HOT NEWS

NELLE SINDROMI LINFOPROLIFERATIVE:
inarrestabile dinamicità

Un caso di linfoma marginale

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UNAHOTELS Decò

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
None							

MILANO

F. , 55 anni – Feb 2020- Quadro all'esordio

- ECOG-PS = **1**
- In anamnesi **pregresso k-mammella** nel 2016 trattata con quadrantectomia bilat +IFRT bilat + ormonoterapia (exemestane, triptorelina)
- 17/01/2020: **linfoadenopatie retroperitoneali** (iliaca comune sx (16x15 mm) iliaca-otturatoria sc (35x20 mm) alla TC con mdc per FU oncologico
- 22/01/2020: **Biopsia LN iliaco est sx (IEO)**→ Linfoma di derivazione da linfociti B periferici della zona marginale, ad insorgenza nodale, **IHC CD20+, cd5-, CD10-, BCL2+(debole). KI67 15%**

MILANO

F. , 55 anni – Sett 2020 - Stadiazione

STAGING->

- ✓ **TC/PET con FDG** (10/02/2020): lesioni ad elevato metabolismo glucidico in sede linfonodale sottodiaframmatica (> 4 sedi ln) + **focale accumulo osso iliaco sx e femore** (**SUV max 5**)
- ✓ **BOM** (10/02/2020) : **negativa** per infiltrazione da linfoma
- ✓ **RM osso** (18/03/2020): **lesioni sostitutive attive** nell'osso iliaco dx e nella cresta iliaca sx + formazione con estensione CC di 13 cm femore sx

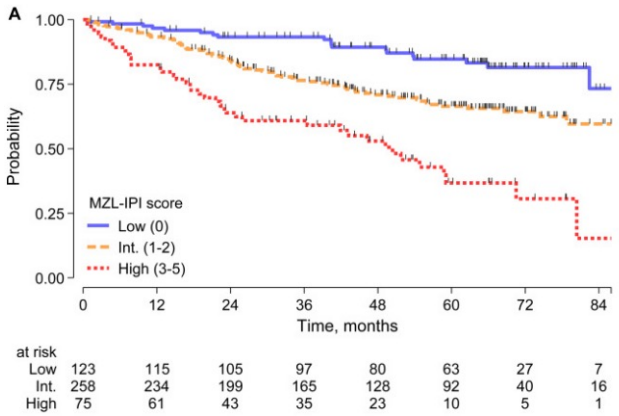
↓ Aprile 2020

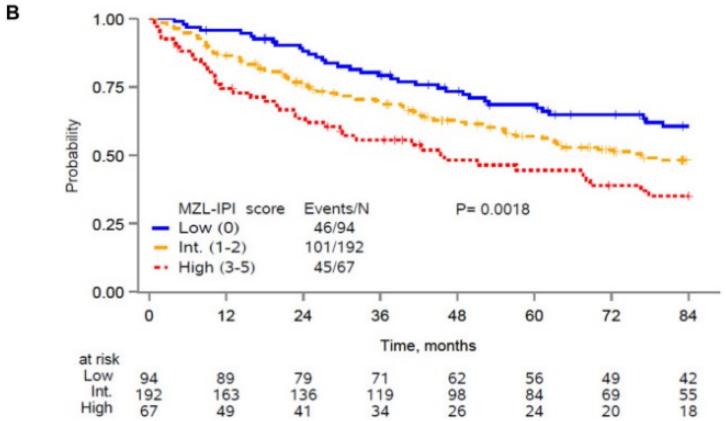
Biopsia neoformazione ala iliaca sx: Localizzazione ossea da LNH a cellule B periferiche, coerente con **linfoma della zona marginale**

MZL-IPI

- ✓ *LDH*
- ✓ *Anemia*
- ✓ *Piastrinopenia*
- ✓ *Linfopenia*
- ✓ *Sottotipo (ENMZL/SMZL vs **NMZL**/ dissMZL)*

Low
Intermediate
High risk





L. Arcaini et. al, eClinicalmedicine,2024

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F. , 55 anni – Mag 2020 – Terapia di I linea

- *Stadio IV E, LDH normale,*
- *Hb 12,8 g/dL, Gb 2700/mmc, Neu 1570/mmc, **Linfociti 800/mmc**, PLTs 228000/mmc*
- *ECOG = 0*

➢ ***MZL-IPI intermediate***

➢ *TERAPIA 1 linea : **Rituximab-Bendamustina** x 6 cicli (Ciclo 1 -> maggio 2020)*

❑ *Tossicità*

→ *dopo primo e secondo ciclo: Neutropenia (G2)*

→ *dopo IV ciclo : **AEA da IgM di tipo freddo** (Hb 8,0 g/dl e indici di emolisi aumentati)*

✓ ***Rivalutazione post IV ciclo (con TC/PET) : RISPOSTA parziale metabolica per persistenza di captazione a livello femorale***

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F., 55 anni – Terapia di I linea personalizzata

- ✓ *TERAPIA 1 linea : **R-Bendamustina x 4 cicl**i , non esegue 5 e 6 ciclo per AEA*

- ✓ *Continua terapia con **Rituximab settimanale x 4 dosi + PDN** (stop terapia 30/10/2020)*

- ✓ ***IFRT consolidamento** III distale femore (36 GY) dal 02/11/2020 al 01/12/2020*

…. da Dicembre 2020 follow up ….

- ➢ Aprile 2021 : TC/PET → **Risposta metabolica completa**

Ottobre 2022 – I recidiva a 2 anni, ***OT 26 mesi***

- Follow up oncologico con PET e RMN osso → comparsa lesioni cresta iliaca sx
- W&W per assenza di sintomi
- Dicembre 2022: RMN osso → progressione vertebrale e costale
- Maggio 2023: biopsia lesione cresta iliaca → localizzazione di LNH

➢ II linea : Inibitore chinasi di Bruton, ZANUBRUTINIB (settembre 2023) sospende ormonoterapia

II linea : Zanubrutinib

Profilo di Tossicità :

- ✓ No citopenia, videat cardio ok
- ✓ Riferisce dolori ossei G1

Rivalutazione risposta :

- ✓ Dopo **6 mesi (febbraio 2024)**: PET/TC total body → **Risposta parziale**
- ✓ Maggio 2024 (+9 mesi) RMN whole body → **confermata risposta parziale**

MAGNOLIA trial

Disease Characteristics

MAGNOLIA

Characteristic	Total (N=68)
MZL subtypes, n (%)	
Extranodal	26 (38.2)
Nodal	26 (38.2)
Splenic	12 (17.6)
Unknown[a]	4 (5.9)
Site of disease for MALT subtype, n (%)	
Gastric	2 (7.7)
Cutaneous	4 (15.4)
Nongastric/noncutaneous	19 (73.1)
Unknown	1 (3.8)
Lymphoma involvement in bone marrow[b], n (%)	29 (42.6)
Bulky disease, n (%)	
LDi >5cm	25 (36.8)
Extranodal disease[c], n (%)	53 (77.9)
Refractory disease[d], n (%)	22 (32.4)
Evidence of FDG-avid disease by IRC, n (%)	
FDG-avid	61 (89.7)
Non-FDG-avid	7 (10.3)

Data cutoff: 18 January 2021

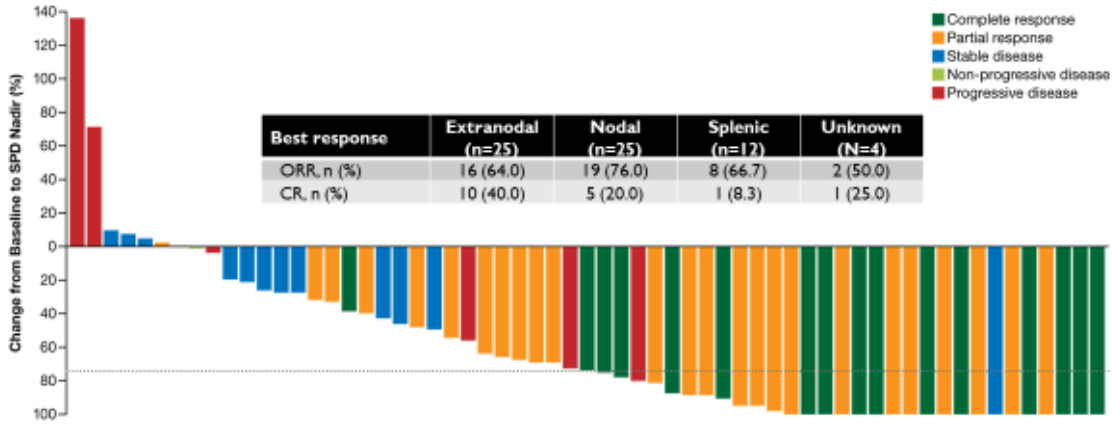
[a]Four patients presented with both nodal and extranodal lesions; investigators were unable to classify the MZL subtype. [b]Derived from baseline bone marrow biopsy/aspiration per investigator assessment. [c]Extranodal disease is defined as patients with extranodal baseline target or nontarget lesions, or bone marrow involvement, as per investigator assessment. [d]Refractory disease is defined as best overall response of stable disease or PD from last prior anticancer regimen.

ECOG PS=Eastern Cooperative Oncology Group performance status; IRC=Independent review committee; MALT=mucosa-associated lymphoid tissue; MZL=marginal zone lymphoma; LDi=longest transverse diameter of a lesion; PD=progressive disease; FDG=fluorodeoxyglucose.

Opat S et al. Clin Cancer Res (2021) 27 (23): 6323–6333. This study is registered on ClinicalTrials.gov (NCT03846427)

Change in Target Lesion SPD by IRC

MAGNOLIA



Best response	Extranodal (n=25)	Nodal (n=25)	Splenic (n=12)	Unknown (N=4)
ORR, n (%)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)
CR, n (%)	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)

Data cutoff: 18 January 2021

Only patients with non-missing BOR, and SPD percentage change were included (n=91). Dashed line: * median reduction in SPD (-74%).

BOR/Note: overall response, CR=complete response, IRC=independent review committee, MZL=marginal zone lymphoma, PD=progressive disease, PR=partial response, SD=stable disease, SPD=sum of products of perpendicular diameters.

Dyer S et al. Clin Cancer Res (2021) 27 (23): 6333–6333. This study is registered at ClinicalTrials.gov (NCT03846427)

Summary

MAGNOLIA

- **The MAGNOLIA study enrolled patients with high-risk features, including:**
  - Elderly patients (median age 70 years)[1]
    - 27.9% of patients were ≥75 years old
  - Heavily pre-treated (median of 2 prior lines of therapy)[2]
    - 34% of patients had ≥3 prior treatments and 98.5% of patients received prior chemotherapies
  - Refractory disease[1]
  - Nodal MZL[1]

- **After a median study follow-up of 15.7 months:**
  - High ORR of 68.2% and CR rate of 25.8% by independent review[1]
    - ORR higher than prespecified null ORR of 30% (P<0.0001)
    - Responses were observed in all MZL subtypes and in high-risk patients*
  - Median PFS and median DOR not reached[1]
    - 93% of responders were progression/death-free at 12 months after initial response
    - PFS rate was 82.5% at 15 months
  - Treatment discontinuation due to AEs occurred in 4 patients; none were considered related to zanubrutinib[1]
  - Grade 5 AEs occurred in 3 patients (including 2 patients who died from COVID-19 pneumonia)[1]
  - Atrial fibrillation/flutter occurred in 2 patients[1]
  - No major hemorrhage was reported[1]

Data cutoff: January 18, 2021.
*Age ≥75: ORR 69%, ≥3 prior lines: ORR 65%, Refractory disease: ORR 71%, Nodal MZL: ORR 64%.
All=all cancer events, COVID=coronavirus disease, CR=complete response, DOR=duration of response, MZL=marginal zone lymphoma, ORR=overall response rate, OS=overall survival, PFS=progression-free survival, PR=partial response, R/R=relapsed/refractory, SD, stable disease.
1. Opat S et al. Poster presented at: EHA 2021; Abstract No. EP783. 2. Opat S et al. ASH 2020. Abstract 329 This study is registered at ClinicalTrials.gov (NCT03846427).

Author Conclusions[1,2]

MAGNOLIA – Final Analysis

- At a median study follow-up of 28 months:
  - Zanubrutinib showed high response rates and durable disease control in R/R MZL
    - ORR of 68% (by PET and/or CT) and 67% (by CT only) with a CR of ~25% by IRC
    - Responses in all MZL subtypes and in difficult-to-treat subgroups
    - At 24 months: PFS rate, 71%; DOR rate, 73%; OS rate, 86%

- Zanubrutinib was generally well tolerated
  - Hypertension and atrial fibrillation/flutter were uncommon; comparable rate to zanubrutinib pooled safety analyses and lower than reported for ibrutinib
  - One (1.5%) patient had major gastrointestinal hemorrhage while receiving concomitant anticoagulant
  - No new safety signals observed

Data cutoff date: 04 May 2021.
CT=computed tomography; DoR=duration of response; CR=complete response; IRC=independent review committee; MZL=marginal zone lymphoma; OS=overall survival; PET=positron emission tomography; PFS=progression-free survival; R/R=relapsed/refractory.
1. Opat S et al. Oral presentation presented at ASH 2021. Abstract 234 2. Opat S et al. Blood Advances 2023 https://doi.org/10.1182/bloodadvances.2022010648