Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Follicular Lymphoma

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Disclosures

Consulting Agreements	AbbVie Inc, Amgen Inc, Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc, Janssen Biotech Inc, Roche Laboratories Inc, Seattle Genetics, Takeda Oncology

Case presentation 6: Dr Favaro

65-year-old asymptomatic man

- 2017: Incidentally discovered 9-cm conglomerate lymph node mass in the small bowel mesentery
  - Asymptomatic Stage II, Grade 3A follicular lymphoma
  - s/p CABG and recurrent bronchitis

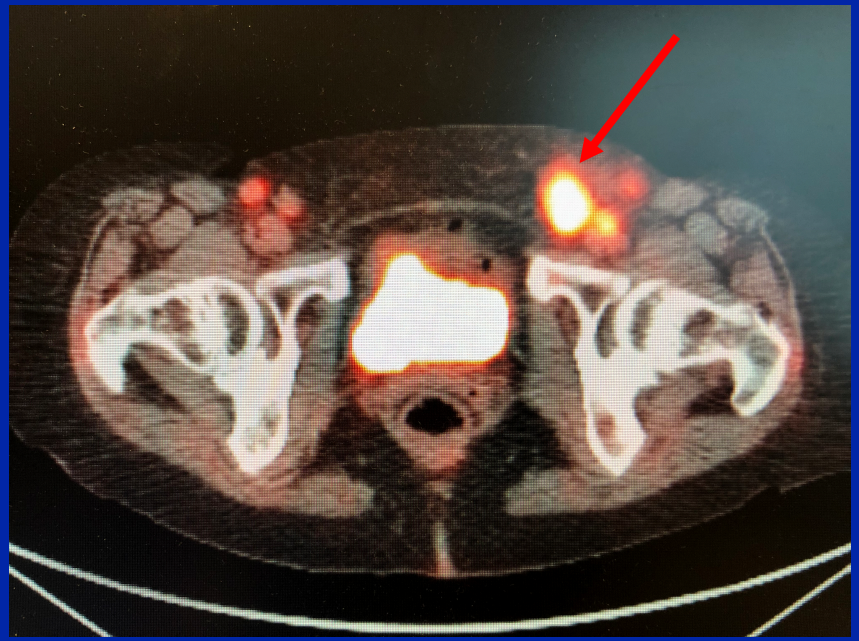
Case presentation 7: Dr Matt-Amaral

86-year-old woman with severe orthostatic hypertension and chronic back pain

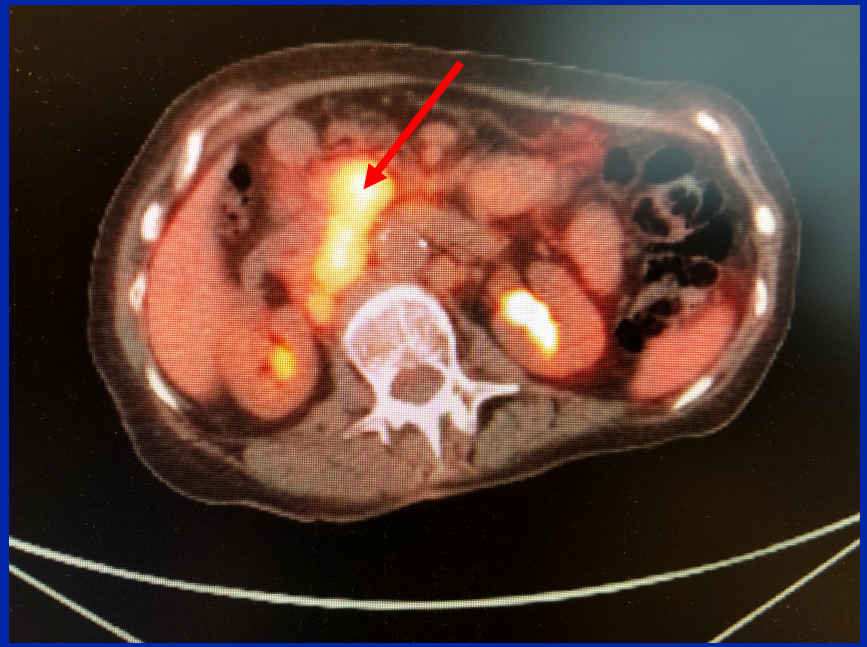
- 2015: Stage IV nonbulky follicular lymphoma (primarily above the diaphragm) with significant B symptoms, including night sweats, fever, chills and weight loss
  - Biopsy: Grade I-II FL
  - PET scan: Highest SUV was 9.6 of a retroperitoneal LN encasing the abdominal aorta; inguinal LN was biopsied with SUV of 8.7
  - LDH borderline elevated
- Rituximab x 4
- Symptom resolution after 2 to 3 treatments; in CR

PET scans

Inguinal LN with SUV of 8.7



Retroperitoneal LN with highest SUV of 9.6 encasing the abdominal aorta

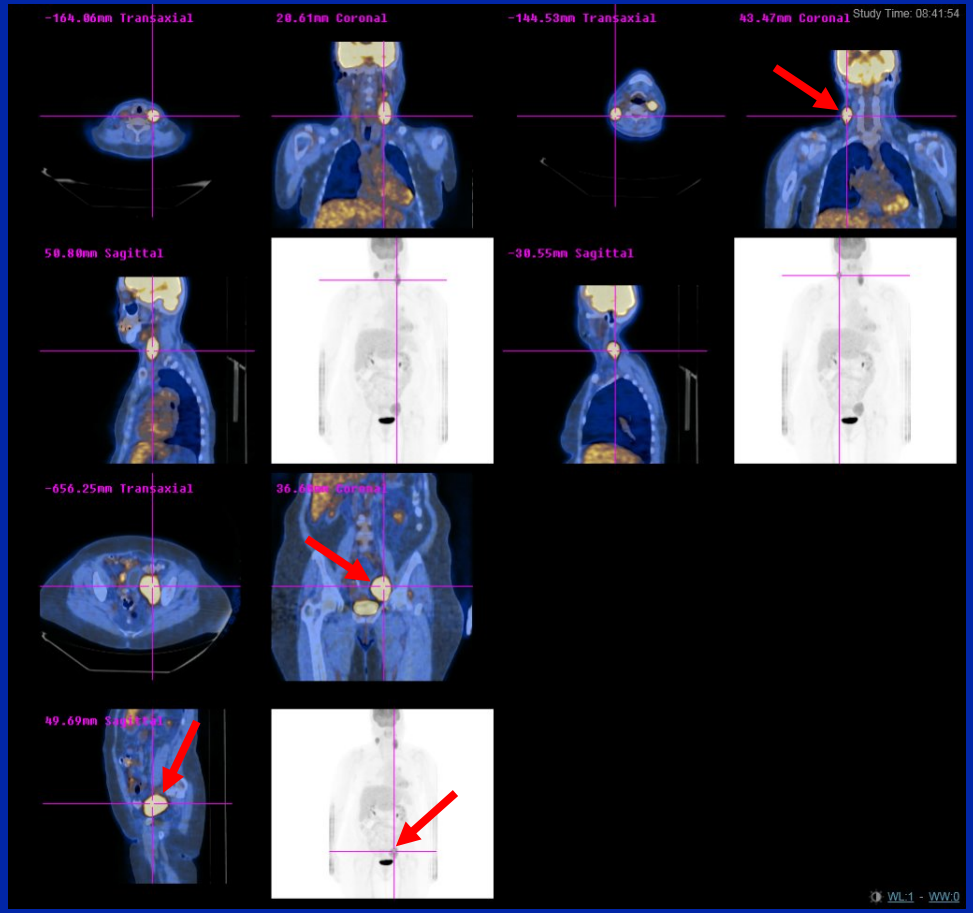


Case presentation 8: Dr Morganstein

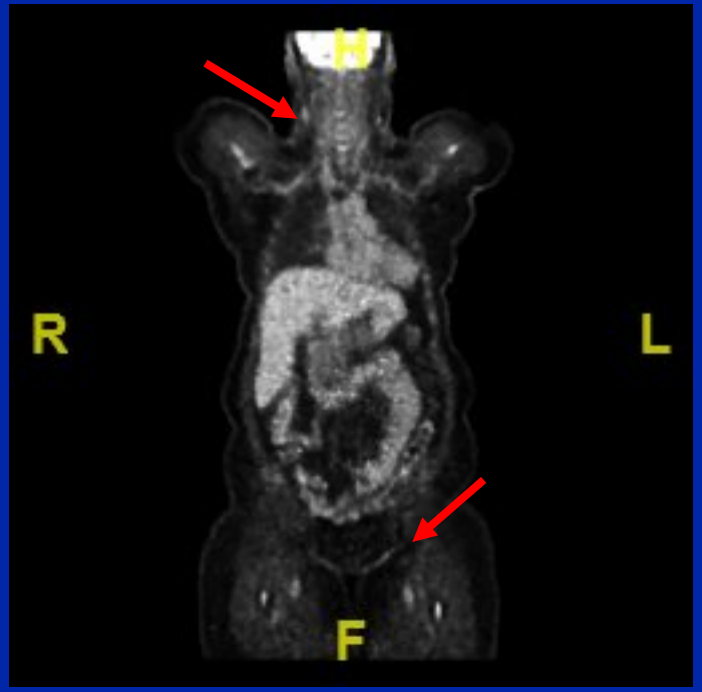
71-year-old woman

- 2017: Presents with large cervical lymph node
- Grade 2 follicular lymphoma
  - PET scan: 8-cm pelvic lymphadenopathy, minimally symptomatic disease
- BR x 6
  - Well tolerated and CR
- Maintenance rituximab
  - After 4 months: Enlarging right cervical lymphadenopathy as only site of disease on PET

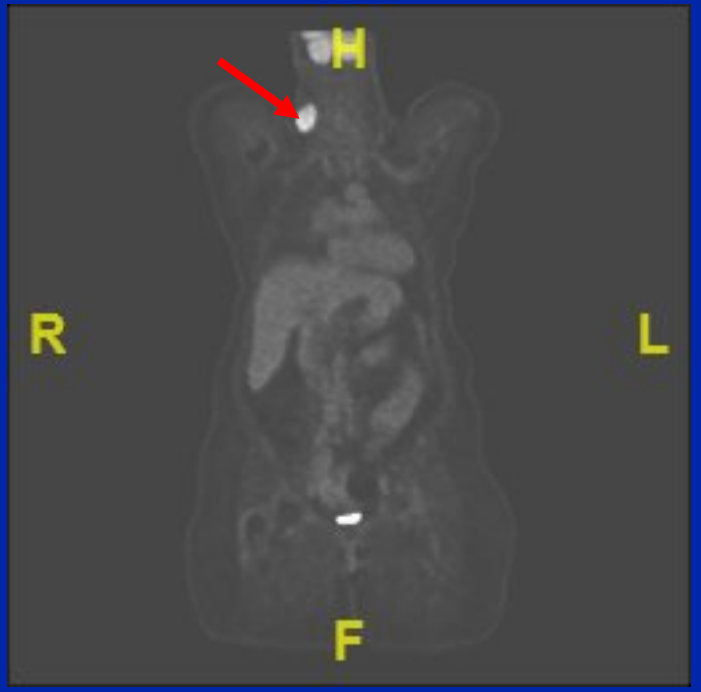
PET scan before BR



After BR: PET-negative



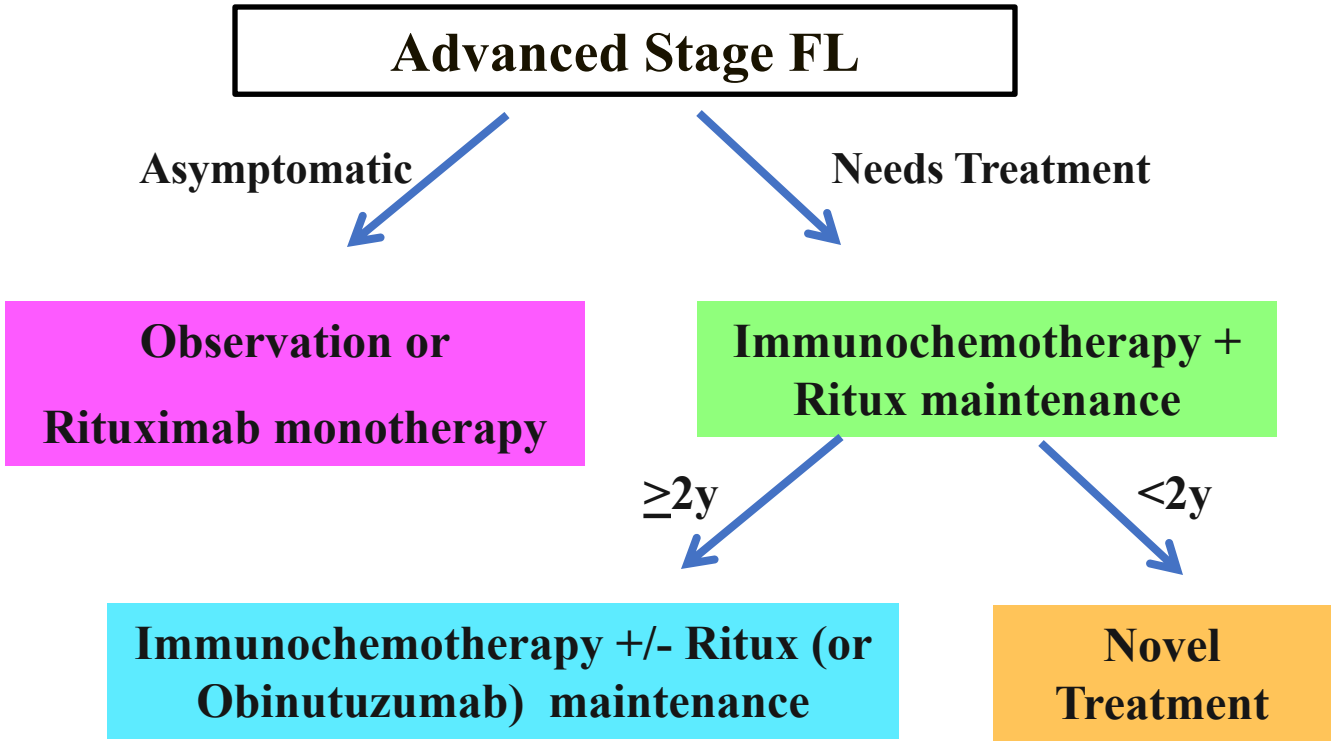
Progression after 4 months



Challenge of Follicular NHL

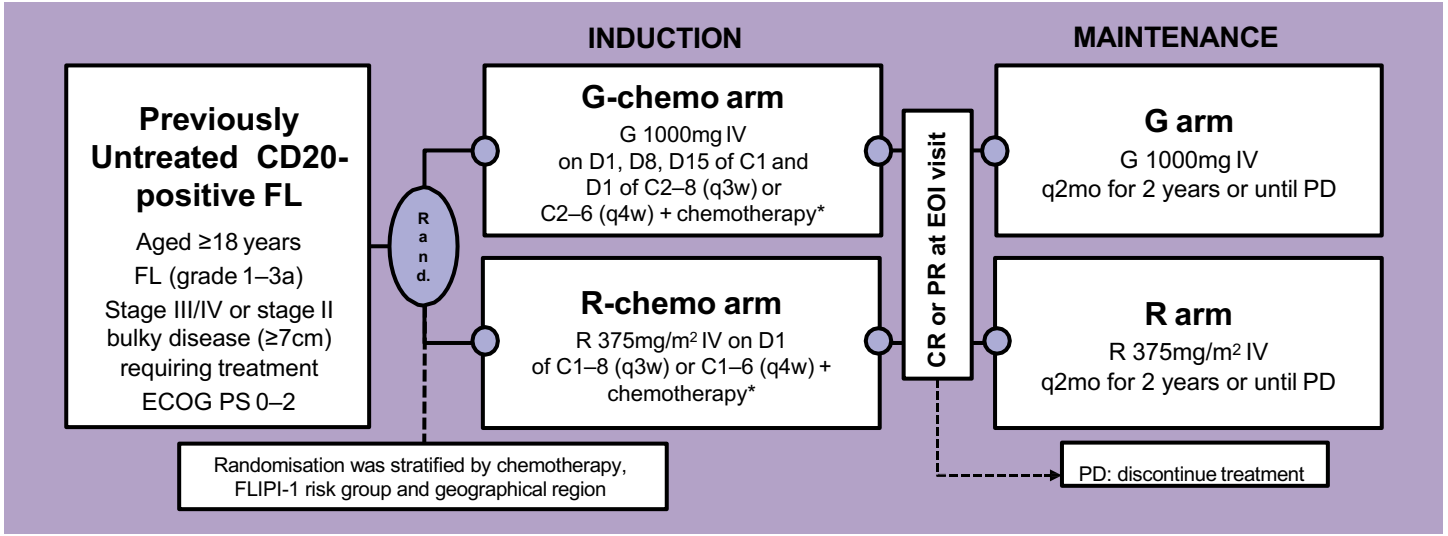
- Indolent behaviour, but remains incurable
- High-risk subset achieves only short-term control
- Novel therapies required to overcome treatment resistance and to reduce toxicity
- Goal is to control the disease, while maintaining quality of life

FL Management Algorithm



Phase 3 GALLIUM Study: Design

International, open-label, randomised Phase III study in 1L pts (NCT01332968)



Primary Endpoint

- PFS (INV-assessed)

Secondary endpoints

- PFS (IRC-assessed)
- OS, EFS, DFS, DoR, TTNALT
- ORR/CR at EOI (+/– FDG-PET)
- Safety
- PROs

***Chemotherapy Regimen:** chosen by site and received by all patients at that site; CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles

Baseline characteristics*

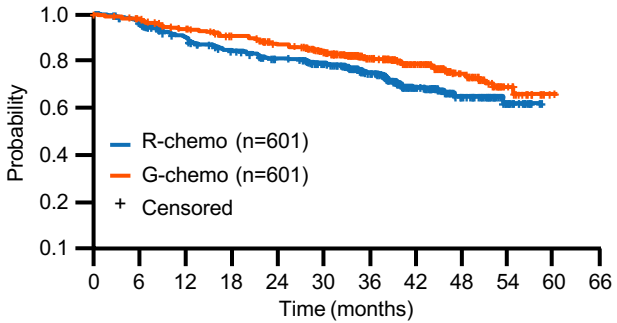
n (%)	*R-chemo, n=601*	*G-chemo, n=601*
Median age, years (range)	**58.0 (23–85)**	**60.0 (26–88)**
Male	280 (46.6)	283 (47.1)
Ann Arbor stage at diagnosis		
I	8 (1.3)†	10 (1.7)‡
II	44 (7.4)†	41 (6.9)‡
III	208 (34.8)†	209 (34.9)‡
IV	337 (56.4)†	338 (56.5)‡
FLIPI risk group		
Low (0–1)	125 (20.8)	127 (21.1)
Intermediate (2)	223 (37.1)	225 (37.4)
High (≥3)	**253 (42.1)**	**249 (41.4)**
Bone marrow involvement	295 (49.3)‡	318 (53.7)§
Extranodal involvement	396 (65.9)	392 (65.2)
Bulky disease (≥7cm)	**271 (45.2)¶**	**255 (42.5)¶**
Median time from diagnosis to randomisation, months (range)	**1.4 (0–168.1)‡**	**1.5 (0.1–121.6)‡**

*ITT population; †n=597; ‡n= 598; §n=592; ¶n=600

Updated from Marcus, et al., NEJM 2017

PFS after 41.1 months median follow-up*

INV-assessed PFS

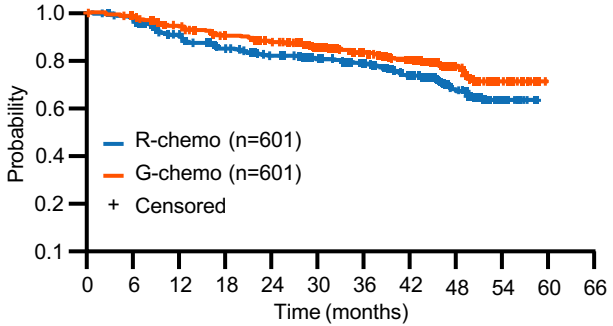


No. of patients at risk

G-chemo	601	561	505	464	438	396	267	149	77	18	
R-chemo	601	569	535	505	478	420	291	176	85	25	1

	R-chemo, n=601	*G-chemo, n=601*
3-yr PFS, % (95% CI)	**75.0 (71.0, 78.5)**	**81.5 (77.9, 84.6)**
HR (95% CI), p-value†	**0.68 (0.54, 0.87), p=0.0016**	

IRC-assessed PFS



No. of patients at risk

G-chemo	601	563	502	463	438	394	271	151	73	16
R-chemo	601	571	532	497	476	414	287	179	79	22

	R-chemo, n=601	*G-chemo, n=601*
3-yr PFS, % (95% CI)	78.9 (75.2, 82.1)	83.4 (79.9, 86.3)
HR (95% CI), p-value†	0.72 (0.56, 0.93), p=0.0118	

*ITT population; †stratified analysis; stratification factors = FLIPI, chemotherapy regimen

Updated from Marcus, et al., NEJM 2017

SAEs and select grade 3–5 AEs of particular interest

n (%) of pts reporting ≥1 one event	*R-chemo, n=597*	*G-chemo, n=595*
Grade 3-5 AEs	409 (68.5)	**449 (75.5)**
SAE	246 (41.2)	**281 (47.2)**
Grade 5 (fatal) AE	21 (3.5)	24 (4.0)
Select AEs		
Neutropenia	236 (39.5)	**278 (46.7)**
Infections	98 (16.4)	**121 (20.3)**
Infusion-related reactions	40 (6.7)	**74 (12.4)**

Updated from Marcus, et al., NEJM 2017

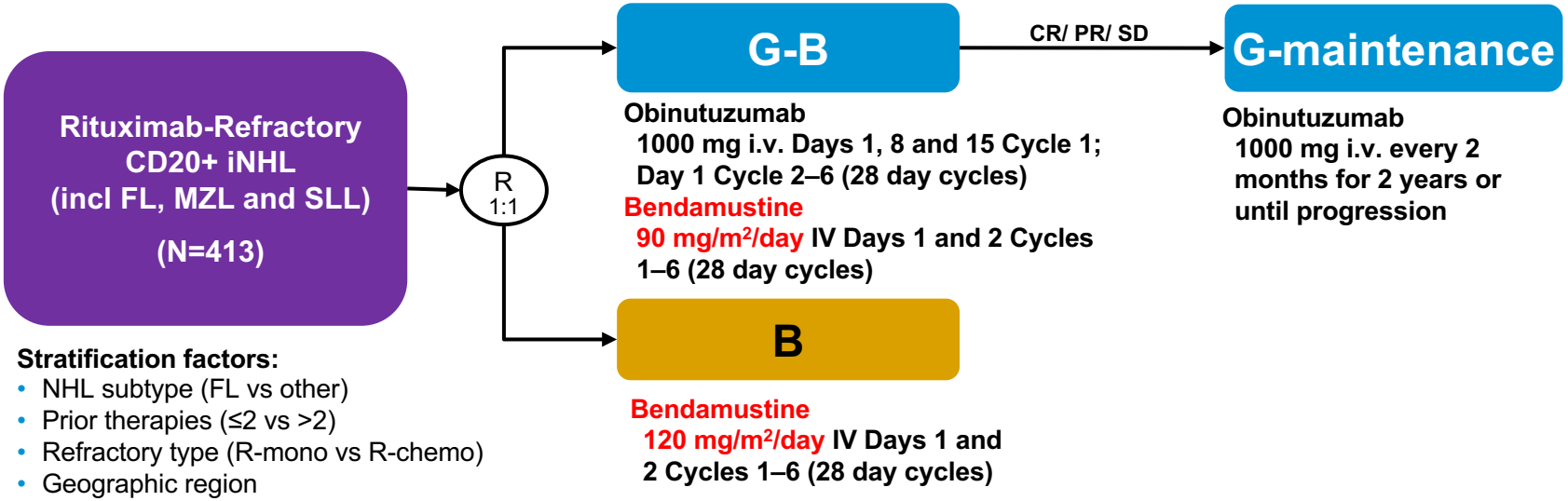
AEs by chemotherapy*

n (%) of pts reporting ≥1 event	*R-benda, n=338*	*G-benda, n=338*	*R-CHOP, n=203*	*G-CHOP, n=193*	*R-CVP, n=56*	*G-CVP, n=61*
Any AE	331 (97.9)	338 (100)	201 (99.0)	191 (99.0)	56 (100)	61 (100)
Grade 3–5 AE	**228 (67.5)**	**233 (68.9)**	151 (74.4)	171 (88.6)	30 (53.6)	42 (68.9)
SAE	160 (47.3)	176 (52.1)	67 (33.0)	76 (39.4)	19 (33.9)	26 (42.6)
Grade 5 (fatal) AE	**16 (4.7)**	**20 (5.9)**	4 (2.0)	3 (1.6)	1 (1.8)	1 (1.6)
AE leading to treatment discontinuation	48 (14.2)	52 (15.4)	31 (15.3)	32 (16.6)	9 (16.1)	11 (18.0)

*Comparisons confounded by imbalances in baseline patient and disease characteristics between chemo groups

Updated from Marcus, et al., NEJM 2017

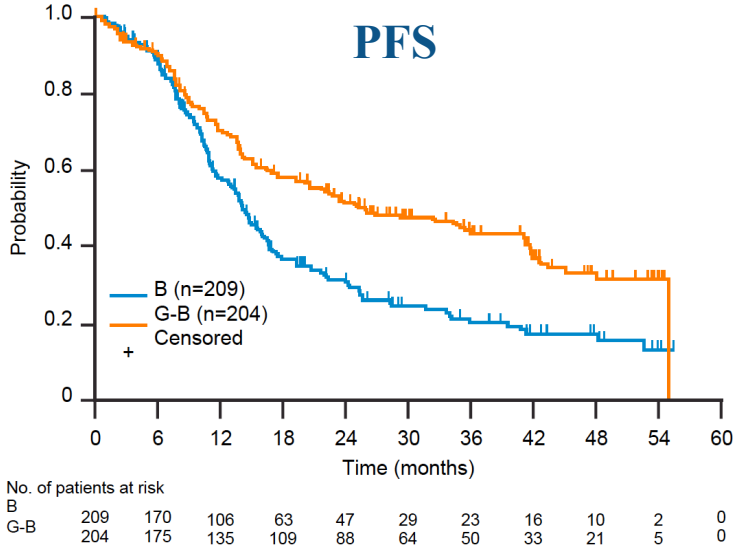
Phase 3 GADOLIN Study: Design

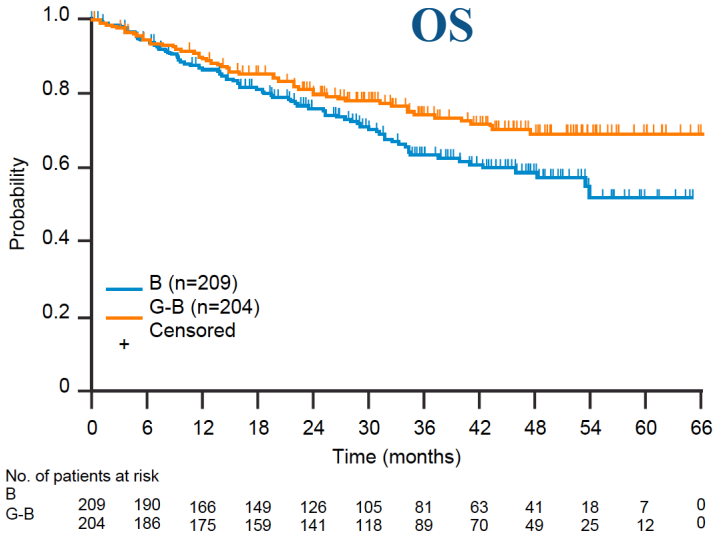


- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

iNHL, indolent non-Hodgkins lymphoma; G-B, obinutuzumab plus bendamustine; G, obinutuzumab

INV-assessed PFS and OS in the iNHL population





HR (95% CI): 0.57 (0.44-0.73)

p-value: <0.0001

HR (95% CI): 0.67 (0.47-0.96)

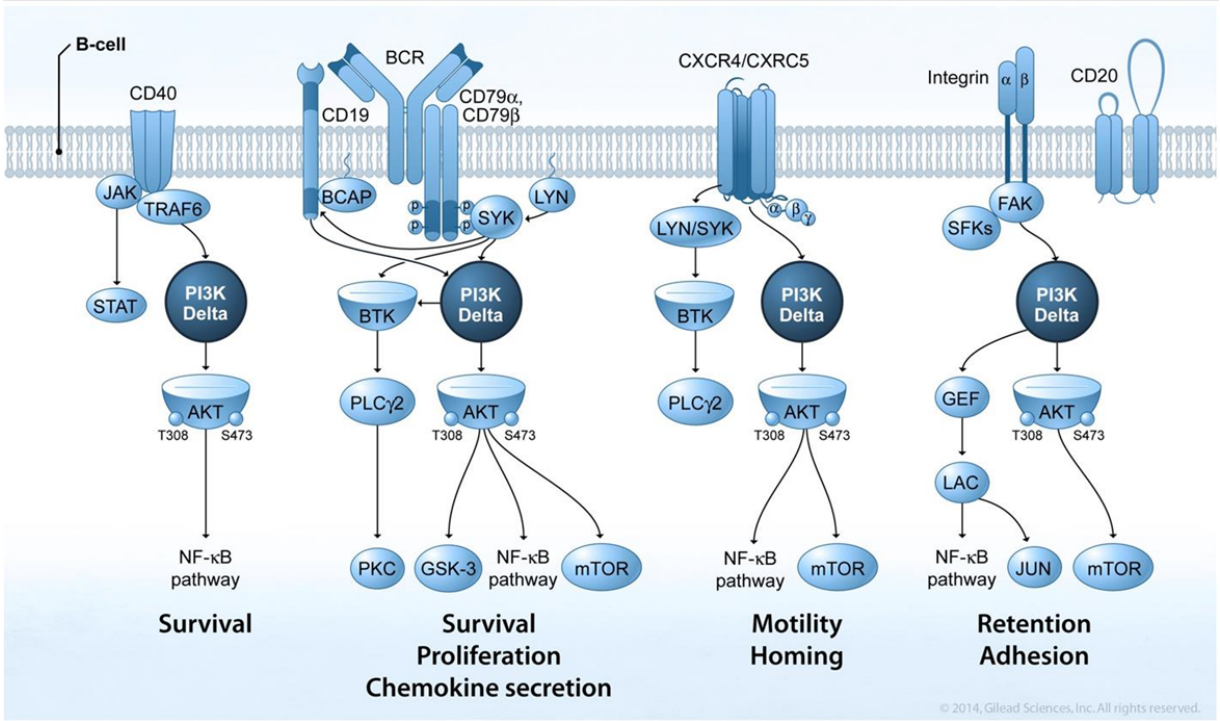
p-value: 0.0269

Median f/up: 31.8 mos

Cheson, B et al, ASH 2016;Abstract 615; Sehn L, et al, Lancet Oncology 2016

PI3K Inhibition

Pathways Using PI3Kδ



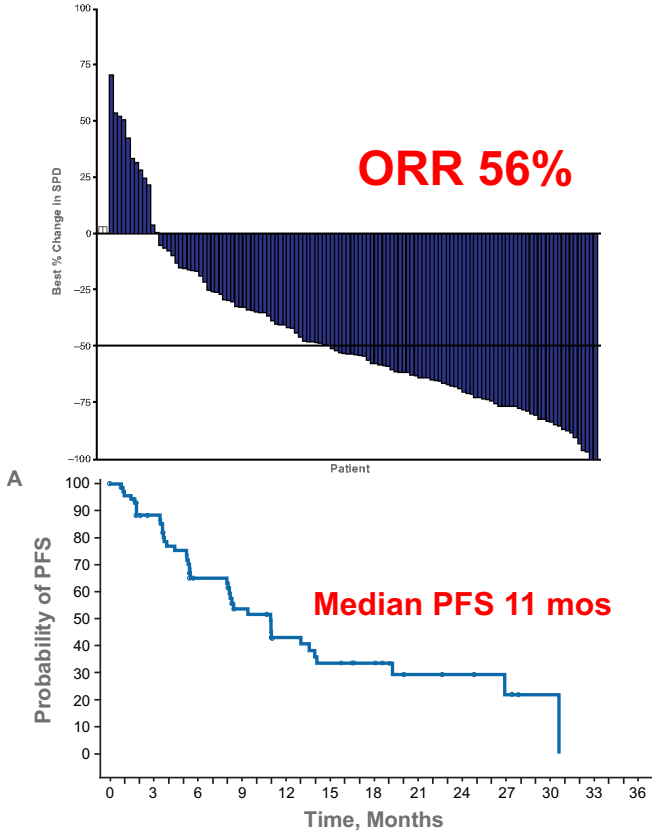
PI3Kδ: largely restricted to hematopoietic cells

Coutre, S et al., Leuk Lymph 2015

Idelalisib – Pivotal Phase 2 Trial in Subgroup of Patients with Relapsed FL

Oral selective inhibitor of PI3Kδ
N=72 patients
Refractory to rituximab and an alkylating agent
Idelalisib 150 mg po bid

Characteristic	N=72
Age, median (range), yr	62 (33-84)
Male, n (%)	39 (54.2)
ECOG, n (%)	
0	31 (43.1)
1	35 (48.6)
2	6 (8.3)
FL Grade, n (%)	
1	21 (29.2)
2	39 (54.2)
3a	12 (16.7)
High-risk FLIPI score, n (%)	39 (54.2)
Ann Arbor Stage III-IV	60 (83.3)
Prior regimens, median (range)	4 (2-12)



Gopal, A et al., NEJM 2014; Salles, G et al., Haematologica 2017

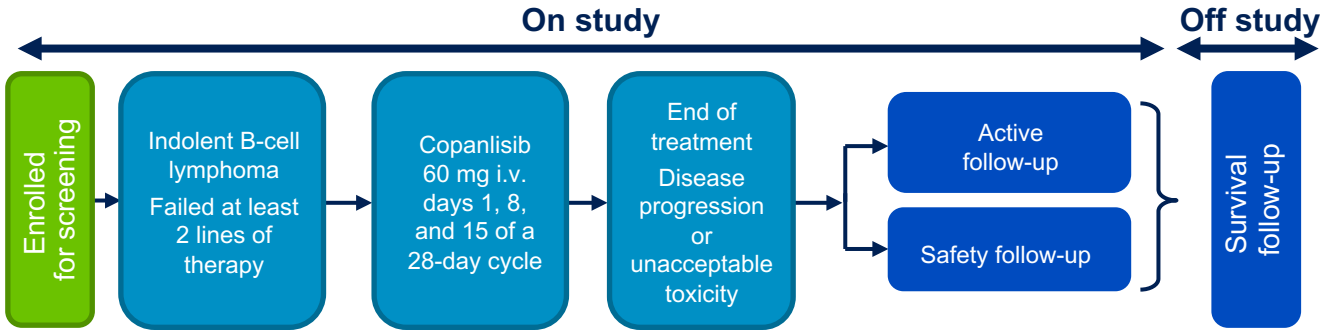
Select Toxicities with Idelalisib in Pivotal Trial in Relapsed Indolent NHL

Adverse Event	Grade	
N = 125	Any (%)	≥ 3 (%)
Diarrhea	43	13
Fatigue	30	2
Cough	29	0
Pyrexia	28	2
Rash	13	2
Pneumonia	11	7
Neutropenia	56	27
Increased ALT	47	13
Increased AST	35	8

- Risk of colitis and pneumonitis, atypical infection when combined

Gopal, A et al., NEJM 2014

Copanlisib Pivotal Phase 2 Trial in Patients with Relapsed or Refractory Indolent NHL: Study Design



Lymphoma types

- FL (grades 1-3a)
- MZL
- SLL
- LPL / WM

Primary Endpoint

- ORR by central review

Secondary endpoints

- PFS
- DoR
- OS
- Safety
- Quality of life

Tertiary endpoints

- Disease control rate
- Duration of stable disease
- ECOG scale
- Lesion size
- EQ-5D questionnaire, visual analog scale

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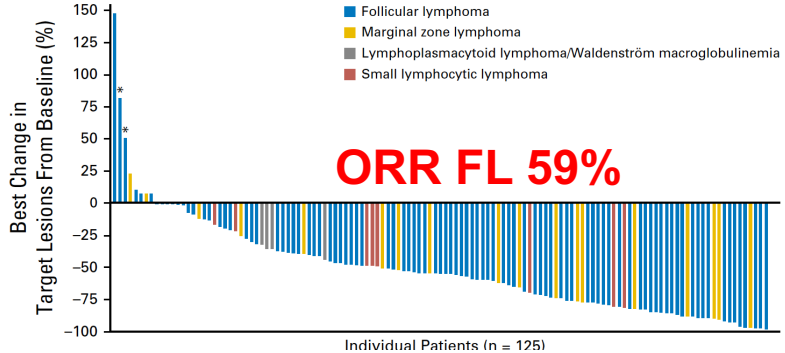
Dreyling M et al, J Clin Oncol 2017

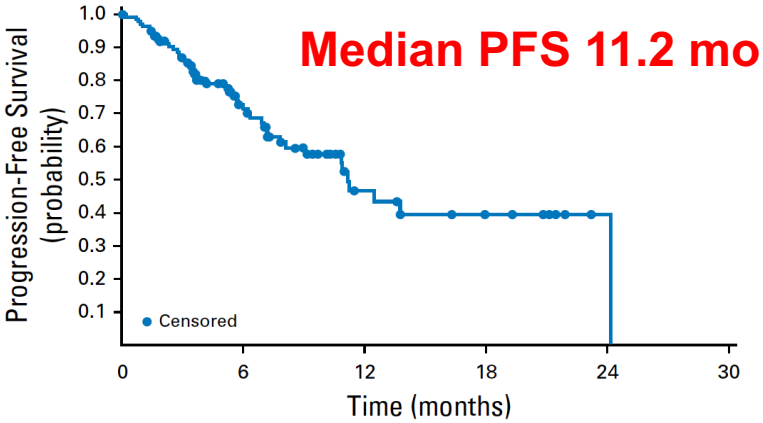
Copanlisib – Pivotal Phase 2 Trial in Relapsed or Refractory Indolent NHL

N=142 patients, 104 with FL

Patient Characteristics

No. of patients	142
Male sex	71 (50)
Median age, years (range)	63 (25-82)
No. of prior anticancer therapy lines	
Median	3
Range	2-9
Histology of tumor†	
FL	104 (73)
Grade 1	22 (21)
Grade 2	52 (50)
Grade 3a	27 (26)
MZL	23 (16)
SLL	8 (6)
LPL/WM	6 (4)
DLBCL‡	1 (1)
Refractory to last regimen	86 (61)
Rituximab	80 (56)
Alkylating agents	60 (42)
Rituximab and alkylating agents	61 (43)





Dreyling M et al, J Clin Oncol 2017

Select Toxicities with Copanlisib in Pivotal Trial in Relapsed Indolent NHL

Common treatment-related AEs, *n* (%)	Total (*N*=142)	
Grade	**All**	**≥3**
Any treatment-related AE	126 (89%)	101 (71%)
Hyperglycemia	69 (49%)	57 (40%)
Hypertension	41 (29%)	32 (23%)
Neutropenia	35 (25)	27 (19%)
Diarrhea	26 (18%)	6 (4%)
Nausea	22 (16%)	1 (1%)
Lung infection	20 (14%)	15 (10%)
Fatigue	17 (12%)	2 (1%)
Laboratory toxicities		
Increased aspartate aminotransferase	39 (28%)	2 (1%)
Increased alanine aminotransferase	32 (23%)	2 (1%)
Treatment-related AEs of special interest		
Pneumonitis (non-infectious)	10 (7%)	2 (1%)
Colitis	1 (1%)	1 (1%)

Dreyling M et al, J Clin Oncol 2017

Phase 2 Trials of Lenalidomide +/- Rituximab in Follicular Lymphoma

Author	Rx	Population	Number with FL	ORR (% CR) in FL
Witzig et al. JCO 2009	**Lenalidomide**	**Rel/refr iNHL**	**22/43**	**27% (9% CR)**
Tuscano et al. BJH 2014	**Lenalidomide + Rituximab**	**Rel/refr iNHL**	**22/27**	**77% (41% CR)**
Leonard et al. JCO 2015	**Lenalidomide *vs* Len + Ritux**	**Relapsed FL**	**91**	**53% (20% CR) *v* 76% (39% CR)**
Fowler et al. Lancet Oncol 2014	**Lenalidomide + Rituximab**	**Untreated iNHL**	**50/110**	**98% (87% CR)**
Kimby et al. ASH 2016	**Rituximab *vs* Len + Ritux**	**Untreated FL**	**154**	**19% (30% CR) *V* 42% (30% CR)**

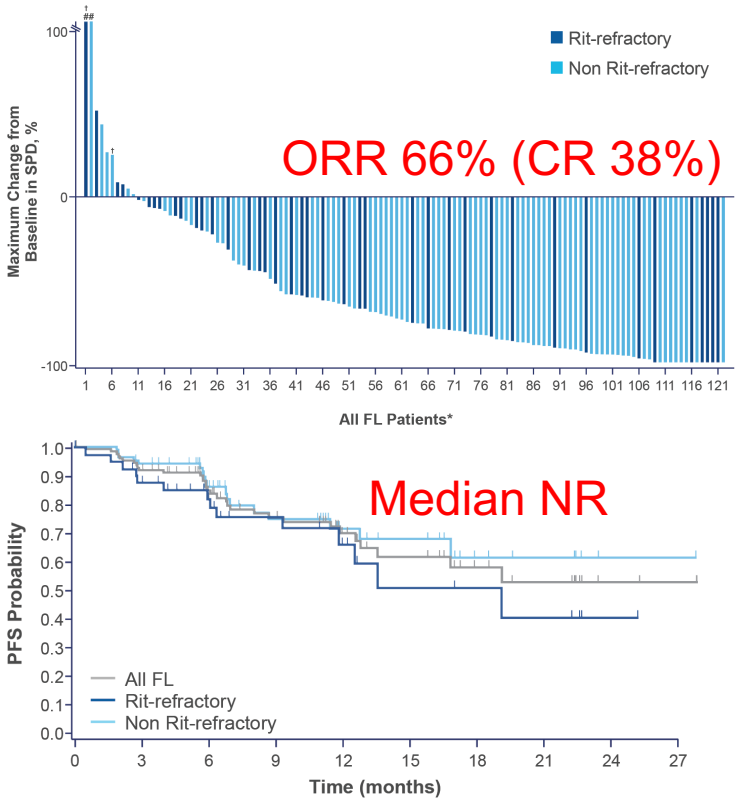
iNHL = indolent NHL

Phase III Studies of Lenalidomide/Rituximab (R^2) in FL

Study (Target Enrollment)	Eligibility	Randomization
AUGMENT (N = 350)	R/R FL, MZL	Arm 1: R^2 Arm 2: Placebo/Rituximab
MAGNIFY (N = 500)	R/R FL grade 1-3b, tFL, MZL or MCL Received R^2 induction, with CR/CRu, PR, or SD	Arm 1: Maintenance R^2 (→ optional Len) Arm 2: Maintenance Rituximab
Relevance (N = 1,000)	Untreated FL	Arm 1: R^2 → Maintenance Len x 1 yr, Rituximab x 2 yrs Arm 2: R-Chemo → Maintenance Rituximab x 2 yrs

Magnify Phase 3B Trial: Preliminary Results in Subgroup with Follicular NHL

Characteristic, n (%)		FL (n=169)
Median age, years (range)		65 (35-91)
Age ≥65 years		91 (54)
Male		95 (56)
ECOG PS at enrollment	0	79 (47)
	1	85 (50)
	2	4 (2)
Disease stage at enrollment	I/II	29 (17)
	III	47 (28)
	IV	93 (55)
Median number of prior systemic anti-cancer therapies		2 (0-9)
>2 prior regimens		59 (35)
Prior rituximab-containing therapy		164 (97)
Rituximab-refractory		53 (31)



Burke JM et al, EHA 2017

Conclusions

- Obinutuzumab has further improved outcomes with immunochemotherapy
- PI3κ inhibitors (idelalisib and copanlisib) offer a novel alternative for rel/refr patients
- Role of rituximab and lenalidomide (R^2) will be clarified by upcoming phase 3 studies
- Novel targeted agents offer promise for the future