
# Lenalidomide nel linfoma mantellare: dati di Real Life

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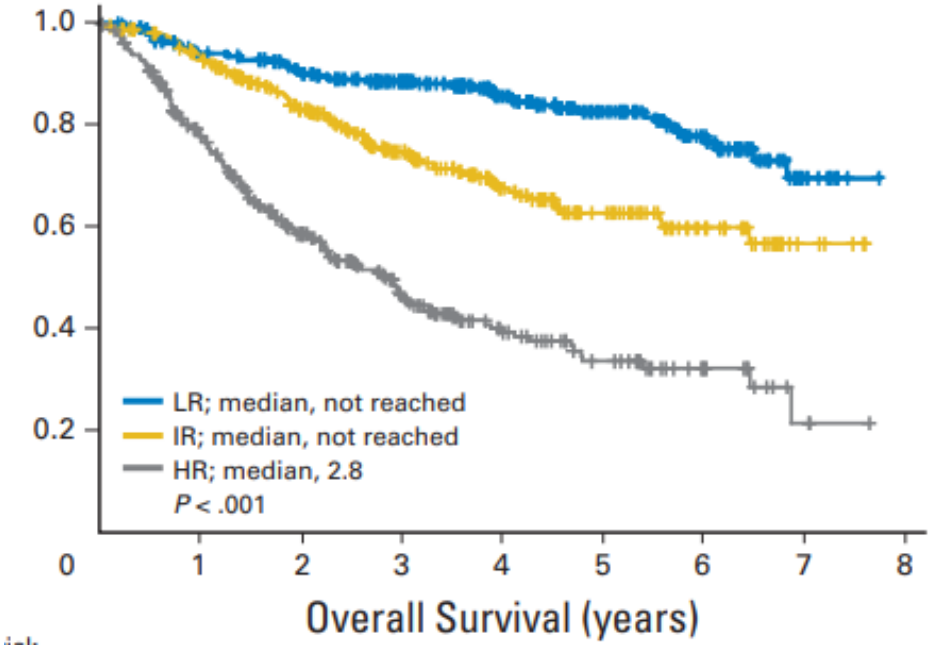
# Background MCL

- MCL accounting for 3-6% of all cases of NHL
- Median age at diagnosis is older than 60 yrs
- MCL often responds to initial treatment but there is a high rate of relapse portending a poor prognosis

- Patient prognosis remains poor with a median OS of 5-6 yrs
- Currently there is no universally accepted standard of care for patient management




OS according to MIPI score
*E.Hoster, JCO 2014*

# Background rrMCL

- With current therapies in the relapsed/refractory setting (ibrutinib, lenalidomide, bortezomib, temsirolimus...) median OS is approximately 2 yrs (Avivi & Goy, 2015)

- in routine practice (i.e., outside a clinical trial setting), the outcome of rrMCL remains overall unchanged both with standard immunochemotherapy and even after HDT-ASCT

- most patients still relapse and frequently develop chemoresistance

- persistent lack of consensus for the treatment of rrMCL

- different geographical approval of single agents (ibrutinib, lenalidomide, bortezomib, temsirolimus) explain the rather impressive variability in the management of these patients across countries

# Lenalidomide in rrMCL

- Lenalidomide is an immunomodulator drug with direct anti-neoplastic effects
- approved use by FDA and EMEA in Mantle Cell Lymphoma
- available in Italy for patients with rrMCL(without any other therapeutic options) since May 2011
- several phase II studies on lenalidomide have provided substantial overall response rate (ORR; 28%–68%) with durable activity in heavily pretreated patients

| ref | Trial | Phase | Diagn. | Dose | n MCL | ORR (CRR) | md DOR | md FU time | PFS (md) | OS (md) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1,2 | NHL-002 | II | R/R NHL | 25 mg | 15 (49 tot) | **53% (20%)** | 14 m (4 NR) | NR | 6 m | |
| 3 | UK (Eve) | II | R/R MCL | 25 mg (15 mg maint.) | 26 | **31% (8%)** | 22 m | 23 m | ITT: 4 m | 10 m |
| 4 | NHL-003 | II | R/R aggr NHL | 25 mg | 57 (217 tot) | **53% (20%)** | 16 m (7 NR) | Resp pts 20 m | | |
| 5, 6 | MCL-001 (EMRGE) | II | R/R MCL post-BOR | | 134 | **28 (8%)** | 17 m | 10 m | 4 m | 19 m |
| 7, 8 | MCL-002 (SPRINT) | II Ran. | R/R MCL | 25 mg | 170 | **68% (40%)** | 16 m | 41 m | 9 m | 28 m |


1)Habermann TM et al, BJH 2009
2)Witzig TE et al, AJH 2017
3)Eve HE et al, BJH 2012
4) Zinzani PL et al, Ann Oncol 2013
5) Goy A. et al, JCO 2013
6) Goy A. et al, BJH 2015
7) Trněný M et al, Lancet Oncol 2016
8) Arcaini L et al, BJH 2018

**Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial**

M. Trneny et al, Lancet Oncol, 2017

study design:

- phase 2
- randomised (2:1)

Enrollment period: from 2009 to 2013

rrMCL
≥ 18 yrs

**254**

170 (67%) → **Lenalidomide**
25 mg orally on days 1–21 every 28, until progressive disease or intolerability

84 (33%) → **single-agent investigator's choice**
(rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine)

| | **Lenalidomide (N=170)** | **Investigator's choice (N=84)** |
|---|---|---|
| Median age, yrs (range) | 65.8 (44-88) | 68.5 (49-87) |
| Age ≥65 yrs | 115 (68%) | 57 (68%) |

treatment arms balanced in baseline characteristics except for:

- high-risk MIPI score
- high tumour burden
- Bulky
- LDH

→ more prevalent among pts randomized to lenalidomide arm

M. Trneny et al, Lancet Oncol, 2017

| | Lenalidom. (N=170) | Investig. choice (N=84) |
|---|---|---|
| **n. of prior anti-lymphoma treatment** | | |
| 1 | 55 (32%) | 37 (44%) |
| 2 | 70 (41%) | 23 (27%) |
| 3 | 36 (21%) | 20 (24%) |
| ≥4 | 9 (5%) | 4 (5%) |
| **Relapsed or refractory to last treatm.** | | |
| Relapsed | 100 (49%) | 59 (70%) |
| Refractory | 70 (41%) | 25 (30%) |
| **Previous anti-lymphoma therapies** | | |
| anthracyclines | 157 (92%) | 78 (93%) |
| rituximab | 156 (92%) | 77 (92%) |
| cytarabine | 62 (36%) | 32 (38%) |
| bortezomib | 21 (12%) | 7 (8%) |
| bendamustine | 6 (4%) | 6 (7%) |
| temsirolimus | 3 (2%) | 1 (1%) |

| | Lenalidom. (N=170) | Investig. choice (N=84) |
|---|---|---|
| **Best response to prior anti-lymph. tr.** | | |
| CR / CRu | 58 (34%) | 29 (53%) |
| PR | 42 (25%) | 30 (36%) |
| SD | 31 (18%) | 9 (11%) |
| PD | 33 (19%) | 10 (12%) |
| unk | 6 (4%) | 6 (7%) |
| **Prior ASCT** | 30 (18%) | 18 (21%) |

# Results

M. Trneny et al, Lancet Oncol, 2017

- median follow-up: 15·9 months (IQR 7·6–31·7) [all patients]
  - lenalidomide group: **15·9 months** [IQR 6·9–32·8]
  - investigator's choice group: **15·3 months** [8·9–15·9].
- 165 (65%) of 254 patients in the ITT population had progressive disease or died

# PFS

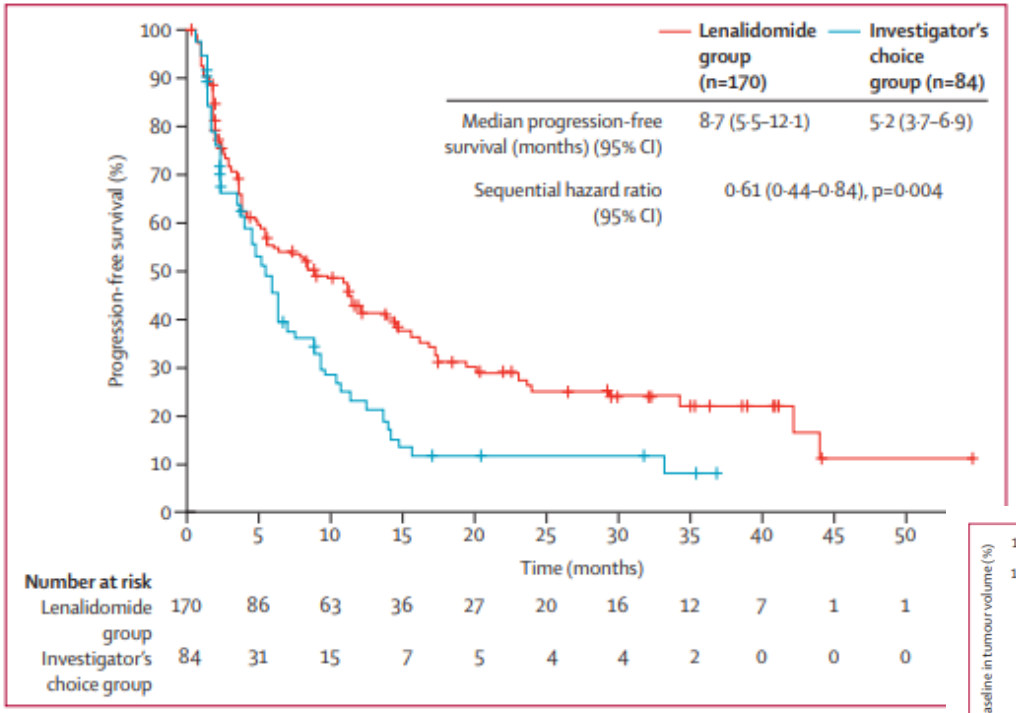



*Figure 2*: Progression-free survival with lenalidomide compared with investigator's choice in relapsed o refractory mantle cell lymphoma (central review)

**Median PFS:**

- **lenalidomide: 8·7 months**

(95% CI 5·5–12·1)

- **inv. choice: 5·2 months**

(95% CI 3·7–6·9)

(HR 0·61, 95% CI 0·44–0·84, **p=0·004**)

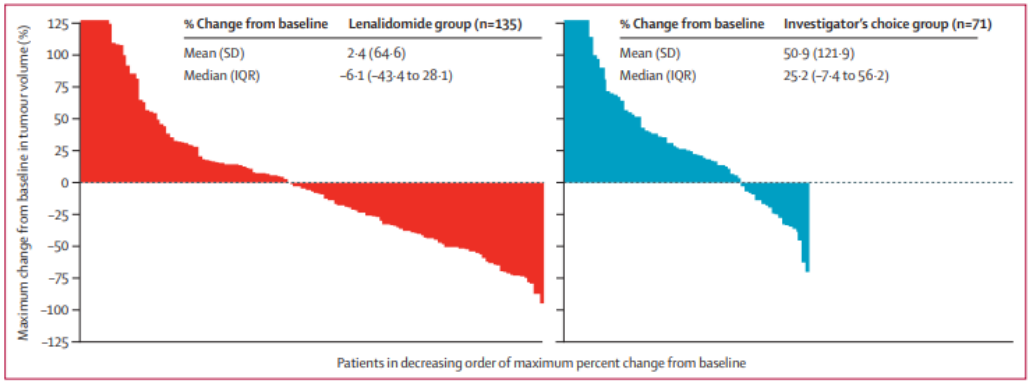



*Figure 3*: Maximum percent change from baseline in measurable tumour volume (central review) in the MCL-002 study

# Response data

M. Trneny et al, Lancet Oncol, 2017

| | **Lenalidom. N=170 n (%) [CI]** | **Investig. choice N=84 N (%) [CI]** | |
|---|---|---|---|
| Objective resp. | 68 (40%) *[33-48 ]* | 9 (11%) *[5-19]* | p<0.001 |
| CR Cru | 8 (5%) | 0 | p=0.043 |
| PR | 60 (35%) | 9 (11%) | |
| SD | 50 (29%) | 44 (52%) | |
| PD | 34 (20%) | 26 (31%) | |
| ND or missing | 18 (11%) | 5 (6%) | |

| | **Lenalidom. N=170 n (%)** | **Investig. choice N=84 N (%)** |
|---|---|---|
| Median time to **first response** | 4.3 (3.9-11.5) | Not reached |
| Median time to **best response** | 6.2 (3.9-11.7) | Not reached |
| **Duration of response** | 16.1 (5.6-12.2) | 10.4 (8.4-19.6) |
| Median **time to progression** | 9.1 (5.6-12.2) | 5.7 (3.7-6.9) |
| Median **OS** | 27.9 (20.0-36.9) | 21.2 (16.0-28.9) |

## Overall Survival

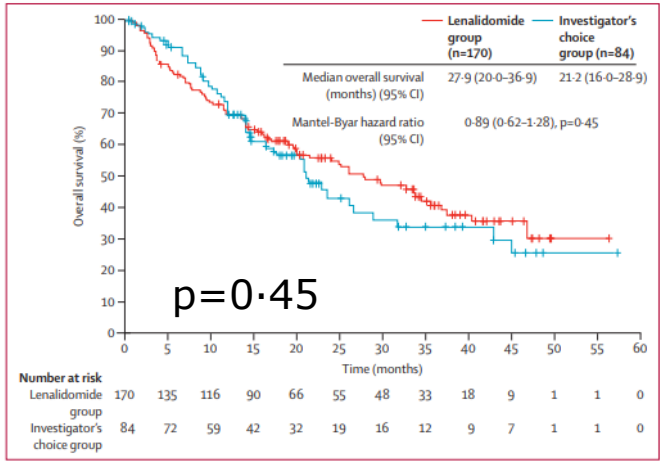



*Figure 4:* Overall survival with lenalidomide compared with investigator's choice in relapsed or refractory mantle cell lymphoma (central review)

# Toxicity

M. Trneny et al, Lancet Oncol, 2017

| | Lenalidomide (n=167) | | | Investigator's choice (n=83) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| **Haematological** | | | | | | |
| Anaemia | 34 (20%) | 12 (7%) | 2 (1%) | 13 (16%) | 5 (6%) | 1 (1%) |
| Thrombocytopenia | 31 (19%) | 25 (15%) | 5 (3%) | 10 (12%) | 16 (19%) | 7 (8%) |
| Leucopenia | 15 (9%) | 11 (7%) | 2 (1%) | 9 (11%) | 5 (6%) | 4 (5%) |
| Neutropenia | 12 (7%) | 40 (24%) | 33 (20%) | 1 (1%) | 13 (16%) | 15 (18%) |
| Febrile neutropenia | 0 | 7 (4%) | 3 (2%) | 0 | 2 (2%) | 0 |
| **Non-haematological** | | | | | | |
| Fatigue | 33 (20%) | 2 (1%) | 0 | 4 (5%) | 0 | 0 |
| Diarrhoea | 32 (19%) | 5 (3%) | 1 (1%) | 8 (10%) | 0 | 0 |
| Constipation | 28 (17%) | 1 (1%) | 0 | 5 (6%) | 0 | 0 |
| Nasopharyngitis | 25 (16%) | 0 | 0 | 5 (6%) | 0 | 0 |
| Asthenia | 24 (14%) | 2 (1%) | 0 | 11 (13%) | 0 | 0 |
| Pyrexia | 24 (14%) | 3 (2%) | 1 (1%) | 9 (11%) | 1 (1%) | 0 |
| Upper respiratory tract infection | 19 (11%) | 1 (1%) | 0 | 4 (5%) | 1 (1%) | 0 |
| Cough | 19 (11%) | 0 | 0 | 3 (4%) | 1 (1%) | 0 |
| Decreased appetite | 18 (11%) | 1 (1%) | 0 | 3 (4%) | 0 | 0 |
| Nausea | 18 (11%) | 0 | 0 | 12 (14%) | 0 | 0 |
| Rash | 18 (11%) | 0 | 0 | 3 (4%) | 0 | 0 |
| Peripheral oedema | 16 (10%) | 1 (1%) | 0 | 9 (11%) | 0 | 0 |
| Vomiting | 10 (6%) | 0 | 0 | 9 (11%) | 0 | 0 |
| Pneumonia | 5 (3%) | 5 (3%) | 1 (1%) | 2 (2%) | 2 (2%) | 0 |

Data are n (%).

*Table 3:* **Treatment-emergent haematological and non-haematological adverse events (≥10% grade 1–2, ≥5% grade 3–4)**

# Conclusions:

M. Trneny et al, Lancet Oncol, 2017

- first randomised study of lenalidomide in patients with rrMCL
- prospectively performed in a large number of patients
- central review assessments for efficacy
- limitation of the study: the lack of comparison with newer agents in MCL
    - eg: ibrutinib, bendamustine, temsirolimus that were not approved in the European Union or considered standard treatment at the time of study initiation
    - more recently considered combination therapy (eg, rituximab plus lenalidomide)
- interpretation of the underpowered OS is limited by the worse baseline disease characteristics of patients in the lenalidomide group, and was potentially confounded as a result of patients who crossed over from investigator's choice to lenalidomide
- **a significant improvement in PFS and and response rates with lenalidomide compared with other single-agent therapies** including rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine in patients with relapsed or refractory mantle cell lymphoma

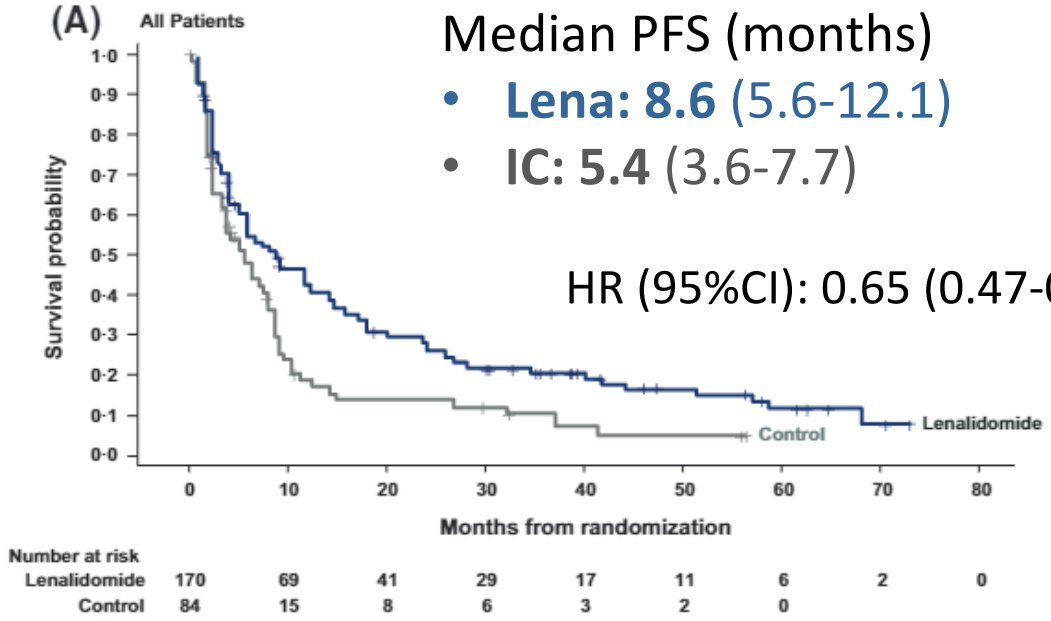
bjh research paper

**Prospective subgroup analyses of the randomized MCL-002 (SPRINT) study: lenalidomide *versus* investigator's choice in relapsed or refractory mantle cell lymphoma**

L. Arcaini et al, BJH 2018

- long term follow up (median f.u. 41.3 months; + 20 months from Trneny paper)
- subgroup exploratory analyses from MCL-002 to evaluate the potential impact of demographic factors, baseline clinical characteristics and prior therapies on PFS

# Progression Free Survival



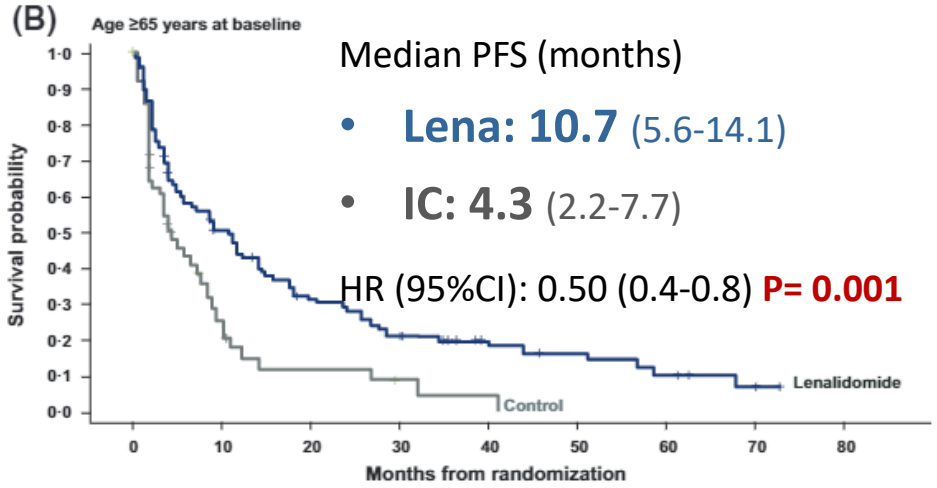

Median PFS (months)

- **Lena: 8.6** (5.6-12.1)
- **IC: 5.4** (3.6-7.7)

HR (95%CI): 0.65 (0.47-0.87) p= 0.006

L. Arcaini et al, BJH 2018

## PFS (age ≥ 65 yrs at baseline)

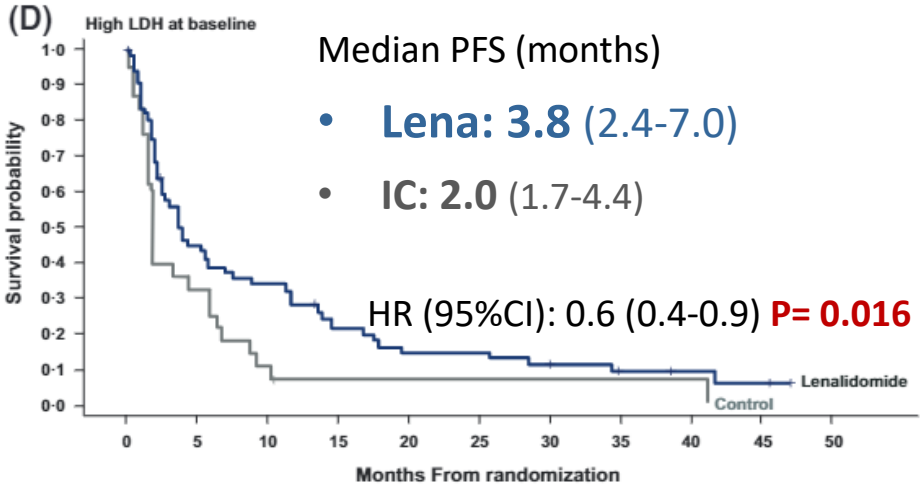



Median PFS (months)

- **Lena: 10.7** (5.6-14.1)
- **IC: 4.3** (2.2-7.7)

HR (95%CI): 0.50 (0.4-0.8) **P= 0.001**

## PFS (LDH at baseline)

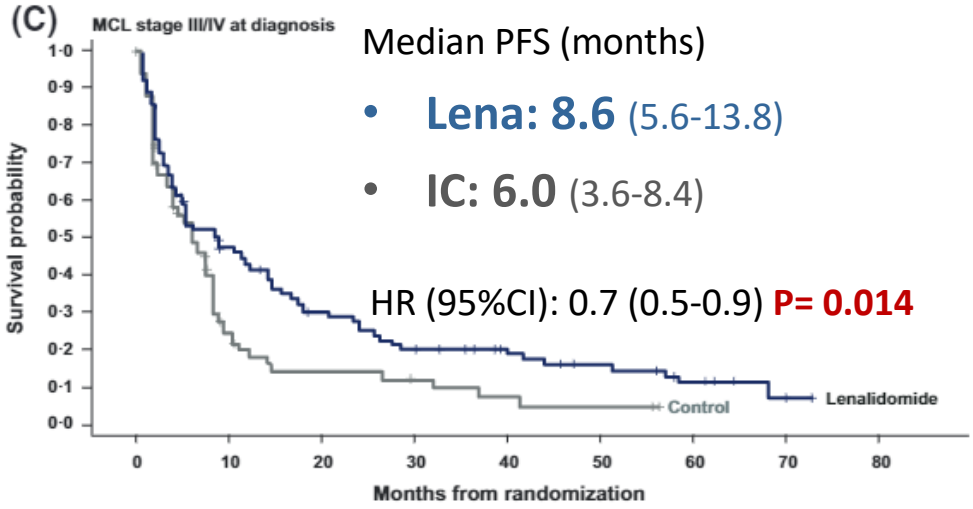



Median PFS (months)

- **Lena: 3.8** (2.4-7.0)
- **IC: 2.0** (1.7-4.4)

HR (95%CI): 0.6 (0.4-0.9) **P= 0.016**

## PFS (stage III/IV at diagnosis)

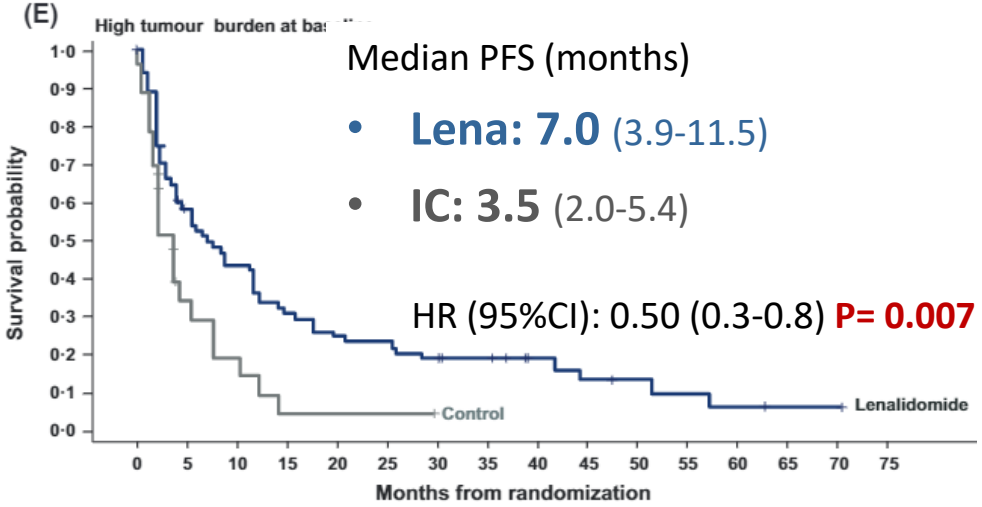



Median PFS (months)

- **Lena: 8.6** (5.6-13.8)
- **IC: 6.0** (3.6-8.4)

HR (95%CI): 0.7 (0.5-0.9) **P= 0.014**

## PFS (high tumor burden)



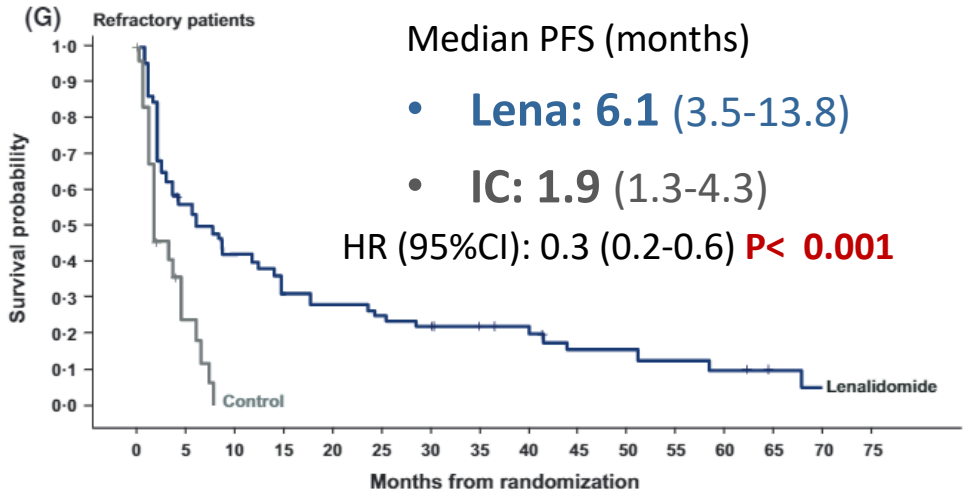

Median PFS (months)

- **Lena: 7.0** (3.9-11.5)
- **IC: 3.5** (2.0-5.4)

HR (95%CI): 0.50 (0.3-0.8) **P= 0.007**

L. Arcaini et al, BJH 2018

# PFS (refractory)




Median PFS (months)

- **Lena: 6.1** (3.5-13.8)
- **IC: 1.9** (1.3-4.3)

HR (95%CI): 0.3 (0.2-0.6) **P< 0.001**

multivariate Cox regression analysis:

factors associated with significantly longer PFS (other than lenalidomide treatment):

•normal LDH levels (P< 0.001)

•nonbulky disease (P= 0.045)

•<3 prior antilymphoma treatments (P= 0.005)

•≥6 months since last prior treatment (P= 0.032)

Lenalidomide improves PFS compared with single-agent IC therapy
in patients with relapsed/refractory MCL,
independent of most patient demographic and clinical characteristics,
and prior treatment history.

# A Systematic Review of Treatments of Relapsed/Refractory Mantle Cell Lymphoma

Madeliene Parrott,[1] Simon Rule,[2] Michael Kelleher,[3] Jayne Wilson[4]

**Table 1** Trial Design of Included Studies

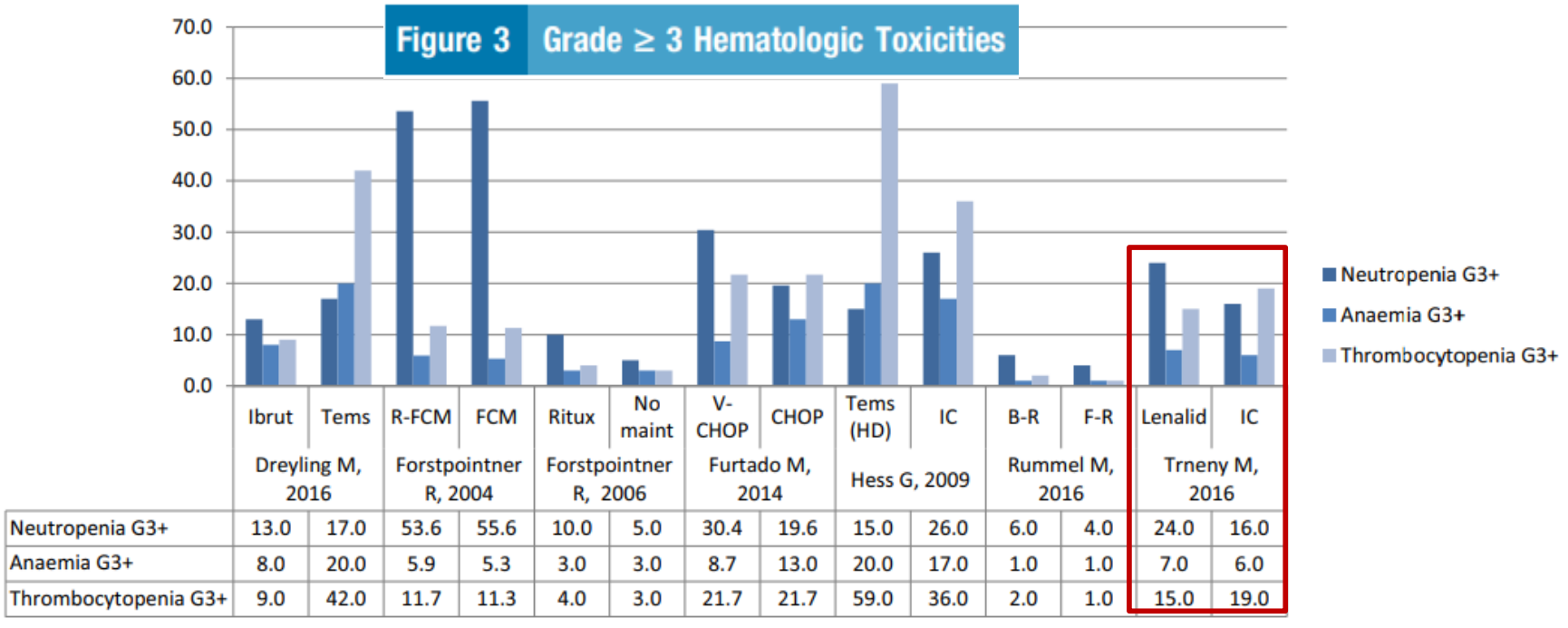
| Investigator | Design | Treatment | | MCL Patients (n) | | Inclusion Criteria |
|---|---|---|---|---|---|---|
| | | ID | Control | ID | Control | |
| Dreyling et al,[15] 2016 | Phase III, multicenter, open label, randomized 1:1, ITT, IWG 2007 | Ibrutinib | Tems | 139 | 141 | R/R MCL, ≥1 previous rituximab-containing therapy, ECOG PS 0-1 |
| Forstpointner et al,[16] 2004 | Phase III, multicenter, open label, randomized 1:1, ITT, IWG 1999 | R-FCM | FCM | 24 | 26 | R/R MCL (35%), FL (49%), lymphoplasmacytic (11%), other (5%); ≥1 previous chemotherapy, including HSCT; PS not stated |
| Forstpointner et al,[17] 2006 | Phase III, multicenter, open label, randomized 1:1, ITT, IWG 1999 | Rituximab maintenance | No Tx | 24 | 26 | R/R MCL, FL; patients achieving CR or PR on induction R-FCM; PS not stated |
| Furtado et al,[18] 2014 | Phase II, multicenter, open label, randomized 1:1, ITT, IWG 2007 | V-CHOP | CHOP | 23 | 23 | R/R MCL, ≥1 previous therapy, ECOG PS ≤2 |
| Hess et al,[19] 2009 | Phase III, multicenter, open label, randomized 1:1:1, ITT, IWG 2007 | Tems HD vs. LD | IC[a] | HD 54; LD 54 | 53 | R/R MCL, 2-7 previous therapies, must have included an alkylating agent, an anthracycline, and rituximab; ECOG PS ≤2 |
| Rummel et al,[20] 2016 | Phase III, multicenter, open label, randomized 1:1, per protocol analyses; response criteria not stated | B-R | F-R | 24 | 23 | R/R MCL (21%), FL (51%), MZL (8%), WM (11%), unclassified (9%), ≥1 previous therapy, WHO PS 0-2 |
| Trneny et al,[21] 2016 | Phase II, multicenter, open label, randomized 2:1, ITT, IWG 2007 | Lenalidomide | IC[a] | 170 | 84 | R/R MCL, ≥1 previous combination chemotherapy with an alkylating agent plus ≥1 of anthracycline, cytarabine, or fludarabine with or without rituximab; ECOG PS 0-2 |

Clinical Lymphoma Myeloma and Leukemia, 2018

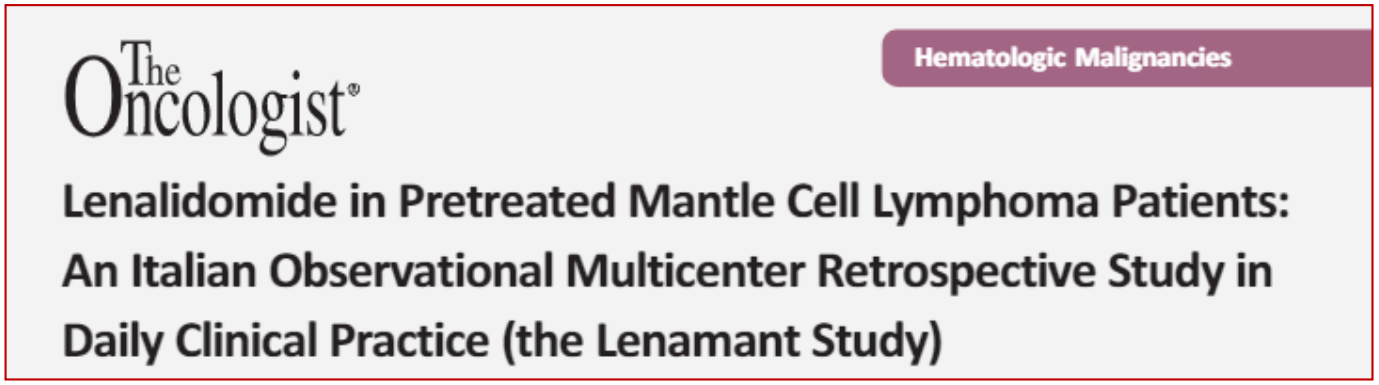
**Table 4** Efficacy Outcomes for MCL Patients in Included Trials

| Investigator | OA | PFS (mo) | | | OS (mo) | | | ORR (%) | | | CR (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | M | HR (95% CI) | *P* Value | M | HR (95% CI) | *P* Value | ORR | OR (95% CI) | *P* Value | CR | OR (95% CI) | *P* Value |
| **IBR vs TEMS** | ITT | 14.6 vs. 6.2 | 0.43 (0.32-0.58) | <.0001 | NR[a] vs. 21.3 | 0.76 (0.53-1.09) | .1324 | 72 vs. 40 | NR[b] | .0001 | 19 vs. 1 | 3.98 (2.38-6.65) | NR[b] |
| **RFCM vs FCM** | ITT | 8 vs. 4 | NR[b] | .3887 | NR[a] vs. 11 (est) | NR[b] | .0042 | 58 vs. 46 | NR[b] | .282 | 29 vs. 0 | NR[b] | NR[b] |
| **R maint vs No Ther** | Initial R-FCM therapy | 14 vs. 12[c] | NR[b] | .049 | 45% vs. 9%[d] | NR[b] | NR[b] | NR[b] | NR[b] | NR[b] | NR[b] | NR[b] | NR[b] |
| **VCHOP vs CHOP** | ITT | 16.5 vs. 8.1 | 0.6 (0.31-1.15) | .12 | 35.6 vs. 11.8 | 0.37 (0.16-0.83) | .01 | 82.6 vs. 47.8 | 0.14 (0.3-0.62) | .01 | 34.8 vs. 21.7 | 0.52 (0.14-1.93) | .33 |
| **Tems (HD vs LD) vs IC** | ITT | 4.8 vs. 1.9 | 0.44 (0.25-0.78) | .0009 | 12.8 vs. 9.7 | 0.80 (0.50-1.28) | .3519 | 22 vs. 2 | NR[b] | .0019 | 2 vs. 2 | NR[b] | NR[b] |
| **BR vs FR** | Per protocol | 17.6 vs. 4.7 | 0.45 (0.22-0.76) | .01 | 35.3 vs. 20.9 | NR[b] | NR[b] | 70.8 vs. 26.1 | NR[b] | NR[b] | 37.5 vs. 13 | NR[b] | NR[b] |
| **Lena vs IC** | ITT | 8.7 vs. 5.2 | 0.61 (0.44-0.84) | .004 | 27.9 vs. 21.2 | 0.89 (0.62-1.28) | .45 | 40 vs. 11 | NR[b] | .001 | 5 vs. 0 | NR[b] | NR[b] |

**Figure 3** Grade ≥ 3 Hematologic Toxicities




| | Ibrut | Tems | R-FCM | FCM | Ritux | No maint | V-CHOP | CHOP | Tems (HD) | IC | B-R | F-R | Lenalid | IC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dreyling M, 2016 | | Forstpointner R, 2004 | | Forstpointner R, 2006 | | Furtado M, 2014 | | Hess G, 2009 | | Rummel M, 2016 | | Trneny M, 2016 | |
| Neutropenia G3+ | 13.0 | 17.0 | 53.6 | 55.6 | 10.0 | 5.0 | 30.4 | 19.6 | 15.0 | 26.0 | 6.0 | 4.0 | 24.0 | 16.0 |
| Anaemia G3+ | 8.0 | 20.0 | 5.9 | 5.3 | 3.0 | 3.0 | 8.7 | 13.0 | 20.0 | 17.0 | 1.0 | 1.0 | 7.0 | 6.0 |
| Thrombocytopenia G3+ | 9.0 | 42.0 | 11.7 | 11.3 | 4.0 | 3.0 | 21.7 | 21.7 | 59.0 | 36.0 | 2.0 | 1.0 | 15.0 | 19.0 |




V. Stefoni et al, The Oncologist , 2018

**Study design:**

- multicenter
- retrospective
- observational

**study aim:**

collecting data on the effectiveness and the safety of lenalidomide requested pursuant to Italian law 94/1998 in rrMCL patients

**study population:**

all patients treated  in Italy with lenalidomide from 2011 to 2013

**70 patients**

- 18: combined therapy
  - 13 lenalidomide + dexamethasone
  - 5 lenalidomide + rituximab
- 52: lenalidomide monotherapy

| Characteristics | N=70, n (%) |
|---|---|
| Median age, yrs (range)<br>≥ 65 yrs | 65 (45-85)<br>13 (18.6) |
| Male | 50 (71.4) |
| Stage III/IV | 56 (80) |
| ECOG ≥ 2 | 20 (28.6) |
| B symptoms | 10 (14.3) |
| Refractory to most recent therapy | 32 (45.7) |
| Refractory to first line | 16 (22.8) |
| median number of previous therapies (range) | 2.5 (1-10) |
| Prior ASCT | 36 (51.4) |
| Lenalidomide single agent | 52 (74.3) |
| Lenalidomide in combination | 18 (25.7) |

V. Stefoni et al, The Oncologist , 2018

# Results

V. Stefoni et al, The Oncologist , 2018

- 688 cycles completed
- N. of cycles (median): 8 (range 1-55)
- Dose depended on physician choice

- Daily dose
  - 10 mg/day: 11(15.7%)
  - 15 mg/day: 16 (22.8%)
  - 25 mg/day: 43 (61.5%)
  - Combination therapy: 4 pts (10-15 mg/day)

**Overall Response Rate ORR (n=70): 47.1%**

- CR: 22 (31.4%)
- PR: 11 (15.7%)
- SD: 6
- PD: 31

**Lenalidomide monotherapy n=52**

- **ORR: 36.5%**
- CR: 14 (26.9%)
- PR: 5 (9.6%)

**Lenalidomide combined therapy n=18**

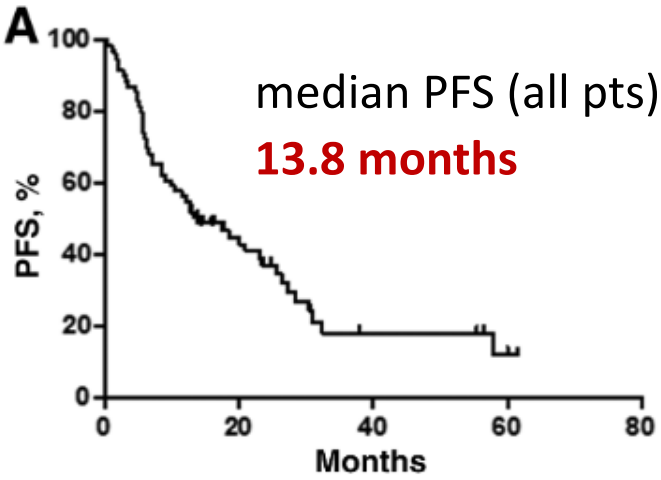
- **ORR: 77.7%**
- CR: 8 (44.4%)
- PR: 6 (33.3%)

- ORR: higher in patients who responded to last previous therapy (52.6%)
- Progressive disease: 56.3% (refractory), 39.5% (responding patients)
- No significative difference in ORR between younger (38.5%) and older (45.6%)
- Median DoR was 17.8 months (monotherapy), 19.4 months in patients treated with monotherapy and combined therapy

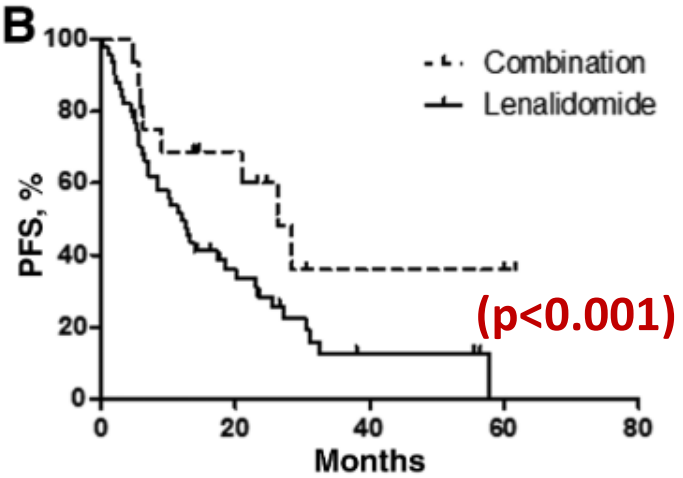
## Outcome median follow-up: 26 months (13.8–62.7)

At the latest available follow-up: 14 patients in continuous CR (6 combined, 8 lena single agent)

### Progression Free Survival




median PFS (all pts):
**13.8 months**

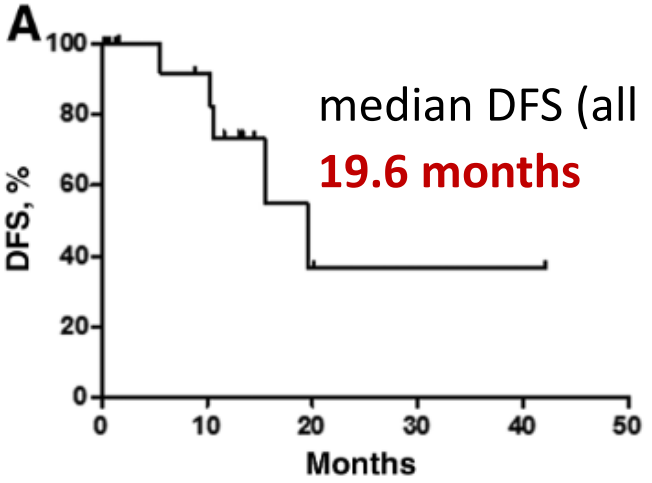



**(p<0.001)**

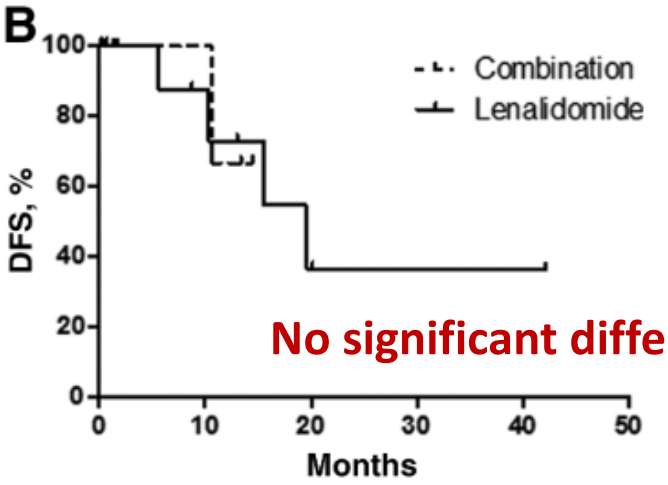
median PFS (monotherapy): **12.1 months**

median PFS (combined): **26.3 months**

### Disease Free Survival




median DFS (all pts):
**19.6 months**



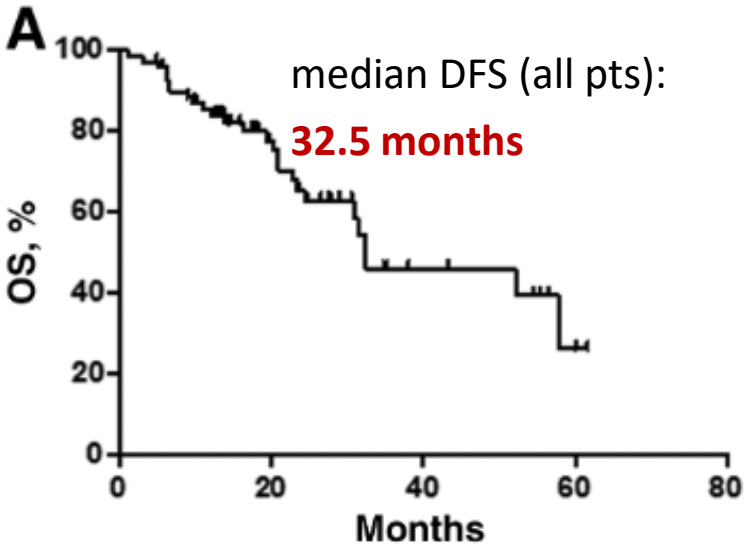

**No significant difference**

median DFS (monotherapy): **19.6 months**

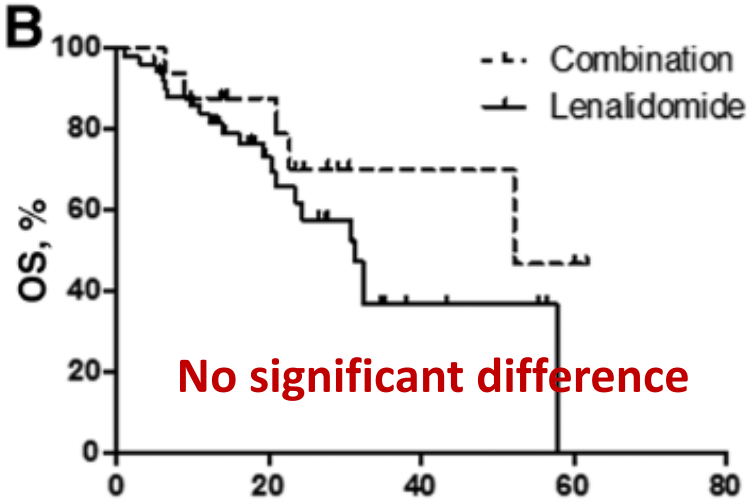
median DFS (combined): **not reached**

V. Stefoni et al, The Oncologist , 2018

# Overall Survival




median DFS (all pts):
**32.5 months**




median OS (monotherapy): **31.4 months**
median OS (combined): **52.2 months**

- 26 patients died
- 34 patients (26 lena alone, 8 in combination) underwent further treatment after lenalidomide failure
- median time TTNT: 3.4 months

## Safety

**AEs: 42 patients (60%)**

neutropenia: 25
thrombocytopenia: 6
anemia: 6
gastrointestinal toxicity: 4

**SAEs: 9 patients (12.8%)**

lung ca: 1
myocardial infarction: 2 (not related to drug)
infection: 1
gastrointestinal toxicities: 4

V. Stefoni et al, The Oncologist , 2018

## Conclusions

- large retrospective analysis on rrMCL
- standard daily clinical practice outside a trial setting (real life experience)
- ORR and CR rate were similar to those observed in clinical trials
- Monotherapy: ORR 36.5%, 26.9% CR, 9.6% PR
- Combined: ORR 77.7%, CR 44.4%
- similar effectiveness among younger and older patients
- Lenalidomide is a feasible treatment option for patients with rrMCL, even in real life
- Lenalidomide was used in a wide spectrum of patients with varied underlying diseases and a broad range of concomitant medications
- the present data have the best picture of the drug's behavior in routine use

Treatment with lenalidomide is effective and tolerable in everyday clinical practice,

with superimposable results to those obtained in clinical trials,

and it must be considered in the therapeutic algorithm of rrMCL as a targeted approach

V. Stefoni et al, The Oncologist , 2018

RESEARCH

# Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004)

M. Wang et al,
Journal of Hematology and Oncology, 2017

study design:

- observational
- retrospective

study aim:

outcomes in patients with rrMCL who received lenalidomide-based therapy after ibrutinib failure or intolerance

study population:

- at least one dose of ibrutinib (monotherapy or combination) **and**
- ibrutinib failure (relapse, PD refractory), **and/or**
- intolerance (discontinuation of ibrutinib for reasons other than PD)

Lenalidomide was not required to immediately follow ibrutinib.

primary endpoint: investigator assessed ORR

## **N. of patients: 58** (enrollment 2009-2016)

- 13: lenalidomide monotherapy
- 45: combined therapy (11 lenalidomide +R, 34 other combination)

| **Characteristics** | **Lena mono N=13, n (%)** | **L+ R N=11, n (%)** | **L+ other N=34, n (%)** | **Overall N=58, n (%)** |
|---|---|---|---|---|
| Median age, yrs (range)<br>≥ 65 yrs | 67 (54-83)<br>6 (46) | 70 (58-84)<br>9 (82) | 71 (50-89)<br>26 (76) | **71 (50-89)**<br>**41 (71)** |
| Male | 11 (85) | 8 (73) | 25 (74) | **44 (76)** |
| Tumor Burden (high) | 4 (31)<br>Missing 3 | 1 (9)<br>Missing 5 | 12 (35)<br>Missing 9 | **17 (29)**<br>**Missing 22** |
| ECOG ≥ 2 | 3 (23)<br>Missing 8 | 1 (9)<br>Missing 5 | 4 (12)<br>Missing 14 | **8 (14)**<br>**Missing 22** |
| Bulky disease (yes) | 2 (15)<br>Missing 9 | 0 (0)<br>Missing 5 | 6 (18)<br>Missing 11 | **8 (14)**<br>**Missing 25** |
| Time from diagnosis to first lenalidomide dose (months)<br>*median (range)* | 58 (15-144) | 47 (6-105) | 46 (4-214) | **49 (4-214)** |
| Time from end of last prior anti-lymphoma therapy to first dose of L (weeks)<br>*median (range)* | 0.7<br>(0.1-3.5) | 0.3<br>(0.1-21.7) | 0.7<br>(0.1-12.6) | **0.7 (0.1-21.7)** |

M. Wang et al, J Hematol Oncol, 2017

# Treatment History

| | Lena mono N=13, n (%) | L+ R N=11, n (%) | L+ other N=34, n (%) | Overall N=58, n (%) |
|---|---|---|---|---|
| N. of prior antilymphoma treatment regimens, median (range) | 4 (3-7) | 3 (2-8) | 4 (1-13) | **4 (1-13)** |
| **Type of ibrutinib treatment** | | | | |
| Combination regimen | 1 (8) | 1 (9) | 10 (29) | **12 (21)** |
| Monotherapy | 12 (92) | 10 (91) | 24 (71) | **46 (79)** |
| **Ibrutinib status** | | | | |
| Relapse/PD | 6 (46) | 2 (18) | 15 (44) | **23 (40)** |
| Refractory | 2 (15) | 8 (73) | 15 (44) | **25 (43)** |
| Intolerant | 3 (23) | 0 (0) | 3 (9) | **6 (10)** |
| Duration of ibrutinib treatment median (range) | 4.8 (1.2-13.9) | 3.9 (2.0-16.6) | 4.3 (0.5-47.6) | **4.3 (0.5-47.6)** |
| **Reason for ibrutinib discontinuation** | | | | |
| Lack of efficacy | 9 (69) | 11 (100) | 31 (91) | **51 (88)** |
| Toxicity to ibrutinib | 3 (23) | 0 (0) | 2 (6) | **5 (9)** |
| Toxicity attibution unknown | 0 (0) | 0 (0) | 1 (3) | **1 (2)** |
| Completed ibrutinib teratment | 1 (8) | 0 (0) | 0(0) | **1 (2)** |

M. Wang et al, J Hematol Oncol, 2017

# Efficacy

- Median duration of treatment:
  - Lena monotherapy: 8.4 weeks
  - Lena combination: 7.4 weeks

| Outcome | **Lena mono N=13, n (%)** | **L+ R N=11, n (%)** | **L+ other N=34, n (%)** | **Overall N=58, n (%)** |
|---|---|---|---|---|
| **Best response by investigator's assessment** | | | | |
| ORR (95% CI) | 2 (15) 2-45% | 3 (27) 6-61% | 12 (35) 20-54% | **17 (29) 18-43%** |
| CR | 0 (0) | 1 (9) | 7 (21) | **8 (14)** |
| PR | 2 (15) | 2 (18) | 5 (15) | **9 (15)** |
| SD | 0 (0) | 1 (9) | 3 (9) | **4 (7)** |
| Relapse/PD | 8 (62) | 3 (27) | 16 (47) | **27 (47)** |
| Unknown | 3 (23) | 2 (18) | 3 (9) | **8 (14)** |
| Missing | 0 (0) | 2 (18) | 0 (0) | **2 (3)** |
| **Duration of response, weeks** Median (95% CI) | 3 (NA to NA) | 20 (NA to NA) | NA (16.4 to NA) | **20* (2.9 to NR)** |

*14 of 17 responders were censored from the DOR analysis due to lack on follow up data

M. Wang et al, J Hematol Oncol, 2017

# Lenalidomide exposure

| | Lena mono N=13 | L+ R N=11 | L+ other N=34 | Overall N=58 |
|---|---|---|---|---|
| **Lenalidomide treatment duration, weeks** | | | | |
| Median (range) | 8.4 (0.4-30.0) | 14.0 (0.9-37.9) | 7.0 (1.1-77.9) | **8.4 (0.4-77.9)** |
| **Number of lenalidomide cycles** | | | | |
| Median (range) | 2.0 (1.0-7.0) | 2.0 (1.0-9.0) | 1.0 (0.0-11.0) | **2.0 (0.0-11.0)** |
| **Duration of other therapy combined with lenalidomide, weeks** | | | | |
| Median (range) | NA (NA) | 8.3 (0.1-35.9) | 7.2 (0.7-77.7) | **7.4 (0.1-77.7)** |

- Most patients received lenalidomide 10–25 mg/day on days 1–21 of each 28-day cycle.

- 54 patients had discontinued lenalidomide-based therapy
- 4 patients continue to receive lenalidomide.

- **reasons for lenalidomide discontinuation:**
  - were lack of efficacy (n = 27)
  - toxicity (n = 10)
  - other reasons (n = 9) [initiation of another therapy, ASCT, primary clinician/patient decision to stop therapy]
- completion of lenalidomide treatment: 5
- missing data: 3

M. Wang et al, J Hematol Oncol, 2017

## Safety

- 48 (83%) had one or more Adverse Events (AE) during lenalidomide treatment
- **20 (34%) patients had at least one serious AE**
  - lenalidomide alone 23%; lenalidomide + rituximab 36%; lenalidomide + others 38%

- The most frequently reported **serious AEs of any grade** were:
  - febrile neutropenia (n = 4; 7%)
  - hypotension (7%)
  - deep vein thrombosis (DVT) (n = 3; 5%)
  - pneumonia (5%)
  - pancytopenia (5%)
  - fall (5%)
  - acute kidney injury (5%)
  - dyspnea (n = 2; 3%)
  - sepsis (3%)
  - respiratory failure (3%).

- **9 pts (16%) patients had at least one AE leading to dose discontinuation**
(lenalidomide alone 8%; lenalidomide + rituximab 18%; lenalidomide + others 18%)

- 28 pts (48%) died
  - 12 during treatment
  - 15 follow up
  - 1 unk

- Cause of death
  - 20 (34%) for MCL or its compications
  - 5 unk causes
  - 1 renal disease
  - 2 AEs

M. Wang et al, J Hematol Oncol, 2017

## Conclusions

- Study limits:
  - retrospective, limited follow up, AEs probably underestimated
  - heterogeneity of regimens combined with lenalidomide: difficult to confidently discern the amount of response due to lenalidomide versus the other therapies used in combination

- lenalidomide-based therapy has clinically significant activity as a monotherapy and in combination regimens to treat heavily pretreated patients with refractory or relapsed MCL after ibrutinib therapy or who cannot tolerate ibrutinib

- lenalidomide addresses an unmet medical need and widens the therapeutic options in a difficult-to-treat patient population

M. Wang et al, J Hematol Oncol, 2017

David A. Bond et al, ASH 2019

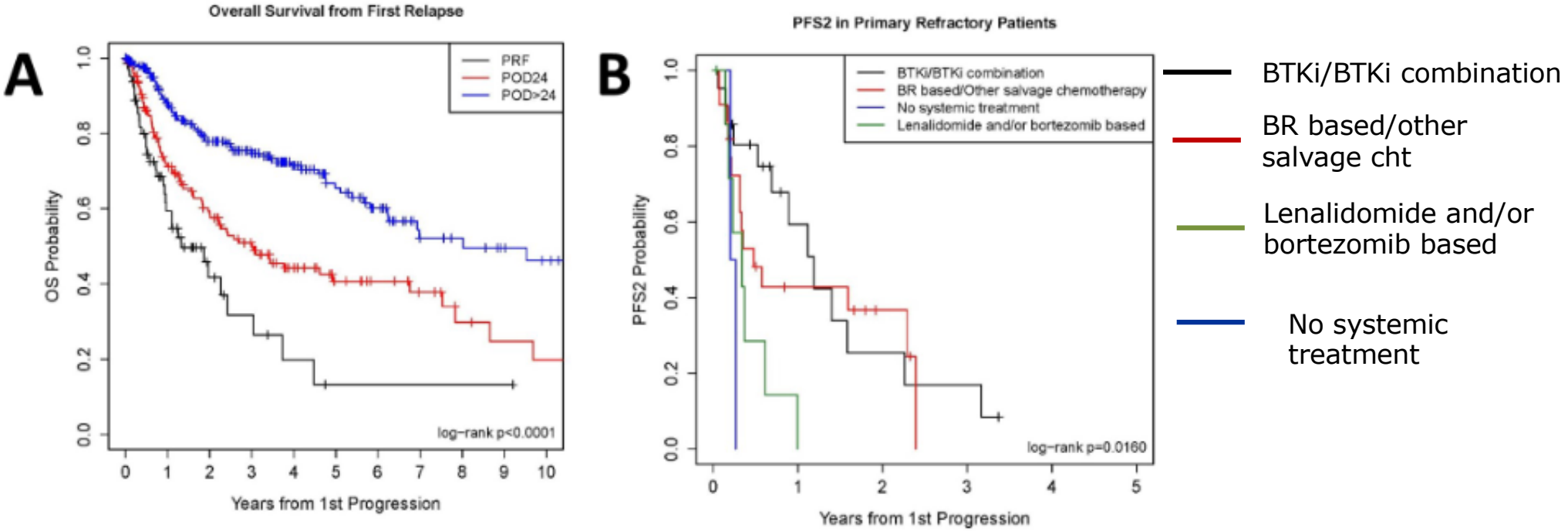
Clinical and outcome data for 453 MCL pts treated between 2000 and 2017 (12 US centers)

three groups:

(a) refractory disease to frontline therapy or POD within 6 months of frontline therapy

(b) POD between 6 to 24 months of therapy was termed POD24

(c) POD beyond 24 months was termed POD>24.




- Of currently available second line therapies, BTKi were associated with improved PFS2 in refractory pts.
- Outcomes are particularly poor for pts who receive intensive induction therapies yet still relapse early, representing a population at high risk for early mortality related to MCL.
- Novel treatment approaches should be evaluated in this population, including CAR-T cell

# Caso Clinico 1

Femmina (1947), aa 67

## Esordio di malattia:

Febbraio 2014: diagnosi di MCL, stadio IV B (sudorazione notturna), MIPI: alto rischio

- BOM (28/02/2014): infiltrato 90%, MIB 10%
- PET (14/02/2014): captazioni linfonodali diffuse

## Terapia di prima linea

Terapia: **R CHOP x 6** (terminati il 17/07/14)

Restaging:

- PET (20/08/2014): score Deauville 2
- BOM (20/08/2014): positiva, infiltrato midollare < 5%

Remissione Parziale (ottima, minimo residuo midollare del 5%)

Consolidamento con ibritumomab (18/09/14)

- BOM (22/12/14): minima localizzazione residua di MCL (<5%)

# Caso Clinico 1

Ottobre 2015: netta progressione di malattia

• pancitopenia, incremento della milza (20 cm vs 14 cm), linfoadenomegalie superficiali

• BOM (16/10/2015): massiva localizzazione di MCL (infiltrato 90%)

• PET (19/10/2015): captazioni linfonodali diffuse

## Terapia di seconda linea

Terapia: **R-BAC 500 x 5** (completati l'11/02/16)

*(non eseguito il 6° ciclo per pancitopenia persistente)*

•PET (08/04/2016) score Deauville 1

•BOM (13/04/2016): negativa

Risposta: Remissione Completa

# Caso Clinico 1

Marzo 2017: recidiva di MCL

- PET (15/03/2017): captazioni linfonodali, noduli mammella sx
- Biopsia nodulo mammario: recidiva di linfoma mantellare, blastoide (MIB > 90%)
- BOM (24/03/2017): negativa

Terapia di terza linea

**Lenalidomide (20 mg/die per 21 gg ogni 28 gg)** [L.648/96]

Ciclo 1 day 1: 14/03/2017

- PET 03/05/2017 (post II ciclo): Deauville 4 (notevole miglioramento del quadro)
- PET 18/01/2018 (post X ciclo): Deauville 1. Remissione Completa
- PET 17/07/2018 (post XVI ciclo): Deauville 1. Remissione Completa

**Completati 20 cicli** (02/11/2018)

**Tossicità:** neuropatia g.1, tossicità epatica g1, piastinopenia g3, neutropenia g3, anemia g1

07/11/2018:

- febbre (max 39°), sintomatologia gastrointesinale (nausea, vomito e diarrea); emocolture positive per E.Coli
- riscontro della tumefazione in sede temporomandibolare

--------→ si programma restaging

# Caso Clinico 1

Novembre 2018: recidiva di MCL

- PET (14/11/2018) (post XX ciclo): captazione mammella sx
- Biopsia nodulo mammario (17/12/2018): MCL, varietà blastoide MIB 90%

## Terapia di quarta linea

Proposta terapeutica: Ibrutinib 140 mg x 4/die

Inizio terapia con ibrutinib: 10/01/2019

- PET (23/04/2019): Deauville 2. Remissione Completa
- PET (07/09/2019): progressione [intenso e focale iperaccumulo nel quadrante supero-interno della mammella sinistra.]

Terapia: RT locale (30 Gy dal 10/10/2019 al 16/10/2019), continua ibrutinib

27/12/2019: ibrutinib 140x4 in corso; programmato restaging fine gennaio

# Caso Clinico 2

Maschio (1939), aa 68

## Esordio di malattia:

Febbraio 2007: diagnosi di MCL, stadio IIIA

- BOM (07/11/2007): negativa
- Biopsia linfonodale: MCL varietà classica, nodale.
- TAC (09/11/2007): linfoadenomegalie sovra e sotto diaframamtiche

## Terapia di prima linea

Terapia: **R-CHOP21 x 6** cicli completati il 12/3/2008
Restaging:

- TAC (11/04/2008): negativa - Remissione Completa

Consolidamento con ibritumomab (24/04/2008)

Settembre 2014: 1^ Recidiva, stadio III A, MIPI high risk, leucemizzato

- PET (02/09/2014): captazioni linfonodali sovra e sotto diaframmatiche
- Biopsia linfonodo ascellare (11/09/2014): MCL, MIB 25%
- BOM (12/09/2014): negativa

# Caso Clinico 2

## Terapia di seconda linea

Proposta terapeutica: Ibrutinib 140 mg x 4/die (NPP Name Patient Program)

- Ibrutinib a 420 mg/die dal 18/10/2014 al 10/08/2018 [3 anni e 10 mesi]

Tossicità: episodi di macroematuria in corso di terapia, sospensione transitoria della terapia

Marzo 2011: ADK della prostata, RT (terminata il 19/08/2011).

Giugno 2018: **2^ recidiva di LNH mantellare, stadio IVA, MIPI: high risk**

- BOM (13/06/2018): localizzazione massiva di LNH mantellare (infiltrato 90%)
- 10/08/2018 PET: negativa

## Terapia di terza linea

Proposta terapeutica: **Lenalidomide (20 mg/die per 21 gg ogni 28 gg)** [L.648/96]

# Caso Clinico 2

**16/08/2018: inizio terapia con lenalidomide 20 mg /die**

- 22/08/18: I ciclo di lenalidomide 20 mg/die sospeso per neutropenia febbrile e polmonite basale dx
- 07/09/2018: leucopenia e neutropenia g3, si introduce G-CSF
- 18/09/2018: riprende **lenalidomide 10 mg/die**
- 11/12/2018: neutropenia g3, prosegue G-CSF settimanali

Rivalutazione post IV ciclo: ottima RP di malattia al controllo midollare

- BOM (12/02/2019) infiltrato midollare 10%

- 12/07/2019: lieve incremento della creatinina con Clearance <50; si riduce la posologia della **Lenalidomide a 10 mg a giorni alterni**
- 29/07/2019: si riduce la posologia della Lenalidomide a 10 mg a giorni alterni (cicli XIII e XIV)
- 07/10/2019: ciclo XV: lenalidomide 10 mg/die
- 31/12/2019: ciclo XVIII: lenalidomide 10 mg/die

# Caso Clinico 3

Maschio (1955), aa 51

## Esordio di malattia:

Maggio 2006: diagnosi di MCL, stadio IV A leucemizzato

- Biopsia ileo: MCL, FISH: traslocazione t (11;14)  58% delel cellule
- BOM (18/05/2006): positiva, infiltrato 55%, MIB 10%
- TAC (22/05/2006): captazioni linfonodali diffuse, splenomegalia

## Terapia di prima linea

Programma terapeutico: **R-HyperCVAD/R-MTX-ARA-C 4 cicli** (8 blocchi) ultimati il 9/11/2006.

- BOM (28/12/2006): negativa
- TAC (22/12/2006)  : non linfoadenomegalie
- Colonscopia/Gastroscopia(con biopsie multiple): negativa, istologico negativo

Restaging: Risposta Completa

# Caso Clinico 3

Ottobre 2011: MCL 1^ recidiva, stadio IV A (midollo osseo e adenopatie profonde)

## Terapia di seconda linea

Programma terapeutico: **4 cicli R-BAC** completati il 25/01/2012

- BOM (24/01/2012): negativa
- PET (23/02/2012): captazione linfonodo inguinale
- Agobiopsia linfonodo inguinale: MCL

Restaging: Remissione Parziale

**Consolidamento con ASCT**

Raccolta di cellule staminali (3,8 x 10^6/Kg), ASCT (condizionato con FEAM) in data 15/3/12.

Restaging: Remissione Completa

Aprile 2014: MCL 2^ recidiva, stadio IV (localizzazione diffusa del tessuto sottocutaneo)

- BOM (21/05/2014): negativa
- PET (22/05/2014): numerose captazioni tessuto sottocutaneo
- TAC (26/05/2014): negativa

## Terapia di terza linea

Programma terapeutico: 3/4 R-GDP

RGDP x 4 completati  il 14/08/2014

- PET (12/09/2014): negativa
- TAC (02/10/2014): negativa

Restaging: Risposta Completa. Rifiuta ipotesi di TMO allogenico

**15/09/2014: inzia lenalidomide 15 mg (gg1-21 ogni 28)**

17/07/2015 agli ultimi due controlli-> piastrine in lieve calo

- Restaging + 6 mesi: TAC (16/03/2015): negativa
- Restaging +12 mesi: TAC (10/09/2015): negativa ---> prosegue con lena 15 mg
- Restaging +18 mesi: TAC (20/04/2016): negativa ---> prosegue con lena 15 mg

Sospesa, per volontà del paziente, la terapia con lenalidomide il **13/09/2016** (25 cicli totali)

- Restaging  finale: Remissione Completa
- BOM (14/12/2016): negativa
- TAC (14/12/2016): negativa

Durata risposta: **18 mesi dal termine della Lena [settembre 2016-aprile 2018]**

Aprile 2018: MCL 3^ recidiva (+ 18 mesi dal termine di lenalidomide], stadio IV

- PET (06/04/2018): linfoadenomegalie sovradiaframmatiche, nodulo sottocutaneo
- BOM (12/04/2018): positva per MCL, FISH t(11;14) bcl1 - IgH: Negativa

## Terapia di quarta linea

Programma terapeutico: **ibrutinib 140 mg x 3** (inizio 13/05/2018)

- 07/06/2018: fibrillazione atriale secondaria a ibrutinib [terapia con beta bloccante, senza TAO in considerazione del basso rischio cardioembolico]

Restaging +6

PET (08/11/2018): score Deauville 1

---> accetta **trapianto allogenico. Continua ibrutinib.**

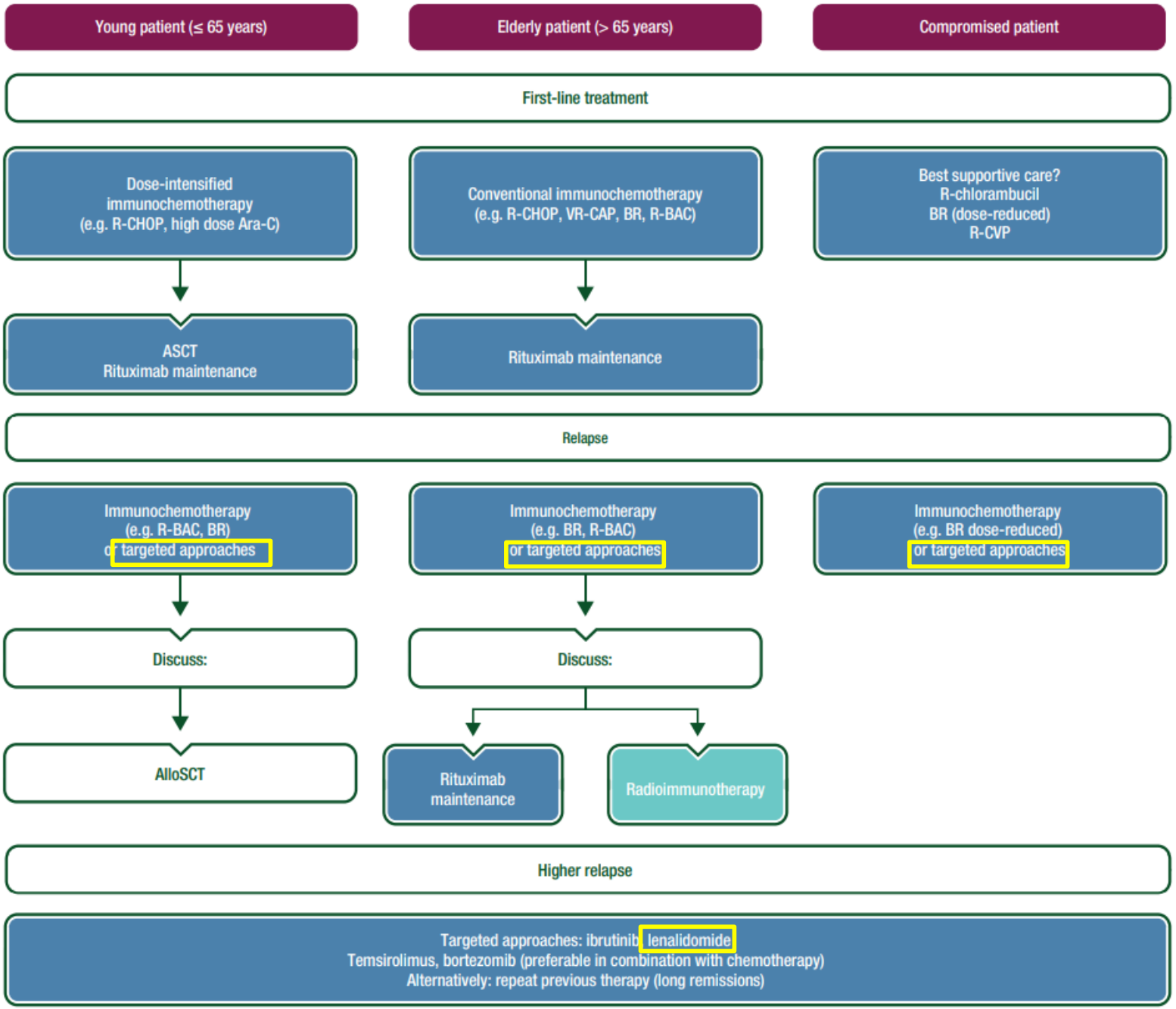
- avvio ricerca MUD
- PET (20/05/2019): score Deauville 1
- PET (16/07/2019): negativa

**Trapianto allogenico da donatore MUD in data 6/9/19**

TAC (27/12/2019): negativa

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

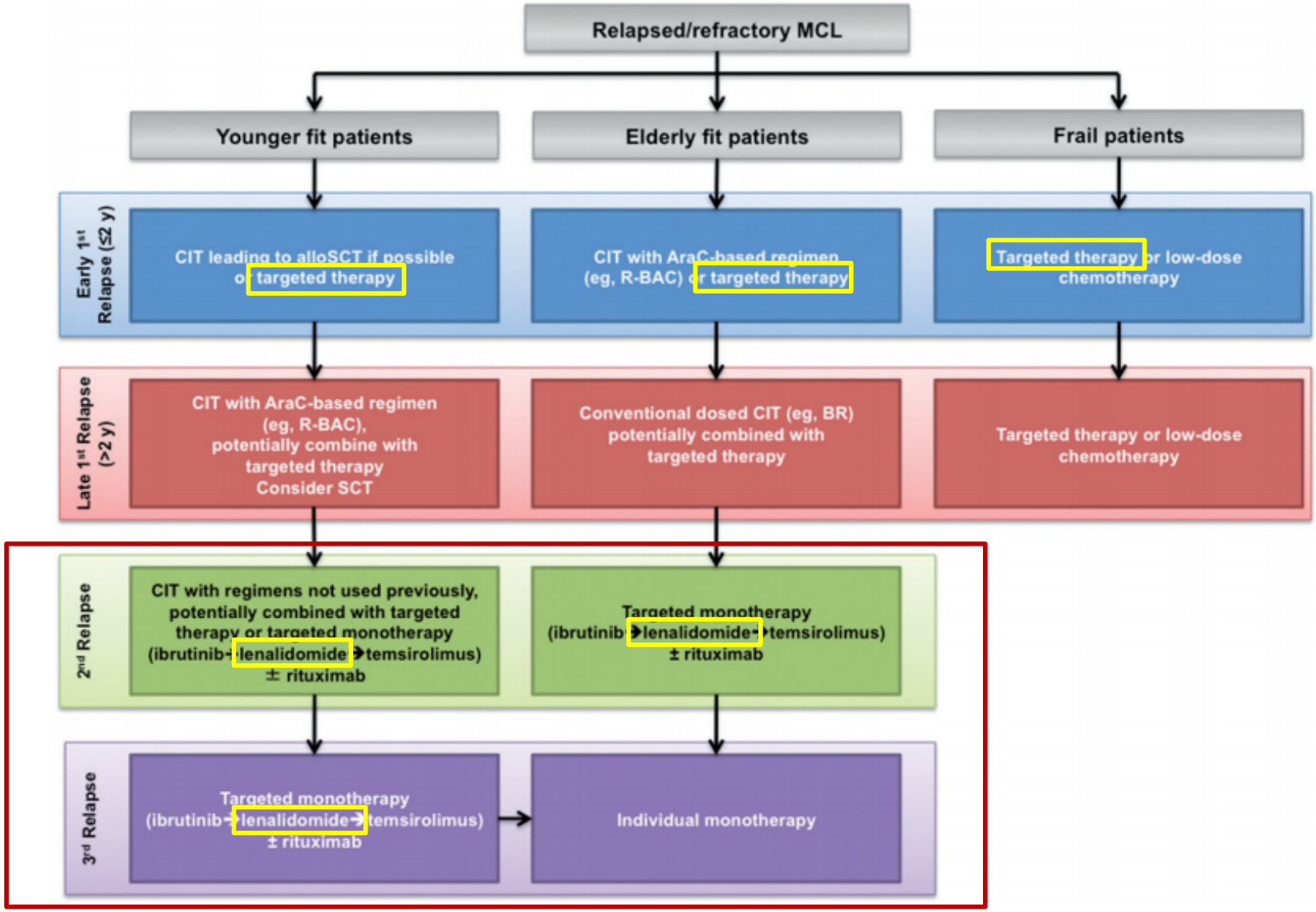
M. Dreyling et al, Annals of Oncology, 2017



# Treatment for patients with relapsed/refractory mantle cell lymphoma: European-based recommendations

Leukemia and Lymphoma, 2018

Martin Dreyling, Igor Aurer, Sergio Cortelazzo, Olivier Hermine, Georg Hess, Mats Jerkeman, Steven Le Gouill, Vincent Ribrag, Marek Trněný, Carlo Visco, Jan Walewski, Francesco Zaja & Pier Luigi Zinzani



# Conclusions

- Lenalidomide shows activity in relapsed/refractory MCL inducing  long-lasting responses even in previously heavily pretreated patients
- It may be considered an option even in bortezomib or ibrutinib exposed patients
- Lenalidomide is effective and tolerable in everyday clinical practice with superimposable results to those obtained in clinical trial
- Although other new generation drugs showed a more prominent role, Lena could be preserved in therapeutic algorithm of MCL, if incorporated in chemo-free regimens

# Overview of reported trials with lenalidomide in MCL

## Combination therapy

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| L + dexamethasone | (28) | | II | R/R MCL | | 33 | | 52% (24%) | 18 m | | md 12 m | md 20 m |
| L + rituximab (R2) | (29) | NCT 00294632 | I/II | R/R MCL | MTD: 20 mg | 44 | | 57% (36%) | md 18.9 m (17.0 NR) | 23 m | md 11 m | md 24 m |
| | (30,31) | | II | Untreated MCL | I: 20 mg c 1, 25 mg c 2–12; R† | 38 | 15 mg, R†/8 w 3 y | 61% | – | 68 m | 3-y PFS 80.3%; 5-y PFS 64% | 3-y OS 92%; 5-y OS 77% |
| L + obinutuzumab | (32) | GALEN | II | R/R aggr. NHL | 20 mg, O 1,000 mg; d 8, 15, 22 c 1, d 1 c2–6, 1/8 w during M | 13 (85 tot) | – | 39% (23%) | md NR | 2.5 y | md 5.8 m | NR |

# Overview of reported trials with lenalidomide in MCL

## R2 + ....

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R2-bendamustine | (33) | R2-FIL | II | R/R MCL | MTD: 10 mg d 1–14/28 d, c 1–4; 15 mg d 1–14/28 d, c 5–6 | 42 | 15 mg d 1–14/28, c 7–18 | Of evaluated 4 c: 88% (44%); 6 c: 79% (58%) | – | 29 m | md 20 m | 2-y OS 67% |
| | (34) | MCL4 (LENA-BERIT) | I/II | Untreated MCL ≥65 y | MTD: 10 mg, c 1–6; 10 [15] mg, c 7–13 | 50 | M L ×7 | ITT 6 c: 80% (64%) | – | 45 m | md 42 m | md 69 m |
| R2-bortezomib | (35) | NCT 00633594 | I/II | Untreated or R/R MCL | MTD: 10 mg d 1–14//21 d BOR‡ | 22 | | Of evaluated 82% (32%) | – | 16 m | 18 m PFS 61% | 18 m OS 79% |
| | (36) | CALBG 5051 | II | R/R MCL | 20 mg d 1–14/21 d, BOR, R† ×8 | 53 | | 40% (15%) | – | 46 m | md 7 m | md 26 m |
| R2-ibrutinib | (37) | MCL6 (PHILEMON) | I + II | R/R MCL | L 15 mg | 50 | I + R | 76% (56%) | – | 18 m | 12-m PFS 57% | 12 m OS 78% |

# Lenalidomide maintenance in R/R MCL

phase II study
relapsed/refractory MCL , >= 18 yrs
at least 2 prior line

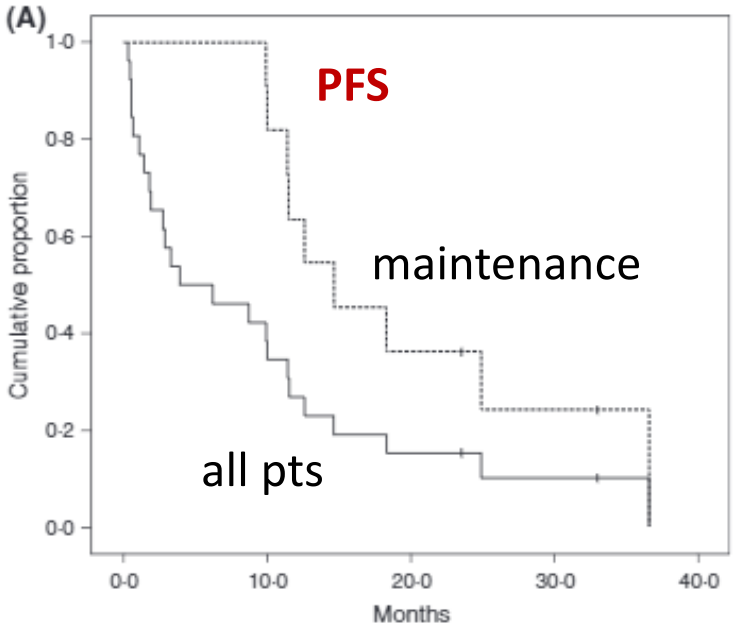
enrolled pts: 26
pts undergoing maintenance: 11

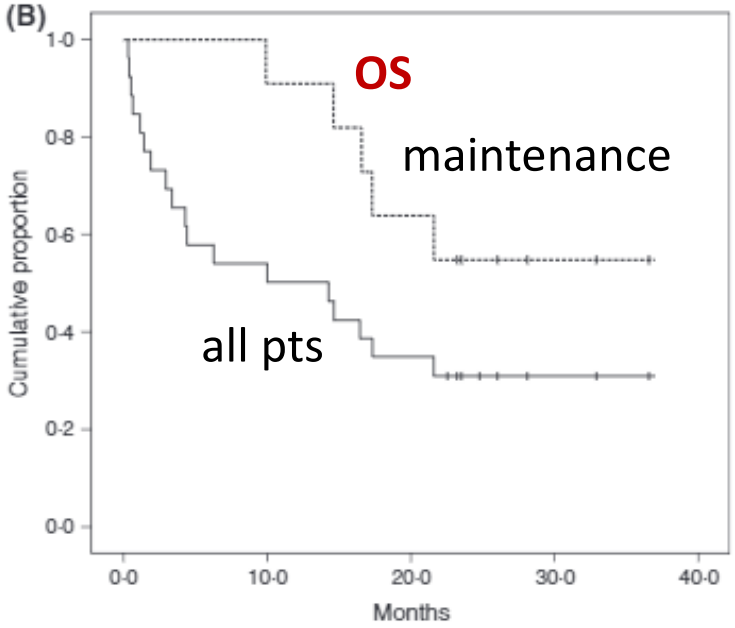
Induction:
Lenalidomide: 25 mg/d on days 1–21 of a 28-d cycle for up to 6 cycles.

If CR, PR or SD

Maintenance:
Lenalidomide: 15 mg/d on days 1–21 of a 28-d cycle until disease progression or unacceptable toxicity

this phase II study further confirms the activity and safety of lenalidomide in relapsed/refractory MCL and suggests it can be used in a maintenance setting at a lower dose



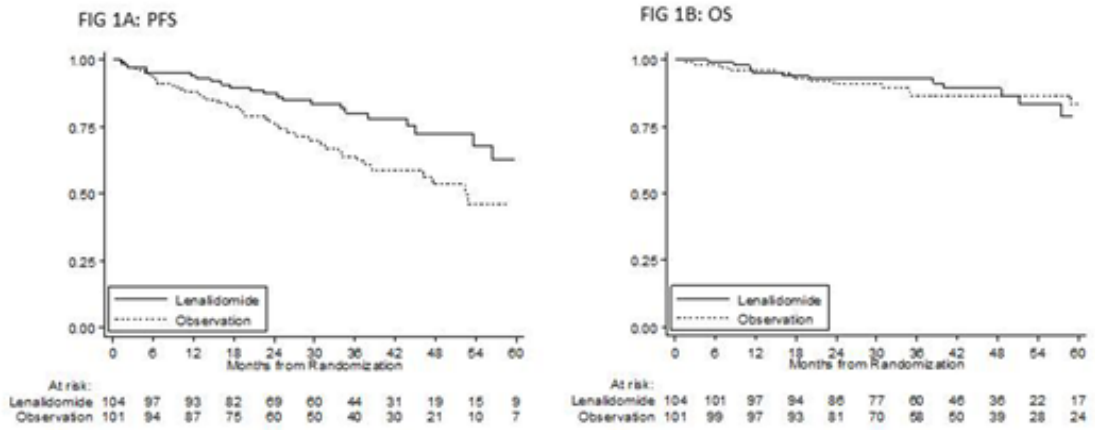



# Studi clinico a supporto

**Table 2. Lenalidomide-based maintenance for MCL.**

| Trial | Induction | Maintenance treatment | No. Maint | Median PFS | Median OS | Common grade 3/4 toxicity during maint | Ref. |
|---|---|---|---|---|---|---|---|
| **Maintenance as front-line** | | | | | | | |
| Ruan et al, 2015 (Front-line) | R2 | Rituximab plus lenalidomide (R2)15mg/day days 1–21 every 28 days until progression | 38 | NR<br>85% 2 yr PFS | NR<br>97% 2 yr OS | Neutropenia 32%<br>Thrombocytopenia 5% | [21] |
| **Maintenance in relapsed/refractory disease** | | | | | | | |
| Eve et al, 2012 (R/R) | Standard dose lenalidomide | Lenalidomide 15mg/day<br>days 1–21 every 28 days until progression | 11 | 14.6 months<br>(95% CI 7.3–21.9) | NR | Neutropenia 62%<br>Thrombocytopenia 42%<br>Infection 39%<br>Anaemia 15% | [23] |
| Zaja et al, 2017 (R/R) | 4 cycles R2B followed by 2 cycles R2 | Lenalidomide 15mg/day<br>days 1–21 every 28 days for 18 months | 42 | 20 months<br>43% 2 yr PFS | NR<br>67% 2 yr OS | Neutropenia 72% | [24] |

- MCL0208 Ash 2018




Results from the MCL0208 trial indicate that LM has a clinically meaningful anti-lymphoma activity in MCL. However, the applicability of LM has some limitations in the context of patients undergoing intensified chemoimmunotherapy. Overall these data support the use of a maintenance regimen after ASCT in young MCL patients.

Two deaths were observed in the LM arm due to pneumonia and thrombotic thrombocytopenic purpura and one in the OBS arm due to pneumonia. Grade 3-4 hematological toxicity was seen in 63% of patients in LM vs 11% in the OBS arm with 59% vs 10% of patients experiencing granulocytopenia. Non-hematological grade 3 toxicity was comparable in the two arms except grade 3-4 infections (11% vs. 4%; Fisher's p=0.10). Second cancers occurred in 7 patients in the LM and 3 in the OBS arm (Fisher's p=0.20).