Role of Radiotherapy

Umberto Ricardi

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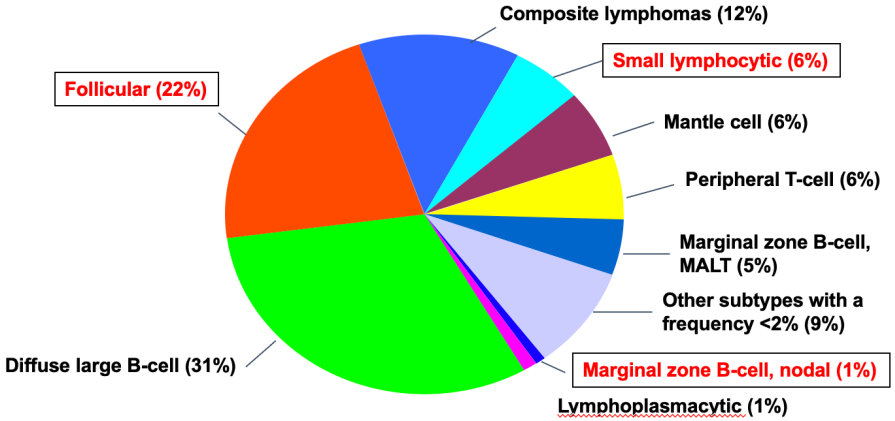
Non Hodgkin B cell Lymphoma:

a heterogeneous disease

Frequency of indolent nodal NHL Subtypes in Adults



Armitage et al. *J Clin Oncol.* 1998;16:2780–2795.

Follicular Lymphoma (FL) is the Second Most Common Type of NHL, Accounting for 22% of NHL

ESTRO School

15,690
FL patients diagnosed annually in the U.S.[1]

12,900
FL patients diagnosed annually in EU5[1]

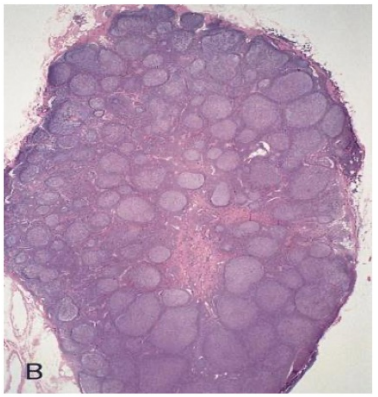
Median survival
~ 14 years

20-33% of FL cases turn into more aggressive diffuse large B-cell lymphoma (DLBCL)

- **Median** age at diagnosis is 62 year
- **Much more common in Caucasians** than in Blacks or Asians - rare in some parts of the world eg Far East and parts of Africa

1. Datamonitor 2012 epidemiology data

Low Grade Follicular Lymphoma



- 20-25% FL have Ann Arbor stage I-II (A)
- Most stage I-II patients have nodal disease only
- Highly radiosensitive

Early Stage Follicular Lymphomas

- Standard treatment: Involved Field Radiotherapy (IFRT), historically 36-40 Gy
- The shape of OS curve suggests a possible plateau in the potential for a cure
- Most relapses occur outside the radiation field

Results of radiotherapy in stage I/II (Stanford, 177 pts):

	5 years	10 years	15 years	20 years
Survival	82%	64%	44%	35%
Relapse-free	55%	44%	40%	37%

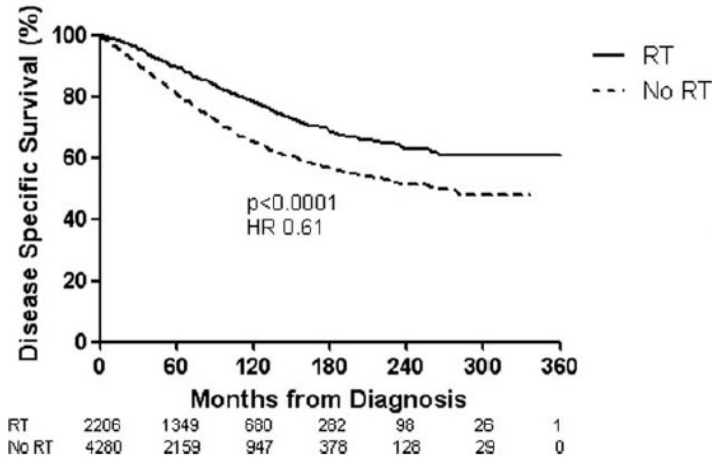
Ref.: MacManus,MP et al.; JCO 14: 1282-90 (1996)

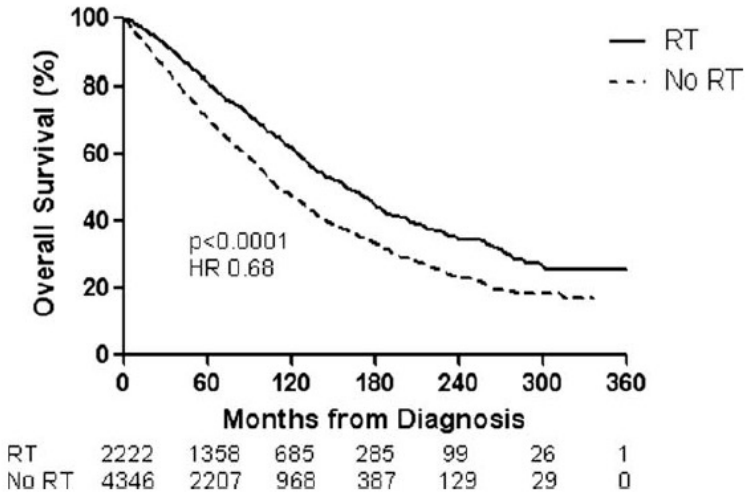
Improved Survival in Patients With Early Stage Low-Grade Follicular Lymphoma Treated With Radiation

Cancer 2010;116:3843–51

A Surveillance, Epidemiology, and End Results Database Analysis

Thomas J. Pugh, MD; Ari Ballonoff, MD; Francis Newman, MS; and Rachel Rabinovitch, MD



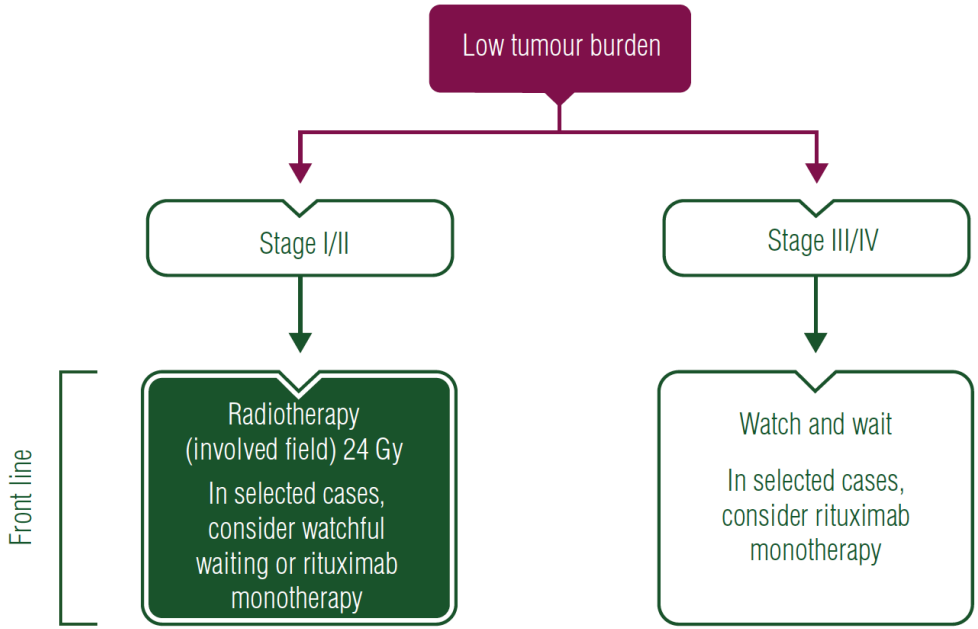


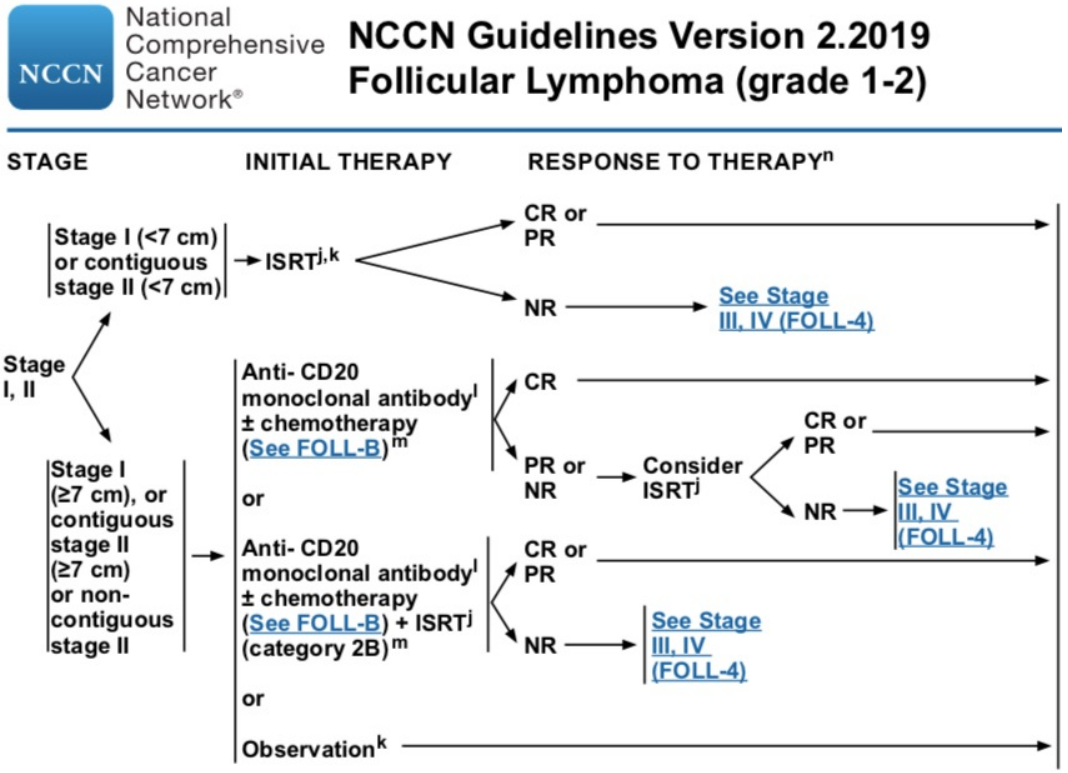
Radiation Therapy has low toxicity and high efficacy

Annals of Oncology 27 (Supplement 5): v83–v90, 2016
doi:10.1093/annonc/mdw400

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

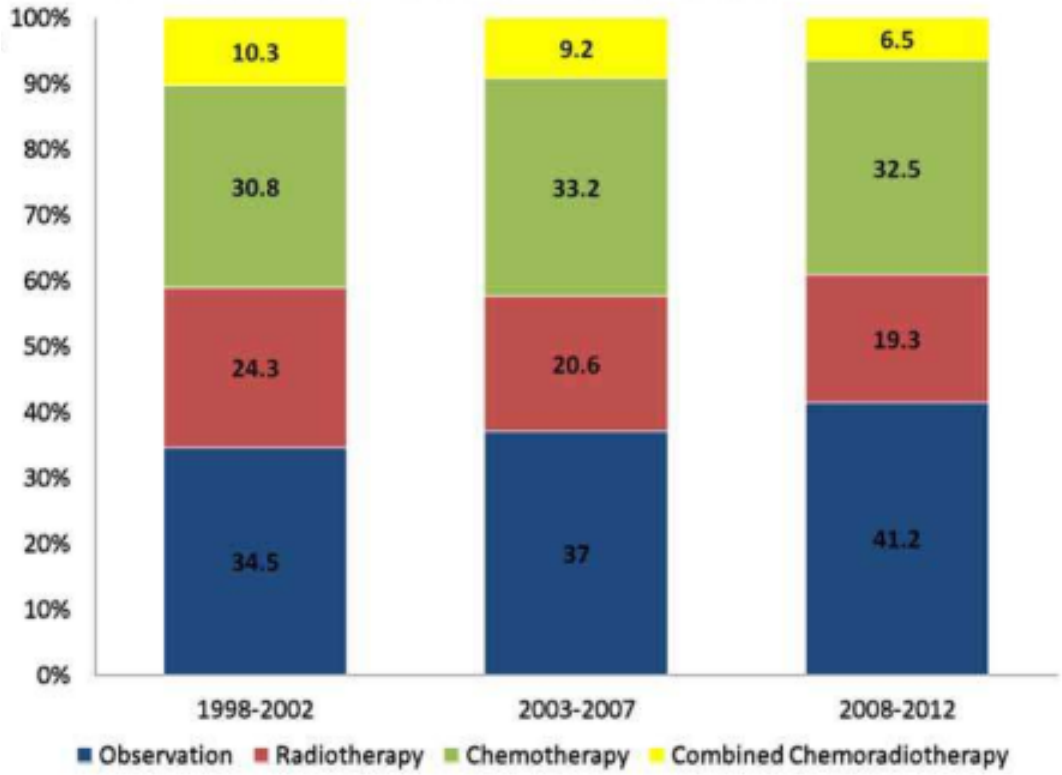
M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4], U. Vitolo[5] & M. Ladetto[6], on behalf of the ESMO Guidelines Committee*

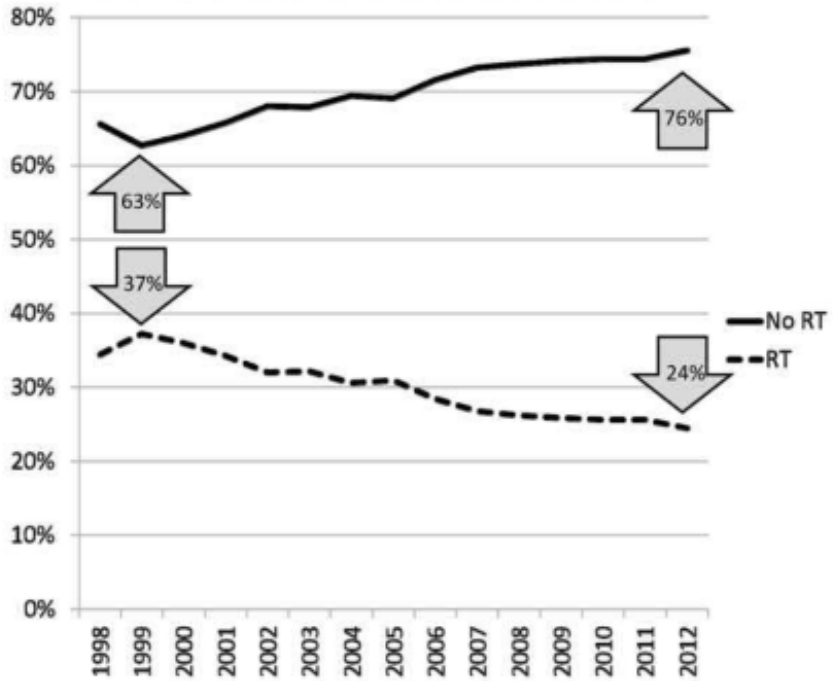




What Is the Optimal Management of Early-Stage Low-Grade Follicular Lymphoma in the Modern Era?

John A. Vargo, MD[1]; Beant S. Gill, MD[1]; Goundappa K. Balasubramani, PhD[2]; and Sushil Beriwal, MD[1]





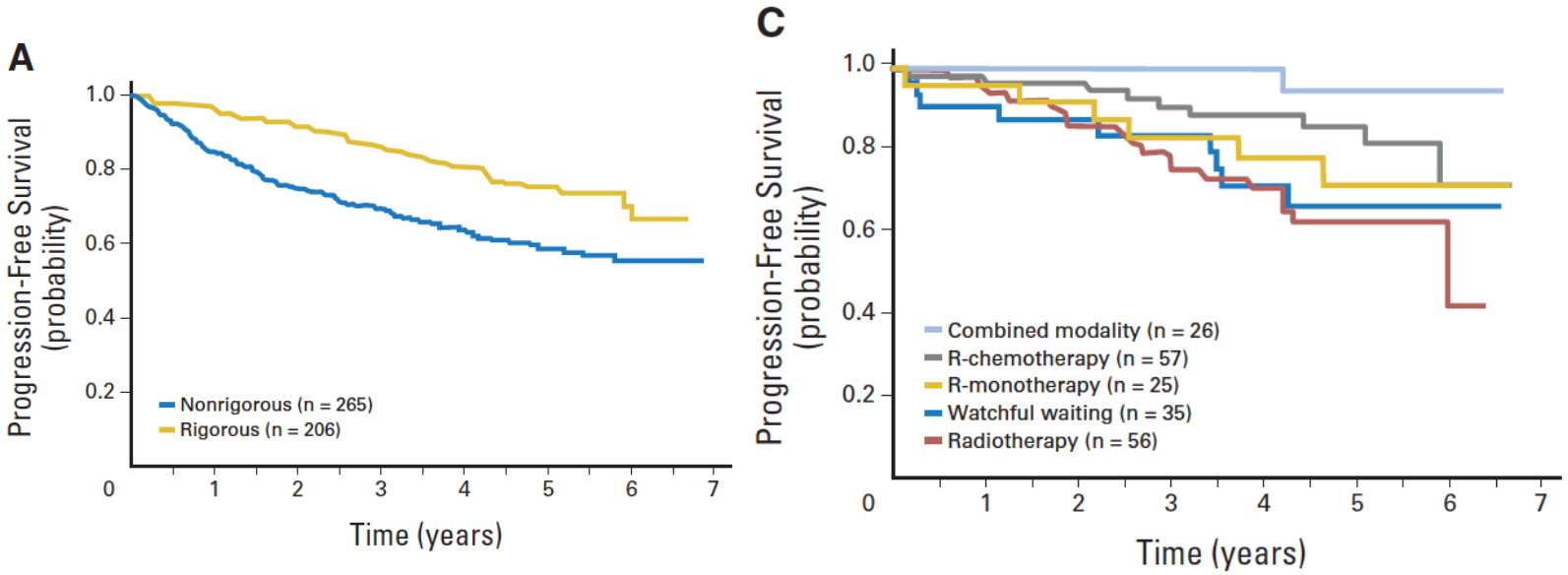
Vargo et al. Cancer 2015

CONCLUSIONS: RT is an increasingly underused treatment approach in the era of modern therapy for patients with early-stage follicular lymphoma

Effectiveness of First-Line Management Strategies for Stage I Follicular Lymphoma: Analysis of the National LymphoCare Study

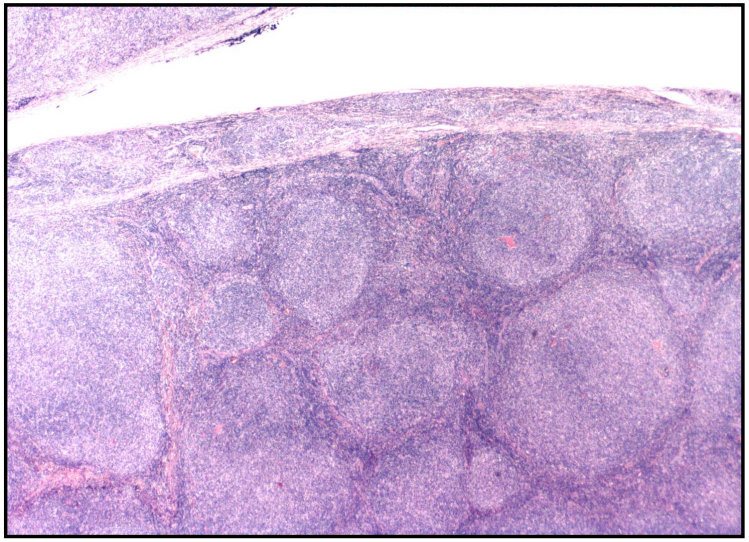
Jonathan W. Friedberg, Michelle Byrtek, Brian K. Link, Christopher Flowers, Michael Taylor, John Hainsworth, James R. Cerhan, Andrew D. Zelenetz, Jamie Hirata, and Thomas P. Miller

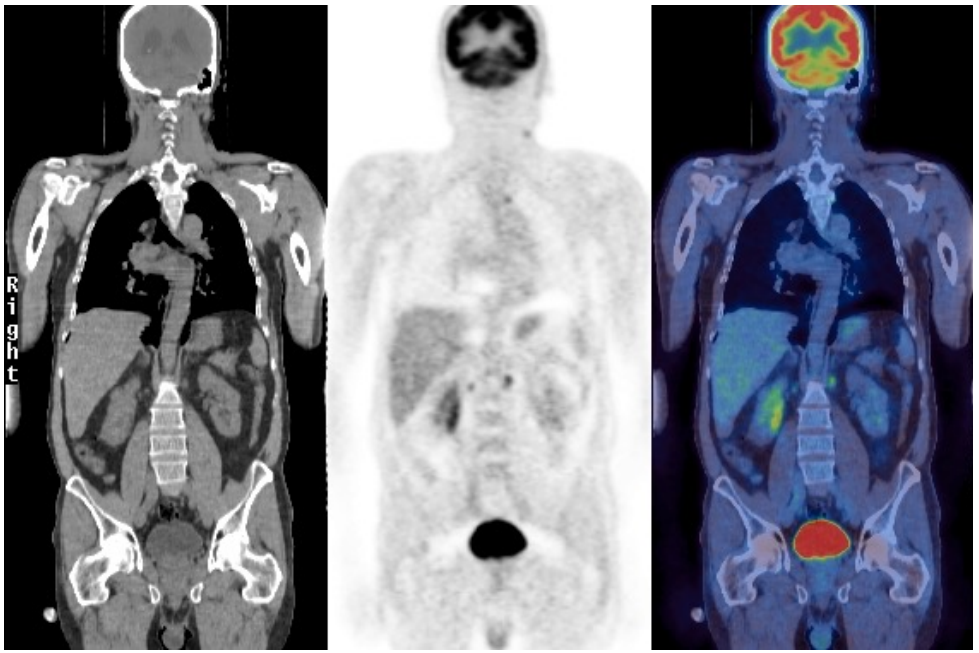
J Clin Oncol 30:3368-3375. © 2012



Of 471 patients with stage I follicular lymphoma, 206 patients underwent rigorous staging

Follicular lymphoma: what staging?





Thorough staging with bone marrow biopsy
and FDG-PET essential

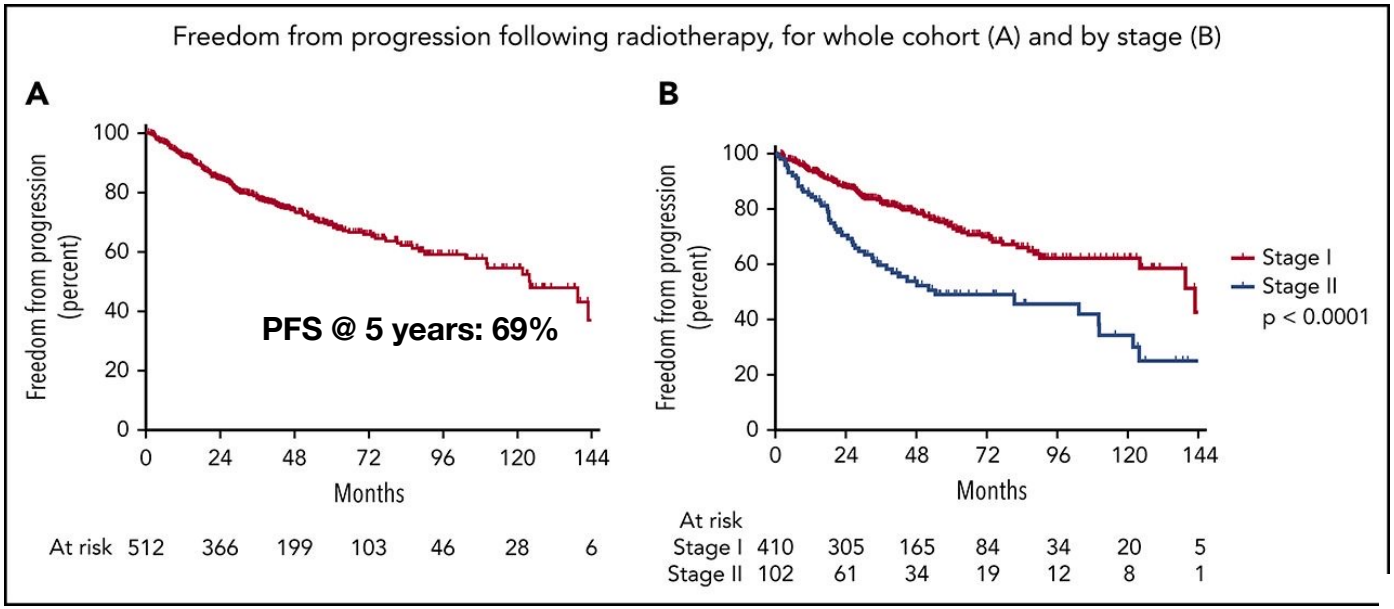
Definitive radiotherapy for localized follicular lymphoma staged by ^{18}F-FDG PET-CT: a collaborative study by ILROG

Jessica L. Brady,[1,*] Michael S. Binkley,[2,3,*] Carla Hajj,[4] Monica Chelius,[4] Karen Chau,[4] Alex Balogh,[5] Mario Levis,[6] Andrea Riccardo Filippi,[6] Michael Jones,[7] Michael Mac Manus,[8,9] Andrew Wirth,[8] Masahiko Oguchi,[10] Anders Krog Vistisen,[11] Therese Youssef Andraos,[12] Andrea K. Ng,[13,14] Berthe M. P. Aleman,[15] Seo Hee Choi,[16] Youlia Kirova,[17] Sara Hardy,[18] Gabriele Reinartz,[19] Hans T. Eich,[19] Scott V. Bratman,[2,3] Louis S. Constine,[18] Chang-Ok Suh,[16] Bouthaina Dabaja,[12] Tarec C. El-Galaly,[11] David C. Hodgson,[7] Umberto Ricardi,[6] Joachim Yahalom,[4] Richard T. Hoppe,[2,3] and N. George Mikhaeel[1]

blood® 17 JANUARY 2019 | VOLUME 133, NUMBER 3

KEY POINTS

- **Outcomes after RT for stage I and localized stage II FL after PET-CT staging are better than those in historical series.**
- **More than two-thirds of patients remain in remission at 5 years, and most relapses occur at distant sites.**



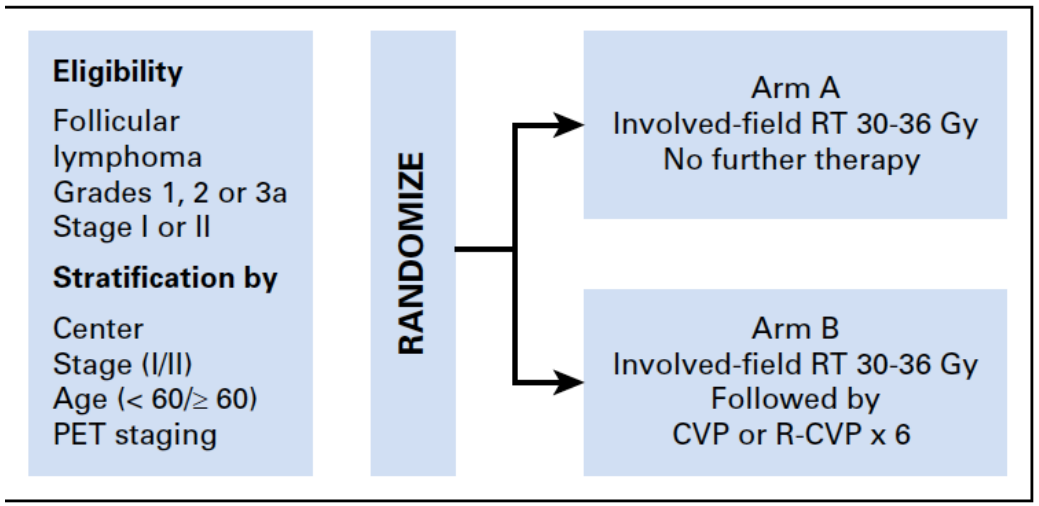
Local control rate of 97.6%

Combined Modality Therapy in Stage I-II FL?

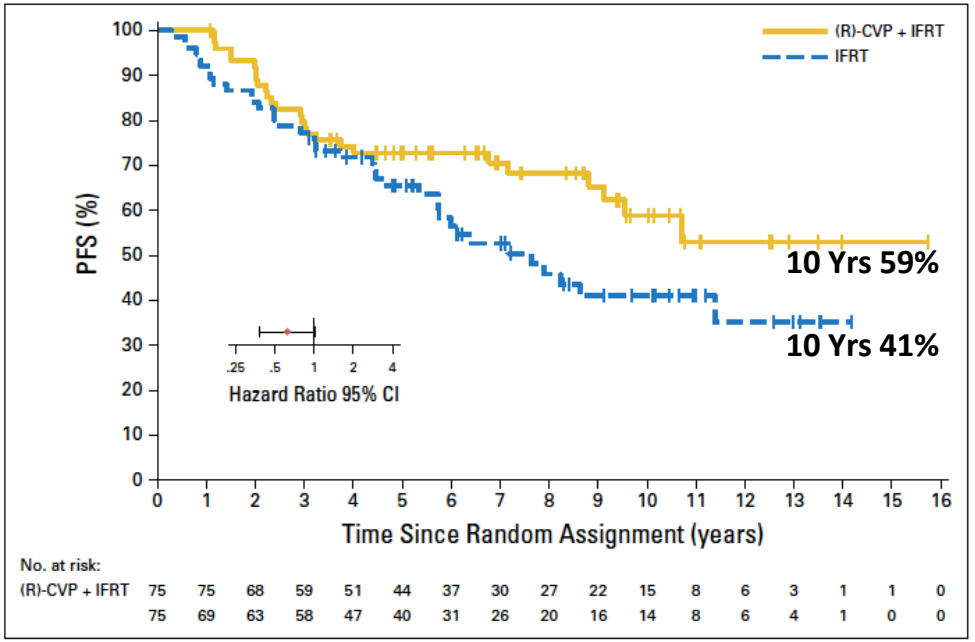
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT J Clin Oncol 36. © 2018

Randomized Trial of Systemic Therapy After Involved-Field Radiotherapy in Patients With Early-Stage Follicular Lymphoma: TROG 99.03

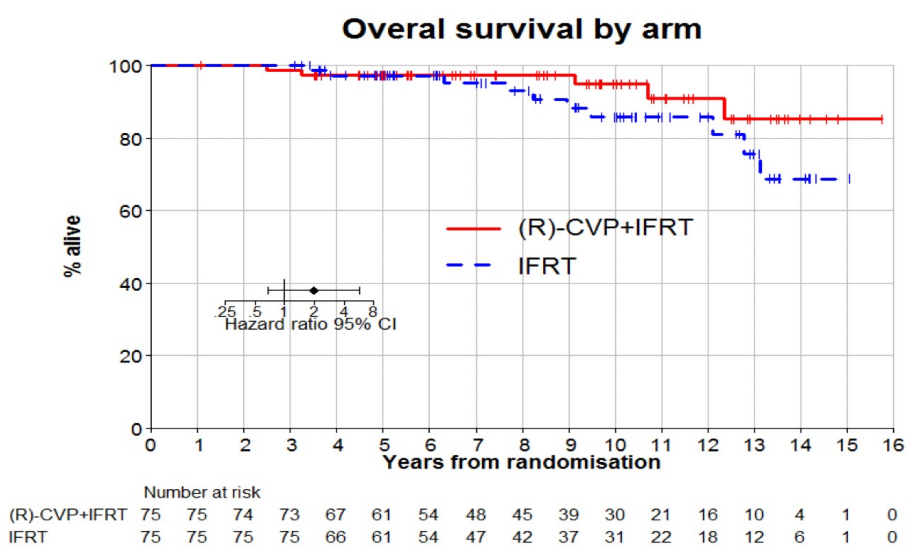
Michael MacManus, Richard Fisher, Daniel Roos, Peter O'Brien, Andrew Macann, Sidney Davis, Richard Tsang, David Christie, Bev McClure, David Joseph, Jayasingham Jayamohan, and John F. Seymour

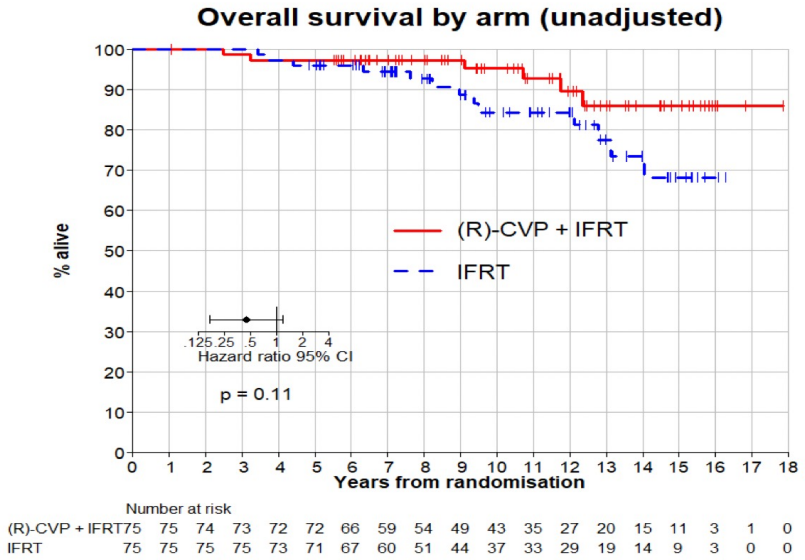


Median age: 57 yrs



Randomized Trial of Systemic Therapy After Involved-Field Radiotherapy in Patients With Early-Stage Follicular Lymphoma: TROG 99.03





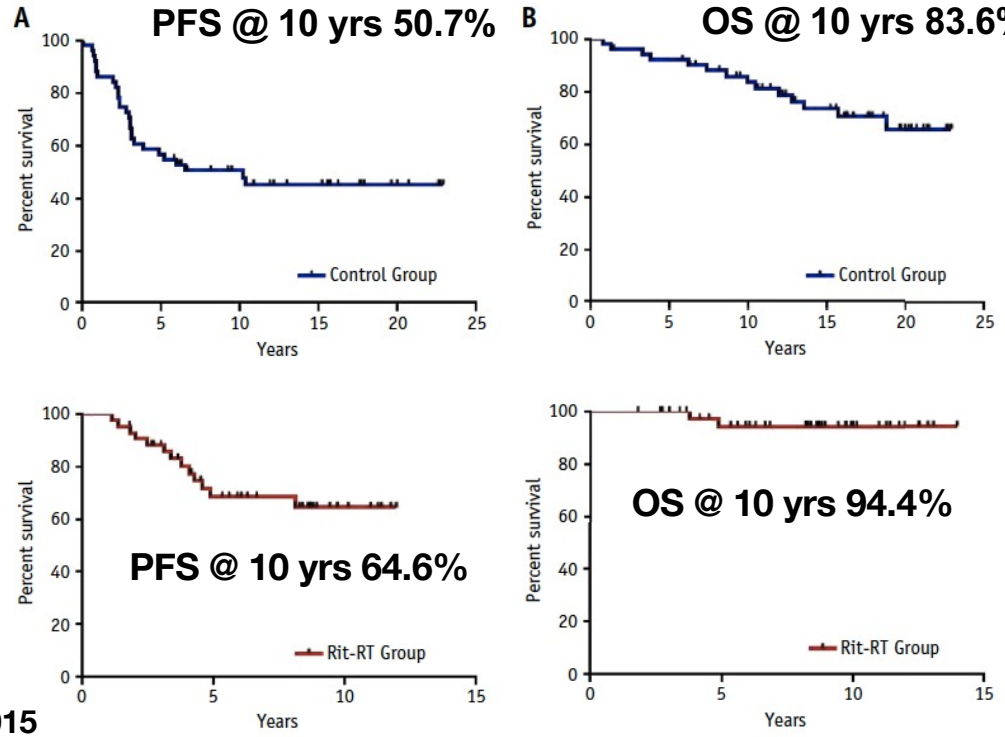
First Analysis p=0.4

Final Analysis p=0.11

MacManus et al. JCO 2018

Addition of Rituximab to Involved-Field Radiation Therapy Prolongs Progression-free Survival in Stage I-II Follicular Lymphoma: Results of a Multicenter Study

Int J Radiation Oncol Biol Phys, Vol. 94, No. 4, pp. 783–791, 2016



4 rituximab courses (375 mg/m^2 , days 1, 8, 15, 22) before RT 36 Gy (Rit-RT)

Ruella et al. IJROBP 2015

Standard RT +/- Rituximab

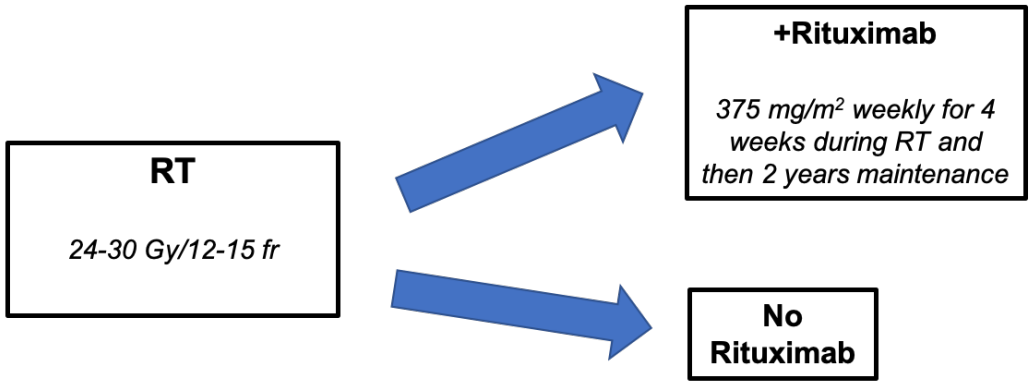
Randomized Trial of Radiation Therapy With and Without Rituximab for Patients With Stage I-II Follicular Lymphoma Grade I/II

M.D. Anderson Cancer Center | Bouthaina Dabaja, MD

Estimated Enrollment 130 patients

Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)

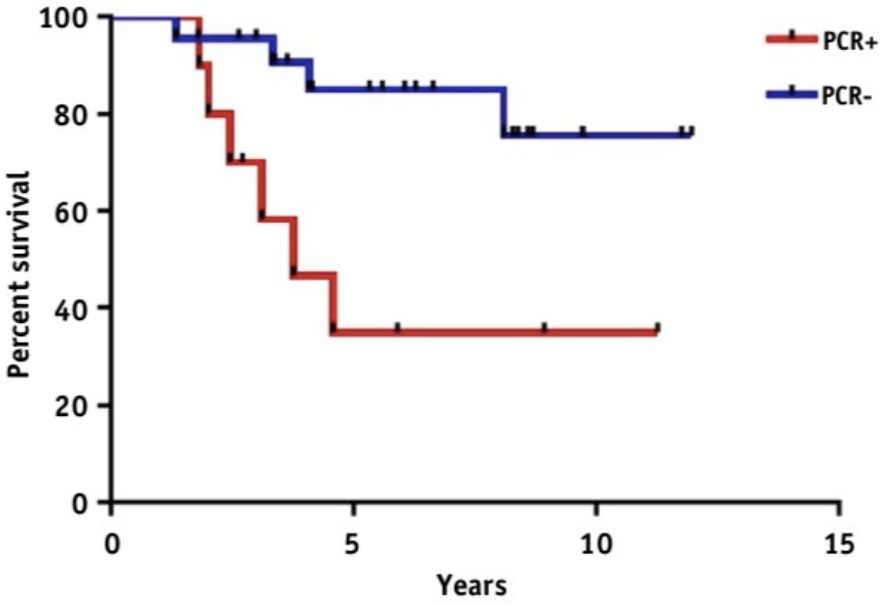
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®



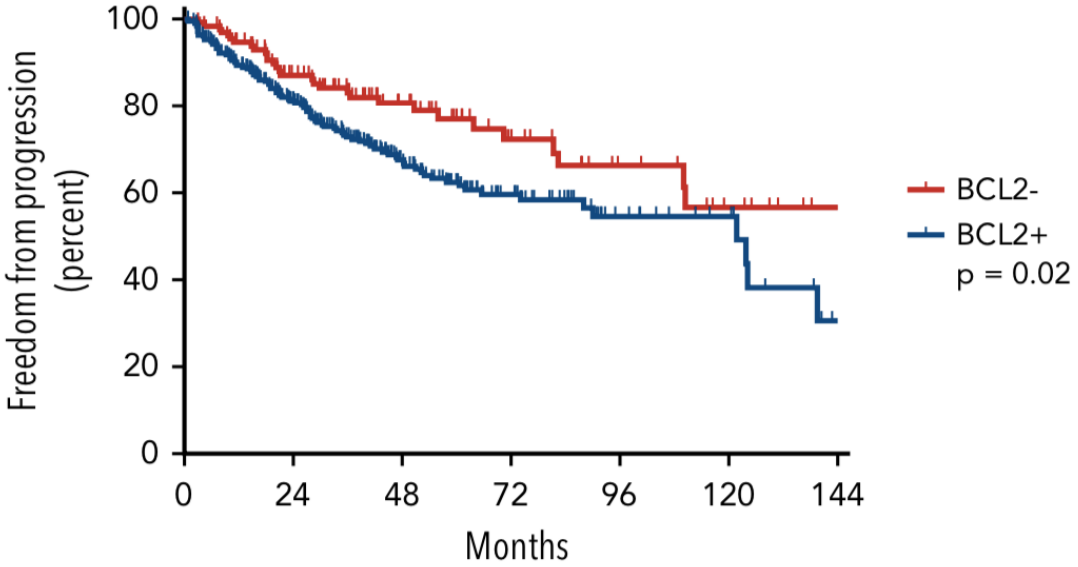
Primary outcome: 10-yrs PFS

Estimated Primary Completion Date	May 2027 (Final data collection date for primary outcome measure)
	Recruiting

Molecular status at baseline impacts on prognosis
(bcl-2/IgH rearrangement)



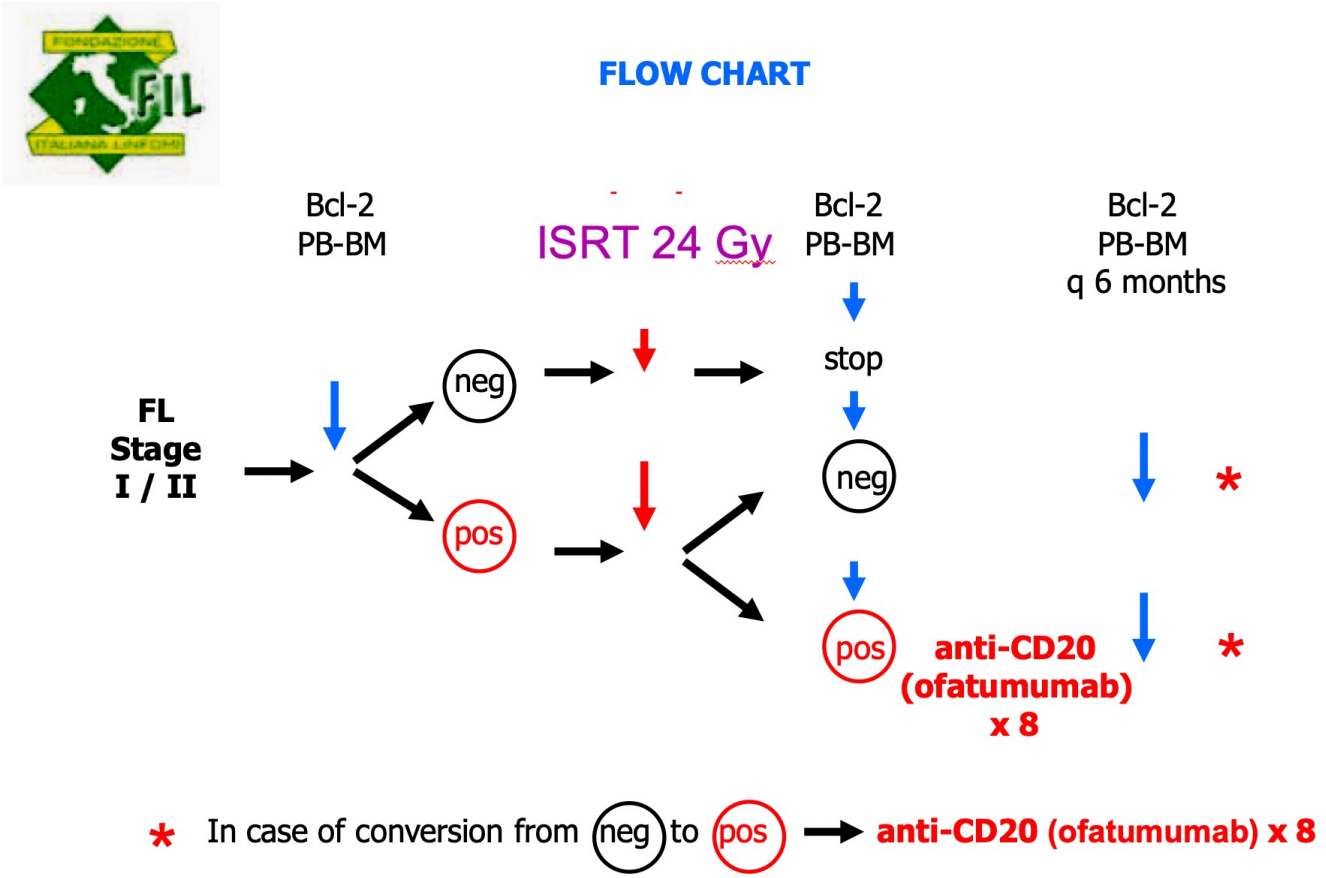
Ruella et al. IJROBP 2015



Definitive radiotherapy for localized follicular lymphoma staged by ^{18}F-FDG PET-CT: a collaborative study by ILROG

Brady et al. Blood 2019

"MIRO'" study (Molecularly Immuno-Radiotherapy Oriented)



Courtesy A. Pulsoni

Ongoing study – Combination of RT + immunotherapy

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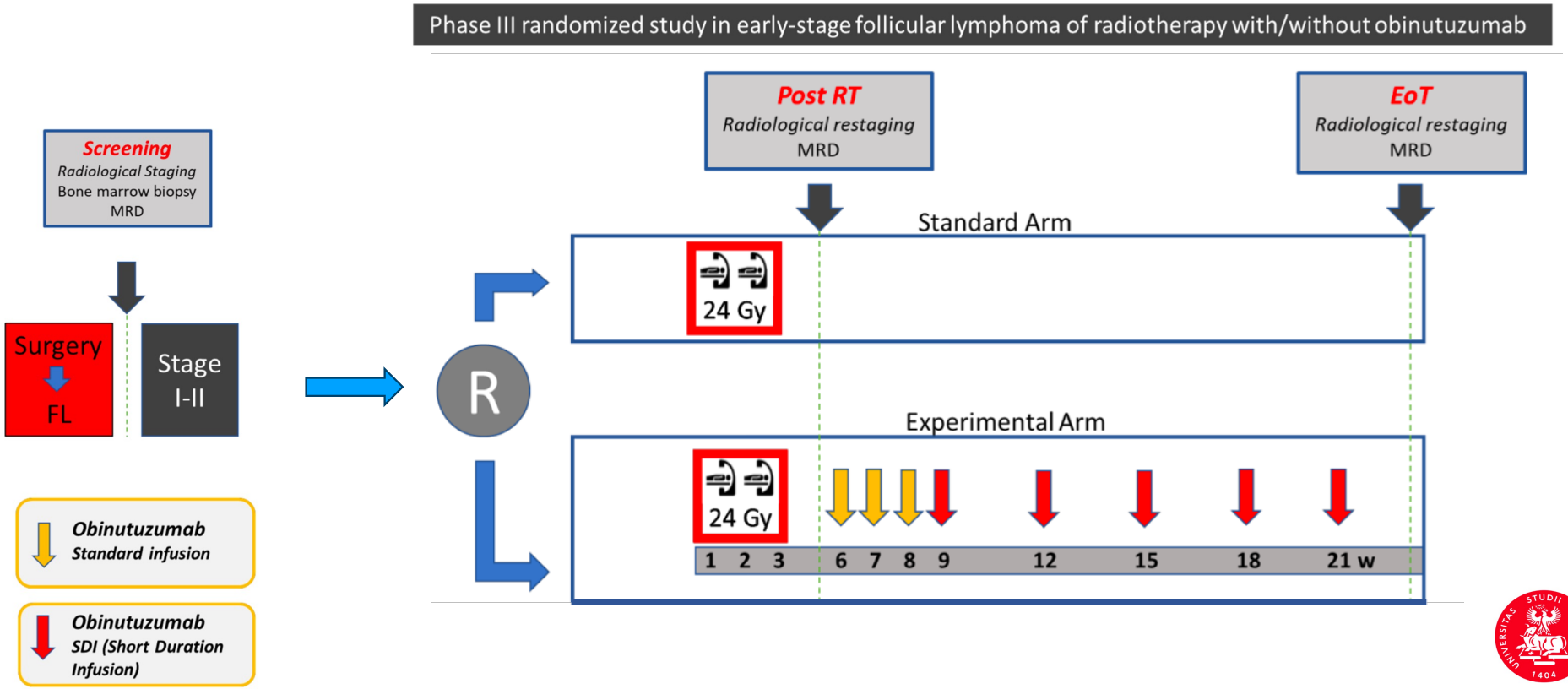
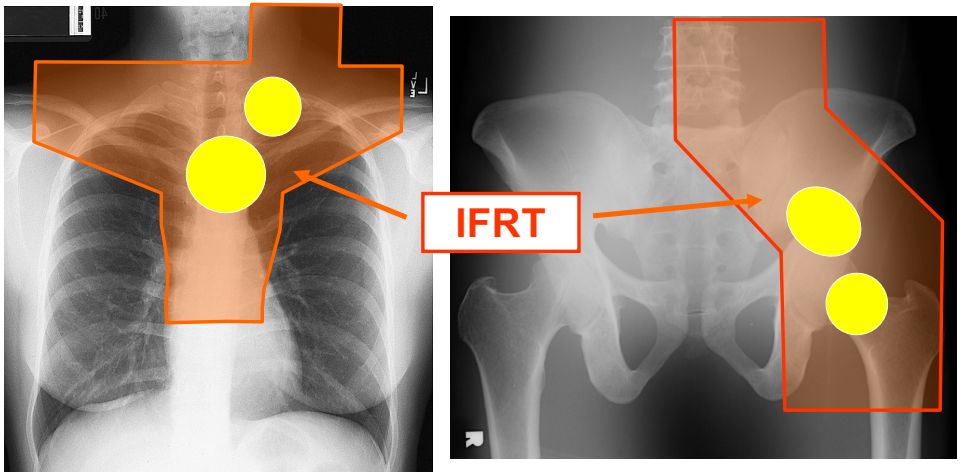
GAZEBO trial (Fondazione Italiana Linfomi study)



Volumes (IFRT vs ISRT/INRT)

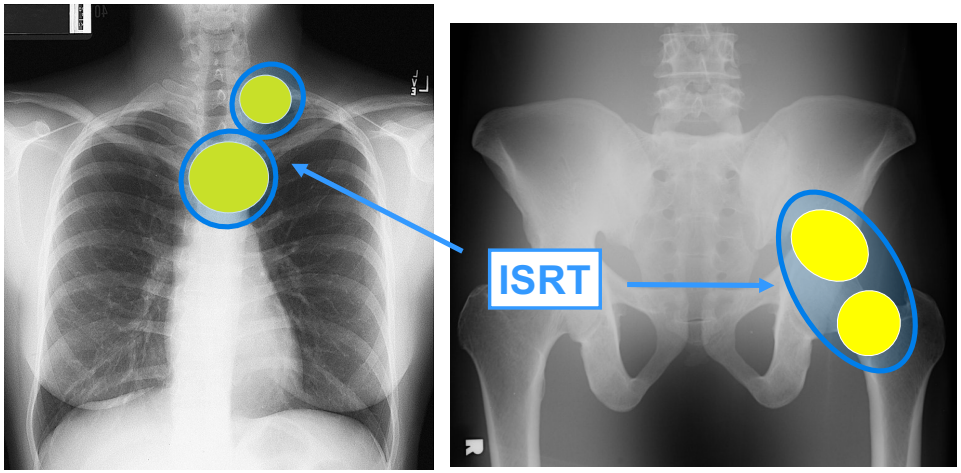
Involved Field (IFRT)

2D planning, based on bony landmark



Involved Site (ISRT)

3D planning, based on lymphoma volume



Long-Term Outcomes for Patients With Limited Stage Follicular Lymphoma

Involved Regional Radiotherapy Versus Involved Node Radiotherapy

- IRRT = involved lymph node group plus ≥1 adjacent, uninvolved lymph node group(s)
- INRT=involved lymph node(s) with margins ≤5 cm
- 237 pts: INRT 95, IRRT 142
- Median follow-up, 7.3 years
- After INRT, 1% of patients had a regional-only recurrence
- No effect of field size on PFS or OS

✓ *Retrospective study*

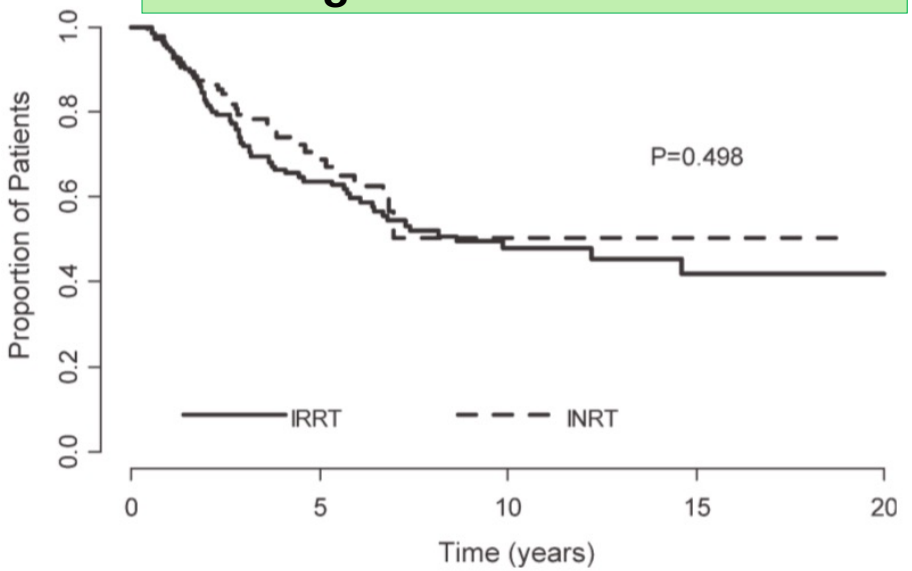
✓ *British of Columbia*

✓ *237 patients*

✓ *Grade 1-3A*

✓ *Timing: 1986-2006*

Progression Free Survival

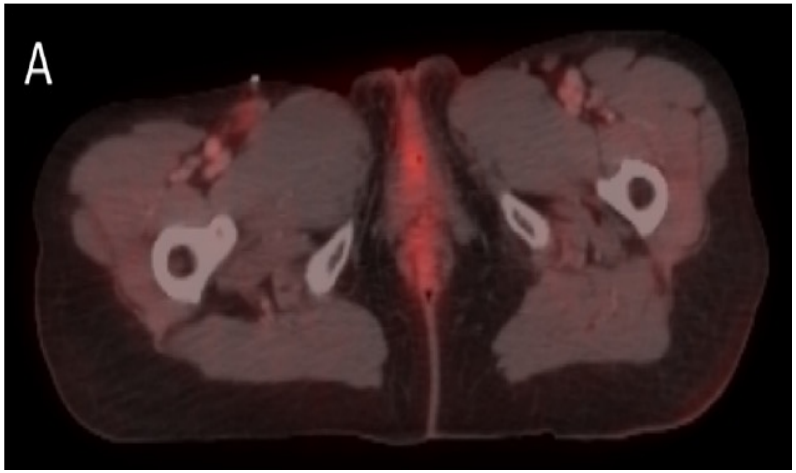


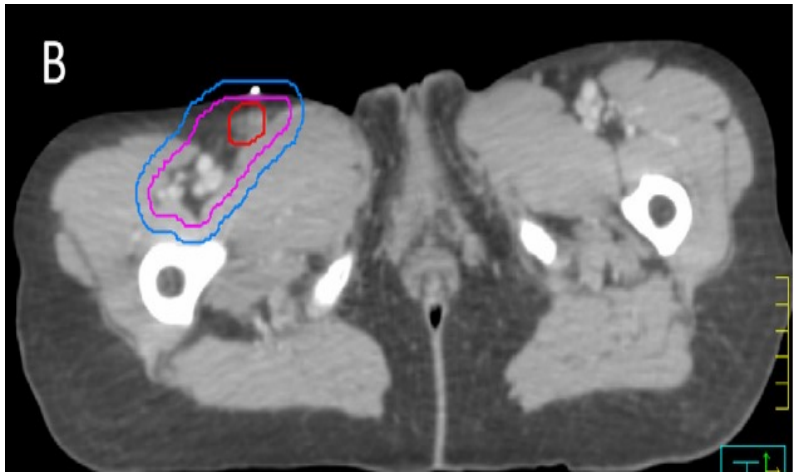
Campbell et al. Cancer 2010

Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Principles of ISRT





The CTV must be designed to encompass suspected subclinical disease based on the pre intervention GTV imaging

The CTV should incorporate GTV and include adjacent lymph nodes in that site and margin dictated by the clinical situation

Illidge T, et l. IJROBP 2014

Reducing doses for FL: background

- Early series: doses often ≥40 Gy
- PMH Toronto series: no dose response above 30 Gy
- Toronto data: plateau in FL after 20 Gy
- EORTC: no improvement in control of FL >25 Gy
- Girinsky/Haas: High response rates with 2 Gy x 2 (ORR 92%)

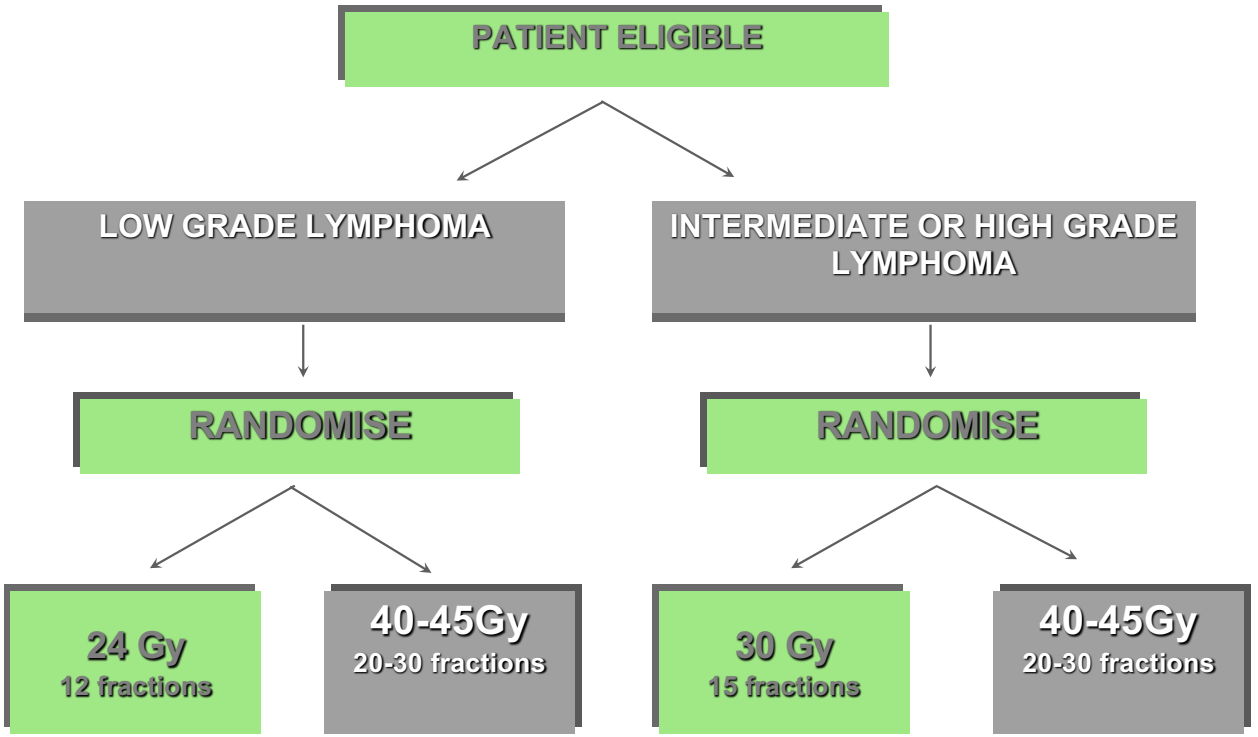
- Informative RCTs needed to answer dose question

Doses (24 vs 40-45 Gy)

Lowry L et al Radiother Oncol, 100, 86-92, 2011

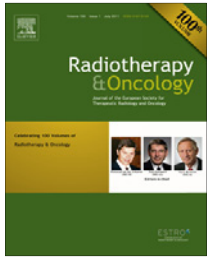
Reduced dose radiotherapy for NHL : A randomised phase III trial

360 indolent NHL (mostly follicular and MZL) randomized

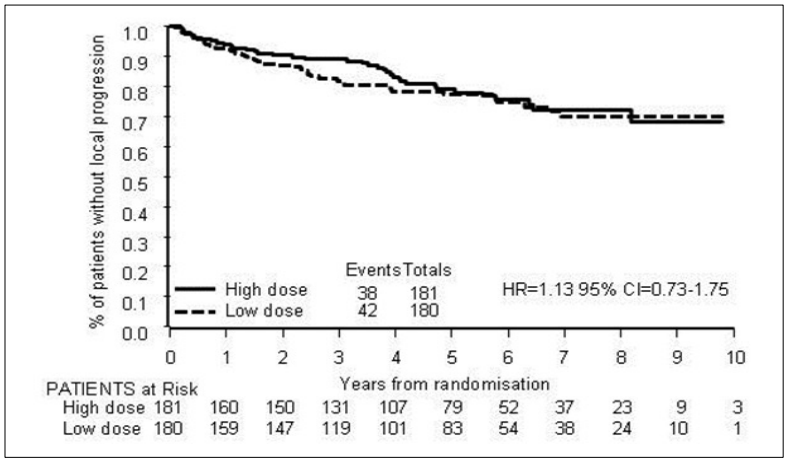


Phase III randomised trial

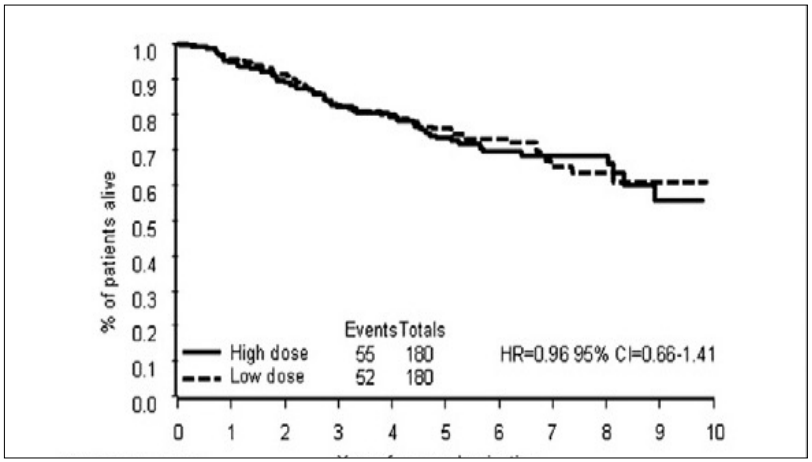
Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆



Local Control



Overall Survival

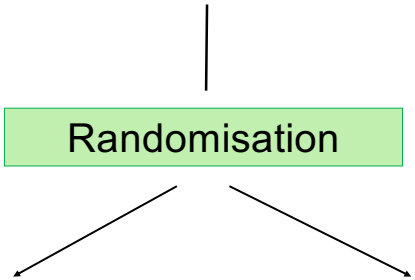


No loss of efficacy associated with radiotherapy doses of 24 Gy in indolent NHL

Lowry et al. Radiother Oncol, 2011

FoRT: A randomised trial of low dose radiotherapy for indolent lymphomas

Histologically proven follicular NHL requiring radiotherapy for definitive treatment of stage IA or IIA disease or for palliation by virtue of tumour bulk or anatomical position



Randomisation

Arm A (Control)

24Gy in 12 fractions

Arm B (Experimental)

4Gy in 2 fractions

Follow up for 5 years

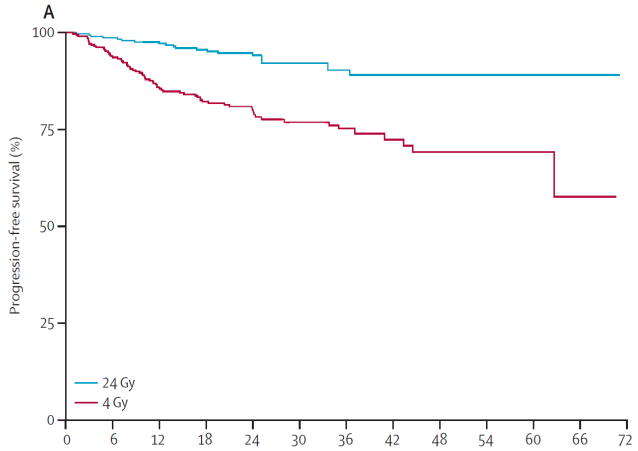
(4 weeks, 12 weeks, 6 months, 12 months, 18 months, 24 months and annually thereafter)

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

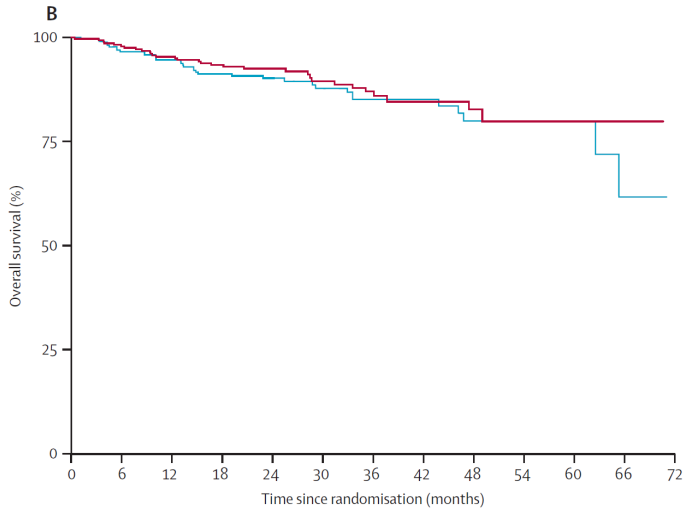
Lancet Oncol 2014

Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Progression Free Survival



Overall Survival



- 24 Gy in 12 fractions is more effective and remains the standard of treatment.
- 4 Gy achieves high response rates (ORR 74%) and is a valid alternative for palliation or retreatment

4 Gy is inferior to 24 Gy in indolent lymphomas

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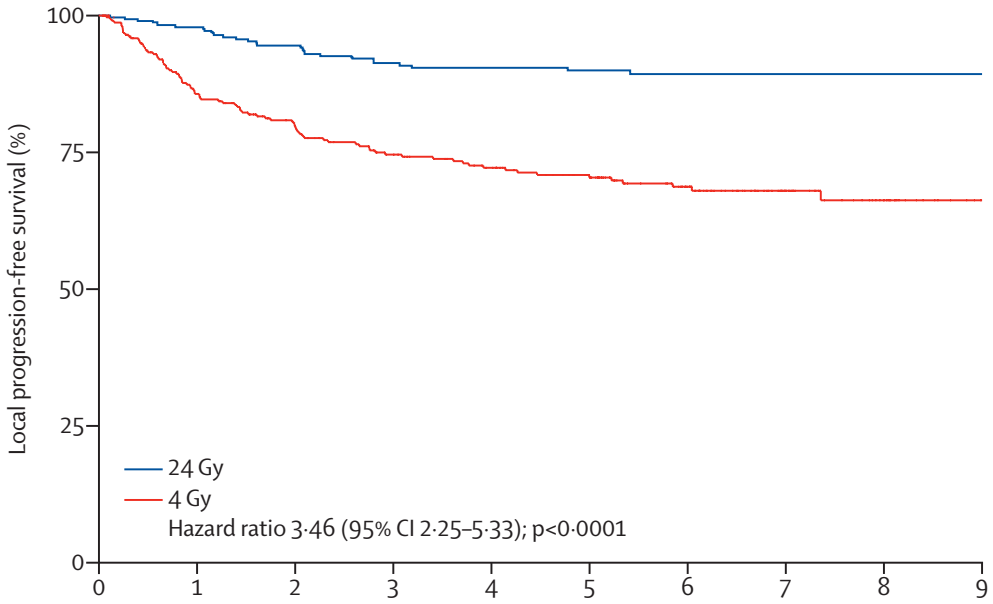
4 Gy versus 24 Gy radiotherapy for follicular and marginal zone lymphoma (FoRT): long-term follow-up of a multicentre, randomised, phase 3, non-inferiority trial

Hoskin et al. Lancet Oncol 2021

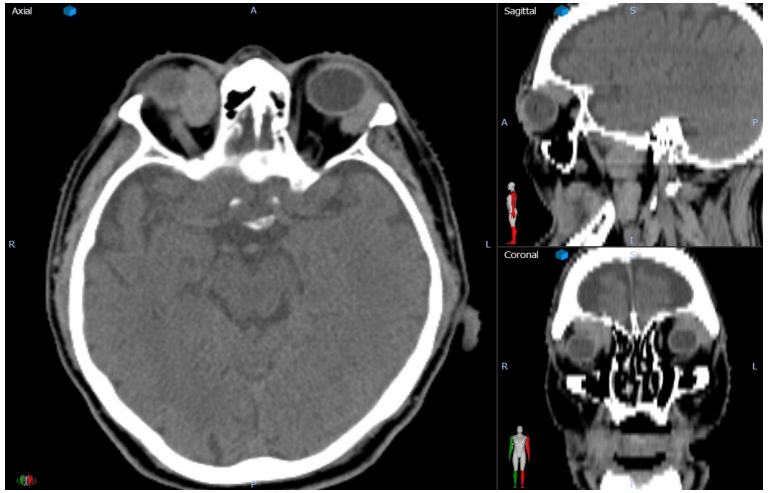
Local Progression Free Survival



Number at risk (number censored)										
24 Gy	299 (26)	266 (42)	241 (61)	214 (82)	192 (108)	165 (162)	110 (219)	53 (247)	25 (262)	10 (271)
4 Gy	315 (15)	256 (33)	221 (48)	192 (60)	174 (84)	146 (124)	103 (173)	53 (197)	28 (215)	10 (225)

FORT trial (UK) 4 Gy vs 24 Gy
Response rate according to histology

	24 Gy	4 Gy
All patients*		
Complete regression	176 (68%)	137 (49%)
Partial regression (>30%)	60 (23%)	90 (32%)
Stable disease (including <30% regression)	22 (8%)	44 (16%)
Progression	2 (<1%)	10 (4%)
Total	260	281
Follicular lymphoma		
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
Marginal zone lymphoma		
Complete regression	24 (71%)	21 (55%)
Partial regression (>30%)	7 (21%)	12 (32%)
Stable disease	3 (1 %)	4 (11%)
Progression	0	1 (3%)
Total	34	38

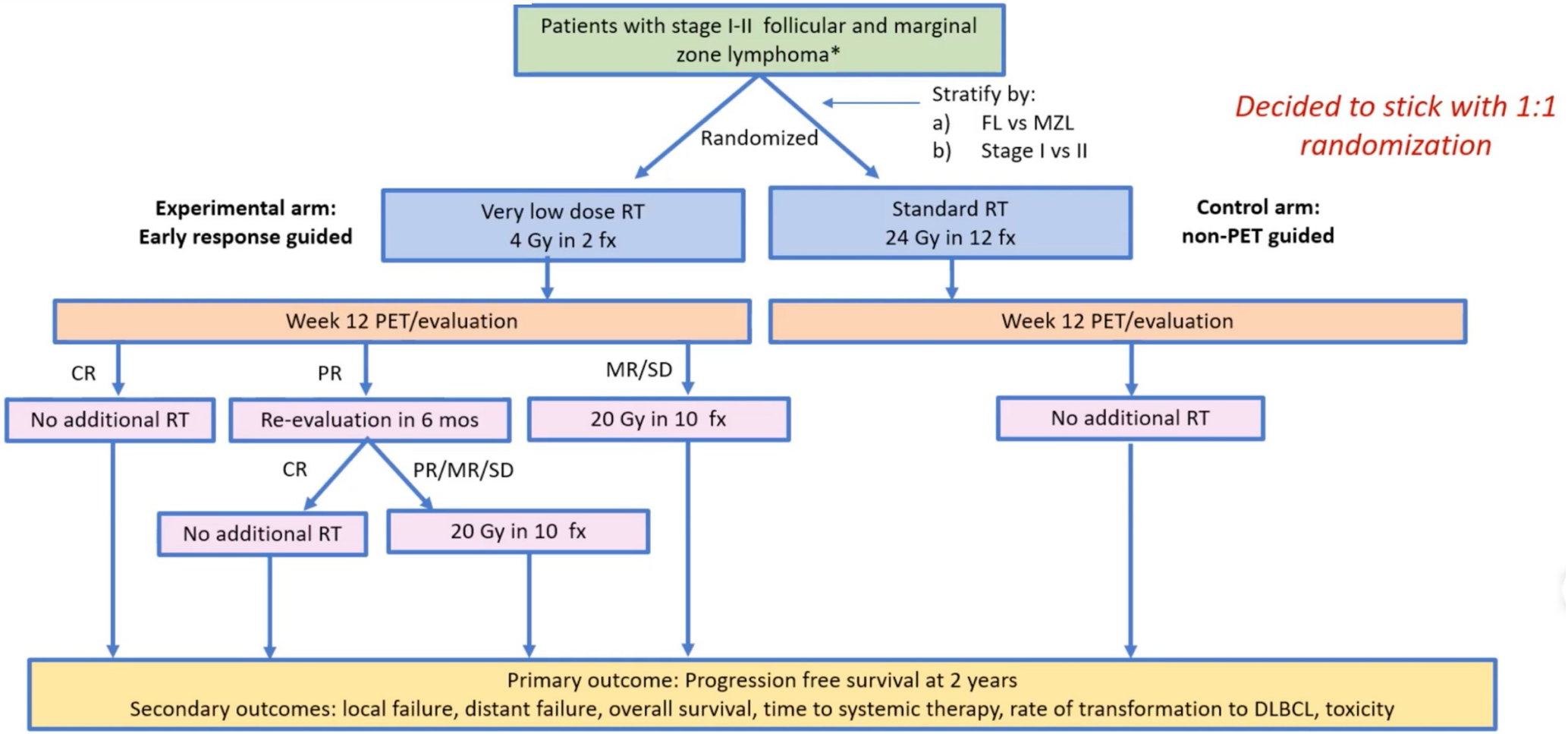


ORR: 90% vs 80%, p < 0.01

ORR: 92% vs 87%, p = 0.71

Hoskin et al. Lancet Oncol 2014

A Phase III Trial of An Early Response-Guided, Adaptive Approach for Potentially Curable Indolent B-cell Lymphomas



Radiation for hematologic malignancies: from cell killing to immune cell priming

- Interplay between radiation and the immune system:
  - radiation therapy «converses» with the immune system to stimulate and enhance anti-tumor immune response
    - pro-immunogenic role of radiotherapy **(immune cell priming)**

Conversing with the immune system

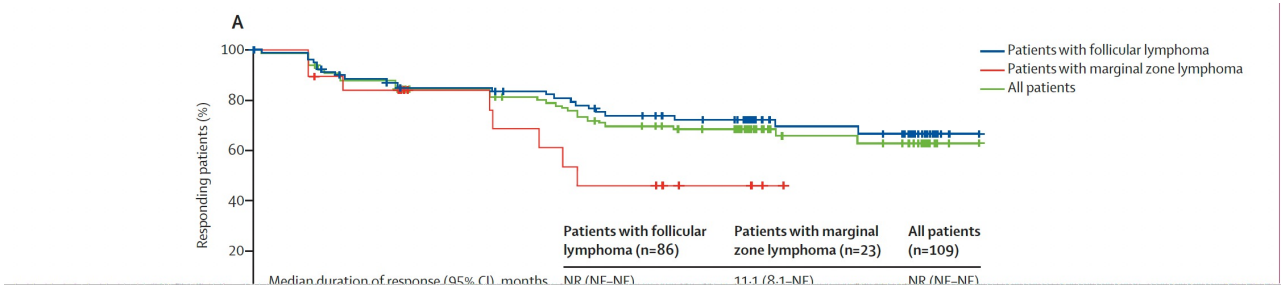
Radiation as a much-needed partner in the current environment of immune and cellular therapies

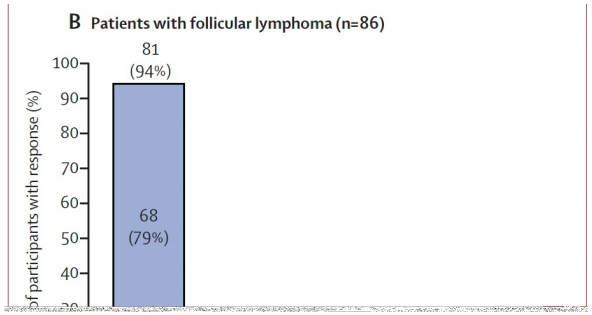
- introduction of immunotherapy
- increased application of cellular therapies like CAR T cell therapy

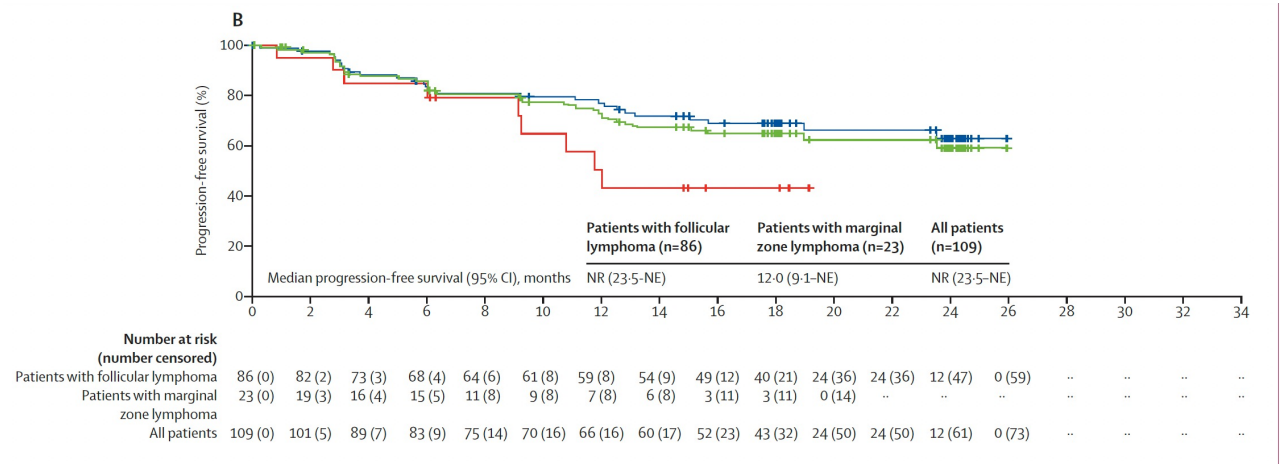
Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

Lancet Oncol 2022; 23: 91–103

Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks, Yin Yang, Remus Vezan, Mauro P Avanzi, Sattva S Neelapu



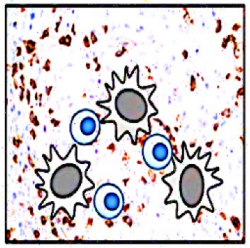




Number at risk (number censored)																		
Patients with follicular lymphoma	86 (0)	82 (2)	73 (3)	68 (4)	64 (6)	61 (8)	59 (8)	54 (9)	49 (12)	40 (21)	24 (36)	24 (36)	12 (47)	0 (59)	..	..	..	..
Patients with marginal zone lymphoma	23 (0)	19 (3)	16 (4)	15 (5)	11 (8)	9 (8)	7 (8)	6 (8)	3 (11)	3 (11)	0 (14)	..	..	..	..	..	..	..
All patients	109 (0)	101 (5)	89 (7)	83 (9)	75 (14)	70 (16)	66 (16)	60 (17)	52 (23)	43 (32)	24 (50)	24 (50)	12 (61)	0 (73)	..	..	..	..

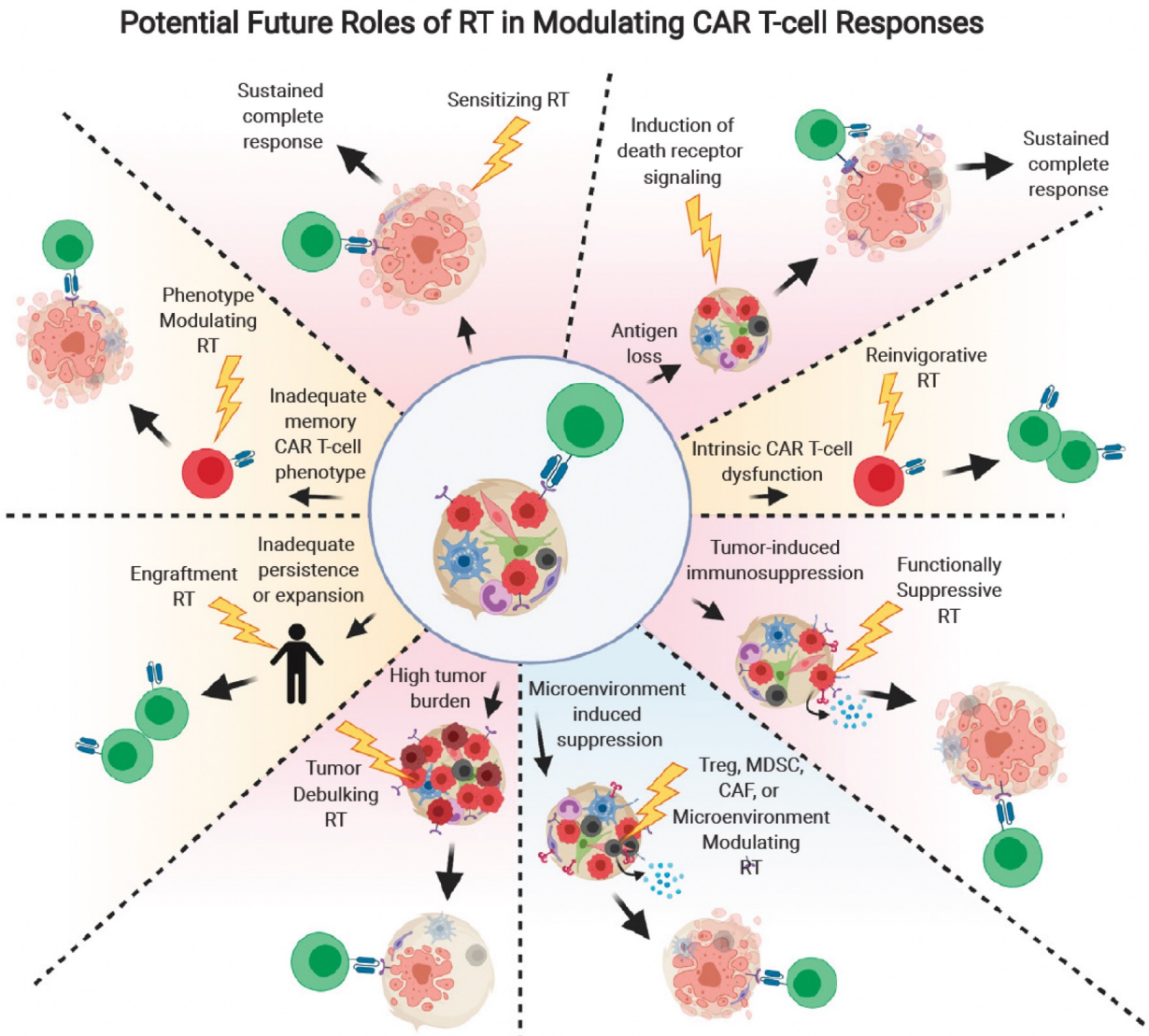
How does Radiation fit in this complicated landscape?

Immunogenic cell death= Priming



Local and abscopal anti-tumor Immune responses

Radiation stimulates tumor antigen release and anti-tumor immunity, activating the adaptive and innate immune response



Deselm C., *BJR (2021)*

Potential future roles of RT in modulating CAR T-cell responses:

- improving the specificity and efficacy of the target
- reinvigorating exhausted T cells
- overcoming Treg- and myeloid cell-mediated immunosuppression
- reducing CD4+ Treg activity
- promoting CD8+ cell activity
- increasing myeloid cell recruitment and antigen presentation

Radiation as bridging therapy prior to CART

- controls the disease during the manufacturing and achieves excellent response rates («to buy time»)
- can decrease the rate and severity of CRS
- debulks/cytoreduces tumor burden
- improves local control and may alter the pattern of relapse post-CART
- may «prime» the immune system and sensitize CART cells, and serve as lymphodepletion therapy

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01622-0

Check for updates

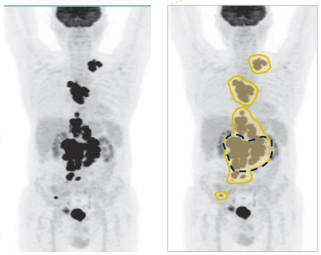
Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

Nathan Hale Fowler[1,2]✉, Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter A. Riedell[16], P. Joy Ho[17], José Antonio Pérez-Simón[18], Andy I. Chen[19], Loretta J. Nastoupil[1], Bastian von Tresckow[20,21], Andrés José María Ferreri[22], Takanori Teshima[23], Piers E. M. Patten[24,25], Joseph P. McGuirk[26], Andreas L. Petzer[27], Fritz Offner[28], Andreas Viardot[29], Pier Luigi Zinzani[30,31], Ram Malladi[32], Aiesha Zia[33], Rakesh Awasthi[34], Aisha Masood[35], Oezlem Anak[33], Stephen J. Schuster[36,38] and Catherine Thieblemont[37,38]

Before infusion, 44 patients (45%) received optional antineoplastic bridging chemotherapy for stabilization. The most commonly used agents (in ≥5% of patients) were rituximab (22%), dexamethasone (11%), gemcitabine (10%), oxaliplatin (7%), prednisolone (7%), etoposide (6%), cyclophosphamide (5%) and vincristine (5%). One patientreceived bendamustine and two received radiotherapy alone

Phase II Study of CAR-T with Bridging RT in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Susan Wu



Screen/consent relapsed/refractory iNHL → Near comprehensive RT* (4Gy)

Bridging steroids at MD discretion

Apheresis → Axi-cel Manufacture → Flu/Cy conditioning → CART Infusion Day 0

Blood

- **Pre RT** T-cell flow
- **Pre-LD chemo** T-cell flow
- **D0, 2, 4, 7, 14** Cytokine 3 panel (SOC)
- **D0, 7, 14, 30** T-cell flow

Biopsy

- **Pre RT biopsy** scRNASeq +scTcRseq + scBCRseq + CosMx
- Additional biomarker collection at 3, 6, 9, 12, 18, 24 months
- **Relapse biopsy*** scRNASeq + scTcRseq scBCRseq CosMx

Other

- **Apheresis product** scRNASeq +scTcRseq
- **Infusion Product** ssRNASeq +TcRSeq

*If sample is clinically indicated

Primary Endpoint:
- AE: Grade 3+ CRS

Secondary Endpoints:
- ORR, CRR, DOR, PFS, MRD
- In-RT field disease control
- Additional adverse events (G1+, G3+)
- Cytokine profile
- T-cell expansion, persistence, immunophenotype

EDITORIAL

Don't Get Stuck on the Shoulder: Radiation Oncologists Should Get Into the CAR With T-Cell Therapies

John P. Plastaras, MD, PhD,* Elise A. Chong, MD,† and Stephen J. Schuster, MD†

Conclusions

- ISRT/INRT remains treatment of choice for majority of stage I/II_1 FL (PET-staged), resulting in long term progression free survival and possible "cure", achievable with very low morbidity

- LDRT (4 Gy) seems to be a very safe and interesting alternative for indolent lymphoma

- **From cell killing to immune cell priming**