- CAR-T “takes a village.”
- CAR-T is very expensive because at this time each CAR-T is made one patient at a time.



REGULATING INNOVATIVE THERAPIES

The afternoon program of the EHA-Patient Joint Policy Symposium highlighted the need for adaptation of regulatory processes to facilitate true patient-centered, personalized medicine.

SESSION 4: REGULATING PERSONALIZED MEDICINE TRIALS

Leading the call for regulatory changes and flexibility was Ulrich Jäger from the Medical University of Vienna, member of EHA's European Affairs Committee. New regulations are needed to enable the tailored decision-making and personalization of trials that are necessitated by the combination of high-risk patients, treatment failures, rare diseases and novel target or drug discoveries. Adaptation is also required from pharmaceutical companies, in order to make multi-drug trials possible.

Human strategic goals and core recommendations

EUROPEAN MEDICINES AGENCY

DRIVING COLLABORATIVE EVIDENCE GENERATION – IMPROVING THE SCIENTIFIC QUALITY OF EVALUATIONS

- Leverage novel non-clinical models and 3Rs
- Optimise capabilities in modelling and simulation and extrapolation
- Foster innovation in clinical trials
- Develop the regulatory framework for emerging clinical data generation
- Expand benefit-risk assessment and communication
- Invest in special populations initiatives
- Develop adaptive pathways via scientific advice in conjunction with key stakeholders
- Exploit digital technology and artificial intelligence in decision-making

Ulrich Jäger, Department of Hematology, Division of Hematology and Hemostaseology²⁰

An encouraging example is Roche which is experimenting with 10-drug trials. Challenges for companies include financial and legal risks, unwanted stimulus for off-label use, and, as Johannes Pleiner-Duxneuner of Roche Austria put it, “the need to turn real-world data into real-world evidence” which requires the combination of databases.

Jan Geissler (CML Advocates Network) stressed the need to involve patients in all the difficult decisions on ethics, regulation and data protection. “If it’s all for the patient, why are we not asked what an acceptable risk is?” He also pointed out that while new regulation may be necessary, much can be done with existing mechanisms such as the Clinical Trials Regulation, Adaptive Pathways and PRIME.

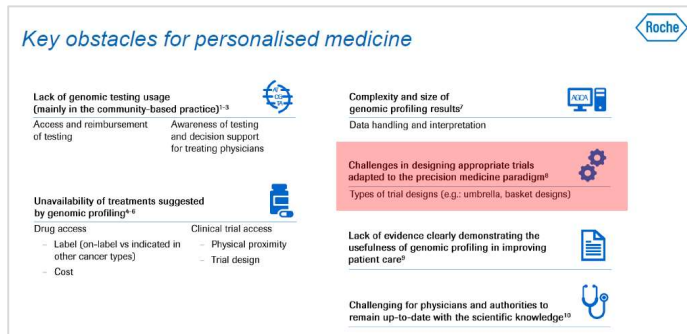
Conclusions

- We must have more trials, more data, more evidence that personalized medicine works – and how.
- Breeding on data nests and withholding effective therapies in the name of ‘good science’ or paternalistic ‘regulation’ is inhumane.
- While new regulation may be necessary, much can already be done with today’s mechanisms. Make use of them. Share the data. Don’t use fingerprinting as an excuse. It will take us years to change the rules.
- If it’s all for the patient, why are we not asked what an acceptable risk is? Get patients involved in ethics, bureaucracy, regulation and data protection.

Jan Geissler <jan@patvocates.net>

Clinical assessor Olga Kholmanskikh Van Criekinging of Belgian medicines agency FAHMP agreed with fellow panel members that new trial designs could help increase the use of biomarkers and personalize treatments, that big data is crucial, and that patient input “along the continuum” is important. She signalled a number of risks, however, including increased operational complexity and challenges to safety oversight,

data integrity and transparency. (Significantly, a survey produced widely diverging patient opinions on data sharing and usage.)



There was agreement among the speakers that the data ownership question is crucial. Registries are seen as part of the solution, and hopes are that valuable lessons can be drawn from the HARMONY project.

SESSION 5: RAISING THE BAR FOR DRUG APPROVALS

The issue most hotly debated on this day was formulated as follows, somewhat provocatively, by session chair Ton Hagenbeek (Amsterdam UMC/EHA European Affairs Committee): “EMA is bound by its mandate, but as a physician I say: there should be a real medical benefit before a medicine can be approved.” Raising the bar for drug approvals, by adding a ‘real added value for patients’ criterion to efficacy and safety, was not something that could, or should, be expected of EMA, as Francesco Pignatti was quick to point out. Not regulators, but doctors and patients should decide on medical benefit. “A paternalistic approach of raising the bar for all is not the answer.” And: “There isn’t a single bar we can all agree on”.

Patient advocate Piarella Peralta (Inspire2Live) proposed refocusing the discussion to “raising the bar for patient care with quality of life”. This requires re-centering healthcare around the “magic combination of patients, clinicians and researchers”.

Responding to Prof. Hagenbeek's challenge that industry trials result in many 'me-too' drugs that are good for industry profits but of little added value to patients, Takeda's Kelly Page acknowledged industry can do better. She insisted, however, that "our responsibility as industry is to run the best studies we can". Page expressed confidence that "patient involvement throughout the development continuum can help ensure value-added outcome".

There was consensus among panel and audience members on the need for meaningful involvement of patients in decisions on benefit, and for alignment of all stakeholders to determine patient-relevant endpoints. In a somewhat prickly exchange on the merits of 'me-too' drugs, however, patients in the room reminded everyone that patients are not a monolithic group with identical preferences. What is of negligible benefit to some may be invaluable to others.

All the slides of the EHA-PATIENT JOINT POLICY SYMPOSIUM are available in google drive:

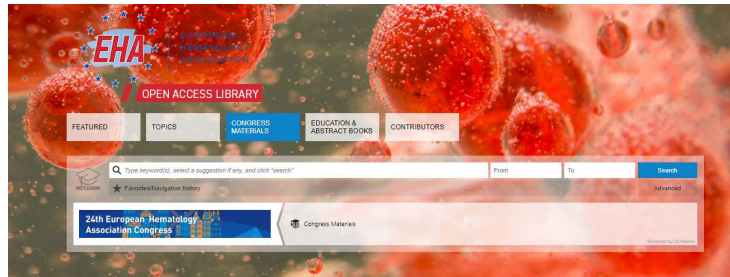
<https://drive.google.com/open?id=1AtCGqhZhGemExR5jPiJPkELTszMsUAsI>

In this folder you will find also some of the presentations included in the Capacity Building session that took place on Thursday June 13, 2019 covering a special topic: Patient involvement in HTA, alongside other important information about how to get the best of the congress. This information is crucial for all patient advocates.

Enjoy!

LYMPHOMAS AT EHA24

This report includes a selection of the lymphoma presentations available at the EHA Annual congress 2019. There are more available and I encourage you to check at the open access platform [EHA OPEN LIBRARY](#)



The 24EHA Congress content is offered in a user-friendly manner, including: congress webcasts, abstracts, e-posters and slides. New content such as expert interviews with leading haematologists are periodically uploaded to ensure users are aware of the latest developments on various haematological topics.

How to read this summary?

The report has been structured following the congress sections. Each title of the selected presentations is a direct link to the expanded content available at the EHA Open Library. In some cases, comments have been added to facilitate the reading, including a captured slide or pieces of information taken from the posters.

Take-home messages

- Evidence on the efficacy of venetoclax and obinutuzumab in treating patients with chronic lymphocytic leukemia (CLL) supports the use of such treatment as a first-line therapy in patients with CLL and co-existing conditions.
- CART work continues as need to know more on how to choose right patients and overcoming relapse and prevent severe adverse effects.
- RCHOP continues being the best option for Diffuse Large B Cell Lymphoma (DLBCL) as other studies results don't show convincing change to progression free survival. Maintenance therapy benefit is still an unmet need as current evidence do not support its incorporation in clinical practice. DLBCL survivors have higher rates of autoimmune disease in comparison to other common solid tumors survivors.
- There are promising drug combinations in Follicular Lymphoma but more studies need to be done to confirm recent findings.
- Ibrutinib is best choice for Waldenström Macroglobulinemia.
- BTKs effective options in R/R Mantle Cell Lymphoma.
- For Marginal Zone Lymphoma patients disease progression is still and unmet need.

I hope you find this summary useful, especially if you could not attend the congress.

Natacha Bolaños
Regional Manager Europe

PRESIDENTIAL SYMPOSIUM

UNTREATED CLL AND COMORBIDITIES

KIRSTEN FISCHER, OTHMAN AL-SAWAF, JASMIN BAHLO, ANNA-MARIA FINK, ET AL.

FIXED-DURATION VENETOCLAX PLUS OBINUTUZUMAB IMPROVES PROGRESSION-FREE SURVIVAL AND MINIMAL RESIDUAL DISEASE NEGATIVITY IN PATIENTS WITH PREVIOUSLY UNTREATED CLL AND COMORBIDITIES

The multinational, open-label, phase 3 CLL14 trial (NCT02242942) compared fixed-duration targeted venetoclax plus obinutuzumab (VenG) treatment with chlorambucil-obinutuzumab (ClbG) treatment in previously untreated patients (patients) with chronic lymphocytic leukemia (CLL) and comorbidities.

<i>Patients' characteristics I</i>	Venetoclax- Obinutuzumab	Chlorambucil- Obinutuzumab	<i>Patients' characteristics II</i>	Venetoclax- Obinutuzumab	Chlorambucil- Obinutuzumab
Number of patients, N	216	216	Number of patients, N	216	216
Median age in years	72	71	IGHV mutational status		
Binet stage			Unmutated	61 %	59 %
A	21 %	20 %	Mutated	38 %	40 %
B	36 %	37 %	Not evaluable	1 %	1 %
C	43 %	43 %	TP53 deleted and/or mutated	12 %	12 %
Median total CIRS score	9	8	Cytogenetic subgroups*		
Median estimated CreaCl in ml/min	65.2	67.5	Deletion in 17p	9 %	7 %
Risk category for TLS			Deletion in 11q	18 %	20 %
Low	13 %	12 %	Trisomy in 12	18 %	21 %
Medium	64 %	68 %	No abnormalities	25 %	22 %
High	22 %	20 %	Deletion in 13q alone	31 %	31 %



<i>All grade 5 adverse events</i>	Venetoclax- Obinutuzumab	Chlorambucil- Obinutuzumab
Number of patients, N	212*	214
Total number of events	16 (8%)	8 (4%)
Events during therapy	5 (2%)**	4 (2%)
Infections and infestations	4 (2%)	3 (1%)
Neoplasms	1 (<1%)	1 (<1%)
Events after completion of therapy	11 (5%)	4 (2%)
Cardiac disorders	3 (1%)	1 (<1%)
Infections and infestations	4 (2%)#	0 (0%)
Neoplasms	2 (<1%)	2 (<1%)
Other reasons	2 (<1%)	1 (<1%)

Conclusion: Fixed-duration VenG induced deep, high (<10⁻⁴ in 3/4 of patients and <10⁻⁶ in 1/3 of patients), and long lasting MRD-negativity rates (with a low rate of conversion to MRD-positive status 1 year after treatment) in previously untreated patients with CLL and comorbidities, translating into improved PFS.

LATE-BREAKING ORAL PRESENTATIONS (BEST ABSTRACTS)

RELAPSED / REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA

PAOLO GHIA, ANDRZEJ PLUTA, MALGORZATA WACH, DANIEL LYSAK, ET AL.

ASCEND PHASE 3 STUDY OF ACALABRUTINIB VS INVESTIGATOR'S CHOICE OF RITUXIMAB PLUS IDELALISIB (IDR) OR BENDAMUSTINE (BR) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Most patients (patients) with CLL respond to initial therapies though nearly all relapse and require subsequent therapy. More effective and tolerable treatments are needed for R/R CLL. Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor with clinical benefit in patients with R/R CLL.

In this randomized, global, multicenter, open-label Phase 3 study (CL-309; ASCEND; NCT02970318), the efficacy and safety of acalabrutinib monotherapy was evaluated vs investigator choice of IdR or BR in R/R CLL.

Methods: Eligible patients with R/R CLL were randomized 1:1 to receive 100 mg oral acalabrutinib BID until progression vs Rituximab + Idelalisib (IdR) (Id 150 mg oral BID in combination with up to 8 IV infusions of R [375 or 500 mg/m²] or +Bendamustine (BR) (70 mg/m² IV B on Day 1 and 2 of each cycle combined with R [375 or 500 mg/m² IV] on Day 1 of each 28-d cycle for up to 6 cycles). Patients were stratified by del(17p) status (yes vs no), ECOG status (0-1 vs 2) and prior lines of therapy (1-3 vs ≥4).

The primary endpoint

- progression-free survival (PFS) assessed by independent review committee (IRC)

Secondary endpoints included

- overall survival (OS),
- IRC-assessed overall response rate (ORR)
- safety

Grade ≥3 AEs and SAEs in ≥5% of Patients in Any Group

Grade ≥3 AEs, n (%)	Acalabrutinib n=154	IdR n=118	BR n=95	SAEs, n (%)	Acalabrutinib n=154	IdR n=118	BR n=95
Any	76 (49)	106 (90)	17 (49)	Any	44 (29)	66 (56)	9 (26)
Neutropenia	24 (16)	47 (40)	11 (31)	Pneumonia	8 (5)	10 (8)	1 (3)
Anemia	18 (12)	8 (7)	3 (9)	Diarrhea	1 (1)	16 (14)	0
Pneumonia	8 (5)	10 (8)	1 (3)	Pyrexia	1 (1)	8 (7)	1 (3)
Diarrhea	2 (1)	28 (24)	0				
Thrombocytopenia	6 (4)	9 (8)	1 (3)				
ALT increased	2 (1)	10 (8)	1 (3)				
Neutrophil count decreased	2 (1)	9 (8)	1 (3)				
Pyrexia	1 (1)	8 (7)	1 (3)				
AST increased	1 (1)	6 (5)	1 (3)				
Transaminases increased	0	6 (5)	0				
Constipation	0	0	2 (6)				

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; SAE = serious AE.

Patients with confirmed progression on IdR/BR could cross over to receive acalabrutinib monotherapy

Conclusion: Acalabrutinib monotherapy significantly improved PFS with a more tolerable safety profile compared with IdR/BR in patients with R/R CLL.

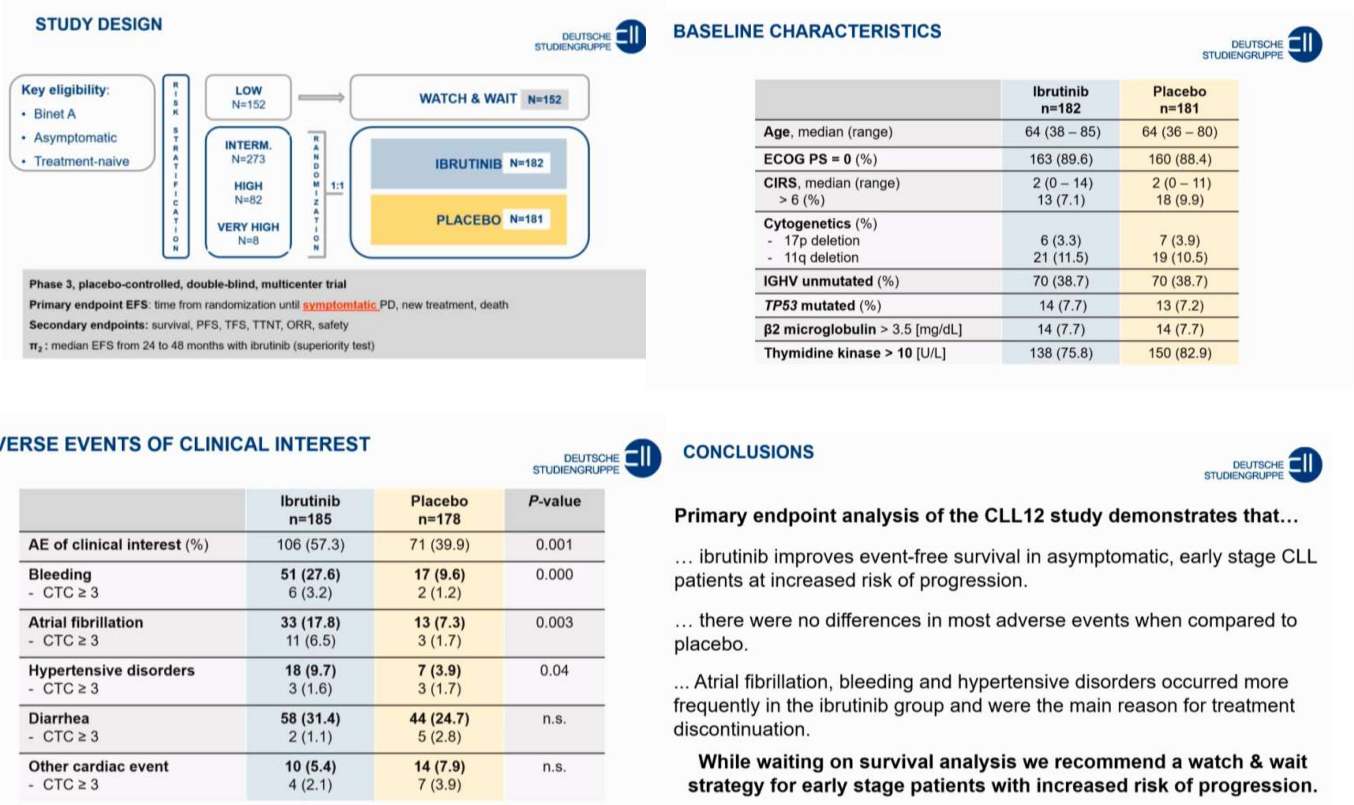
NAÏVE EARLY STAGE CHRONIC LYMPHOCYTIC LEUKEMIA CLL

PETRA LANGERBEINS, JASMIN BAHLO, CHRISTINA RHEIN, HENRIK GERWIN, ET AL.

IBRUTINIB VERSUS PLACEBO IN PATIENTS WITH ASYMPTOMATIC, TREATMENT-NAÏVE EARLY STAGE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PRIMARY ENDPOINT RESULTS OF THE PHASE 3 DOUBLE-BLIND RANDOMIZED CLL12 TRIAL

So far, treatment of asymptomatic, early stage CLL patients has not been proven beneficial. Ibrutinib is a BTK inhibitor with impressive clinical efficacy in advanced or relapsed CLL. It has not been tested in treatment-naïve early stage CLL.

The aim of the double-blind, randomized, placebo-controlled CLL12 trial was to evaluate whether ibrutinib prolongs event-free survival (EFS) in early stage CLL patients with increased risk of progression defined by a recently developed score (Pflug et al., Blood 2014).



Conclusion: The results of this study allow to conclude that ibrutinib significantly improves EFS, PFS and time to next treatment (TTNT*) in patients with treatment-naïve early stage CLL when compared to placebo. There were no significant differences in adverse events between both study arms.

TTNT* were defined as time from randomization until progression/death (PFS) or until the date of initiation of subsequent treatment for CLL (TTNT).

INDOLENT AND MANTLE-CELL NON-HODGKIN LYMPHOMA - CLINICAL

**S LEGOUILL, ASMA BELDI-FERCHIOU, VICTORIACACHEUX, MARION ALCANTARA, ET AL.
OBINUTUZUMAB PLUS DHAP FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION PLUS OBINUTUZUMAB MAINTENANCE PROVIDES A HIGH MRD RESPONSE RATE IN UNTREATED MCL PATIENTS, LYMA-101 TRIAL - A LYSA TRIAL**

The LYMA-101 study is a prospective and open phase II trial testing the effect of Obitunuzumab in untreated MCL patients under 66 years of age and eligible for intensive therapy. Induction consisted of 4 cycles of Obinutuzumab-DHAP (O-DHAP) before consolidation with ASCT (BEAM conditioning plus Obinutuzumab) followed by Obinutuzumab maintenance.

This study found that obinutuzumab plus DHAP (O-DHAP) followed by ASCT plus obinutuzumab maintenance, provided a high minimal residual disease (MRD) response rate in untreated patients with mantle cell lymphoma (MCL). No major toxicities were reported. One-year OS and PFS are encouraging, however longer follow-up is necessary to evaluate patient outcomes. Longer follow up is needed to evaluate patient outcomes. However, both PFS and OS are highly encouraging at one year.

Conclusion: The Lyma-101 trial successfully achieved its primary endpoint (84.9% of MRD BM negativity after induction) and demonstrates the high efficacy of O-DHAP as induction chemotherapy regimen with an unprecedented high level of MRD negativity.

**PAU ABRISQUETA, BRAD KAHL, LALITA BANERJEE, ANDREW MCMILLAN, ET AL.
POLATUZUMAB VEDOTIN (POLA) + OBINUTUZUMAB (G) AND LENALIDOMIDE (LEN) IN PATIENTS (PATIENTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): INTERIM ANALYSIS OF A PHASE IB/II TRIAL**

Pola-G-Len may enhance anti-tumor immune response in R/R FL. A pre-planned interim analysis of the safety/efficacy of induction and maintenance with Pola-G-Len in patients with R/R FL in a phase Ib/II study. Response rates at end of induction with Pola-G-Len are promising, with high complete remission rates (compared with available R/R FL treatment); 90% of patients remain progression free at 12 months.

Conclusion: The safety profile of Pola-G-Len is consistent with known profiles of the individual drugs, Adverse effects were manageable with supportive care. The novel triplet combination could have a potential place as therapy for patients with R/R FL.

Safety summary
Grade 3-4 AEs (≥2 patients)

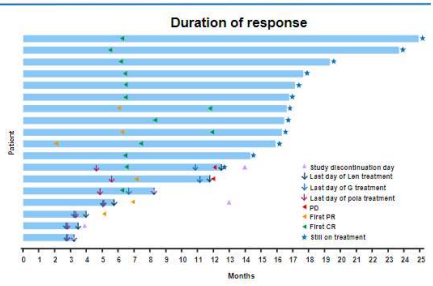
Grade 3-4 AEs	n (%)	n=52
Total no. of patients with grade 3-4 AEs	39 (75)	
Hematologic		
Neutropenia ¹	24 (46)	
Thrombocytopenia	9 (17)	
Anemia	6 (12)	
Febrile neutropenia	2 (4)	
Non-hematologic		
Infections ²	6 (12) ³	
ALT increased	2 (4)	
Lipase increased	2 (4)	
Hypokalemia	2 (4)	
Tumor lysis syndrome	2 (4)	

Clinical cut-off date: 6 July 2018

¹ICSP use reported in 24 (46%) patients; infections presented as Systemic Organ Class terms - all other AEs are reported by preferred terms: ²Lower respiratory tract infection (LRTI), Septic shock, sepsidemia, bacterial sinusitis, pneumonia, and urinary tract infection

Updated follow-up
Interim analysis efficacy evaluable population (n=18)

- Median duration of follow up: **16.6 (3.2-25.1) months**
- Median PFS: **not reached**
- 12-month PFS rate: **90%**
- Of 17 responders, two patients have experienced disease progression to date
- The remaining patients have ongoing responses with the longest >21 months



SIMON RULE, WOLNEY GOIS BARRETO, JAVIER BRIONES, ANGELO MICHELE CARELLA, ET AL.
EFFICACY AND SAFETY OF PROLONGED MAINTENANCE WITH SUBCUTANEOUS RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA: RESULTS OF THE PHASE III MABCUTE STUDY

Rituximab (R)-chemotherapy (chemo) induction plus R maintenance is an established treatment for indolent non-Hodgkin lymphoma (iNHL). However, the optimum duration of R maintenance is unknown. A subcutaneous (SC) form of R (R-SC) is now available.

The phase III MabCute study evaluated the efficacy and safety of subcutaneous rituximab (Rituxan) as maintenance after standard subcutaneous rituximab induction and maintenance in patients who have relapsed or refractory indolent non-Hodgkin lymphoma.

The study was conducted in 639 patients, and 129 progression-free survival after randomization (PFSrand) events were needed to achieve 80% power. The study was not able to fully address this primary endpoint of PFSrand due to the limited number of events observed.

However, the study did show that the safety profile of subcutaneous rituximab during prolonged maintenance was consistent with the known profile of the product, and also demonstrated that the safety profiles of the intravenous rituximab and the subcutaneous option were comparable.

Why was important this study?

Biosimilar rituximab (intravenous) has had a massive impact with respect to cost (can be up to 40 cheaper than MabThera), therefore is taken a relevant portion of the market. However, there's no biosimilar subcutaneous.

In the maintenance setting, the hidden costs of somebody being in a chair all afternoon versus the subcutaneous are massive, not to mention the impact for the patient. That's recognized. So the investigators think there is any role (in maintenance) for an intravenous formulation over a subcutaneous. That's why it is relevant to proof the efficacy and safety work as expected.

Franck Morschhauser, Pierre Feugier, Ian W Flinn, Robin Gasiorowski, et al.

IMPROVED OUTCOMES IN PATIENTS (PATIENTS) WITH BCL2-POSITIVE DLBCL TREATED WITH VENETOCLAX (VEN) PLUS R-CHOP: RESULTS FROM THE PHASE 2 CAVALLI STUDY

The CAVALLI trial, studied the safety and efficacy of venetoclax plus rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP), then compared these outcomes with controls in the phase III GOYA trial who received R-CHOP alone. (GOYA compared anti-CD20 monoclonal antibody obinutuzumab versus rituximab in addition to CHOP chemotherapy in patients with previously untreated DLBCL).

The present study included 208 adults with DLBCL, an International Prognostic Index score of 2 to 5, an ECOG performance status of ≤2, and at least one measurable lesion ≥1.5 cm. Patients were assigned to receive 6 cycles of R-CHOP plus venetoclax. Per study protocol, two additional cycles of venetoclax plus rituximab were permitted per physician choice.

Conclusion: For the substantial portion of patients with DLBCL with overexpression of the BCL2 protein, combining the BCL2 inhibitor venetoclax with standard chemotherapy may improve response rates, according to results from the phase II CAVALLI trial. However, patients who received venetoclax experienced a higher rate of adverse events (AEs) compared with a historical control group who received chemotherapy alone.

Table 2. Safety profile in CAVALLI vs GOYA IPI 2-5

AEs n (%)	CAVALLI N=208*	GOYA IPI 2-5 (N=564)
Any AE	206 (99)	528 (94)
AE with fatal outcome (grade 5)	4 (2)	30(5)
SAE	116 (56)	230 (41)
Grade 3-4 AE	179 (86)	373 (66)
AE leading to w/d from any treatment	50 (24)	56 (10)
AE leading to w/d from Ven treatment	41 (20)	NA

*Protocol violation (includes 2 patients with IPI 1); NA, not applicable; SAE, serious adverse event; w/d, withdrawal.

A higher rate of cytopenia, FN and infections was observed in CAVALLI vs GOYA; however, there was no increase in risk of death, and the RDI of chemotherapy was maintained at similar levels.

AGGRESSIVE LYMPHOMAS - NEW AGENTS

POSTER

Jeremy Abramson, M. Lia Palomba, Jon Arnason, Matthew Lunning, et al.

LISOCABTAGENE MARALEUCEL TREATMENT OF PATIENTS WITH RELAPSED/REFRACTORY B-CELL NON-HODGKIN LYMPHOMA AND SECONDARY CENTRAL NERVOUS SYSTEM LYMPHOMA: INITIAL RESULTS FROM TRANSCEND NHL 001

No clinical studies have yet evaluated chimeric antigen receptor (CAR) T cell therapies in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) who have secondary central nervous system (CNS) lymphoma. This is a new sub-group analyses from the multicenter, phase 1 TRANSCEND NHL 001 study evaluating the investigational therapy lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T-cell product, in adult patients with relapsed/refractory non-Hodgkins lymphoma (NHL) who have secondary CNS lymphoma.

CONCLUSIONS

- This subset analysis represents the first evaluation of CAR T cells in patients with secondary CNS involvement by lymphoma
- Liso-cel had a manageable safety profile and showed preliminary clinical activity in patients with secondary CNS lymphoma
 - No apparent excess risk of NEs was observed
 - 1 patient had NEs (grade 3) and CRS (grade 2)
- Response or resistance to liso-cel was similar in sites of systemic and CNS lymphoma in all patients
- Patients with diverse B-cell NHL histologies and patterns of CNS involvement were treated
 - 4 of 6 patients with CNS involvement at time of first liso-cel infusion responded
 - 2 have ongoing CRs at the time of their last visits on Day 270 and Day 545, respectively, after liso-cel
 - 1 patient progressed systemically on Day 365, but maintained the CNS response up until death
- These preliminary data suggest that further investigation of liso-cel is warranted in patients with CNS lymphoma to:
 - Gather a larger safety and efficacy dataset in patients with secondary CNS lymphoma
 - Explore liso-cel treatment for patients with primary CNS lymphoma for whom few effective therapies are available

RESULTS

Patients

- 3 patients at DL1 and 6 at DL2 had secondary CNS lymphoma
- Patients with secondary CNS lymphoma were enrolled between May 2015 and April 2018
- The median age of patients with secondary CNS lymphoma was 60 years, and they had received a median of 3 prior therapies (**Table 1**)
- Onset of secondary CNS lymphoma varied widely
 - In 6 patients with DLBCL or high-grade B-cell lymphoma, diagnosis of secondary CNS lymphoma occurred before initial liso-cel administration and before subsequent treatment with liso-cel in 2 patients

Efficacy was evaluated per the Lugano criteria. Patients achieving a complete response could be retreated with liso-cel upon progressive disease.

Results: At data cutoff, 9 patients with secondary CNS lymphoma at initial treatment (n = 6), retreatment (n = 2), or cycle 2 (n = 1) received liso-cel. 4 patients were treated at DL1 and 5 at DL2. The median (range) age was 60 (47–73) years and number of prior lines of therapy was 3 (2–7).

Median time to peak CAR+ T cell expansion was 12.5 (7–112) days. 1 of 9 patients had grade (G)2 cytokine release syndrome (CRS) and 1 of 9 patients had a neurological event (NE; G3 decreased level of consciousness).

Giulia Perrone, Anna Guidetti, Anna Doderò, Paolo Corradini

CAR T-CELL THERAPY FOR LYMPHOMAS IN ITALY: THE ISTITUTO NAZIONALE DEI TUMORI OBSERVATIONAL STUDY AFTER THE EMA APPROVAL

Since 2016, our center is the only one approved in Italy and we are now conducting a prospective observational trial to evaluate the feasibility of CART-cell treatment. We report the results after EMA approval. It is worth of note that in Italy the government Drug Agency (AIFA) has not approved yet the commercial treatment.

Since September 2018 The Istituto National Dei Tumori (INT) prospectively register all patients referred at the INT center for CART-cell eligibility evaluation either for the enrolment in the ongoing clinical trial JCAR017 or in the contest of the expanded access program (EAP) open for enrolment since February 2019 only at INT. All patient's data were recorded including disease characteristics, comorbidities, history and present disease status at imaging. Patients were evaluated and screened for inclusion/exclusion criteria of the CART cells program available at that moment and planned for treatment.

Conclusion: Among all patients with r/r DLBCL only 24% presented clinical and disease characteristics suitable for CARTs treatment. Moreover, some eligible patients run the risk to become ineligible because of poor disease control. The 4 week period to obtain CART-cells is a major obstacle to successful treatment. CART-cell treatment needs to be planned earlier in the disease course to optimize the outcome. The feasibility in Italy over the last 6 months of CART cells treatment has been largely unsatisfactory and primarily limited by the lack of commercial products. Our observational study is ongoing.

Sung-Soo Yoon , Matthew Matasar, Laurie H. Sehn, Sarit Assouline, et al.

MANAGING CYTOKINE RELEASE SYNDROME (CRS) AND NEUROTOXICITY WITH STEP-FRACTIONATED DOSING OF MOSUNETUZUMAB IN RELAPSED/REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (NHL)

CONCLUSIONS

- Mosunetuzumab exhibits a promising risk-benefit profile in pts with aggressive and indolent R/R NHL.
- CRS and NAE appear less frequent, milder, and more manageable than with other T-cell directed therapies,¹⁻³ and are mostly confined to the first cycle of dosing.
- Step-up dosing in C1 has enabled continued dose escalation of mosunetuzumab, with no apparent increases in toxicity, indicating a broad therapeutic index.
- Dose escalation of mosunetuzumab, as a single agent, and in combination (atezolizumab, polatuzumab vedotin, chemotherapy) in R/R NHL is ongoing.

Conclusion: Step-fractionation has enabled continued dose escalation of mosunetuzumab with no apparent increases in toxicity, exhibiting a promising risk-benefit profile.

ORAL PRESENTATIONS

Thomas Witzig, Kami Maddocks, Sven de Vos, Roger Lyons, et al.

PHASE 1/2 TRIAL OF ACALABRUTINIB PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

Acalabrutinib, a highly selective, potent, covalent Bruton tyrosine kinase inhibitor, has demonstrated a 24% overall response rate as a single agent in relapsed/refractory diffuse large B-cell lymphoma.

Pembrolizumab targets PD-1, an immune checkpoint that limits anticancer responses; it has showed responses in patients with Richter transformation who failed ibrutinib and can augment acalabrutinib activity in vitro.

Aims: To assess the efficacy and safety of the combination of acalabrutinib plus pembrolizumab for patients with relapsed/refractory diffuse large B-cell lymphoma.

Conclusion: The combination of acalabrutinib plus pembrolizumab was well tolerated, with meaningful activity and some exceptional responders (>24 months) in these patients with relapsed/refractory diffuse large B-cell lymphoma.

Table

	All (N=61)
Overall response rate, n (%) [95% CI]	16 (26) [19-39]
Best response, n (%)	
Complete response	4 (7)
Partial response	12 (20)
Stable disease	18 (30)
Progressive disease	22 (36)
Other ^a	5 (8)
Duration of response, median (95% CI), mo	6.9 (2.3-not estimable)
Progression-free survival, median (95% CI), mo	1.9 (1.6-3.7)

^a Due to death (progressive disease, abdominal abscess [n=1 each]), clinical progressive disease (n=1), and withdrawal because of adverse events (thrombocytopenia, altered mental status [n=1 each]).

Randomized trials of the combination versus single agent are needed.

Ranjana Advani, Nancy Bartlett, Sonali Smith, Mark Roschewski, et al.

THE FIRST-IN-CLASS ANTI-CD47 ANTIBODY HU5F9-G4 WITH RITUXIMAB INDUCES DURABLE RESPONSES IN RELAPSED/REFRACTORY DLBCL AND INDOLENT LYMPHOMA: INTERIM PHASE 1B/2 RESULTS

u5F9-G4 (5F9) is a first-in-class IgG4 antibody targeting CD47, a macrophage immune checkpoint and “don’t eat me” signal on cancers leading to phagocytosis of tumor cells. Pre-clinically, 5F9 synergizes with rituximab to eliminate lymphoma by enhancing antibody-dependent cellular phagocytosis.

5F9+rituximab demonstrated encouraging safety/efficacy in a Phase (Ph) 1b dose escalation cohort in patients with relapsed/refractory (r/r) DLBCL and FL that were rituximab-refractory (Advani et al., NEJM 2018). Herein we report on extended follow up of this Ph1b cohort and preliminary Ph2 data.

Aims: The primary objectives were to determine the safety/efficacy of escalating doses of 5F9+rituximab in patients with r/r DLBCL and indolent lymphoma.

Conclusion: 5F9+rituximab is a novel immunotherapy blocking a key macrophage/cancer checkpoint. It is well tolerated with rapid and durable responses observed in both heavily pre-treated DLBCL and indolent lymphoma patients. Ph2 enrolment is ongoing (NCT02953509). Funded by Forty Seven and the Leukemia and Lymphoma Society.

Thomas Witzig, Lubomir Sokol, Won Seog Kim, Francine Foss, et al.

TIPIFARNIB IN RELAPSED OR REFRACTORY ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL) AND CXCL12+ PERIPHERAL T-CELL LYMPHOMA (PTCL): PRELIMINARY RESULTS FROM AN OPEN-LABEL, PHASE 2 STUDY

Conclusion: Preliminary activity of tipifarnib was observed in PTCL patients, particularly in those with tumors of AITL histology and high CXCL12 expression and enrollment in the CXCL12+ cohort continues.

Rong Tao, Lei Fan, Yongping Song, Yu Hu, et al.

SINTILIMAB FOR RELAPSED/REFRACTORY (R/R) EXTRANODAL NK/T CELL LYMPHOMA (ENKTL): A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (ORIENT-4)

Conclusion: Sintilimab is effective and well tolerated in r/r ENKTL and could be a promising treatment option for these patients. Early disease progression observed by PET scan in this study could be pseudo-progression as it did not correlate with poor outcome, which warrants further investigation. NCT03228836

AGGRESSIVE LYMPHOMAS - FIRST LINE, COMBINATION THERAPY AND REAL-LIFE DATA - AGGRESSIVE NON-HODGKIN LYMPHOMA

Monica Balzarotti, Michele Spina, Chiara Monagheddu, Stephane Chauvie, et al.

PET-DRIVEN RADIOTHERAPY IN PATIENTS WITH LOW RISK DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) : THE DLCL10 MULTICENTER PHASE 2 TRIAL BY FONDAZIONE ITALIANA LINFOMI (FIL)

The role of consolidation radiotherapy (RT) after rituximab-chemotherapy (R-CT) in DLBCL is not completely defined. Historically, bulky sites at diagnosis are irradiated after R-CT, whereas residual disease at other sites is considered as treatment failure. Since 2007, complete remission (CR) is defined as PET negativity and some groups postulated that PET negative areas after R-CT do not need consolidation RT.

Conclusion: Our data suggest that irradiating only sites of unique residual PET uptake, regardless of bulky at onset, can be considered as a reasonable strategy for low risk DLBCL patients. In patients with bulky disease, PET-driven RT allowed RT sparing in approximately half of patients. Moreover, consolidation RT in those with focal residual PET positivity, guaranteed excellent prognosis (17/17 cured) and has to be recommended as a valid option.

Marek Trněný, Irene Canales Ruiz, Maurizio Martelli, Laurie H. Sehn, et al

BASELINE TOTAL METABOLIC TUMOR VOLUME IS HIGHLY PROGNOSTIC FOR REFRACTORINESS TO IMMUNOCHEMOTHERAPY IN DLBCL: AN ANALYSIS OF THE PHASE 3 GOYA TRIAL THE PHASE 3 GOYA TRIAL

Conclusion: TMTV was determined to be the only independent prognostic factor for primary refractoriness in previously untreated patients with DLBCL, suggesting that responsiveness to immunochemotherapy is associated with tumor burden (as measured by TMTV). High TMTV was associated with very poor survival outcomes. Considering TMTV as a prognostic factor may assist in the identification of patients with high-risk disease who may benefit from an alternative therapeutic strategy.

Pieterrella Lugtenburg, Peter Brown, Bronno van der Holt, Francesco D'Amore, et al.

RITUXIMAB MAINTENANCE FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN FIRST COMPLETE REMISSION: RESULTS FROM A RANDOMIZED HOVON-NORDIC LYMPHOMA GROUP PHASE III STUDY

Conclusion: Rituximab maintenance therapy provides no additional benefit for DLBCL patients in first CR after R-CHOP.

Catherine Thieblemont, Steven Legouill, Roberta Di Blasi, Guillaume Cartron, et al.

REAL-WORLD RESULTS ON CD19 CAR T-CELL FOR 60 FRENCH PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA INCLUDED IN A TEMPORARY AUTHORIZATION FOR USE (ATU) PROGRAM

Describes the organization in the 5 authorized centres (APHP, Hôpital Saint-Louis-Paris, CHU Montpellier, CHU Nantes, CHU Lyon, CHU Lille).

Conclusion: The time elapsed between ATU validation and CAR T-cell reception remains substantial and a bridging therapy was necessary for almost all patients. The LYSA group and the CALYM institute (www.calym.org) are organizing a national registration program for these patients with clinical and biological data collection.

POSTER

Sattva S. Neelapu, Caron A. Jacobson, Olalekan O. Oluwole, Javier Munoz, et al.

AXICABTAGENE CILOLEUCEL (AXI-CEL) IN REFRACTORY LARGE B CELL LYMPHOMA: OUTCOMES IN PATIENTS ≥ OR < 65 YEARS OF AGE IN THE PIVOTAL PHASE 1/2 ZUMA-1 STUDY

Table 4. CRS and NEs by Age Group*

AE, n (%)	≥ 65 y (n = 27)		< 65 y (n = 81)		Overall† (N = 108)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
Any CRS^{b,c}	25 (93)	2 (7)	75 (93)	10 (12)	100 (93)	12 (11)
Pyrexia	23 (92)	3 (12)	60 (80)	9 (12)	83 (83)	12 (12)
Hypotension	10 (40)	2 (8)	34 (45)	8 (11)	44 (44)	10 (10)
Hypoxia	7 (28)	3 (12)	16 (21)	6 (7)	23 (23)	9 (9)
Any NE^e	21 (78)	12 (44)	51 (63)	23 (28)	72 (67)	35 (32)
Encephalopathy	12 (44)	8 (30)	28 (35)	17 (21)	40 (37)	25 (23)
Confusional state	9 (33)	2 (7)	20 (25)	8 (10)	29 (27)	10 (9)
Aphasia	4 (15)	0	15 (19)	8 (10)	19 (18)	8 (7)
Agitation	3 (11)	3 (11)	7 (9)	2 (2)	10 (9)	5 (5)
Delirium	3 (11)	3 (11)	0	0	3 (3)	3 (3)

*Events shown include those with ≥ 10% Grade ≥ 3 events in either age group
^bCRS was graded per a modified grading system proposed by Lee et al.
^cIndividual symptoms of CRS and NEs were graded per Common Terminology Criteria for Adverse Events, v 4.03.
^eAE, adverse event; CRS, cytokine release syndrome; NE, neurologic event.

- Rates of Grade ≥ 3 cytokine release syndrome and neurologic events were generally similar across age groups (Table 4)
- Numerically higher rates of some neurologic event-associated symptoms in patients ≥ 65 vs < 65 years were consistent with older age

CONCLUSIONS

- The 2-year follow-up analysis of ZUMA-1 demonstrates that axi-cel induces a high rate of durable responses with a manageable safety profile for patients ≥ and < 65 years of age
- No age-related differences in efficacy or safety were observed, suggesting that age ≥ 65 years should not be a limiting factor in axi-cel treatment decisions
- Axi-cel offers substantial clinical benefit for older patients with refractory large B cell lymphoma who otherwise have limited treatment options

Max S. Topp, Tom van Meerten, Martin Wermke, Pieternella J. Lugtenburg, et al.

AXICABTAGENE CILOLEUCEL (AXI-CEL) IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B CELL LYMPHOMA: PRELIMINARY RESULTS OF EARLIER STEROID USE

Conclusion: Early use of steroids may help in managing severe CRS and NE by potentially reducing their incidence in patients treated with CAR T cell therapy without affecting response rates. Optimizing AE management may help to further improve the benefit:risk profile of CAR T cell therapy.

Cristina Barrenetxea, Concha Alaez, Susana Herraiez, Samuel Romero, et al.

PREBEN, PIXANTRONE, RITUXIMAB, ETOPOSIDE AND BENDAMUSTINE, IN AGGRESSIVE NON-HODGKIN LYMPHOMA

Pixantrone offers an alternative for R/R DLBCL patients with efficacy and a favorable safety profile based on a phase 3 clinical trial, which permitted its approval by the EMA. In this study, pixantrone was given as a single-agent salvage therapy in pre-treated patients that did not respond to at least two previous chemotherapy regimens, either relapsed or refractory. Patients achieved good responses with low toxicity. Thirty percent of patients achieved objective responses and 20% CR and not confirmed CRs. There have been some polychemotherapy combinations with Pixantrone previously described, which obtained better global and CR rates.

Conclusion: In our series, R/R aggressive non-hodgkin lymphoma patients treated with PREBEN achieved 67% of global responses, which are higher than with other schemes in poly-treated patients. Toxicity was limited and no unexpected adverse effects were observed. Altogether, these results provide evidence that PREBEN therapy is effective and safe and encourage us to use it in elderly and young patients as a bridge-to-transplantation.

HODGKIN LYMPHOMA - CLINICAL

Thierry Leblanc, Paul Harker-Murray, Christine Mauz-Körholz, Maurizio Mascarin, et al.

NIVOLUMAB AND BRENTUXIMAB VEDOTIN-BASED, RESPONSE-ADAPTED TREATMENT IN PRIMARY REFRACTORY AND IN PEDIATRIC PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA IN CHECKMATE 744

Current first salvage therapies (tx) for younger patients (pts) with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) are associated with variable cure rates and long-term toxicities. New strategies are required, especially in primary refractory and pediatric pts. In adult R/R cHL, first salvage with nivolumab + brentuximab vedotin (BV) resulted in 82% objective response rate (ORR) with 61% complete metabolic response (CMR; Herrera et al. Blood 2018).

CheckMate 744 (NCT02927769) is an ongoing phase 2 study evaluating a risk-stratified, response-adapted approach using nivolumab, BV, and bendamustine in children, adolescents, and young adults with R/R cHL. In the standard-risk cohort, the regimen was well tolerated and resulted in high CMR rates prior to consolidation with high-dose chemotherapy and autologous transplantation (auto-HCT; Harker-Murray et al. ASH 2018).

Aims: To assess efficacy and safety of this risk-stratified, response-adapted approach in primary refractory pts, and in pediatric pts (aged <18 y) in CheckMate 744, with a focus on the nivolumab + BV induction phase.

Conclusion: Response-adapted tx with nivolumab + BV achieved high CMR rates in primary refractory patients with cHL after 4 cycles of induction. In pediatric patients with a standard risk of relapse, induction with nivolumab + BV, followed by BV + bendamustine intensification for suboptimal response, demonstrated high CMR rates and a favorable safety profile prior to consolidation.

Andrea Gallamini, David Straus, Monika Dlugosz-Danecka, Sergey Alekseev, et al.

FRONTLINE BRENTUXIMAB VEDOTIN WITH CHEMOTHERAPY FOR STAGE 3/4 CLASSICAL HODGKIN LYMPHOMA: 3-YEAR UPDATE OF THE ECHELON-1 STUDY

The phase 3 ECHELON-1 study demonstrated that brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine (A+AVD) was superior to doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), in terms of modified progression-free survival (PFS) per independent review and per investigator, for the frontline treatment of stage 3/4 classical Hodgkin lymphoma (cHL) (Connors JM, et al. N Engl J Med 2018;378: 331–344).

The RATHL, and SWOG S0816 studies utilized positron-emission tomography (PET) scan-adapted strategies performed after cycle 2 (PET2), demonstrating short- and long-term toxicities in PET2-positive (PET2+) patients switched to bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), or escalated BEACOPP, and frequent relapses in PET2-negative (PET2-) patients. Long-term follow-up of patients with stage 3/4 disease who were aged ≤60 years in the RATHL and SWOG S0816 studies demonstrated 3-year PFS of 79.8% (PET2-, 82.1%), and 5-year PFS of 74% (PET2-, 76%), respectively.

Aims: Here we present a 3-year update of the ECHELON-1 study to compare the effects of frontline A+AVD vs ABVD in patients with stage 3/4 cHL, including PFS per investigator and outcomes by PET status for the intention-to-treat (ITT) population.

Conclusion: Follow-up at 3 years demonstrates that frontline treatment of stage 3/4 cHL with A+AVD provides a durable treatment benefit compared with ABVD that is independent of PET2 status. While direct comparisons cannot be made, efficacy with A+AVD appears favorable in the context of findings with PET-adapted strategies, without requiring interim PET assessment, escalation of therapy, or bleomycin.

Michael Fuchs, Helen Goergen, Carsten Kobe, Hans Eich, et al.

PET AFTER 2 CYCLES OF ABVD IN PATIENTS WITH EARLY-STAGE FAVORABLE HODGKIN LYMPHOMA TREATED WITHIN THE PHASE 3 GHSG HD16 STUDY

Conclusion: In early-stage favorable HL, a positive PET after 2xABVD is associated with a larger tumor volume and represents a risk factor for PFS among patients treated with standard CMT, particularly when DS4 is considered as cutoff for positivity. PET-guided treatment intensification in this high-risk subgroup might help to reduce the frequency of relapses.

Hidde L.A. Posthuma, Josée M. Zijlstra, Otto Visser, Pieternella J. Lugtenburg, et al.

PRIMARY THERAPY AND SURVIVAL AMONG ADULT PATIENTS WITH NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL): A POPULATION-BASED ANALYSIS IN THE NETHERLANDS, 1993-2016

Conclusion: In this large, nationwide population-based study, survival among various **subgroups of patients with NLPHL** during a 23-year period was largely comparable to the survival of the general population. Further, we noted no improved survival after the introduction of rituximab into the therapeutic arsenal of NLPHL since 2003. Future prospective studies in NLPHL are necessary to establish evidence-based treatment recommendations that consider the delicate balance between efficacy, toxicity, and quality of life.

NOVEL AGENTS AND THERAPIES FOR CLL

Eugen Tausch, Jasmin Bahlo, Sandra Robrecht, Christof Schneider, et al

GENETIC MARKERS AND OUTCOME IN THE CLL14 TRIAL OF THE GCLLSG COMPARING FRONT LINE OBINUTUZUMAB PLUS CHLORAMBUCIL OR VENETOCLAX IN PATIENTS WITH COMORBIDITY

Conclusion: Prognostic value of genomic aberrations, IGHV and gene mutations were confirmed for G-Clb, while with Ven-G only del(17p) and TP53mut were associated with short PFS and only del(17p) with short OS. Unmutated IGHV was identified as a predictive factor characterizing a group of patients with particular benefit from Ven-G.

Othman Al-Sawaf, Esther Liliënweiss, Jasmin Bahlo, Sandra Robrecht, et al.

HIGH EFFICACY OF VENETOCLAX PLUS OBINUTUZUMAB IN PATIENTS WITH COMPLEX KARYOTYPE (CKT) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PROSPECTIVE ANALYSIS FROM THE CLL14 TRIAL

Conclusion: CKT can be frequently observed in older, treatment-naïve CLL patients. While CKT correlates well with CLL-IPI high/very high risk, 2/3 of these patients do not show TP53 aberrations. Presence of CKT in patients treated with ClbG is associated with shorter PFS and OS, including patients without TP53 aberrations. In contrast, VenG is able to overcome the adverse risk associated with CKT. These findings support the clinical importance of chromosome analysis before choosing frontline therapy, and underline the particular value of VenG in CLL CKT patients.

Alessandra Tedeschi, Jan Burger, Paul M. Barr, Tadeusz Robak, et al.

FIVE-YEAR FOLLOW-UP OF PATIENTS RECEIVING IBRUTINIB FOR FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

Conclusion: Single-agent ibr had sustained PFS and OS benefit, including for patients with high-risk genomic features, in the longest follow-up to date from a phase 3 study of first-line BTK-directed therapy. Responses to ibr improved over time with nearly three-fold more patients achieving CR/CRi with long term follow up. With up to 66 months follow up, more than half of patients remain on long-term continuous ibr treatment. No new safety signals emerged.

Arnon P Kater, Julie Dubois, Sabina Kersting, Lisbeth Enggaard, et al.

SAFETY ANALYSIS OF VENETOCLAX AND IBRUTINIB FOR PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (R/R CLL): SECOND INTERIM ANALYSIS FROM THE PHASE II VISION HO141 TRIAL

Conclusion: Treatment with ibrutinib and venetoclax in the setting of R/R CLL shows a favorable benefit-risk profile and a complete remission in 61% of patients after 9 cycles of treatment with an increasing uMRD rate to 52% after one year of treatment. The DSMB recommends continuing of the study.

Tanya Siddiqi, Kathleen Dorritie, Jacob Soumerai, Deborah Stephens, et al.

TRANSCEND CLL 004: MINIMAL RESIDUAL DISEASE NEGATIVE RESPONSES AFTER LISOCABTAGENE MARALEUCEL (LISO-CEL) IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA

Conclusion: In this study of heavily pretreated patients with standard- and high-risk CLL/SLL and previous ibrutinib treatment, liso-cel-related toxicities (ie, CRS and NEs) were manageable. Patients rapidly achieved CR/CRi and uMRD. The phase 2 component of the study is currently enrolling patients for treatment at dose level 2. Additional follow-up will be presented.

POSTER PITCH

Jenny Wu, Christopher Bolen, John F Seymour, Peter Hillmen, et al.

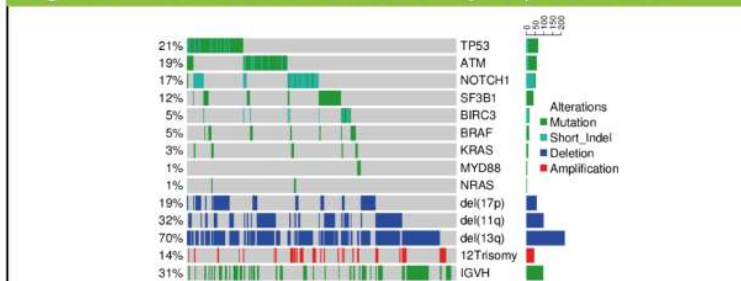
IMPACT OF MAJOR GENOMIC ALTERATIONS ON OUTCOME OF RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED WITH VENETOCLAX PLUS RITUXIMAB IN THE PHASE 3 MURANO STUDY

RESULTS

Genomic profile and characteristics

- Cytogenetics and mutational clone sizes were well balanced between treatment arms.
- All 313 patients had non-silent, deleterious mutations (range 25–205; mean 47 deleterious mutations per patient); approximate mean 0.97 ± 0.3 mutations per megabase (0.5–4.3).
- Of the 9 most frequently mutated genes examined, ≥ 1 frequent mutation was identified in 202/313 (65%) patients from both arms; and 69/313 (22%) patients harboured ≥ 2 frequent mutations.
- Frequency and distribution of mutations in key frequent mutations, genomic alterations and IGVH status are shown in **Figure 2**.

Figure 2. Incidence and distribution of key frequent mutations



Conclusion: We assessed the mutational landscape of R/R CLL by WES and confirmed prior mutation frequency reports.

A superior PFS benefit was observed for VenR vs BR in all clinical and molecular subgroups assessed, including the key CLL driver mutations reported here. NOTCH1 mutations may define a new high-risk pt subgroup for VenR. MVA, further validation and deep sequencing for subclones are needed, given the small size of the mutated cohort, and to address the biological basis of the findings.

POSTER

Richard Greil, Graeme Fraser, Brian Leber, Reinhard Marks, et al.

EFFICACY AND SAFETY OF IBRUTINIB IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS PREVIOUSLY TREATED WITH VENETOCLAX IN THE MURANO STUDY

Conclusion: IBR demonstrated an acceptable tolerability profile with no new safety signals as well as good clinical activity in this series of R/R CLL patients who received IBR following VenR treatment in MURANO. IBR treatment, therefore, seems an acceptable option for patients with CLL who relapse following VenR.

More data will be gathered from the MURANO study for patients treated with VenR who progress and subsequently receive treatment with IBR.

- 4 patients had IBR dose modification or interruption due to neutropaenia (n=2), clarithromycin treatment (n=1), or cutaneous nevus biopsy (n=1).
- A list of adverse events seen with IBR is provided in **Table 2**; no instances of major bleeding were reported.
- To date, all patients are still alive.

Table 2. Safety profile for IBR

Adverse event	n (%)
Arthralgia*	2 (25.0)
Atrial fibrillation	2 (25.0)
Neutropaenia	2 (25.0)
Pneumonia†	1 (12.5)
Skin abscess‡	1 (12.5)

*1 case almost resolved on follow-up; †Without hospitalisation; ‡Multiple skin abscesses reported.

Farrukh Awan, Rebecca Chan, Lin Gu, Guan Xing, et al.

TREATMENT EMERGENT ADVERSE EVENTS VARY WITH DIFFERENT PI3K INHIBITORS

INTRODUCTION

- Idelalisib (IDELA) is a daily oral PI3Kδ inhibitor approved in both the United States and the European Union as a monotherapy for relapsed or refractory (R/R) follicular lymphoma and in combination with anti-CD20 for R/R chronic lymphocytic leukemia (CLL).
- Duvelisib (DUVA), a daily oral PI3Kδ/γ inhibitor, is approved in the United States for both R/R follicular lymphoma and R/R CLL.
- Copanlisib (COPA) is an intravenous PI3Kδ/α inhibitor approved in the United States for R/R follicular lymphoma and is administered once a week using a 3 weeks on, 1 week off schedule.
- These drugs demonstrate comparable efficacy; therefore, route of administration, dosing schedule, and anticipated treatment emergent adverse events (TEAEs) are important considerations in guiding selection of PI3Kδ inhibitor therapy.

OBJECTIVES

To compare the safety profiles of IDELA vs. COPA and IDELA vs. DUVA and to evaluate the effect of pre-existing conditions on IDELA-induced TEAEs.

RESULTS

Table 2A. TEAEs or Lab Abnormalities in IDELA- vs. COPA-Treated Patients.

IDELA mDOT = 27 wks COPA mDOT = 22 – 26 wks TEAE or Lab Abnormality	aGr			Gr3/4		
	IDELA N=163 n (%)	COPA N=142 or 168 n (%)	P-Value	IDELA N=163 n (%)	COPA N=142 or 168 n (%)	P-Value
Colitis	7 (4.3)	1 (0.7)	0.0719	4 (2.5)	1 (0.7)	0.3769
Diarrhea	77 (47.2)	60 (35.7)	0.0347	22 (13.5)	8 (4.8)	0.0068
Fatigue	51 (31.3)	37 (26.1)	0.3753	2 (1.2)	3 (2.1)	0.6667
Hyperglycemia	11 (6.7)	90 (53.6)	<.0001	2 (1.2)	66 (39.3)	<.0001
Hypertension	9 (5.5)	59 (35.1)	<.0001	2 (1.2)	46 (27.4)	<.0001
Infection (multiple preferred terms)	24 (14.7)	35 (20.8)	0.1539	17 (10.4)	23 (13.7)	0.4018
Nausea	51 (31.3)	43 (25.6)	0.2737	3 (1.8)	1 (0.6)	0.3653
Neutropenia (including febrile neutropenia)	44 (27)	53 (31.5)	0.3987	35 (21.5)	42 (25)	0.5156
Pneumonitis	7 (4.3)	11 (7.7)	0.2297	4 (2.5)	2 (1.4)	0.6889
Pyrexia	54 (33.1)	38 (26.8)	0.2608	4 (2.5)	6 (4.2)	0.5228
Rash (including exfoliative skin reactions)	35 (21.5)	26 (15.5)	0.2017	4 (2.5)	3 (1.8)	0.7200
Thrombocytopenia	28 (17.2)	20 (14.1)	0.5293	8 (4.9)	7 (4.9)	1.0000
Increased AST (lab parameter)	71 (43.6)	39 (27.7)	0.0042	21 (12.9)	2 (1.4)	0.0001
Increased ALT (lab parameter)	85 (52.1)	32 (22.7)	<.0001	29 (17.8)	2 (1.4)	<.0001

Table 2B. TEAEs or Lab Abnormalities in IDELA- vs. DUVA-Treated Patients.

IDELA mDOT = 28.1 wks DUVA mDOT = 39.1 wks TEAE or Lab Abnormality	aGr			Gr>3		
	IDELA N=261 n (%)	DUVA N=442 n (%)	P-Value	IDELA N=261 n (%)	DUVA N=442 n (%)	P-Value
Anemia (lab parameter)	84 (32.2)	198 (44.8)	0.0011	13 (5.0)	66 (14.9)	<.0001
Arthralgia	17 (6.5)	46 (10.4)	0.1004	0	1 (0.2)	1.0000
Constipation	27 (10.3)	57 (12.9)	0.3377	0	1 (0.2)	1.0000
Cough	80 (30.7)	111 (25.1)	0.1115	4 (1.5)	2 (0.5)	0.2019
Diarrhea or colitis	109 (41.8)	222 (50.2)	0.0347	30 (11.5)	101 (22.9)	0.0002
Dyspnea	36 (13.8)	52 (11.8)	0.4793	7 (2.7)	8 (1.8)	0.4325
Fatigue	88 (33.7)	126 (28.5)	0.1503	5 (1.9)	22 (5.0)	0.0433
Lower respiratory tract infection	4 (1.5)	46 (10.4)	<.0001	1 (0.4)	11 (2.5)	0.0381
Mucositis	0	61 (13.8)	<.0001	0	6 (1.4)	0.0897
Musculoskeletal pain	10 (3.8)	90 (20.4)	<.0001	1 (0.4)	6 (1.4)	0.2681
Nausea	68 (26.1)	104 (23.5)	0.4683	3 (1.1)	4 (0.9)	0.7146
Neutropenia (lab parameter)	138 (52.9)	276 (62.4)	0.0140	74 (28.4)	184 (41.6)	0.0005
Pneumonia (multiple preferred terms)	47 (18.0)	91 (20.6)	0.4328	41 (15.7)	67 (15.2)	0.9138
Pneumonitis	10 (3.8)	22 (5.0)	0.5761	6 (2.3)	NA*	N/A**
Rash (multiple preferred terms)	70 (26.8)	136 (30.8)	0.3035	8 (3.1)	41 (9.3)	0.0019
Thrombocytopenia (lab parameter)	75 (28.7)	170 (38.5)	0.0089	27 (10.3)	65 (14.7)	0.1059
Increased AST (lab parameter)	108 (41.4)	163 (36.9)	0.2616	32 (12.3)	24 (5.4)	0.0022
Increased ALT (lab parameter)	114 (43.7)	177 (40)	0.3834	41 (15.7)	34 (7.7)	0.0014

*NA = not available; **N/A = not applicable.

Conclusion: Although the approved PI3K δ inhibitors may be perceived to be associated with synonymous AE profiles (“class effect”), this intra-class comparison highlights specific AE risks associated with each compound. The potential emergence of specific AEs associated with each agent should be considered when selecting a PI3K δ inhibitor, though drug exposure differences and major limitations of cross-trial comparisons should be noted.

GENE THERAPY, CELLULAR IMMUNOTHERAPY AND VACCINATION - CLINICAL

M. LIA PALOMBA, CONNIE BATLEVI, ISABELLE RIVIERE, BRIGITTE SENECHAL, ET AL.

A PHASE I FIRST-IN-HUMAN CLINICAL TRIAL OF CD19-TARGETED 19-28Z/4-1BBL "ARMORED" CAR T CELLS IN PATIENTS WITH RELAPSED OR REFRACTORY NHL AND CLL INCLUDING RICHTER TRANSFORMATION

Conclusion: Treatment with 19-28z/41BBL armored CAR T cells is safe. No severe CRS was observed and severe NTX occurred in 8% of the patients. The overall CR rate of 57% is encouraging, CR rates were higher in patients with large cell lymphoma (78%) compared to CLL (20%), though small number of patients limits any firm conclusions.

Patients with CLL may require higher doses of CAR T cells or incorporation of the CAR therapy in earlier lines of treatments. Detailed cytokine and CAR T cell expansion analysis as well as updated data will be presented.

POSTER

SURBHI SIDANA, AMYLOU DUECK, MICHELLE BURTIS, JOAN GRIFFIN, ET AL.

QUALITY OF LIFE IN PATIENTS UNDERGOING CHIMERIC ANTIGEN RECEPTOR (CAR) - T CELL THERAPY VS. AUTOLOGOUS AND ALLOGENEIC STEM CELL TRANSPLANT FOR HEMATOLOGIC MALIGNANCIES

The overall goal of our study is to evaluate quality of life and symptom burden over time in patients receiving CAR-T cell therapy and compare them to that of prospective cohorts of patients undergoing autologous and allogeneic SCT for hematologic malignancies.

Conclusion: Preliminary data show that patients undergoing CAR-T cell therapy do not experience a more significant dip in QOL compared with autologous and allogeneic SCT, with some indication of better PWB in the short-term. Accrual & follow-up are ongoing. Updated results, including 3-month follow up will be presented at the meeting.