Caso Clinico – Linfoma Follicolare

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FIRENZE

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Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X	X	
Gilead					X	X	
Takeda						X	
Janssen						X	
BMS-Celgene						X	
BeiGene						X	
Incyte							X
Novartis					x		
Lilly						X	
Roche					X		

M.E.M, MALE, 02/10/1975

Past medical history:

- Occult HBV infection → Lamivudine
- Hypothyroidism → Levothyroxine
- Non-Functioning Pituitary Adenomas

Diagnosis: September 2006

- Inguinal lymph node biopsy: **Follicular Lymphoma grade 1**
- Stage IVA (bone marrow), FLIPI: 1
- GELF criteria: ≥ 3 nodal sites involved with a diameter of >3 cm

WHICH THERAPY WOULD YOU HAVE CHOSEN?

1) R-CHOP
2) R-CVP
3) R-FM
4) R-BENDAMUSTINE
5) Chlorambucil
6) Clinical Trial

Minimum Clinical Recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphoma, Hiddeman W. et al, Annals of Oncology 2005

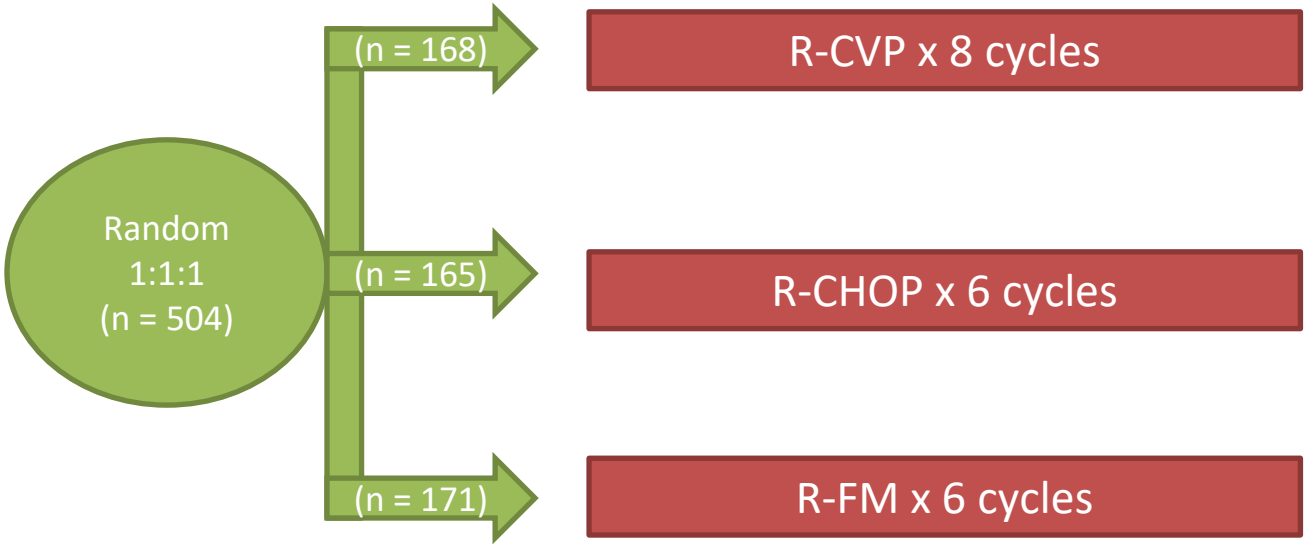
FOLL05 Trial: prospective, randomized, open-label, multicenter phase III trial including untreated patients with advanced stage symptomatic FL

Key eligibility criteria:

- Age: 18 - 75
- Untreated Follicular Lymphoma grade 1, 2 or 3A
- Stage: II - IV
- ECOG 0 – 2
- Active disease (according to SIE guidelines)

Key exclusion criteria:

- Follicular Lymphoma grade 3B
- Transformation into an aggressive lymphoma
- Stage I
- CNS involvement
- History of previous malignancy



- Enrollment period: from March 2006 to September 2010
- Median follow-up: **34 months** (range 1 - 70)

Primary end point

- **Time to treatment failure (TTF)**

FIRST LINE: FOLL05 TRIAL (phase 3)

- R-CVP x 8 cycles → CR (2007)

1° Relapse: 29/06/2011 (+ 4 aa)

- Axillary lymph node biopsy: **Follicular Lymphoma, grade 1/2**
- **Stage IVA** (bone marrow)

WHICH THERAPY WOULD YOU HAVE CHOSEN?

1) R-CHOP
2) R- Bendamustine
3) Ibritumumab - Tiuxetan
4) High-Dose Chemotherapy (R-IEV/R-ICE/R-DHAP) + ASCT
5) Clinical Trial

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Dreyling M. et al, Annals of Oncology 2011

SECOND LINE: STANDART TX

- R-CHOP X 6 cycles → CR (2012)
- Consolidation with ASCT:
  - Cyclophosphamide 4 g/mq and HSC Harvesting
  - BEAM + ASCT (14/05/2012) → CR (September 2012)

2° Relapse: 11/12/2020 (+ 8 aa)

- Abdominal lymph node biopsy: **Follicular Lymphoma, grade 1/2**
- **Stage IVA** (bone marrow, skeleton)

WHICH THERAPY WOULD YOU HAVE CHOSEN?

1) Obinutuzumab - Bendamustine
2) Rituximab - Lenalidomide
3) Clinical trial
4) High-Dose Chemotherapy (R-IEV/ R-ICE/R-DHAP)
5) Idelalisib

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Dreyling M. et al, Annals of Oncology 2020

BGB 3111 – 212_ROSEWOOD trial: an international, phase 2, open-label, randomized study of zanubrutinib + obinutuzumab vs obinutuzumab monotherapy in r/r FL

Key eligibility criteria:
- ≥18 years
- R/R FL (gr 1 – 3a)
- ≥ 2 previous lines of therapy (including an anti-CD20 Ab and alkylator-based regimen)

Key exclusion criteria:
- CNS involvement
- t - FL
- Prior BTKi
- Required ongoing therapy with CYP3A inhibitor or inducer

Random 2:1 (n = 217)

n =145 → Zanubrutinib 160 mg BID until PD/unacceptable toxicity + Obinutuzumab 1 g on days 1, 8, 15 of cycle 1 and on day 1 of cycles 2 – 6. Then 1 g every 8 weeks up to 20 doses maximum

(n = 72) → Obinutuzumab monotherapy (same schedule)

Optional crossover*

- Primary analysis cut off: 08/10/2021
- Median follow-up: **12.5 months**

Primary end point: ORR by IRC
Secondary end point: ORR by IA, CR, DOR, PFS, OS, TTR, Safety, PK
Exploratory end point: ORR after crossover

* if centrally confirmed PD (at any time) or no response at 12 months

BGB 3111 – 212: Obinutuzumab + Zanubrutinib: ROSEWOOD trial

Patients characteristics	ZO (n = 145)	O (n = 72)
Median age (years)	64	64
Median number of previous lines of therapy	3	3
> 3 previous lines of therapy (%)	28	25
High FLIPI (%)	53	51
Refractory to any previous anti-CD20 therapy (%)	54	50
Refractory to last line of therapy (%)	32	40
POD 24	28	32

Results	ZO (n = 145)	O (n = 72)
ORR (%)	68.3	45.8
CRR (%)	37.2	19.4
18 – mo DOR (%)	70.9	54.6
Median PFS (mo.)	27.4	11.2
Median time to new anti-lymphoma therapy or crossover (mo.)	NR	12.1
18 – mo OS (%)	85.4	72.6

29 patients crossed over: **ORR 24.1%**

ROSEWOOD: A phase II randomized study of Zanubrutinib plus obinutuzumab versus Obinutuzumab Monotherapy in patients with relapsed or refractory follicular lymphoma. Zinzani P.L et al, 2023 J Clin Oncol.

BGB 3111 – 212: Obinutuzumab + Zanubrutinib: ROSEWOOD trial

Any grade AE in the ZO cohort	% of patients
Thrombocytopenia	34.3
Neutropenia	27.3
Diarrhea	16.1
Fatigue	14
Cough	11.9

Grade ≥3 AE in the ZO cohort	% of patients
Neutropenia	22.4
Thrombocytopenia	14%
Atrial Fibrillation	0.7
Major bleeding	1.4%

AE leading to death: 5.6% (ZO cohort) vs 9.9% (O cohort)

Zanubrutinib + Obinutuzumab demonstrated superior efficacy to Obinutuzumab monotherapy in treatment of patients with R/R FL, with a favorable benefit-risk

ROSEWOOD: A phase II randomized study of Zanubrutinib plus obinutuzumab versus Obinutuzumab Monotherapy in patients with relapsed or refractory follicular lymphoma. Zinzani P.L et al, 2023 J Clin Oncol.

THIRD LINE: CLINICAL TRIAL (phase 2)

Obinutuzumab + Zanubrutinib (BGB 3111 - 212) x 10 cycles from 26/01/2021 to 28/10/2021 → **ORR: CR**

- **PET-FDG after 3° cycle: PR**
- **PET-FDG after 6° cycle: CR**
- PET-FDG after 10° cycle: CR
- BOM after 10° cycle: negative for lymphoma

Adverse events:

- Oral and genital HSV reactivation (during cycle 9)

WOULD YOU HAVE CONSOLIDATE?

Allo - SCT

- **DONOR**: 24 years male, matched unrelated (MUD), HLA 10/10
- **SOURCE OF HSC**: PBSC
- **BLOOD TYPE**: AB0 minor incompatibility (Donor 0+/Recipient B+)
- **CMV SIEROLOGY**: donor IgG-/recipient IgG+

- **CONDITIONING REGIMEN**: Thiotepa, Fludarabine, Cyclophosphamide (from 11/11/2021 to 14/11/2021)
- **GVHD PROPHYLAXIS**: ATG 6 mg/kg (from day – 6 to day – 2), CSA 3 mg/kg/die (from day – 1), MTX 10 mg/m² on day + 1, + 3 and + 6.

- **INFUSION: 17/11/2021**

→ 6.94 x 10^8/kg total nucleated cells
→ 5.76 x 10^6/kg CD34+ cells
→ 145.8 x 10^6/kg CD3+ cells

Allo - SCT

ACUTE COMPLICATIONS:

1. Parainfluenza virus type 3 infection → symptomatic treatment
2. S. epidermidis infection → Daptomycin + Piperacillin – Tazobactam
3. Deep vein thrombosis of the right internal jugular vein → LMWH

CHRONIC COMPLICATIONS:

1. + 3 months: COVID infection with mild symptoms → Sotrovimab early treatment
2. No GVHD occurred

EVALUATION OF DISEASE:

→ PET-FDG + 3 months: CR. FISH 99.4% donor. Blood type 0+ (donor)

→ PET-FDG + 6 months: CR. FISH 100% donor

→ **PET-FDG + 12 months: CR**