



15-ICML International Conference on Malignant Lymphoma



Selection of sessions 15-ICML

July 2019



THIS IS A SELECTION OF LYMPHOMA NEWS, PATIENT ADVOCACY AND/OR POLICY RELATED TOPICS PRESENTED AT THE 15 INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA THAT TOOK PLACE IN LUGANO, FROM JUNE 18 TO JUNE 22

THE SUMMARIES ARE TAKEN FROM THE ABSTRACTS AND MATERIALS AVAILABLE ON THE ICML WEBSITE

FOR ANY QUESTION PLEASE GET IN TOUCH:

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Introduction

The International Conference on Malignant Lymphoma (ICML) has become, since its first edition in 1981, a must-attend event for the scientific community involved in the study and treatment of lymphoid neoplasms.

This year, the 15th International Conference on Malignant Lymphoma (ICML) was held in Lugano, Switzerland, from 18 – 22 June 2019. ICML 2019 gathered almost 3'800 professionals in lymphoma from all over the world: haematologists, clinical oncologists, radiation oncologists, paediatricians, pathologists and leading researchers involved in the study and treatment of lymphoid neoplasms, to discuss the cutting-edge updates from hot topics across lymphoma disciplines.

Highlights covered chemo-free regimens, the latest trial data, and CAR T-cell discussions. The diseases explored included Hodgkin lymphoma and non-Hodgkin lymphoma, including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL). Chronic lymphocytic leukemia (CLL) was also a focus of the meeting.

There was also space to discuss about the high prices of innovative drugs.

- The conference Program Book, with detailed program, maps and all information about the conference, was distributed onsite to all attendees and it can be downloaded [here](#).
- The 15-ICML Educational Book can be accessed [here](#).
- The 15-ICML Abstract Book can be accessed here. It is also possible to download the supplement [here](#).
- Access the Posters of the International Conference on Malignant Lymphoma 15-ICML https://www.postersessiononline.eu/pr/aula_poster.asp?congreso=869655787
- You can also find several videos (filmed presentations) and podcasts [here](#)



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Take home messages

- There was a workshop on bridging liquid biopsy into the management of patients with lymphoma. The conclusions are that the technique for liquid Biopsy will be different depending on what you want to discover but it clearly provides an important new strategy that will aid in the treatment of lymphoma. Immunoglobulin sequencing provides a tumor specific marker for disease activity. Furthermore, it can provide an estimate of tumor bulk and tumor response dynamics during treatment. Interim monitoring can identify patients at high risk of treatment failure and surveillance monitoring can identify patients months before radiographic disease progression. Tumor specific mutations can also be detected and may reflect an averaging of mutations present within multiple tumor masses. Such analysis may aid in the molecular characterization of tumors and selection of targeted treatments for precision medicine.
- CART work continues as need to know more on how to choose right patients and overcoming relapse and prevent severe adverse effects.
- Genetic differences identified in DLBCL have prognostic implications and lead to substantial variations in clinical course and response to therapy - it is not a cats basket anymore. This differences can also enable the molecular classification of DLBCL into specific subtypes.
- Mantle cell Lymphoma - always a model to lymphoproliferative neoplasias: Patients with many comorbidities and transplant ineligible could benefit most from ibrutinib plus rituximab in the front-line setting (a chemo-free regimen).
- Response-oriented maintenance based on MRD and PET is feasible in patients with follicular lymphoma (preliminary analysis, more evidence needs to be gathered).
- RCHOP continues being the best option for DLBCL as other studies results don't show significant benefit to change progression free survival (particularly the ROBUST study adding Lenalidomide to RCHOP regimen). Maintenance therapy benefit is still an unmet need as current evidence do not support its incorporation in clinical practice.
- Diffuse Large B Cell Lymphoma 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.
- One of the key events was the first Lymphoma Hub's symposium, with 4 experts discussing on different lymphoma and CLL entities the prospects of chemo-free regimens. Slides of this event are available at:
 Professor Ulrich Jäger <https://www.youtube.com/watch?v=OpRJ0IAHzg0>
 Professor Michael Hallek <https://www.youtube.com/watch?v=QPxlx2mhM0Y>
 Professor Nathan Fowler <https://www.youtube.com/watch?v=EknzAJxSMio&t=2s>
 Professor Simon Rule <https://www.youtube.com/watch?v=BKNHs9Km-j4>
- Last but not least, high price of medicines occupied a relevant space in the conference, with one lecture and one big debate.

I hope you find this summary useful, especially to those who could not attend the congress!

VINCENT RAJKUMAR ON THE HIGH PRICE OF CANCER DRUGS

The ICML included very inspiring presentations on the topic of the high price of cancer drugs

Can a life-saving drug be too expensive?

Dr. Vincent Rajkumar of the Mayo Clinic talks about the high price of cancer drugs--drugs that can cost much more than \$300,000 per year and require multiple years of treatment. Rajkumar explains how little a role market forces play in setting prices and what might be done to improve the situation.

Every single drug is expensive, referring to newer approved myeloma therapies that cost up to \$192,000/year individually, and up to \$590,000/year in triplet or quadruplet combination regimens, according to estimates.

Research shows medical bankruptcies are not associated with drug copayments, he added, but rather other medical expenses, such as hospital and physician bills, along with loss of income and limited savings.



Dr. Rajkumar urged action on several fronts, including value-based pricing or tying the price of a drug to how much value it produces.

How to lower the cost of cancer drugs to make them more affordable and accessible to patients in the U.S. and around the world? Dr. Rajkumar cites the following reasons for the high cost of cancer drugs:

1. A monopolistic nature to drug innovation (although he feels that pharmaceutical companies are not to be blamed for this).
2. Medicare is not able to negotiate directly with drug companies.
3. The U.S. does not allow drugs to be imported.
4. There are barriers to generic competitors entering the market.

Dr. Rajkumar then proposes the following solutions among others:

1. Allow Medicare to directly negotiate for the price of new drugs.
2. Allow personal importation of cancer drugs to patients with prescriptions for such drugs.
3. Allow easy entry of generic drugs into the U.S. (in a manner that doesn't stifle innovation).



MAYO CLINIC

What we say matters

Drug	Zoledronic Acid	Denosumab
ASP	60	2150

Be careful with words like "Standard of Care"

F. CAVALLI

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2. Conduct Strategic Trials

- Modified Dosing: to reduce cost
 - SAKK 39/16 OptiPOM Trial
 - Thilo Zander
- Limited Duration Therapy

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3. Facilitate easy entry of generics & biosimilars

Generic Competition and Drug Prices

Number of Generic Manufacturers	Average Relative Price Per Dose
1	100%
2	52%
3	44%
4	39%
5	33%
6	28%
7	23%
8	21%
9	20%
10	20%
11	22%
12	20%
13	24%
14	16%
15	13%
16	11%
17	9%
18	8%
19	5%

<https://georgevanantwerp.com/2010/11/18/how-generic-prices-drop-with-number-of-manufacturers/>

F. CAVALLI

HEALTH AFFAIRS BLOG

RELATED TOPICS: PHARMACEUTICALS | FDA APPROVALS PROCESS | DRUG PRICING | PRESCRIPTION DRUGS | MARKETS | PHARMACEUTICAL INDUSTRY | PHARMACEUTICAL PATENTS | PHARMACEUTICAL INNOVATION | PHARMACEUTICAL RESEARCH AND DEVELOPMENT | PHARMACEUTICAL MARKETING | PHARMACEUTICAL SALES | PHARMACEUTICAL DISTRIBUTION | PHARMACEUTICAL REGULATION | PHARMACEUTICAL POLICY | PHARMACEUTICAL ECONOMICS | PHARMACEUTICAL HISTORY | PHARMACEUTICAL FUTURE

Policy Options For Increasing Generic Drug Competition Through Importation

Matthew Cohen, Ravi Gupta, Thomas J. Bolyky, Joseph S. Ross, Aaron S. Kesselheim

JANUARY 7, 2019

10.1377/hblog20190103.333047

F. CAVALLI

Are new and expensive anti-lymphoma drugs worth the money?

A SELECTION OF SLIDES



Are BCR pathway inhibitors worthwhile the money?

No rumble in the jungle!

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KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK III

S. RULE | G. SALLES | A. SUREDA | L.H. SEHN | M. GHELMINI

PATIENT AND PHYSICIAN TREATMENT "COSTS"

Patient goals: Quality of life, Few side-effects, High efficacy

Physician goals: High response rate, Long remission, Low toxicity

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HEALTH SYSTEM/ SOCIETY'S TREATMENT "COSTS"

- Inward treatment vs. „once daily a pill“
- patient's working hours
- GB/NICE: Rituximab monotherapy registered not on PFS, OS, but „social productivity“

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Are BCR pathway inhibitors worthwhile the money?

- ✓ Patient's „cost“
- ✓ Health system: inward vs. once daily a pill
- ✓ pricing reasonable considering the benefit
- ✓ Patient's productivity

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Incremental cost-effectiveness ratio (ICER)

The difference in cost between two possible interventions, divided by the difference in their effect.

$$ICER = \frac{(C_1 - C_0)}{(E_1 - E_0)}$$

- ICER for ibrutinib over R-chemo €62,650
- €49,849 per QALY if used at first recurrence (just at NICE threshold for end of life)

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Can we afford this?
(the pound is rubbish so lets say £1+\$1+€1+1CHF)

Median net annual income in EU = €17,032

Ibrutinib monthly cost for MCL = €6,132

If median exposure 11.1 months cost per patient = €61,933

Longest patient on continuous therapy 76.9 months = **€477,069**

I guess we can do a 10 hip replacements a year for €1,933..think about the Quality of life improvement there...

Pay for 25 of the 18,000 pacemakers the NHS inserts every year

Or the cost of 350 emergency ambulance call outs

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Now this is getting economically crazy

phase 2 study of daily oral ibrutinib and venetoclax in patients with MCL (n=28)

After a median follow-up of 15.9 months, the median progression-free survival had not been reached

mCR ≥62% at week 16.

MRD clearance (flow) was 67% ; ASO-PCR in 38%

Yon et al. NEJM 2018

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Vote with me..NO

- So whilst your individual territory may be able to shoulder the burden, the societal costs are massive.
- Think about impact upon other healthcare needs. There is a limit to any budget.
- There are effective alternatives
- We need to encourage better design of clinical trials, with comparators that represent true practice.

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Cost - Thalidomide 100mg

- 2003 - Comparable with statin (approx. £30/month)
- 2019 - £596.96 + VAT / month

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Are new expensive anti-lymphoma drugs worth the money?

IMID's = NO

Gilles SALLES

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In Conclusion ...

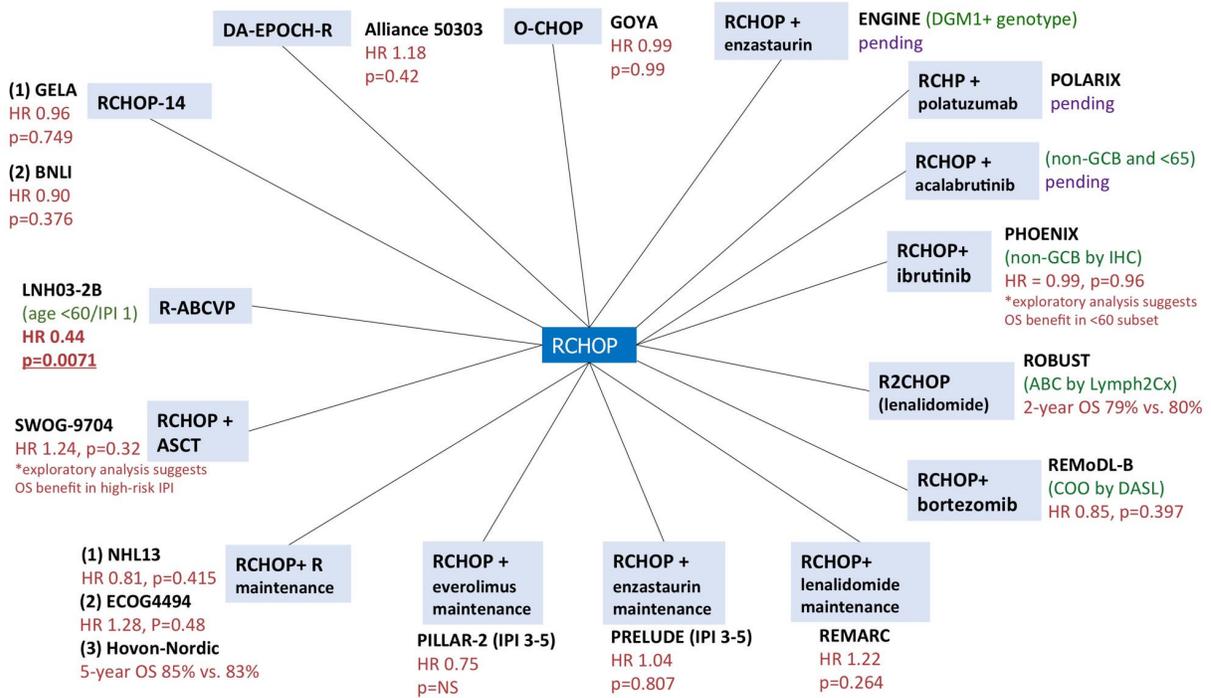
- CART cell therapy is an expensive therapy but ...
 - Effective in a population of patients with RR DLBCL with a huge need of new approaches; more follow up is needed
 - One shot therapy
 - Acceptable toxicity profile
 - Need to identify the adequate candidates for this procedure
- New molecules, ADC strategies, bi-specific MoAb:
 - Promising results
 - Not devoid of side effects
 - In some cases, treatment until relapse / toxicity
 - Unknown price so far ...

Institut Català d'Oncologia

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Pivotal phase III trials over the last 20 years (HRs for OS comparison of challengers vs RCHOP21)

RCHOP in DLBCL remains the standard



The modern approach to mantle cell lymphoma -S.Rule

Mantle Cell Lymphoma is a rare and generally aggressive form of non-Hodgkin lymphoma. Our understanding of the pathophysiology of this disease is improving and whilst risk factors are understood, treatments are not yet tailored towards these. The treatment algorithm in the front line is well established for older and younger patients and observation is the norm for a subset of patients although these are not well characterised as yet.

In the relapse setting the role of novel agents, especially the BTK inhibitors is becoming established and combination approaches look promising. Trials are beginning to challenge the role of chemotherapy against the novel agents especially as part of front line therapy. As a consequence it is likely we will see a paradigm shift in the management of this disease in the next few years.

Table of Various Treatment for R/R MCL

Treatment	Study or Literature Reference	N	ORR	CR	Median DOR (months)	Median PFS (months)	Median OS (months)
Ibrutinib	PCYC-1104-CA	111	68%	21%	17.5	13.9	Not reached
Bortezomib	Fischer 2006	155 ^a	33%	8%	9.2	6.5	23.5
Lenalidomide	Goy 2009	134	28%	8%	16.6	4.0	19.0
Temsirolimus ^b	Hess 2009	54	22%	2%	7.1	4.8	12.8
Acalabrutinib	Wang 2017	124	81%	40%	Not reached	Not reached	Not reached

CR=complete response; DOR= duration of response; ORR=overall response rate; OS=overall survival;
PFS= progression-free survival.
^a Of the 155 patients enrolled, 141 were assessable for response.
^b Results are presented for temsirolimus 175/75 mg dose group.

Summary of non intensive induction regimens*

	N	Age	ORR	CR	mPFS
R-CHOP	244	66	89%	42% (CT)	14.4 mo
VR-CAP	243	65	92%	53% (CT)	24.7 mo
BR**	188	70	~90%	~45% (CT)	35-48 mo
RBAC500	57	71	91%	91% (PET)	Not reached

*no maintenance therapy
**pooled data from 3 trials

- Summary**
- Treat when clinically indicated
 - Young patients
 - Cytarabine is the key drug
 - What you add to it is not clear
 - Older patients
 - CHOP or Bendamustine based treatment appropriate
 - New agents are rapidly moving into the front line
 - Likely to be part of the standard of care soon
 - Clinical trials are how we improve outcomes

Learn more: <https://onlinelibrary.wiley.com/doi/full/10.1002/hon.2596>

HOW TO APPROACH CLL IN CLINICAL PRACTICE -M.Hallek

The management of patients with CLL has undergone profound changes and led to an improved outcome of patients over the last 20 years. This development was initiated when it was shown that the addition of CD20 antibodies to chemotherapy as initial therapy of CLL created a survival benefit for CLL patients. More recently, the advent of targeted agents such as ibrutinib, idelalisib, or venetoclax, has further increased our therapeutic armamentarium for CLL. Initially, kinase inhibitors and venetoclax were shown to specifically improve the outcome for patients with TP53 dysfunction or at relapse. During the last months, large phase III trial results also demonstrated a benefit of these agents for first line CLL therapy. Finally, CAR-T cells are also effective therapies for some CLL patients, although their definitive value remains to be determined.

With the many potent options available for first-line treatment of CLL, a number of factors need to be considered in clinical decision-making. They are mostly defined by potential side effects of novel agents. These factors include comorbidities (e.g. cardiomyopathies, arrhythmia, renal failure), comedication (e.g. CYP inhibitors, anticoagulants), individual preference (time limited vs indefinite treatment) but also economic considerations. Despite its efficacy and widespread use, indefinite ibrutinib monotherapy of CLL patients comes with essential drawbacks: an increased financial burden, need for frequent controls under therapy, relatively high rates of cardiac arrhythmias as well as resistance mutations and rapid relapses after discontinuation of the drug in some cases. Therefore, it appears highly important to create fixed-duration combination therapies with venetoclax, ibrutinib, and/or obinutuzumab that aim to achieve MRD-negative, durable responses while being safe and tolerable. Results from the phase III FLAIR, CLL13, and CLL14 trials are awaited to move this concept into the first-line treatment.

First line treatment of CLL, in 2019

Stage	Fitness	del (17p) or p53mut	IGVH	Therapy
Binet A-B, rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or rai III-IV	Go go	No	M	FCR (BR above 65 y) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 y)*
	Slow go	No	Irrelevant	Ibrutinib, venetoclax or idelalisib + rituximab (if contraindications for ibrutinib)
			M	Chlorambucil + obinutuzumab or ibrutinib*
	Yes	Yes	U	Ibrutinib or Chlorambucil + obinutuzumab*
			Irrelevant	Ibrutinib or venetoclax (+ obinutuzumab) or idelalisib + rituximab (if contraindications for ibrutinib)

* Consider and discuss with patient: long-term vs fixed (6 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies [?] for CIT; cardiac toxicity, bleeding, and autoimmune disease for Ibru).

Second line treatment of CLL in 2019

Response to 1-L therapy	Fitness	Therapy
Refractory or progress within 3 y	Go go	Change to one of the following options: ibrutinib, idelalisib + R, venetoclax + rituximab, FA, FCR (after BR), venetoclax, Alemtuzumab plus - dexamethasone, lenalidomide (+ R), BR (after FCR). Discuss consolidation with allogeneic SCT.
	Slow go	Change to one of the following options: ibrutinib, idelalisib + R, venetoclax (+rituximab), Alemtuzumab, FCR-lite, BR, lenalidomide (+R), ofatumumab, HD R
Progress after 3 y	All	Repetition of 1-L therapy is possible.

The management of CLL is undergoing dynamic changes. Targeted drugs such as obinutuzumab, ibrutinib, idelalisib, or venetoclax when used in combination or additional, new agents will further improve the treatment options for CLL patients. Therefore, in order to learn how to optimize our current therapeutic strategies we should continue to include our patients into clinical trials.

Learn more: <https://onlinelibrary.wiley.com/doi/10.1002/hon.2583>

SUCCESS OF VENETOCLAX AND OBINUTUZUMAB USE IN PATIENTS WITH CLL TREATMENT

It was discussed the efficacy of venetoclax and obinutuzumab in treating patients with chronic lymphocytic leukemia (CLL). The focus was on how to use such treatment as a first-line therapy in patients with CLL and co-existing conditions.

Venetoclax is a selective inhibitor of BCL2, a protein responsible for regulating cell death that is overexpressed in CLL cells. By inhibiting this protein, venetoclax functions to rapidly induce apoptosis in these malignant cells. Obinutuzumab is an anti-CD20 monoclonal antibody that can bind and destroy CLL cells.

With pre-clinical data suggesting a maximal additive effect for venetoclax when used in concert with obinutuzumab, this study was conducted to test the efficacy of such treatment in elderly patients with previously untreated CLL. Current treatments for CLL patients are continuous and indefinite targeted therapy or fixed duration chemoimmunotherapy. Venetoclax-obinutuzumab treatment presents as a new fixed duration targeted treatment regimen that could potentially bolster CLL care.

This CLL14 study was created by the German CLL Study Group to evaluate a non-chemotherapeutic fixed-duration treatment consisting of venetoclax and obinutuzumab. The efficacy of this treatment was compared to that of a standard chemoimmunotherapy treatment with chlorambucil and obinutuzumab in untreated patients with CLL and other comorbidities.

Data on minimal residual disease (MRD) from the CLL14 study:

It was found that the use of venetoclax and obinutuzumab yielded better outcomes than chlorambucil and obinutuzumab did regarding progression free survival. 88% of the patients treated with venetoclax-obinutuzumab showed no disease progression two years after treatment, compared to only 64% of those treated with chlorambucil-obinutuzumab.

In addition, 76% of the patients treated with venetoclax-obinutuzumab showed no MRD in the blood three months after treatment, compared to 35% in the standard group.

The researchers concluded that venetoclax–obinutuzumab fixed-duration targeted therapy can safely be used in elderly CLL patients with co-existing conditions. Such treatment was superior to chlorambucil-obinutuzumab treatment in progression free survival, overall response rate, complete response rate, MRD negative responses, and in all relevant subgroups including IGVH unmutated, del(17p) or TP53 mutated patients. The team also noted that venetoclax–obinutuzumab treatment could present as an alternative to continuous indefinite BTK inhibitor treatment.

This approach yielded the highest rate of MRD negative results observed in a such a study thus far.

NEW DATA ON T-CELL AND OTHER LYMPHOMAS

M. Federico, Modena (Italy), et al.

THE RELEVANCE OF OBSERVATIONAL REGISTRIES: THE CASE OF T CELL LYMPHOMA PROJECTS 1.0 AND 2.0

The T-Cell Project (TCP; NCT01142674), is an academic effort sponsored by the International T-Cell Lymphoma Project (ITCLP), was set up in 2006, and builds on the retrospective study carried on by the network.

Many lessons come from this project: 1) the risk of incorrect diagnostic classification is high, with the consequence need to find reliable tools, specific markers and objective criteria to improve accuracy in the routinely diagnostic work-up for these entities; 2) the outcome of PTCL continues to be dismal in the majority of cases and no improvement was found in OS in the majority of subtypes, compared to older series; 3) treatment remains challenging and new therapies are welcome. Moreover, this project allowed to build a new prognostic model for patients with PCTL-NOS, based on advanced stage, poor ECOG-PS, low serum albumin level and elevated absolute neutrophil counts.

Recently, several new findings have contributed to further understanding of biological, clinical, and therapeutic aspects of PTCLs. Thus, the International T-cell non-Hodgkin's Lymphoma Study Group recently launched the T-cell Project 2.0, being again a prospective, longitudinal, international, observational study of patients with PTCLs. This study adapts to changes made in diagnosis, classification, staging and response evaluation, in order to have a contemporary, real-time understanding of the evolving landscape of T-cell lymphoma biology and treatment, together with the application of contemporary technologies to further identify of new therapeutic targets. A final accrual of 1,000 cases has been planned. At present, 60 Institutions from 18 different countries already joined the project. So far, 151 patients have been registered by 25 active sites, 34% of whom with diagnosis of PTCL-NOS.

Conclusion: A final accrual of 1,000 cases has been planned. At present, 60 Institutions from 18 different countries already joined the project. So far, 151 patients have been registered by 25 active sites, 34% of whom with diagnosis of PTCL-NOS.

NEW DRUG COMBINATIONS - DLBCL

G. Salles, Lyon (France), et al.

PRIMARY ANALYSIS RESULTS OF THE SINGLE-ARM PHASE II STUDY OF MOR208 PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (L-MIND)

A chemotherapy-free combination of lenalidomide and the novel anti-CD19 antibody tafasitamab (MOR208) continues to show encouraging clinical activity against relapsed/refractory DLBCL, with durable responses and promising progression-free and overall survival.

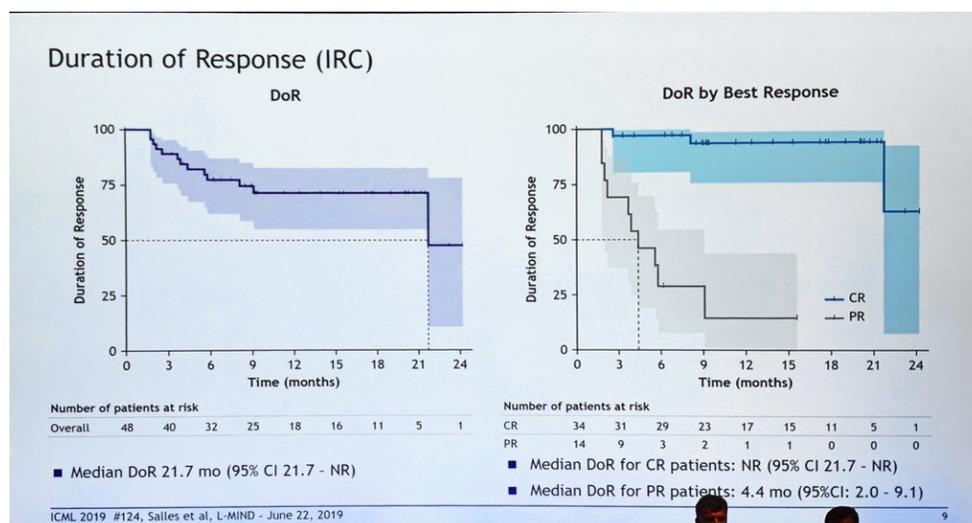
After a median follow-up of 17.3 months, the overall response rate (ORR) – the primary endpoint in the single arm trial – was 60%, consisting of 42.5% complete responses (CR) and 17.5% partial responses (PR). There is consistently high activity in transplant-ineligible subgroups, patients who have limited treatment options and who have really poor prognosis.

The median duration of response in the entire cohort was 21.7 months. For patients with a CR, the median duration of response had not been reached at the time of data cutoff. For patients with a PR, the median duration of response was 4.4 months.

- Hematologic treatment-emergent toxicities occurring in 10% or more of patients included (in descending order of frequency) neutropenia, anemia, thrombocytopenia, leukopenia, and febrile neutropenia.
- Non-hematologic treatment-emergent events occurring in at least 10% of patients included diarrhea, asthenia, peripheral edema, pyrexia, rash, decreased appetite, hypokalemia, fatigue, and similar events, the majority of which were grade 1 or 2 in severity.

Conclusion: The combination of MOR208 and LEN was well tolerated and has shown encouraging activity and long lasting responses in pts with R-R DLBCL, who have poor prognosis and urgently need effective therapies.

The durable responses and favorable overall survival I would say represent a remarkable outcome, and this combination of lenalidomide with tafasitamab results in a new chemo-free immunotherapy for patients with relapsed/refractory DLBCL.



MOR208+ Len data... key point not overtly expressed that probably should have been. mDOR for patients in PR is ~2x that in ZUMA-1 (4.4 mo vs 1.9 mo).

Scientific Forum: REVOLUTIONARY THERAPIES FOR CANCER

Four true giants in cancer research met to speak on “Revolutionary therapies for cancer“:

- *Carl June*, US Researcher, pioneer of CAR-T cells and director of the Center for Cellular Immunotherapies of the University of Pennsylvania;
- *Michael Hall*, professor at the Biozentrum of the University of Basel, and initiator of an area of study on the mTOR protein (crucial for the growth of cells), which has led to the development of drugs to treat different types of tumors; and
- *Alberto Mantovani*, professor at the Humanitas University of Milan and scientific director of the Humanitas Research Hospital, who with his research was one of the first scientists to get involved in immune-oncology.
- *Solange Peters*, the future President of the European Society for Medical Oncology (ESMO), talked about how “precision medicine” has changed the way of treating several types of lung cancer.

Below is a summary of the new avenues of research outlined by the speakers.

Alberto Mantovani

It is without doubt that in the last twenty years studies in the immunology sector have changed, and will continue to change, our way of dealing with cancer. We have discovered that the body’s defence system can identify cancer cells, surround them and infiltrate them, but then, in certain cases, it stops, without destroying them. Our goal now is to get to the point of ensuring that the body is able to defend itself “fully”, without being slowed down by tumors.

Among those that “police” the immune system, macrophages play a particularly active role in helping tumors. These cells are a key component in inflammation: they act as a very important defence mechanism, but in certain cases can also set the stage for tumors. Today we have proof of macrophage recruitment, by cancerous cells, and of the functional skewing of these “corrupt agents”. Of course, as we gradually identify these mechanisms, it will also become possible to find new therapies to block them. Through our lifestyles, however, we can do a lot to reduce the risk of cancer. There is a very simple formula: zero, five, thirty. What I mean is: zero cigarettes, five portions of fruit and vegetables a day and thirty minutes of exercise. If we applied this little rule consistently every day, we could avoid hundreds of thousands of new cases of cancer.

Michael Hall

The TOR protein regulates the growth of cells and, also because of this, plays a central role in the development of many tumors. This protein can be slowed down by a drug called rapamycin, or by other similar drugs. However, a new generation of molecules capable of blocking the TOR protein with mechanisms of action that differ from rapamycin are also being studied. In this regard, we are waiting for the results of the first clinical experiments conducted.

TOR is found in all eukaryotes (i.e. in those, like us, that possess cells with a clearly defined nucleus, containing DNA), from yeast to plants, worms, flies and even mammals, and therefore humans. It is implicated in the development of cancer, but appears to play a key role also in aging and in disorders such as cancer, cardiovascular disease, obesity, and diabetes.

In light of this evidence, the possibility of not limiting the use of drugs that inhibit TOR only to cancer is being discussed. However, many studies will be necessary, because the role played by TOR in coordinating and integrating overall body growth and metabolism is not yet clear, whereas the role that this protein plays in controlling the growth of single cells has been more clearly identified.

Carl June

CAR-T cells are T lymphocytes (fundamental elements of the immune system) that are taken from the blood of the patient and genetically modified, using special viruses, to ensure that they recognize cancer cells (thanks to special receptors), and are then reinfused into the same patient, after being multiplied millions of times in the laboratory.

CAR is the acronym of Chimeric Antigen Receptor. CAR-T cells are an important cancer therapeutic, capable of treating diseases that cannot be cured with other drugs and, hence, have been approved by the US, Canadian and European health authorities for the treatment of B cell malignancies in pediatric and adult patients (acute lymphoblastic leukaemia and several types of advanced lymphomas). Now the challenge is to extend the use of this therapy also to solid tumors (not only, therefore, to those of the blood and lymphatic system).

CAR-T cells, as we said, have demonstrated, after many years of study and attempts, that immune cells empowered through genetic engineering can be used as an important new class of cancer therapeutics. However, it will most probably be appropriate, or necessary, to integrate this new pillar of medicine with the more classic pillars of chemotherapy and radiation therapy.

Another challenge for research is that of rendering CAR-T cells increasingly reliable, effective and safe. In this regard, the continuing emergence of new techniques for cellular genetic engineering provides a set of tools for programming immune cells in an increasingly precise manner, making way for the next generation of smart T cells.

Grading and assessment of neurotoxicity on CAR-T

CTCAE v4.03 grading of neurotoxicity

Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
Level of consciousness	Mild drowsiness / sleepiness	Moderate somnolence, limiting instrumental ADL	Obtundation or stupor	Life-threatening needing urgent intervention/ mechanical ventilation
Orientation / Confusion	Mild disorientation / confusion	Moderate disorientation, limiting instrumental ADL	Severe disorientation, limiting self-care ADL	Life-threatening needing urgent intervention/ mechanical ventilation
Encephalopathy	Mild limiting of ADL	Limiting instrumental ADL	Limiting self-care ADL	Life-threatening needing urgent intervention/ mechanical ventilation
Speech	Dysphasia not impairing ability to communicate	Dysphasia with moderate impairment in ability to communicate spontaneously	Severe receptive or expressive dysphasia, impairing ability to read, write or communicate	-
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures
Tremors	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	-
Motor weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self-care ADL, disabling	-
Bowel or bladder incontinence	-	-	Intervention indicated; limiting self care ADL	-
Cerebral edema	-	-	-	Life-threatening; urgent intervention indicated

ASTCT Consensus Encephalopathy Assessment Tool

CARTOX Tool	Immune-Effector Cell-Associated Encephalopathy (ICE) Tool
<ul style="list-style-type: none"> Orientation: Orientation to year, month, city, hospital, President: 5 points Naming: Name 3 objects (e.g., point to clock, pen, button): 3 points Writing: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point Attention: Count backwards from 100 by ten: 1 point 	<ul style="list-style-type: none"> Orientation: Orientation to year, month, city, hospital: 4 points Naming: Name 3 objects (e.g., point to clock, pen, button): 3 points Following commands: (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): 1 point Writing: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point Attention: Count backwards from 100 by ten: 1 point

NSelapu et al. Nat Rev Clin Oncol, Jan 2018 | Lee et al. Biol Blood Marrow Transplant, 2019 Apr;25 (4):625-638

Impaired handwriting is a sensitive sign of neurotoxicity

Day 4 9 am	I love Shawnee, KS.	MMSE score 29/30
Day 5 01:30 PM Toci 8 mg/kg		27/30
Day 5 03:30 PM	I'm sure you'll...	27/30
Day 6 9 am	I miss my kids.	29/30

PLENARY SESSION

C. Rushton, M. Alcaide, M. Cheung, N. Thomas, et al.

IDENTIFYING MUTATIONS ENRICHED IN RELAPSED-REFRACTORY DLBCL TO DERIVE GENETIC FACTORS UNDERLYING TREATMENT RESISTANCE

Conclusion: DLBCL patients with mutations in relapse-enriched genes are at a higher risk of treatment failure. Mutations in these genes, specifically hotspot deletions, may have power as biomarkers to identify patients at a high risk of relapse and could inform on the mechanism of acquired resistance to components of R-CHOP.

U. Vitolo, T.E. Witzig, R.D. Gascoyne, D.W. Scott, et al.

ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R²-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma

Conclusion: Overall, the ROBUST study did not meet the primary endpoint of progression free survival for lenalidomide/R-CHOP vs placebo/R-CHOP in previously untreated patients with ABC-DLBCL, although a positive trend favoring lenalidomide/R-CHOP has been observed in advanced-stage and higher-risk patients. The safety profile of lenalidomide/R-CHOP was consistent with those of individual medicines, and no new safety signals were identified with the combination.

G.S. Nowakowski, F. Hong, D.W. Scott, R. Macon, et al.

ADDITION OF LENALIDOMIDE TO R-CHOP (R2CHOP) IMPROVES OUTCOMES IN NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FIRST REPORT OF ECOG-ACRIN1412 A RANDOMIZED PHASE 2 US INTERGROUP STUDY OF R2CHOP VS R-CHOP

Conclusion: The addition of lenalidomide to R-CHOP (R2CHOP) in this phase II study improved PFS in newly diagnosed DLBCL.

P. Langerbeins, J. Bahlo, C. Rhein, H. Gerwin, et al.

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

Conclusion: The results of this study allow to conclude that ibrutinib significantly improves EFS, PFS and 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.

INDOLENT NON-FOLLICULAR LYMPHOMA

A. Conconi, Ponderano (Italy), et al.

EARLY PROGRESSION OF DISEASE (POD24) PREDICTS SHORTER SURVIVAL IN MALT LYMPHOMA PATIENTS RECEIVING SYSTEMIC TREATMENT

Conclusion: In patients with EMZL who received front-line systemic treatment, POD24 is associated with poorer survival and may represent a useful endpoint in future prospective clinical trials.

A.J. Ferreri, Milan (Italy), et al.

INTRALESIONAL RITUXIMAB SUPPLEMENTED WITH AUTOLOGOUS SERUM IN RELAPSED CD20+ INDOLENT LYMPHOMAS OF THE CONJUNCTIVA: ACTIVITY AND SAFETY RESULTS OF THE "IRIS" TRIAL

Conclusion: Intralesional rituximab is a safe and active treatment in pts with conjunctival indolent lymphoma. The addition of autologous serum is associated with improved response in some cases. Retreatment of local relapses can result in a second long-lasting response.

A. Bruscatto, Bellinzona (Switzerland), et al.

MULTI-OMICS LANDSCAPE OF SPLENIC MARGINAL ZONE LYMPHOMA (SMZL) - INTERIM ANALYSIS OF IELSG46 STUDY

Conclusion: Genetic analysis of a large cohort of SMZLs cases identified four molecular subtypes characterized by unique deregulated genetic pathways, clinical outcome and potentially a molecular phenotype. These results can provide the basis for proposing the classification of SMZL into provisional molecular subtypes, that may lead to a conceptual edifice for developing precision therapies for SMZL patients.

P.L. Zinzani, Bologna (Italy), et al.

UMBRALISIB MONOTHERAPY DEMONSTRATES EFFICACY AND SAFETY IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA: A MULTICENTER, OPEN-LABEL, REGISTRATION DIRECTED PHASE 2 STUDY

Conclusion: PI3K-delta inhibition with single-agent umbralisib is active and well tolerated in pts with R/R MZL, achieving durable responses with chemotherapy-free therapy.

J. Castillo, Boston, MA (USA), et al.

IBRUTINIB FOR THE TREATMENT OF BING-NEEL SYNDROME: A RETROSPECTIVE, MULTICENTER STUDY

Conclusion: Ibrutinib monotherapy can induce durable responses with acceptable toxicity in patients with BNS. Despite symptomatic and radiological improvements in the majority of patients, half of the patients can have persistence of disease in the CSF, and this should not represent treatment failure.

S.P. Treon, Boston, MA (USA), et al.

IBRUTINIB MONOTHERAPY PRODUCES LONG- TERM DISEASE CONTROL IN PREVIOUSLY TREATED WALDENSTROM'S MACROGLOBULINEMIA: FINAL REPORT OF THE PIVOTAL TRIAL (NCT01614821)

Conclusion: The findings confirm that ibrutinib is highly active, and produces long-term responses in previously treated WM. Prolonged ibrutinib therapy is associated with deeper responses, including VGPR. Response activity, time to major response, and PFS are impacted by MYD88 and CXCR4 mutation status.

ADVANCES IN CAR T-CELL TREATMENT

L.W. Kwak, Duarte, CA (USA), et al.

NOVEL BAFF-R CAR T-CELL THERAPY FOR CD19 ANTIGEN-LOSS RELAPSED B CELL TUMORS

Conclusion: Taken together, our data suggest that BAFF-R is amenable to CAR T-cell therapy and that targeting it may add to existing alternative strategies to overcome relapse from CD19 antigen loss, such as CD22 CAR T cells. Future strategies combining dual targeting of CD19 and BAFF-R may also be effective.

C.L. Batlevi, New York, NY (USA), et al.

PHASE I 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/4-1BBL armored CAR T cells is safe with no severe CRS. Grade 3 neurotoxicity was noted in 3 pt (11%) with no case of cerebral edema. The overall CR rate is 57% with 8 patients remaining in CR at the time of this report. Future studies are warranted to develop and improve on existing CAR T cell therapies.

C.A. Ramos, Houston, TX (USA), et al.

CD30-CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS FOR THERAPY OF HODGKIN LYMPHOMA (HL)

Conclusion: Twelve patients have been evaluated at 6 weeks after infusion. Seven have had a CR lasting up to >15 months, 1 had a partial response, and 4 had disease progression. In 2 patients who relapsed after CR and were re-biopsied, immunohistochemistry evidenced persistent tumor expression of CD30. Hence, infusion of CD30.CARTs after cytoreductive chemotherapy is well tolerated at the doses used. Inclusion of cytoreduction pre-infusion substantially improves CD30 CART expansion and appears associated with superior anti-tumor activity in relapsed patients.

J. Gauthier, Seattle, WA (USA), et al.

DURABLE RESPONSES AFTER CD19-TARGETED CAR-T CELL IMMUNOTHERAPY WITH CONCURRENT IBRUTINIB FOR CLL AFTER PRIOR IBRUTINIB FAILURE

Conclusion: In conclusion, CD19 CAR-T cell therapy with concurrent ibrutinib for R/R CLL was feasible and led to high rates of durable responses, without \geq grade 3 CRS.

A.V. Hirayama, Seattle, WA (USA), et al.

HIGH RATE OF DURABLE COMPLETE REMISSION IN FOLLICULAR LYMPHOMA AFTER CD19 CAR-T CELL IMMUNOTHERAPY

Conclusion: CD19 CAR-T cell immunotherapy is highly effective in adults with clinically aggressive R/R FL, with durable CR in a high proportion of FL pts.

DLBCL: Clinical Data

L. Ceriani, Bellinzona (Switzerland), et al.

INTEGRATION BETWEEN METABOLIC TUMOUR VOLUME AND METABOLIC HETEROGENEITY PREDICTS OUTCOME OF DLBCL LYMPHOMA PATIENTS IN THE SAKK 38/07 STUDY COHORT

Conclusion: Baseline MTV is a powerful predictor of clinical outcomes in patients with DLBCL treated with R-CHOP. High MTV values predict a worse response to treatment especially in patients with non-GCB subtype. A prognostic model based on the combination of MTV and MH may allow the early identification of patients at high risk of disease progression following conventional treatment. The validation of these results in an independent retrospective cohort of patients treated with R-CHOP21 is ongoing and full data will be presented.

J.R. Westin, Houston, TX (USA), et al.

SMART START: RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB ALONE PRIOR TO COMBINATION WITH CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA

Conclusion: The Smart Start trial demonstrates the chemotherapy-free combination of rituximab 375 mg/m², ibrutinib 560 mg, and lenalidomide 25mg is highly effective in patients with newly diagnosed non-GCB DLBCL. Further studies are planned with other novel agents and with fewer cycles of chemotherapy consolidation for patients achieving a CR with RLI alone.

P. Lugtenburg, Rotterdam (Netherlands), 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.

T. Shree, Stanford, CA (USA), et al.

IMPAIRED IMMUNE HEALTH IN SURVIVORS OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A LARGE POPULATION-BASED STUDY

Conclusion: These findings, from a large, population-based cohort, show that immune-related conditions in DLBCL survivors are wide-ranging, and increased risk for these conditions is long-lasting. These data highlight a need to understand the mechanisms of immune dysfunction and to define predictors of clinical risk among DLBCL survivors.

DLBCL patient characteristics in CAR-T clinical trials and the real world

DLBCL patient characteristics in CAR-T clinical trials and the real world

	JULIET ^{1,2}	ZUMA-1 ³	TRANSCEND ⁴	RWE (axi-cel) ⁵	RWE (axi-cel) ⁶	Elderly (≥65) (axi-cel) ⁷
N apheresed (infused)	167 (115)	119 (108) ^a	(69) in DLBCL cohort	295 (274)	104 (91)	17
Age, years (range)	56 (22-76)	58 (51-64)	61 (26-82)	60 (21-83)	63.8 (21-80)	68 (64-77)
Age ≥ 65 years, %	23	24	–	33	–	–
DLBCL, %	80	76	–	68	43	76
tFL, %	18	16	–	26	–	24
Double/triple hit, n/N	19/70 ¹	5/47	At least 16/69	–	21/104 and 4/104	–
# of prior therapies, %						
1	5	3	Median: 3	–	–	–
2	44	28	Range: 1-12	–	–	–
3+	51	69		75	–	–
Prior autoSCT, %	49	21	46 (any prior transplant)	33	27	–
Prior alloSCT, %	Not permitted	Not permitted		2	3	–
Refractory, %	54	76	67 (chemorefractory)	42	91	–
Bridging therapy, %	90	Not permitted	Permitted	55	40	Not permitted

The purpose of this table is to summarize data. Head-to-head studies have not been performed and no comparisons can be made.

alloSCT, allogeneic SCT; autoSCT, autologous SCT; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; RWE, real-world evidence; SCT, stem cell transplantation; tFL, transformed follicular lymphoma.

^aBaseline characteristics shown only for 101 patients in phase 2 of trial.

1. Schuster SJ, et al. *N Engl J Med.* 2019;380:45; 2. Schuster, SJ, et al. *Blood.* 2018;132:1684; 3. Locke FL, et al. *Lancet Oncol.* 2019;20:31; 4. Abramson JS, et al. *Blood.* 2017;130:581; 5. Nastoupil LJ, et al. *Blood.* 2018;132:91; 6. Jacobson CA, et al. *Blood.* 2018;132:92; 7. Sano D, et al. *Blood.* 2018;132:96.

DLBCL patient outcomes in CAR-T clinical trials and the real world

	JULIET ^{1,2}	ZUMA-1 ³	TRANSCEND ^{4,5}	RWE (axi-cel) ⁶	RWE (axi-cel) ⁷	Elderly (≥65) (axi-cel) ⁸
N evaluable for efficacy/safety	99/111	101/108	68 in DLBCL cohort/102	274	95	17/17
ORR, %	54 (43-64)	74	75	81 at 90 days	71	–
CR rate, %	40	54	56	57 at 90 days	44	47 at 30 days
DOR, %	6-mo: 66% 12-/18-mo: 64%	Median: 11.1 months (4.2-NE)	–	–	Median: 4.9 months	–
Grade 3/4 CRS, %	23	11	1	7	16	18
Tocilizumab received, %	15	45	29	63	67	–
Grade 3/4 NE, %	11	32	14	33	39	29
Steroids received, %	11	29	48 ^a	55	64	–

The purpose of this table is to summarize data. Head-to-head studies have not been performed and no comparisons can be made.

CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; NE, neurological events; ORR, overall response rate; RWE, real-world evidence.

^aAccording to the 2019 ASCO presentation, 21/44 patients with CRS and/or NE received dexamethasone treatment.

1. Schuster SJ, et al. *N Engl J Med.* 2019;380:45; 2. Schuster, SJ, et al. *Blood.* 2018;132:1684; 3. Locke FL, et al. *Lancet Oncol.* 2019;20:31; 4. Abramson JS, et al. *Blood.* 2017;130:581; 5. Abramson JS, et al. *J Clin Oncol* 2019 (suppl); abstr 6637; 6. Nastoupil LJ, et al. *Blood.* 2018;132:91; 7. Jacobson CA, et al. *Blood.* 2018;132:92; 8. Sano D, et al. *Blood.* 2018;132:96.

W. Zhao, Shanghai (China), et al.

DIFFUSE LARGE B-CELL LYMPHOMA: USING IMMUNE BIOMARKERS TO DEFINE NOVEL THERAPIES

Conclusion: Together, immune dysregulation plays an important role on disease progression and may become potential therapeutic targets. Further mechanism study is helpful for the identification of biological subsets sensitive to immunotherapy and eventually to realize precision treatment in DLBCL.

EXTRANODAL LYMPHOMAS

A. Hayden, Vancouver, B.C. (Canada), et al.

OUTCOME OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA: IMPACT OF A PET-GUIDED APPROACH

Conclusion: Overall outcomes of PMBCL pts primarily treated with R-CHOP are favourable with a 5 y OS of 89%. Changing to a PET-adapted approach has reduced the use of CRT by over 60% without compromising cure rates. EOT PETneg scan is associated with excellent outcomes with 90% cure rate using modern D criteria. In contrast, D5 have a very poor outcome and may benefit from alternate treatment approaches.

P.L. Zinzani, Bologna (Italy), et al.

NIVOLUMAB COMBINED WITH BRENTUXIMAB VEDOTIN FOR RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA: EFFICACY AND SAFETY FROM THE PHASE 2 CHECKMATE 436 STUDY

Conclusion: In patients with R/R PMBL, nivolumab + BV demonstrated a high investigator-assessed ORR of 73%, with 37% CR. TRAEs were consistent with the safety profiles of nivolumab and BV treatment alone. The combination of nivolumab + BV may be synergistic and is active in patients with R/R PMBL.

D. Jagadeesh, Cleveland, OH (USA), et al.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD) AFTER SOLID ORGAN TRANSPLANT (SOT): SURVIVAL AND PROGNOSTICATION AMONG 570 PATIENTS (PTS) TREATED IN THE MODERN ERA

PTLDs are rare, aggressive and clinically heterogeneous diseases that may arise in the setting of immunosuppression following SOT. There remains an absence of a standard frontline treatment approach in the real world setting. We conducted a comprehensive multicenter retrospective study to analyze disease characteristics and outcomes of post-SOT PTLD in the modern era.

Conclusion: These data represent the largest cohort of SOT-related PTLD pts reported to date. Collectively, pts with lung and heart SOT-related PTLD had significantly inferior OS and depth of response to 1st line therapy was a critical determinant for long-term RFS and OS. Our data demonstrates improved outcomes in pts with newly diagnosed PTLD treated in the era of novel agents.

FOLLICULAR LYMPHOMA

Despite recent advances, relapsed or refractory follicular lymphoma remains a challenging and heterogeneous disease. Oral therapies that can address multiple signalling pathways and overcome chemo-resistance without cumulative side effects are urgently needed.

S. Dirnhofer, Basel (Switzerland), et al.

PROGNOSTIC IMPLICATIONS OF THE MICROENVIRONMENT IN FOLLICULAR LYMPHOMA UNDER RITUXIMAB AND RITUXIMAB+LENALIDOMIDE THERAPY; A TRANSLATIONAL STUDY OF THE SAKK35/10 TRIAL

Conclusion: Based on data from this prospective clinical trial on FL, we identified tumor microenvironmental characteristics which may allow prognostic stratification with respect to immuno- and combined immuno- and immunomodulatory therapy. Our analysis implicates that lenalidomide might help to overcome the adverse prognostic implication of higher amounts of regulatory T cells in the microenvironment of follicular lymphoma and that it may have particularly favorable effects in cases with higher amounts of TH2-equivalents as demonstrated by GATA3-positive T-cells. Additional analysis by gene expression profiling of the microenvironment may further contribute to a better understanding of this so far still underestimated component of follicular lymphoma.

P. Perez Galan, Barcelona (Spain), et al.

DECIPHERING THE CONTRIBUTION OF MACROPHAGES TO FOLLICULAR LYMPHOMA PATHOGENESIS: NEW INSIGHTS INTO THERAPY

Conclusion: In summary, these results support the role of M2 macrophages in FL pathogenesis and suggest that therapies manipulating FL-M2 crosstalk may be a new strategy, especially in combination with anti-B cell therapies.

C.L. Batlevi, New York, NY (USA), et al.

IMPACT OF PET IMAGING AND HISTOLOGIC TRANSFORMATION ON THE PROGNOSIS OF EARLY DISEASE PROGRESSION IN FOLLICULAR LYMPHOMA

Conclusion: Our study provides evidence that in the modern era of PET-based staging, PFS24 may not be a robust surrogate endpoint for OS. The improved outcomes in PET-staged patients with early progression may be associated with identification and exclusion of patients with transformed disease at time of therapy. Patients with early progression are at risk for early death. In contrast, patients with early progression and no evidence of transformation have an extended OS, suggesting aggressive upfront therapies may not be warranted in these patients.

M. Federico, Modena (Italy), et al.

RESPONSE ORIENTED MAINTENANCE THERAPY IN ADVANCED FOLLICULAR LYMPHOMA. RESULTS OF THE INTERIM ANALYSIS OF THE FOLL12 TRIAL CONDUCTED BY THE FONDAZIONE ITALIANA LINFOMI

Conclusion: In patients with intermediate-high risk FL according to FLIPI2 and requiring systemic therapy, omission of R-maintenance resulted in a significantly lower 3-year PFS, despite the attainment of a post-induction complete metabolic response.

HODGKIN LYMPHOMA

M.S. Binkley, Stanford, CA (USA), et al.

STAGE I-II NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA IN THE MODERN ERA: A MULTI-INSTITUTIONAL EXPERIENCE OF ADULT PATIENTS BY ILROG

Conclusion: OS for pts with stage I-II NPLHL is excellent and did not differ based on treatment after adjusting for age and stage. There was no PFS benefit for pts with stage II NPLHL receiving CMT over RT alone although there was a suggestion that pts with IAP C-F may benefit from CMT. PFS was superior among pts who received RT as a component of initial therapy.

S. Ansell, Rochester, MN (USA), et al.

NIVOLUMAB PLUS DOXORUBICIN, VINBLASTINE AND DACARBAZINE FOR NEWLY DIAGNOSED ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA: CHECKMATE 205 COHORT D 2-YEAR FOLLOW-UP

Conclusion: With extended follow-up, nivolumab followed by N-AVD demonstrated a 21-mo PFS rate of 83% per investigator, a high metabolic response rate with 75% CMR at EOT per IRC, with no new safety signals. Incorporation of Deauville assessment improved the concordance of CR between IRC- and investigator-assessed responses. Nivolumab followed by N-AVD provides a promising alternative Tx option in newly diagnosed AS cHL.

A. Gallamini, Nice (France), et al.

CONSOLIDATION RADIOTHERAPY COULD BE OMITTED IN ADVANCED HODGKIN LYMPHOMA WITH LARGE NODAL MASS IN COMPLETE METABOLIC RESPONSE AFTER ABVD. FINAL ANALYSIS OF THE RANDOMIZED HD0607 TRIAL

Conclusion: cRT could be safely omitted in aHL pts presenting with a LNM and both a negative PET-2 and EoT-PET, irrespective from the LNM size. As in more than 80% of the pts the site of LNM at baseline was in mediastinum, this could translate in a significant reduction of late-onset treatment related mortality for secondary tumours and coronary arterial disease.

A. Prica, Toronto, ON (Canada), et al.

COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF MULTIPLE TREATMENT STRATEGIES USING ABVD AND/ OR BEACOPP IN THE TREATMENT OF ADVANCED-STAGE HODGKIN LYMPHOMA

Conclusion: The preferred treatment strategy for patients with newly diagnosed advanced-stage Hodgkin lymphoma is the AHL2011 PET-adapted regimen. This strategy maximizes life expectancy, quality-adjusted life years, and is the most cost-effective strategy, accounting for increased rates of hematologic toxicity, secondary malignancy, and infertility caused by exposure to at least 2 cycles of BEACOPP.

HIGH RISK LARGE B-CELL LYMPHOMAS

S. Leppä, Helsinki (Finland), et al.

[YOUNG HIGH RISK PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA INCLUDING BCL-2/MYC DOUBLE HIT LYMPHOMAS BENEFIT FROM DOSE-DENSE IMMUNOCHEMOTHERAPY WITH EARLY CNS PROPHYLAXIS](#)

Conclusion: The results are encouraging with favorable survival rates, low toxic death rate and low number of CNS events.

F. Morschhauser, Lille (France), et al.

[IMPROVED OUTCOMES IN PATIENTS \(PTS\) WITH BCL2- POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA \(DLBCL\) TREATED WITH VENETOCLAX \(VEN\) PLUS R-CHOP: RESULTS FROM THE PHASE 2 CAVALLI STUDY](#)

Conclusion: Adding Ven to R-CHOP improved efficacy in BCL2 IHC+ 1L DLBCL pts versus matched GOYA controls. A higher rate of cytopenia, FN and infection was observed in CAVALLI vs GOYA; however, there was no increase in risk of death and the RDI of chemotherapy was similar.

E.A. Chong, Philadelphia, PA (USA), et al.

[CD19-DIRECTED CAR T CELL THERAPY \(CTL019\) FOR RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL AND FOLLICULAR LYMPHOMAS: FOUR YEAR OUTCOMES](#)

Conclusion: At a median follow-up over four years, we demonstrate that a single infusion of CTL019 provides durable remissions in pts with relapsed/refractory DLBCL and FL. This is the longest follow-up for CTL019 therapy for relapsed/refractory B-cell lymphomas reported to date.

CLL AND MORE

A. Tedeschi, Milan (Italy), et al.

[FIVE-YEAR FOLLOW-UP OF FIRST-LINE IBRUTINIB FOR TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA](#)

Conclusion: Single-agent ibr sustained superior PFS and OS compared to chl, including for pts with high-risk genomic features, in the longest follow-up to date from a phase 3 study of first-line BTK-directed therapy. After up to 66 mo follow-up, responses to ibr improved over time with almost three-fold more pts achieving CR/CRi with long-term follow-up. More than half of pts remain on long-term continuous ibr treatment, and no new safety signals emerged.

O. Al-Sawaf, Cologne (Germany), 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, which can be observed frequently in older, treatment-naïve CLL pts, correlates with CLL-IPI high/very high risk, although 2/3 of these pts do not show TP53aberrations. CKT is associated with shorter PFS and OS in pts treated with ClbG, including pts without TP53 aberrations.

VenG can overcome this adverse risk. These data support the importance of chromosome analysis before frontline therapy, and the value of VenG in CLL CKT pts.

J. Wu, San Francisco, CA (USA), et al.

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

Conclusion: We assessed the mutational landscape of R/R CLL by WES and confirmed prior mutation frequency reports. 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. To address the biological basis of the findings, MVA, further validation in larger cohorts and deep sequencing for subclones are needed.

S. Handunnetti, Melbourne (Australia), et al.

AN UNDETECTABLE peripheral blood (PB) Minimal Residual Disease (MRD) STATUS SHOULD BE THE THERAPEUTIC GOAL WITH VENETOCLAX THERAPY IN RELAPSED/ REFRACTORY CLL

Conclusion: PB uMRD commonly correlates with BM uMRD in CLL patients treated with Ven, and serves as an equivalent predictor of long term outcome. Patients who have not achieved PB uMRD by 24 months are unlikely to do so. This group is enriched for TP53 dysfunction and complex karyotype. While patients achieving uMRD have prolonged TTP, CLL eventually recrudesces, supporting a drive to time-limited combination therapy.

T. Siddiqi, Duarte, CA (USA), et al.

TRANSCEND CLL 004: MINIMAL RESIDUAL DISEASE AFTER LISOCABTAGENE MARALEUCEL IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/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 of CRS and NE were manageable and grade 3 or higher events were limited. Patients rapidly achieved CR/CRi and undetectable MRD. The phase 2 component of the study is currently enrolling patients for treatment at dose level 2. Additional follow-up will be presented.

Tiacci, Perugia (Italy), et al.

THE BRAF INHIBITOR VEMURAFENIB PLUS RITUXIMAB PRODUCES A HIGH RATE OF DEEP AND DURABLE RESPONSES IN RELAPSED/REFRACTORY HAIRY CELL LEUKEMIA: UPDATED RESULTS OF A PHASE-2 TRIAL E.

Conclusion: Vemurafenib plus rituximab is a brief, safe and non-myelotoxic regimen inducing MRD-negative durable responses in most relapsed/refractory HCL patients. Randomized testing against the chemotherapy-based standard of care in the frontline setting is warranted.

T-CELL LYMPHOMAS

P. Ghione, New York, NY (USA), et al.

RISK OF BREAST IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL) IN A COHORT OF 3546 WOMEN PROSPECTIVELY FOLLOWED AFTER RECEIVING TEXTURED BREAST IMPLANTS.

Conclusion: This study, evaluating the risk of women with textured breast implants from a prospective database with long-term follow-up, demonstrated that the incidence rate of BIA-ALCL may be higher than previously reported. These results can help inform implant choice for women undergoing breast reconstruction.

Y. Song, Beijing (China), et al.

20-YEAR SURVIVAL DATA ANALYSIS OF PTCL PATIENTS IN PEKING UNIVERSITY CANCER HOSPITAL

Conclusion: According to our experiences, CHOPE regimen improved the efficacy and survival of PTCLs in front-line; addition of gemcitabine resulted in more adverse events without benefit of survival. Patients with AITL and advanced-stage NKTCL who achieved CR after first-line therapy should be recommended to receive HDT/ASCT.

L. de Leval, Lausanne (Switzerland), et al.

NEW DATA IN THE MOLECULAR PATHOLOGY OF T CELL LYMPHOMAS

Conclusion: The GATA3 (TH2) and TBX2 (TH1) subgroups of PTCL-not otherwise specified defined by specific molecular signatures, are associated with different copy abnormalities and oncogenic pathways, indicating distinct oncogenic evolution.

M. Lopez-Parra, Salamanca (Spain), et al.

AUTOLOGOUS STEM CELL TRANSPLANTATION AS PART OF FIRST-LINE THERAPY IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA: A MULTICENTER GELTAMO/FIL STUDY

Conclusion: Our results indicate that ASCT in 1st CR improves the survival of patients with PTCL other than ALK+ anaplastic large-cell lymphoma. These results should be confirmed in a prospective randomized study. A propensity score matching analysis is planned.

O. Tournilhac, Clermont-Ferrand (France), et al.

FIRST-LINE THERAPY OF T-CELL LYMPHOMA: ALLOGENEIC OR AUTOLOGOUS TRANSPLANTATION FOR CONSOLIDATION - FINAL RESULTS OF THE AATT STUDY

Conclusion: AlloSCT or autoSCT given to consolidate response in pts with PTCL showed no significant survival differences. While exerting a strong GvL-effect alloSCT resulted in substantial TRM. For younger pts with PTCL autoSCT remains the preferred consolidation, in particular, because pts relapsing after autoSCT can be successfully salvaged with alloSCT.

A. Zoellner, M. Unterhalt, S. Stilgenbauer, K. Hübel, et al.

AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST REMISSION SIGNIFICANTLY PROLONGS PROGRESSION-FREE AND OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA

Conclusion: After a prolonged median follow up of 14 years the mature results of our trial confirm a significantly prolonged PFS and OS after ASCT in first remission of mantle cell lymphoma. However, there was only a non-significant trend for PFS and no difference in OS in the subset of patients treated with a Rituximab-containing induction therapy, potentially due to the reduced statistical power of this subgroup analysis. In the current study generation, the substitution of ASCT by the BTK inhibitor Ibrutinib is evaluated.

S. Le Gouill, A. Beldi-Ferchiou, V. Cacheux, G. Salles, et al.

OBINUTUZUMAB PLUS DHAP FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) PLUS OBINUTUZUMAB MAINTENANCE PROVIDES A HIGH MRD RESPONSE RATE IN UNTREATED MCL PATIENTS, RESULTS OF LYMA-101 TRIAL, A LYSA GROUP STUDY

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 before ASCT with an unprecedented high level of MRD negativity, which predict better PFS and OS. Longer FU is needed to evaluate patient outcome after O-DHAP/ASCT/Obinutuzumab on-demand maintenance. However, both PFS and OS are highly encouraging at one year.