Dr. Jim Armitage: Hello, welcome to Practical Hematologist.com. My name is Jim Armitage and I'm a Professor of Medicine at the University of Nebraska Medical Center. Today, I am happy to be joined by Dr. Gilles Salles. Gilles and I have been friends for a long time. We were just talking that his name is mispronounced even more commonly than my name is. The correct way is you leave off the S on his last name.

Gilles has quite a career. He was one of the most famous hematologists in France, not in small part because he led the extraordinarily important PRIMA study that showed that follicular lymphoma has its outcome changed with maintenance rituximab. After a long career and very outstanding career there, he recently was recruited to Memorial Sloan Kettering, where he is the chief of the lymphoma service.

Faculty Disclosures

James O. Armitage, MD
Honorarium: Cardiff Oncology, Inc.

Gilles Salles, MD
Consulting: AbbVie, Inc., BeiGene, Bristol Myers Squibb Company, Celgene Corporation – A Bristol Myers Squibb Company, Debiopharm Group, Epizyme, Inc., Genentech - A Member of the Roche Group, Genmab A/S, Incyte Corporation, Ipsen, Janssen Pharmaceuticals, Inc., Kite Pharma/Gilead Sciences, Inc., Loxo Oncology, Miltenyi Biotec, Molecular Partners, MorphoSys AG, Nordic Nanovector ASA, Novartis AG, RAPT Therapeutics, Takeda Pharmaceuticals U.S.A., Inc., VelosBio, Inc.

Honorarium: AbbVie, Bayer AG, Incyte, Kite/Gilead, MorphoSys, Novartis, and Regeneron Pharmaceuticals, Inc.

Stakeholder: Owkin

Now you will see our disclosures.

Learning Objectives

- Discuss recent evidence/publications on emerging therapies for frontline follicular lymphoma (FL) treatment
- Describe implications for current/future practice of new clinical trial data in the frontline treatment of FL

Today's presentation is going to address current and emerging directions in the frontline treatment of patients with follicular lymphoma. In this presentation, Dr. Salles will discuss recent advances in emerging therapies and describe implications for current and future practice. I hope that we will have a chance for a little bit of discussion afterwards.

I now will turn the presentation over to Dr. Salles.

Dr. Gilles Salles: Thank you so much, Dr. Armitage, and thank you to the organizers for having me. What I'm going to try today is review with you the way we do manage patients with follicular lymphoma diagnosis, and what is emerging in the field.

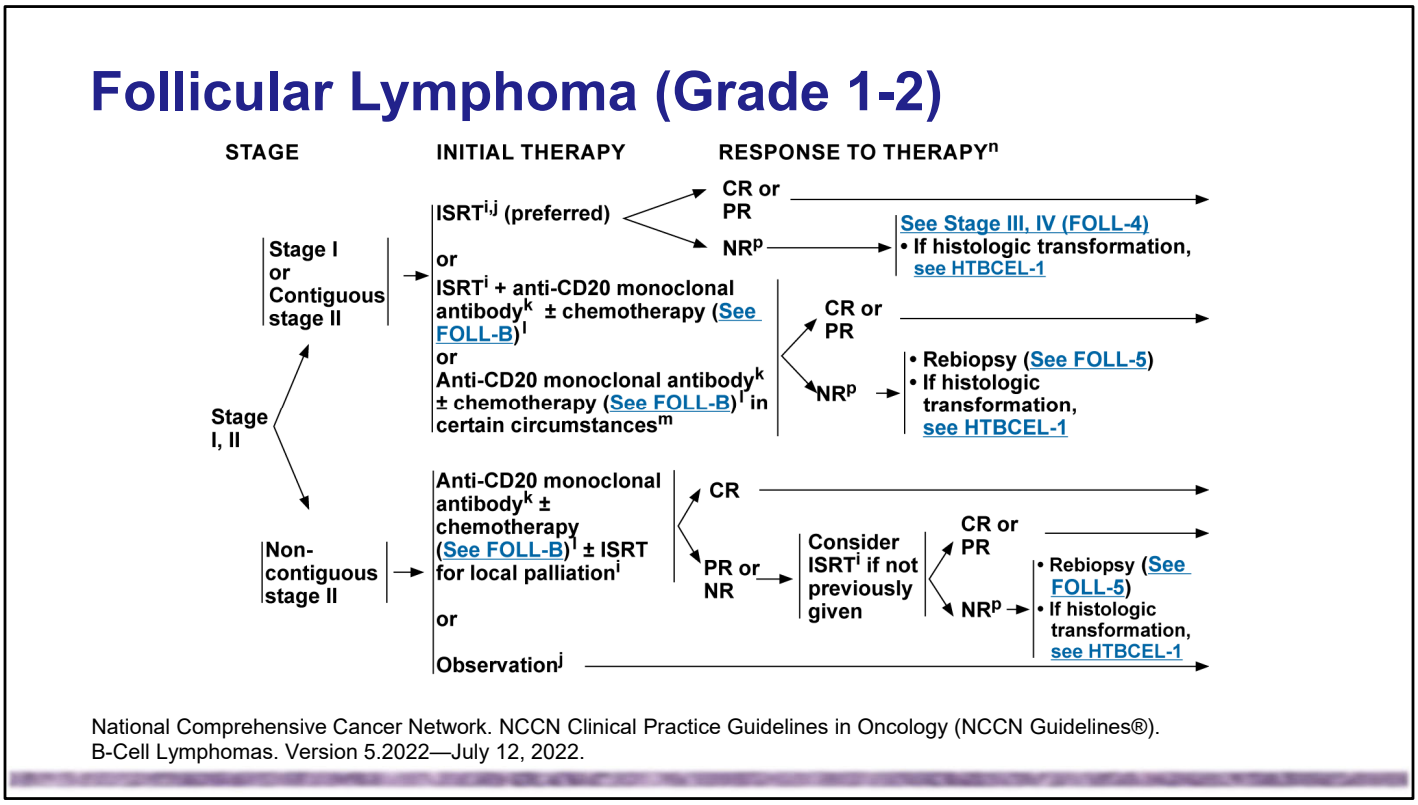
First-line Management of Patients with Follicular Lymphoma in 2022

1) In patients with localized disease

2) In patients with low tumor burden and/or asymptomatic disease

3) For other patients with high tumor burden in need of systemic treatment

The first thing that we need to consider when we meet patients with follicular lymphoma, we tend to separate patients into three categories. This will be the way I will address the management of the patient. We first have patients with localized disease.



National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). B-Cell Lymphomas. Version 5.2022—July 12, 2022.

What we learned from the NCCN guidelines but also from many retrospective studies is that these patients, when they have stage one disease or contiguous stage two, are usually best managed using involved site radiation therapy to bring them into response. There is a potential of combining radiation therapy with anti-C20 antibodies. There was an Australian study suggesting that there was a benefit, but I will say that's not necessarily common practice for these patients, especially nowadays in the COVID pandemic era.

For the other patients with noncontiguous stage two, we will then assess the tumor bulk and how this patient does, and eventually adapt another way of treating them.

For Stage I patients, radiation therapy has long been considered standard of care

Radiation for Follicular Lymphoma[1]

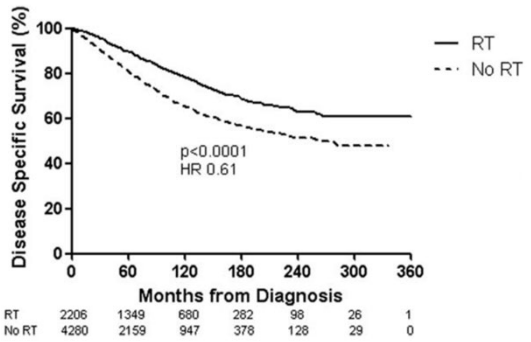


Figure 1. Non-Hodgkin lymphoma-specific survival with or without upfront external beam radiation therapy (RT) is shown. HR indicates hazard ratio.

A 24 Gy RT dose
- **provides equivalent results to 40-45 Gy[2]**
- **provides superior control vs. 4 Gy[3]**

In patients with high-risk features (bulk, high LDH, grade 3, …), other options are recommended[4]

Staging using PET-CT and BM recommended[5]

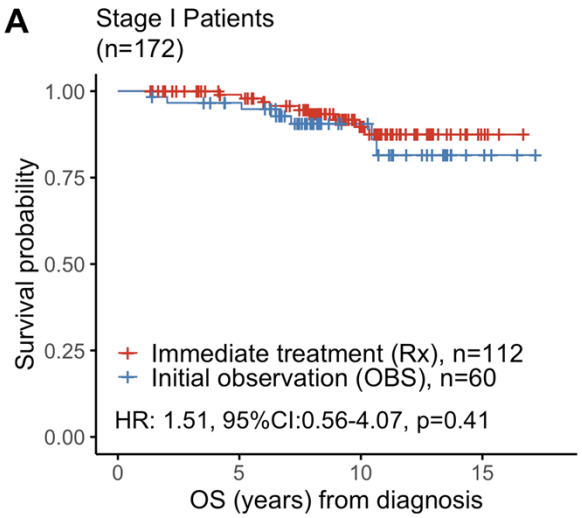
Relapses are not infrequent

[1]Pugh et al. *Cancer*. 2010., [2]Lowry et al. *Radiother Oncol*. 2011., [3]Hoskin et al., *Lancet Oncol*. 2021., [4]NCCN & ESMO Guidelines., [5]Friedberg, et al. *J Clin Oncol*. 2012. [6]Plancarte et al. *Eur J Haematol*. 2006.

Again, this is very old data, indicating that the patients that receive radiation therapy with localized disease had actually a better long-term survival than the patients that did not receive radiation therapy. Over the years, there has been a refinement of the dose of radiation therapy, dose of 40 to 42 Gy has been abandoned to get to a standard dose of 24 Gy.

It does provide superior disease control that an abbreviated shorter course of therapy with 2 by 2 Gy, or 4 Gy, although the overall survival of the patient receiving 24 of 4 Gy is identical. Usually, we consider that patients with high-risk features such as high bulk, large node, high LDH, or grade 3 will probably better be managed with other options. An optimal staging of these patients nowadays will include PET-CT, and eventually bone marrow examination.

Is overall survival improved in stage 1 patients receiving initial radiation therapy?



- The rate of **transformation** increased steadily over time and was 4.2% at 5 years and 10.8% at 10 years

Number at risk				
Rx	112	95	43	4
OBS	60	53	21	4

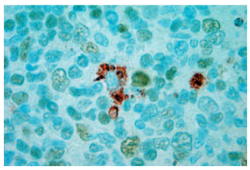
Sha F, et al., *Blood Cancer J.* 2022;12(2):29.

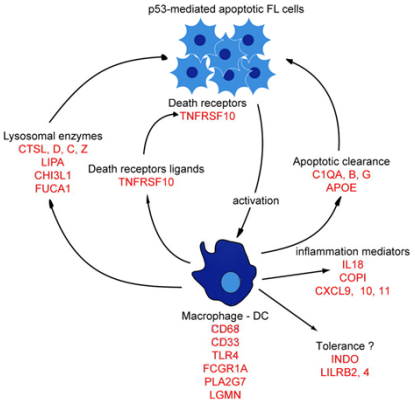
What has been shown recently in one of the studies that we perform at Memorial Sloan Kettering Cancer Center is that delivering initial radiation therapy did not necessarily influence the overall survival as compared to observation.

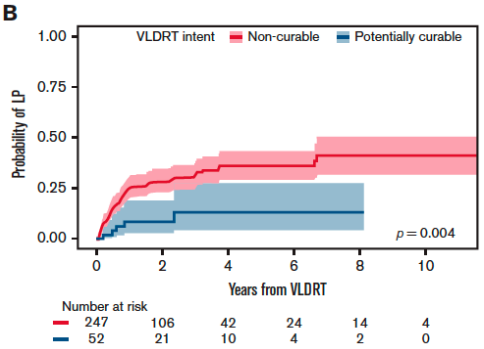
Again, these patients will probably prefer to have treatment. We have to keep in mind that these patients may eventually relapse, and that the rate of transformation increased steadily over time and was in this study up to 10% in that 10 years.

Current and Emerging Directions in the Frontline Treatment of Follicular Lymphoma: Implications for Practice

Low dose (2x2 Gy) radiation therapy in FL

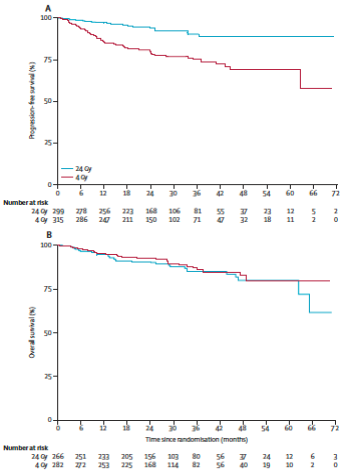






Retreatments:
Median time to new lesion out of field: # 1.5 years

Follicular Lymphoma	24 Gy	4 Gy
Complete regression	152 (67%)	116 (48%)
Partial regression (>30%)	53 (23%)	78 (32%)
Stable disease (including <30% regression)	19 (8%)	40 (16%)
Progression	2 (<1%)	9 (4%)
Total	226	243



Progression-free survival for all sites (A) and overall survival for one site per patient (B)

Knoops L, et al., *Blood*. 2007;110(4):1116-1122.; Hoskin PJ, et al., *Lancet Onc*. 2014;15(4):457-463.; Saleh K, et al., *Cancer Med*. 2020;9(11):3725-3732.; Imber B, et al., *Blood Adv*. 2021;5(20):4185-4197.

Just a few words regarding low-dose radiation therapy, which is one of the practices we have commonly. Again, you can see on the left that there is a biological rationale for this low-dose radiation therapy. You can see that the median time to new lesion out of field is one to two years.

On the right, you can see randomized trial data indicating that the better disease control with 24 Gy as compared to 4 Gy, but again, no overall survival difference.

First-line Management of Patients with Follicular Lymphoma in 2022

1) In patients with localized disease

2) In patients with low tumor burden and/or asymptomatic disease

3) For other patients with high tumor burden in need of systemic treatment

Let's move now to the other patients with more extended disease rather than localized disease. The way we tend to consider these patients is to separate patients with a low tumor burden and/or asymptomatic disease from those with a high tumor burden.

Despite progress in understanding FL biology, clinical features still guide treatment decision

GELF criteria	BNLI criteria	NCCN criteria
✓ High tumor bulk defined by either: - a tumor > 7 cm - 3 nodes in 3 distinct areas each > 3 cm - symptomatic splenic enlargement - organ compression * - ascites or pleural effusion	✓ Rapid disease progression in the preceding 3 months ✓ Life threatening organ involvement ✓ Renal or liver infiltration ✓ Bone lesions	✓ GELF criteria present (original definition) ✓ Threatened end-organ function ✓ Steady or rapid progression (eliminate transformation +++) ✓ Appropriate clinical trial
✓ Presence of systemic symptoms ✓ Cytopenia (leukocytes/platelets) § ✓ Leukemic phase § ✓ Serum LDH or β2-microglobulin above UNL *	✓ Systemic symptoms or pruritus ✓ Hb<10 g/dL or WBC< 3.0×10^9/L or Plat.<100×10^9/L ; related to marrow involvement	

Note: these criteria were eventually withdrawn (§) or added (*) in some subsequent studies (FL2000, PRIMA, RELEVANCE)

Ardeshna KM, et al, *Lancet*. 2003;362(9383):516–522. Brice P, et al., *J Clin Oncol*. 1997;15(3):1110–1117., National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). B-Cell Lymphomas. Version 5.2022—July 12, 2022.

This is done usually using what we used to call the GELF criteria that we established in our group more than 20 years ago, indicating that patients with a high tumor bulk, a large tumor greater than 7 centimeters, three nodes in three distinct areas of 3 centimeters, or some organ involvement by the disease, the presence of systemic symptoms, cytopenia, or eventually high biological features will be the one for whom we would like to initiate treatment. In United Kingdom, there were other criteria that were defined but very similar in fact, if you compare them side by side.

The NCCN criteria actually use the GELF criteria and add to that threatened end-organ function, steady or rapid progression. Obviously, if we have an appropriate clinical trial for patients with a low tumor burden, we may consider it.

First-line Management of Patients with Follicular Lymphoma in 2022

1) In patients with localized disease

2) In patients with low tumor burden and/or asymptomatic disease

3) For other patients with high tumor burden in need of systemic treatment

What do we do for those patients with low tumor burden or asymptomatic disease.

Follicular lymphoma: first line strategy
Low tumor burden / asymptomatic patients

- Difficulties (?) in adopting a watchful waiting strategy and wish to delay the use of chemotherapy
- Good efficacy / safety profile of rituximab as single agent [1-4]
  - > 3 out of 4 patients respond, half of them with CR
  - > but median PFS: 2 to 3 years (but time to next treatment initiation longer ?)
- Several clinical trials have investigated prolonged rituximab treatment:

  RWW, RESORT, SAKK

[1]Hainsworth JD, et al. *Blood*. 2000;95(10):3052-3056.; [2]Colombat P, et al. *Blood*. 2001;97(1):101-106 [3]Ghielmini M, et al. *J Clin Oncol*. 2005;23(4):705-711; [4]Witzig TE, *J Clin Oncol*. 2005; 23(26):6409-6414.

As you know, the standard of care for these patients for many years has been watch and wait, watchful waiting strategy, it was never demonstrated that an early intervention for these patients will change the natural history of this disease.

Because patients have cancer sometimes it is difficult to adopt a watchful waiting strategy, and some patients may not be able to fulfill our expectation to come back for surveillance, and there was also the wish of delaying the use of chemotherapy. For this reason, rituximab single agent was proposed for this patient, gave identical results in several studies, which means that three out of four patients respond, and half of them achieve a CR. However, within two to three years, this will be the median time of starting a new therapy for this patient.

Several trials have attempted to prolong rituximab treatment, but none of them have clearly shown a benefit. In particular in the United States, the RESORT trial where patients receive initially four infusions of rituximab and were randomized to maintenance versus retreatment at the time of progression didn't show an overall survival benefit, showed that there were more side effects in prolonging rituximab treatment, and ultimately this was not a recommendation of the author that recently was updated as a result.

Follicular lymphoma: First line strategy Low tumor burden / asymptomatic patients

- Delaying treatment initiation remains an acceptable option in 2022
  - The objective to use rituximab single agent in order to delay R-chemo (shown to influence overall survival) is questionable
- There is no benefit of prolonged rituximab treatment in patients having a FL with a low tumor burden
- Other approaches, as long as they display a low toxicity profile, are worth being investigated:
  - Immunomodulation, new antibodies, epigenetic drugs, …

I think in 2022, delaying treatment initiation remains an acceptable option. We don't need to use rituximab single agent to delay the use of R-chemo since we know that R-chemo is one of the options that is really improving overall survival when it's needed. There is no benefit of prolonged rituximab treatment in patients with follicular lymphoma and a low tumor burden. Obviously, we would like to continue to investigate, if there are any interventions with more specific drugs, so for instance, drug targeting the epigenetic machinery that can be used in these patients, and continue to design clinical trial for these patients.

First-line Management of Patients with Follicular Lymphoma in 2022

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Let's move now for patients with a high tumor burden, which actually comprise a little bit more than half of the patients we see in our clinic nowadays.

Rituximab + chemotherapy has improved overall survival

Study Name and Author	Follow-up	Overall Survival (%)		*P*
		Control	Rituximab	
M3902; Marcus, et al.[1]	4 years	77	83	✓
GLSG; Hiddemann, et al.[2]	5 years	84	90	✓
M39023; Herold, et al.[3]	4 years	75	89	✓
FL2000; Salles, et al.[4]	5 years	79	84	✓ (high risk pts)

Cochrane analysis:
HR = 0.63 [0.51–0.79]
Schulz H et al. Cochrane Database *Syst Rev*. 2007 Oct 17;(4):CD003805.

[1]Marcus R, et al. *J Clin Oncol*. 2008;26:4579–4586.; [2]Buske C, et al. *Blood*. 2008;112:abstract 2599.; [3]Herold M. *J Clin Oncol*. 2007; 25:1986–1992.; [4]Salles G, et al. *Blood*. 2008;112:4824–4831.

For these patients, the major change as you know, 20 years ago, was the introduction of rituximab, the anti-CD20 antibody in combination with chemotherapy. You see here a couple of different regimens, and a couple of clinical trials that have shown that this was an improvement of overall survival. In Cochrane analysis, a reduction of the risk of this was at 30% for these patients. This has become the standard of care.

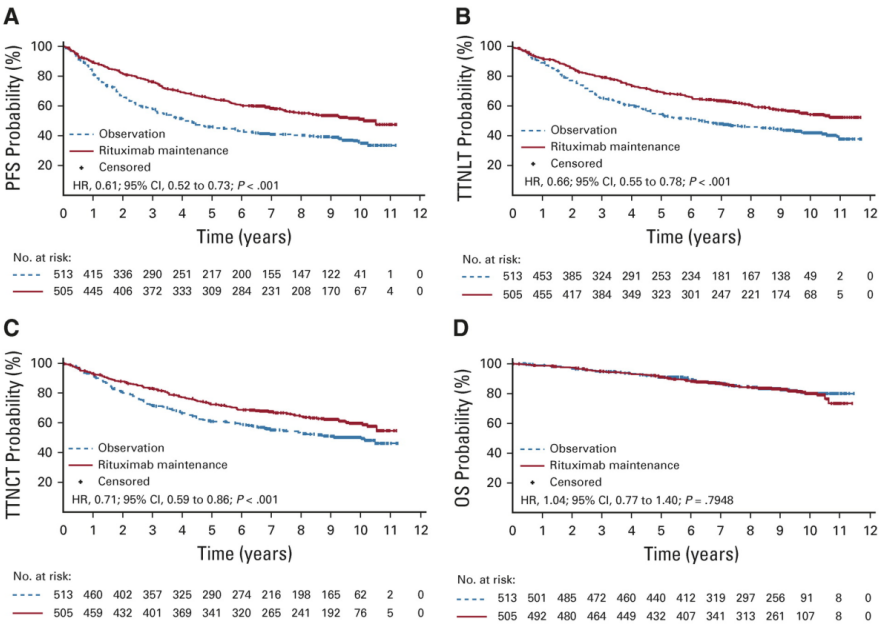
R-chemo + R-maintenance (PRIMA) 10-year updated results

10-year PFS estimates

Observation 35%
R Maintenance 51%

Median time to new treatment initiation

Observation 6.1 y
R Maintenance > 10 y (not reached)



Bachy E, et al. *J Clin Oncol*. 2019;37(31):2815-2824.

What we have shown in the PRIMA study is that after this combination of rituximab and chemotherapy, the use of rituximab maintenance was bringing a benefit in terms of progression-free survival, as shown here. As you can see at 10 years, the progression-free survival for those patients receiving maintenance were 51% versus only 35% for those patients that did not receive maintenance. What I think was interesting was at the time of new treatment initiation was also prolonged, being of six years for these patients without maintenance, and up to 10 years or greater than 10 years for those that receive maintenance.

Despite the fact that's shown on the last curve on the right bottom of the slide, that there was no overall survival difference, this brought to the patients a longer treatment interval.

R-chemo + R-maintenance (PRIMA) 10-year updated results

10-year PFS estimates

Observation 35%
R Maintenance 51%

Median time to new treatment initiation

Observation 6.1 y
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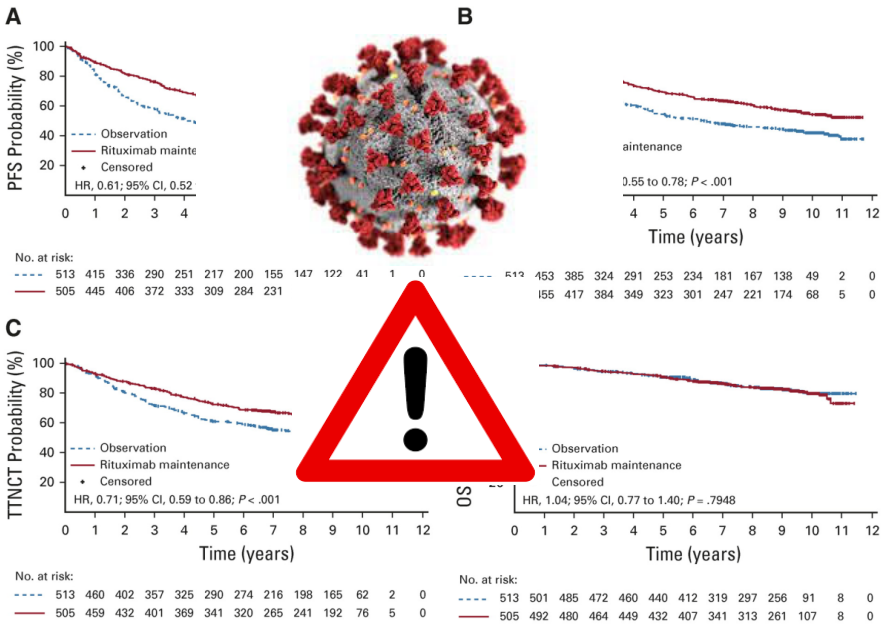
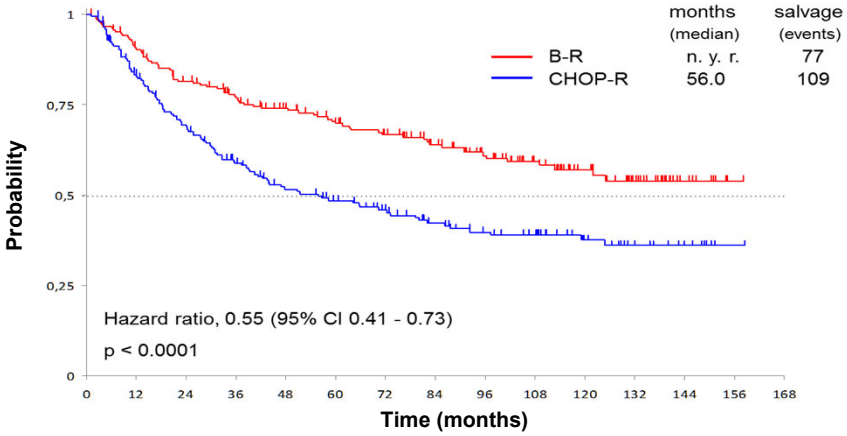


I think we just have to remind ourselves today that in the time of this COVID-19 pandemic, maybe the use of rituximab maintenance may not be as safe as it used to be, may eventually blunt any response to vaccination, and many of us have diminished the use of rituximab maintenance nowadays.

10-year update of the StiL Study

Median f-up 117 months – All histologic subtypes of iNHL

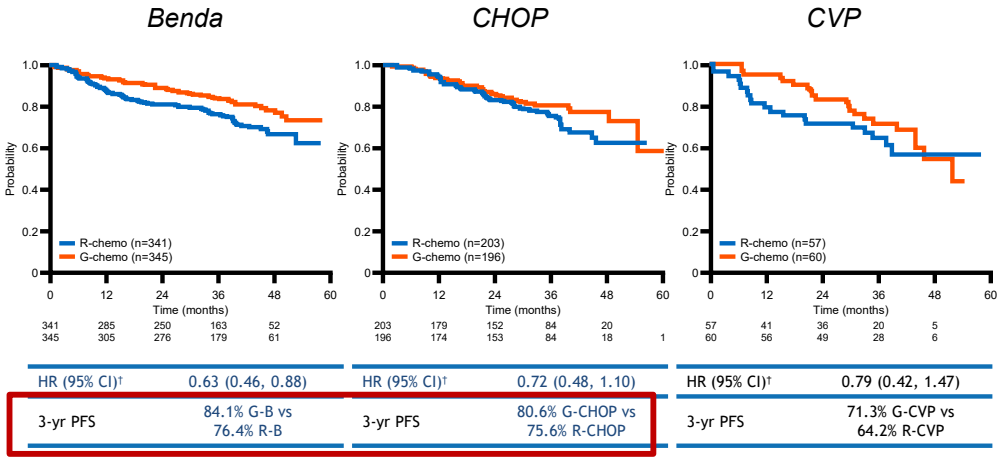
Used TNTT as a surrogate for PFS



Rummel MJ, et al. Abstract #7501. Presented at the 2017 American Society of Clinical Oncology Annual Meeting, June 3, 2017; Chicago, Illinois

The second question is related to the kind of chemotherapy you use. Our colleague in Germany has done this trial, comparing bendamustine versus CHOP in combination with rituximab, and published his early result of data a few years ago, indicating that bendamustine was associated with a better control of the disease than CHOP. I think this led many people to adopt bendamustine as a standard of care, given also the less cytopenia with bendamustine, no hair loss, and the possibility to keep anthracycline regimen for the time of relapse, especially if there was a histologic transformation.

GALLIUM study: INV-assessed PFS by chemo*



HR (95% CI)†	0.63 (0.46, 0.88)	HR (95% CI)†	0.72 (0.48, 1.10)	HR (95% CI)†	0.79 (0.42, 1.47)
3-yr PFS	84.1% G-B vs 76.4% R-B	3-yr PFS	80.6% G-CHOP vs 75.6% R-CHOP	3-yr PFS	71.3% G-CVP vs 64.2% R-CVP

- By chemo analysis not powered to demonstrate statistically significant differences between treatment arms

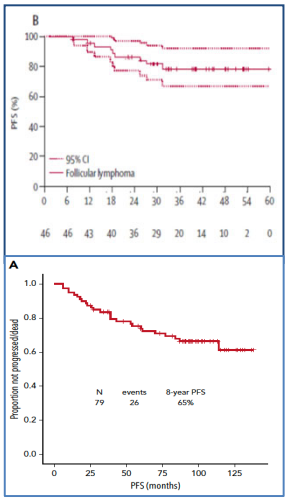
*ITT population; †analysis stratified by IPI (as well as chemotherapy regimen)

Hiddemann W, et al., *J Clin Oncol*. 2018;36(23):2395-2404.

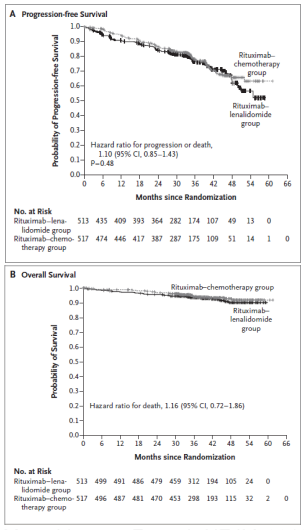
I just would like to point that in the GALLIUM study where there were no randomizations between bendamustine, CHOP, or CVP, the patient received these kinds of chemotherapy and according to the presentation, there were, as you can eventually see, no major difference between bendamustine/CHOP or CHOP/rituximab. The study also evaluated the use of another antibody called obinutuzumab, but as you can see, the benefit of using obinutuzumab in the red curve was not major compared to rituximab, and given the side effect associated with obinutuzumab, was not necessarily brought to standard clinical practice, at least in this part of the world.

Moving away from chemotherapy? Rituximab-Lenalidomide: RELEVANCE

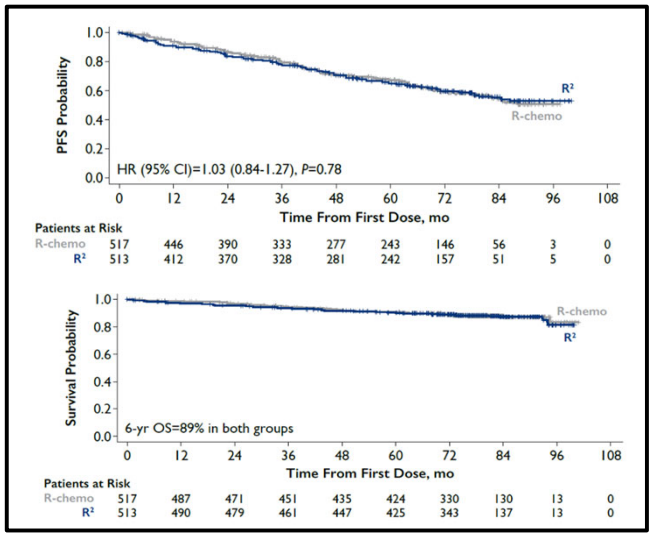
6 years update



Fowler N, et al., *Lancet Onc.* 2014
Strati P, et al., Blood.2021.



Morschhauser F, et al. *NEJM*. 2018.



Morschhauser F, et al. *J Clin Oncol*. 2022.

The question is, are we going to move away from this result? Investigators, Dr. Nathan Fowler and colleagues, published years ago a combination of rituximab and lenalidomide in the first line setting of patients with follicular lymphoma. The initial phase two results prompted an international study called RELEVANCE, where we compare head-to-head this combination of rituximab/lenalidomide to a classical immunochemotherapy regimen, which in most cases was including either R-CHOP or R-bendamustine.

The preliminary results were published four years ago shown in the middle of the slide.

You can see here on the right, the recent update we published showing that there is clearly no difference between rituximab/lenalidomide and rituximab chemotherapy in terms of progression-free survival and overall survival. While the trial design initially attempted to improve PFS, we failed to meet this primary endpoint. Then rituximab/lenalidomide was not approved in the first line setting by FDA, but it's one of the options recommended by the NCCN guidelines. I think many patients can receive that nowadays.

Patients with high tumor burden in need treatment: anti-CD20 + chemo remains the standard of care

- R-Benda ≥ R-CHOP >> R-CVP for PFS, but no difference in OS
  - Different toxicity profiles?
  - CHOP might be privileged in some subgroups (grade 3A, high SUV, bulk or high LDH?)
- Rituximab maintenance improves PFS (but not OS)
  - At 10 years, 63% of pts have not received another chemo after maintenance (PRIMA)
  - Risk/benefit after bendamustine unclear
- Obinutuzumab improves PFS over R (but not OS)
  - Toxicities in some patients?
  - Could G-CVP be an interesting option for certain patients?
- R2 (Rituximab - lenalidomide) is not superior to-chemo
  - And represents a good alternative to avoid cytotoxic agents…

What are the conclusion regarding the management of the patients? We have options which are consisting of rituximab/bendamustine, rituximab/CHOP, or eventually rituximab/CVP. It is an improvement of R-Benda and R-CHOP against R-CVP in terms of PFS, and maybe R-Benda versus R-CHOP, but overall there is no difference in overall survival. They may have different toxicity profiles, and you may choose one or the other depending on patient's characteristics and further individualize treatment.

Maybe CHOP might be privileged in some patients with particular presentation such as grade 3A follicular lymphoma, where we haven't really worried for the possibility of transformation. Similarly for patients with a high SUV on the accumulation of the PET scan, or patients with large bulk or LDH, but again, there is no demonstration that one is really better than the other.

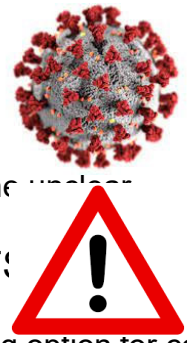
Again, rituximab maintenance improves progression-free survival but not overall survival, and in the PRIMA study at 10 years, two-thirds of the patients did not have to receive another treatment after chemo plus maintenance. The risk-benefit of using maintenance after bendamustine remains unclear.

Obinutuzumab, another anti-CD20 antibody improved PFS over rituximab but not always, but maybe accompanied with some toxicity for patients. I may draw your attention to the fact that this combination of obinutuzumab plus CVP really increases the value of the CVP regimen, and may be an interesting option for frail patients in which we may be worried about the side effect of bendamustine in terms of T-cell depletion.

Finally, rituximab/lenalidomide is not superior to R-chemo but represents a good alternative especially in young patients if we want to avoid a cytotoxic agent.

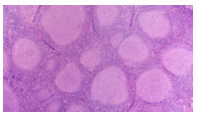
Patients with high tumor burden in need treatment: anti-CD20 + chemo remains the standard of care

- R-Benda ≥ R-CHOP >> R-CVP for PFS, but no difference in OS
  - Different toxicity profiles?
  - Should a particular regime[illegible] e subgroups (grade 3A ? High SUV?)
- Rituximab maintenance [illegible] t not OS)
  - At 10 years, 63% of pts ha[illegible] er chemo after maintenance (PRIMA)
  - Risk/benefit after bendamustine [illegible]
- Obinutuzumab improves PF[illegible] ɔut not OS)
  - Toxicities in some patients?
  - Could G-CVP be an interesting option for certain patients?
- R2 (Rituximab - lenalidomide) is not superior to-chemo
  - But seems a good alternative…



Again, in the field of the COVID pandemic, we may be willing to adapt the options for those patients according to the way they can protect themselves, vaccinated or not, or eventually benefit from antibody coverage.

Bi-specifics CD3 x CD20 in patients with R/R FL (updated April 2022)

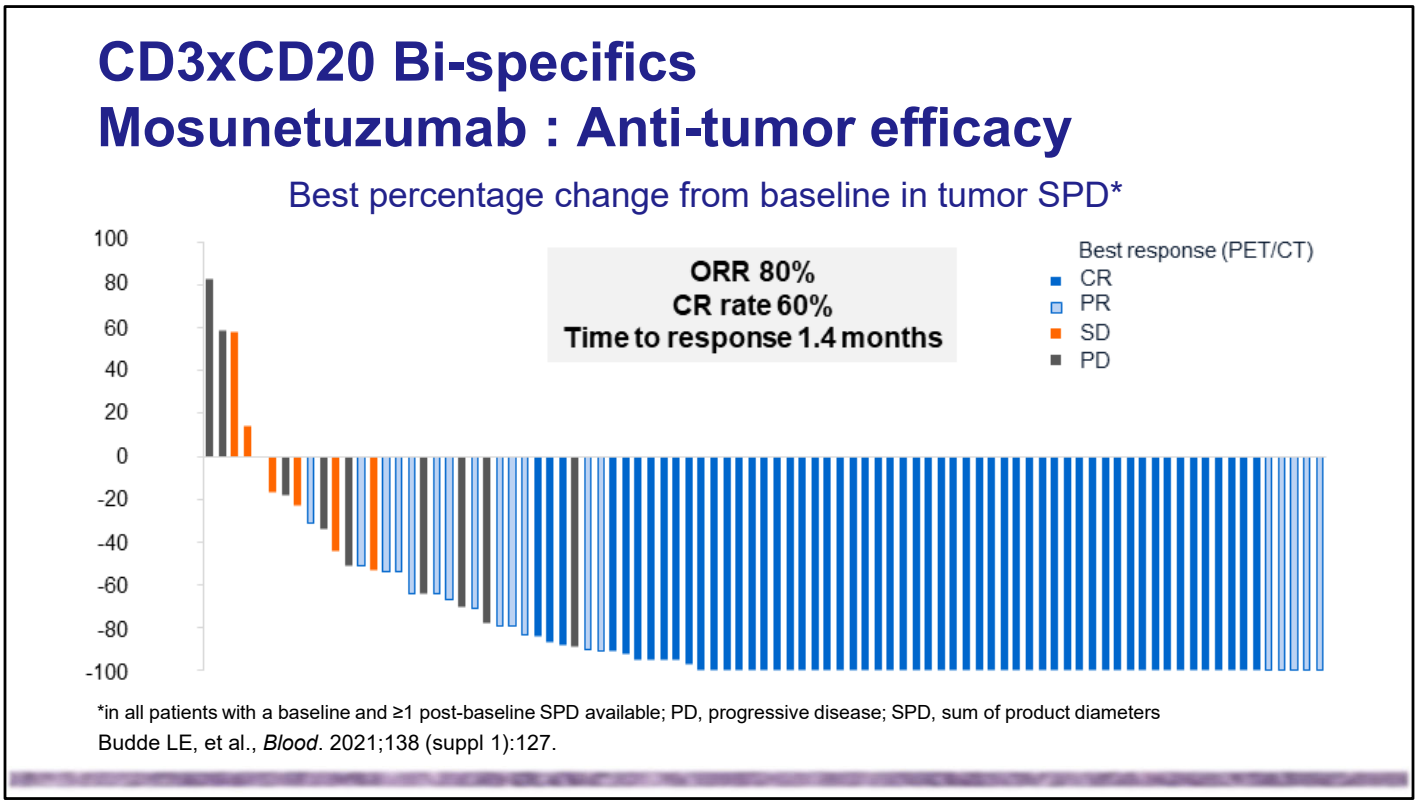


	Mosunetuzumab (RG7828)[1]	Odronextumab (REGN1979)[2]	Glofitamab (RG6026)[3]	Epcoritamab (GEN3013)[4]
Patients	90	32	53	10
ORR	80%	93%	81%	90%
CR	60%	72%	70%	50%

Budde LE, et al., *Blood*. 2021;138 (suppl 1):127. [2]Bannerji R, et al., *Lancet Haematology*., [3]Morschhauser F, et al. *ASH 2021*., [4]Hutchings M, et al., *Lancet Onc*. 2021.

What is coming up in the field and what is emerging are a new class of drug which we call bi-specific antibody. These bi-specific antibodies bind on one side of the tumor and on antigen which is CD20 that we all know well, and on the other side, on the other arm of the antibody, engage the T-cell receptor with the CD3 antigen. These bi-specific antibodies, have first been developed in the relapse setting. You can see here on this table the recent results that were presented with four different drugs being similar in the design targeting CD3 and CD20.

As you can see, the overall response rate was very high in the relapse setting, and the complete response rate was ranging from 50% up to 72%. It's possible that in the near future, this bi-specific antibody will be in clinical trial for the first line management of patients with follicular lymphoma, and may further push us away from the classical immunochemotherapy combination.



Just here are shown the result of mosunetuzumab, which can be delivered also now as a subcutaneous antibody in the relapse setting. Again, an overall response rate of 80%, a CR rate of 60%. Several clinical trials are being performed in different parts of the country investigating this drug in the first line setting.

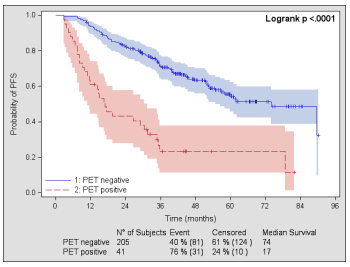
EOI-PET is highly predictive of PFS & OS in FL:

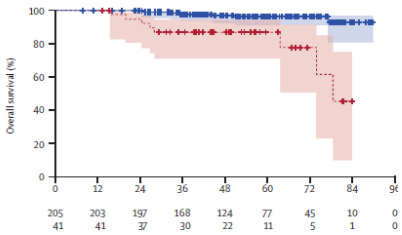
… FL is no longer an indolent disease for the PET-positive

> 4 x risk of progression

>5-fold risk of death

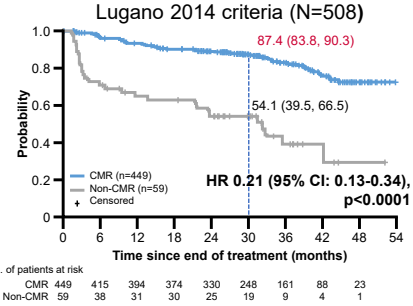
FOLL-COLL:
(PRIMA, FOLL05,
PET-FOLLICULAIRE)
Trotman, *Lancet Haematology*, 2014.



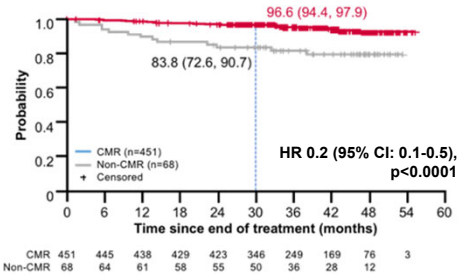


GALLIUM:
Trotman, *Lancet Oncology*, 2018.

Lugano 2014 criteria (N=508)

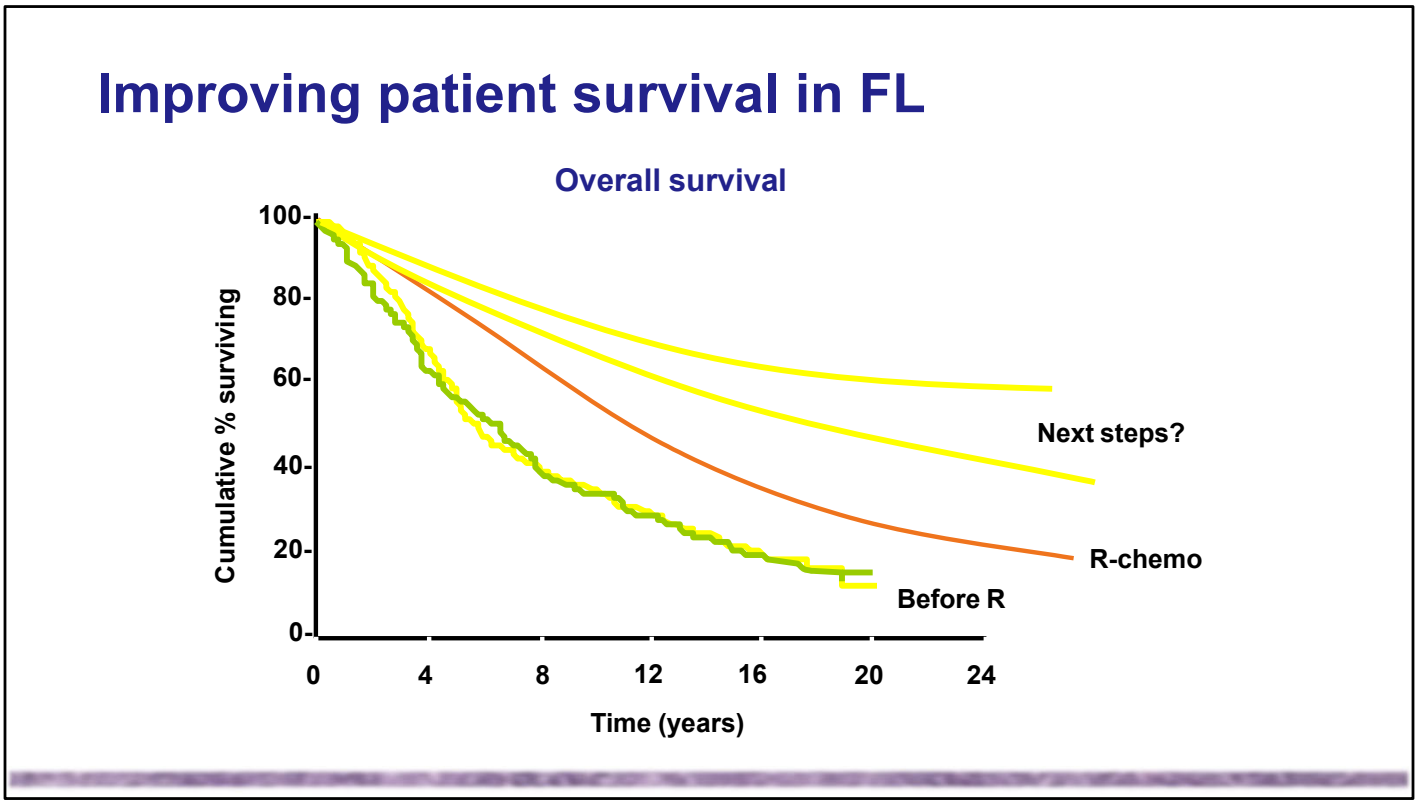


Lugano 2014 criteria (N=519)



5yr PFS 70% vs 29% in non-CMR
5yr OS 92% vs 80%.
POD24 risk 8.8 fold in non-CMR

I would like to deliver a last message regarding the evaluation of patients after having completed either immunochemotherapy or the R-squared regimen, which is the evaluation of these patients using PET-CT. From retrospective data, looking at the patients that were in several clinical trial such as PRIMA, FOLL05, a dedicated trial using PET, or even in the GALLIUM trial, it was shown that those patients that at the end of what we call induction therapy, the six months of immunochemotherapy or R-squared, had positive PET results, had a higher risk of progression and a higher risk of death than the other one. Maybe this includes a couple of patients who
may develop a disease that is transformed during this induction therapy. Maybe that is just a testimony of resistance to a classical agent. We should consider for these patients a possibility to do a new biopsy or to observe them closely and eventually to adapt their treatment if they progress.



Our ultimate goal obviously for patients with follicular lymphoma has been to continue to improve overall survival even if at this time we are not able to say that we cure patients. Rituximab has clearly brought benefit compared to chemotherapy only. Maintenance may bring another benefit. I think that our goal is to continue to leverage this curve and have patients benefiting from longer treatment-free interval, and optimally improving their overall survival.

That's my way of handling patients with newly diagnosed follicular lymphoma and I will be happy to discuss these options with you, Dr. Armitage.

Dr. Jim Armitage: Thank you, Gilles. That was a wonderful presentation. Because we have a few minutes, I'm going to ask you a few things that I think are interesting, and I hope the audience will think is interesting.

First comment is you commented, most people would say low-grade follicular lymphoma is not a curable disease, but I know you must have, because I have patients who are in remission 30 or 40 years after their initial treatment, even going back to the days before rituximab. I tend to tell people, most people are not cured. Most people will require other therapy if you wait long enough, but some people appear to be, at least they never relapsed during their life. We'll hope that you're one of those people who might be cured if cure means you die of something else before the lymphoma comes back. How do you tell patients about that? How do you tell them about their future?

Dr. Gilles Salles: That's a very interesting question. I usually am cautious with the patient when I meet them for the first time. I obviously present the fact that we have a good way to treat them and offer them a treatment that will bring them in a complete response or very good complete response, and that they may benefit from very long treatment-free interval. I also mention to them that we have efficient treatment at the time of relapse. When I meet a patient that is maybe 10 years off of his first line chemotherapy, I say that I don't know if the disease will recur or not.

I think that we have data suggesting that the risk of recurrence diminishes with time, but we all have seen patients alive without recurrence for 20 plus years, but also very late relapse at 15 years. I think we should continue to watch these patients. Again, we may discuss with them what we tend to call functional cure, which is basically having a normal life. Even if you have one or two lymph nodes of 1 or 2 centimeters, you don't need to re-initiate a treatment, and you don't have probably to impose to this patient a very regular imaging scan and things like that. Rather, adopt a more clinical follow-up for this patient, and only go for imaging if something happens.

Dr. Jim Armitage: Thank you. I agree with you. All right. Second thing, some of our audience might have seen and wonder how you deal with it. What do you do with a patient that has what people might call diffuse follicular lymphoma? It's a low-grade follicular lymphoma, but diffuse growth pattern. Used to be different, today it's in the same disease category. Does it make any difference to you if a pathologist tells you that?

Dr. Gilles Salles: I think there are different presentations of this patient with diffuse involvement in the lymph node. Some of these patients vary schematically because not all are the same. A young woman with inguinal nodes and this diffuse histological pattern, we know now that these are probably follicular lymphoma a little bit different. They don't necessarily carry the BCL2 IGH translocations. They have other mutation pattern, and these patients do extremely well. Either watch and waiting or just radiation therapy, these patients may go on for years without having to start another treatment. Things are a little bit different for those patients with more disseminated disease, lymph nodes above and below the diaphragm will rather handle and propose to this patient the same strategies as those patients with other forms of the disease.

Dr. Jim Armitage: Thank you very much. As I said, I think that can be a confusing thing to be told that you think they have follicular lymphoma if the growth pattern is different, and I'm very interested in your responses. Along that same line, what to you is high-grade follicular lymphoma that should be treated differently?

Dr. Gilles Salles: That's a very important question. We clearly have follicular lymphoma that are, I will say, homogeneous, and that are grade 1/2 follicular lymphoma. Then we have the patients who present in the lymph node with an increased number of large cell. Those roles were called grade three, and further subdivided between grade 3A where this pattern was really mixed with small cells, or grade 3B where there were follicles that were essentially consistent in large cell. If there are diffuse areas of large cell, this is clearly a different disease, and this is the coexistence of follicular lymphoma and diffuse large B cell lymphoma.

What is a little bit unknown at this time is really how these patients with follicular 3A or 3B behave. I think most of us consider that this follicular 3A do similarly well that follicular grade 1/2, while we think that the patient with follicular 3B should be managed probably with an anthracycline-based regimen, essentially with R-CHOP. The issue is that it's sometimes not very easy unless you have experienced pathologists working with you to make this distinction between 3A and 3B. If you have any doubt, I will say that may be an argument to go for an anthracycline-based regimen.

There have been some suggestions that some of these patients may have even a lower risk of relapse at grade 1/2. Also, there is no clear definitive answer to this question. I will say that's a gray area. My advice is if you hear that this is a grade three, ask your pathologist to review the case, go into more details. If you are grade 3B, clearly the management of this patient is high risk, and should be similar to the management of DLBCL. For grade 3A, maybe integrate the other clinical variables such as the tumor burden, the level of LDH, the presentation, and adapt your strategy individualized based on these findings.

Dr. Jim Armitage: Thank you. A couple other quick therapeutic questions. Bi-specifics are really interesting drugs. Maybe poor person's CAR T-cell therapy, they're exciting, but how to use them is interesting. Do you see them as a single agent, assuming that they continue to work, everything pans out, there's no new toxicities? Do you see them eventually as a single agent as initial therapy, or do you see them as consolidation therapy after remission induced otherwise, in attempted cure, or what? How would you see these are going to be used?

Dr. Gilles Salles: I think it's a field full of investigation. First of all, a few comments regarding bi-specifics, because as you said, although they are usually considered to be safe drug, they're associated with side effects which are essentially side effects during the first one, two, or three infusions of the drug, consisting of systemic symptom, similar to what we see with CAR T, but to a much lesser extent of severity. Grade 1/2 cytokine release syndrome, potentially rashes. If this is a sub-Q drug, rashes at the site of injection. Very, very limited number of so-called neurological events.

I think these patients can be easily managed, but you have to train physician and your clinical team, nurse, physician assistant to manage these patients. Right now, most of those will go to an ambulatory care management, what we call step-up dosing with increasing dose of the antibody with the first injections.

What we do right now, we have a study where we use them as single agent, because I believe that the numbers that have been shown in terms of overall response rate and CR rate in the relapse setting are probably going to be better in the first line setting. Obviously, this is a clinical trial.

Other clinical trials are combining them with lenalidomide, or are eventually combining them with chemotherapy. My hope still is that this drug will help us to move away from chemotherapy in the first line setting. Whether they are used alone, whether they are used with lenalidomide, with an antibody drug conjugate, or another drug, I think that's how I see them. What we don't know, and that's a major question, is the duration of the response achieved with this drug. The results are very premature, but I think it's worth trying and it's worth investigating this field. I believe that this drug will play a major role in the management of our patients in the near future.

Dr. Jim Armitage: One last therapeutic question that I suspect given your history with this regimen, people would like to know how you really today use lenalidomide and rituximab, the so-called R-squared regimen. Outside of a study, you have a patient who doesn't fit or doesn't want to be in a clinical trial, which one of those would you personally recommend that regimen over BR or something else?

Dr. Gilles Salles: As I mentioned, I still have a little a group of patients in which I prefer to have an anthracycline-based regimen; 3A, high LDH, high bulk. Let's take all the other patients. I usually tell them that R-squared is a good option that will allow them to have a life without many side effects, although there are some side effects with this combination. That could be an option to consider. Obviously, they have to be covered by insurance for lenalidomide, which is an expensive drug. If the patient is amendable to this possibility, I propose to start this regimen.

There is usually during the first month four infusion of rituximab as a loading process. I start lenalidomide at a dose of 20 milligram per day, 21 day out of 28. I warn the patient about the possible side effects of lenalidomide, a few cytopenias, but that are usually not clinically relevant. Eventually, a few GI symptoms, and in about 10% to 15% of the patient, rashes that are easily manageable with a little bit of antihistamines, or steroids, interruption of lenalidomide. Eventually in patients that are more frail or elderly, I tend to adapt very quickly the dose of lenalidomide dropping down to 15 or 10 milligram. I try to bring this patient in over the first six months regularly with this scheme.

If they achieved a complete response, I drop lenalidomide. I continue for another year the combination, and in patients that are ready to accept that, continue with some maintenance features as it was initially developed in RELEVANCE. I think it's an easy regimen for patients that are willing to accept. The surveillance in the initial period, managing the side effect, and the patient to whom I offer that were rather happy on this regimen. I think we should envision it if it's feasible in terms of the insurance coverage, and if this represent a good option for them, despite the fact that the treatment is more prolonged.

Dr. Jim Armitage: Do you give anybody anticoagulation? What do you do about that?

Dr. Gilles Salles: No, I usually give only aspirin for these patients. I think these patients are pretty ambulatory. The risk of deep thrombosis is inferior in lymphoma as compared to what it is in myeloma, they don't have the same hyperviscosity. Unless this is a patient that has a previous history of DVT or thrombosis, or a patient that is not really agile and things like that, I will just tend to give aspirin for these patients.

Dr. Jim Armitage: Gilles, thank you very much. I suspect that our audience will get the pleasure that I do when you get to listen to a person who's a real expert, who really does this, has a huge amount of experience, and in your case has actually changed the field. It's wonderful to have a chance to listen to you. I know that the people that will watch this will also get great pleasure. I thank them for viewing. Thank you very much.

Dr. Gilles Salles: Thank you very much, Jim.