Caso Clinico 2

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AOU Careggi

Firenze

LEUCEMIA LINFATICA CRONICA:
L'INNOVATIVITÀ TERAPEUTICA ED OLTRE...

28-29 MARZO 2023 BOLOGNA ROYAL HOTEL CARLTON

B.M 1966

- Uomo
- Diagnosi di LLC nel 2008
- Anamnesi familiare positiva per CLL (madre, zia e una cugina)
- Nel 2009 effettua trattamento secondo schema FCR ottenendo CR
- Non disponibili dati FISH o molecolari

Marzo 2015

- Recidiva di malattia inizio 2014
- Gennaio 2015:
  - GB 139x10^9/l, ALC 128x10^9/L hb 9,1 g/dl, plt 297x10^9/L
  - LDH normale, non carenza di b12 e folati, bilancio marziale normale
  - Non infezioni in atto
  - Linfoadenomegalie laterocervicali bilateralmente (max 2 cm a dx), sovraclaveare sinistra pacchetto di 3 linfonodi centimetrici, sovraclaveare dx 1 linfonodo di circa 1 cm, ascellare sinistra subcentimetrici, ascellare destra circa 1cm, inguinali subcentimetrici bilateralmente.
  - Non sintomi sistemici

Criteri di trattamento in R/R

- Almeno uno fra:
  - Insufficienza midollare (sviluppo o peggioramento di anemia o piastrinopenia)
  - Splenomegalia massiva (almeno 6 cm dall'arcata) o progressiva o sintomatica
  - Bulky linfonodale(almeno 10 cm) o linfoadenomegalia progressiva o sintomatica (sviluppo o aumento del 50%)
  - Linfocitosi progressiva (aumento del 50% in due mesi o tempo di raddoppiamento inferiore a 6 mesi)
  - Anemia o piastrinopenia autoimmune poco responsivi ai trattamenti standard
  - Sintomi costituzionali (perdita di peso, fatigue, febbre, sudorazioni)

Terapie disponibili

- Ripetere chemio immunoterapia
- Compassionevoli ibrutinib o rituximab idelalisib
- Arruolamento in protocolli

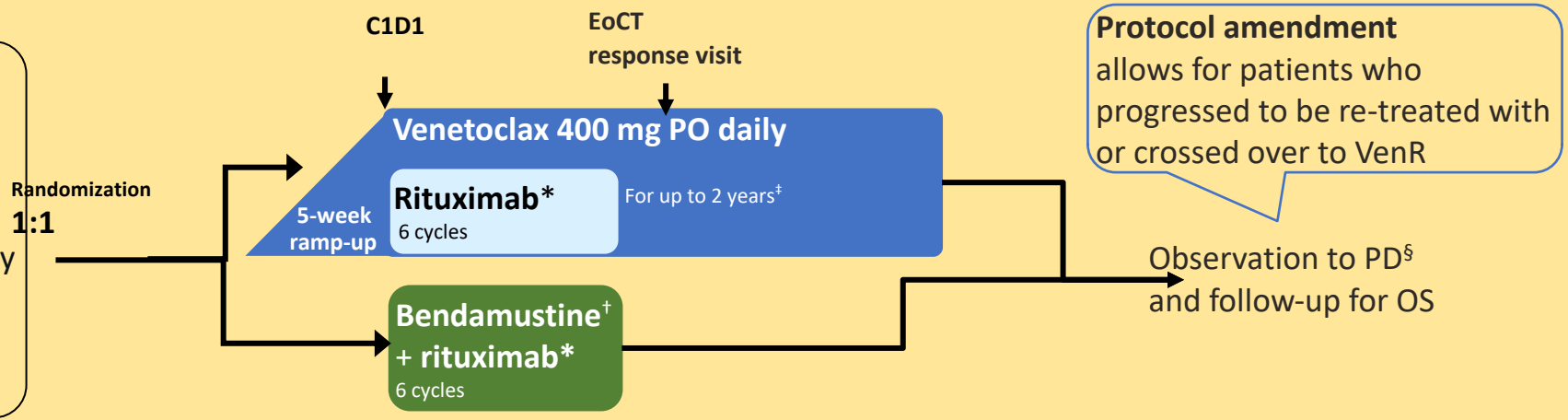
Studio Murano

Multicenter, Phase 3, Open-Label, Randomized Study to Evaluate the Benefit of Venetoclax + Rituximab (VenR) vs Bendamustine + Rituximab (BR) in Patients with R/R CLL

R/R CLL (N=389)

Key Inclusion Criteria

- 1–3 lines of prior therapy, including ≥1 chemotherapy-containing regimen
- Prior bendamustine only if DoR was ≥2 y (i.e. not refractory or resistant to prior BR)
- ECOG PS ≤1



Primary Endpoint:

- INV-assessed PFS

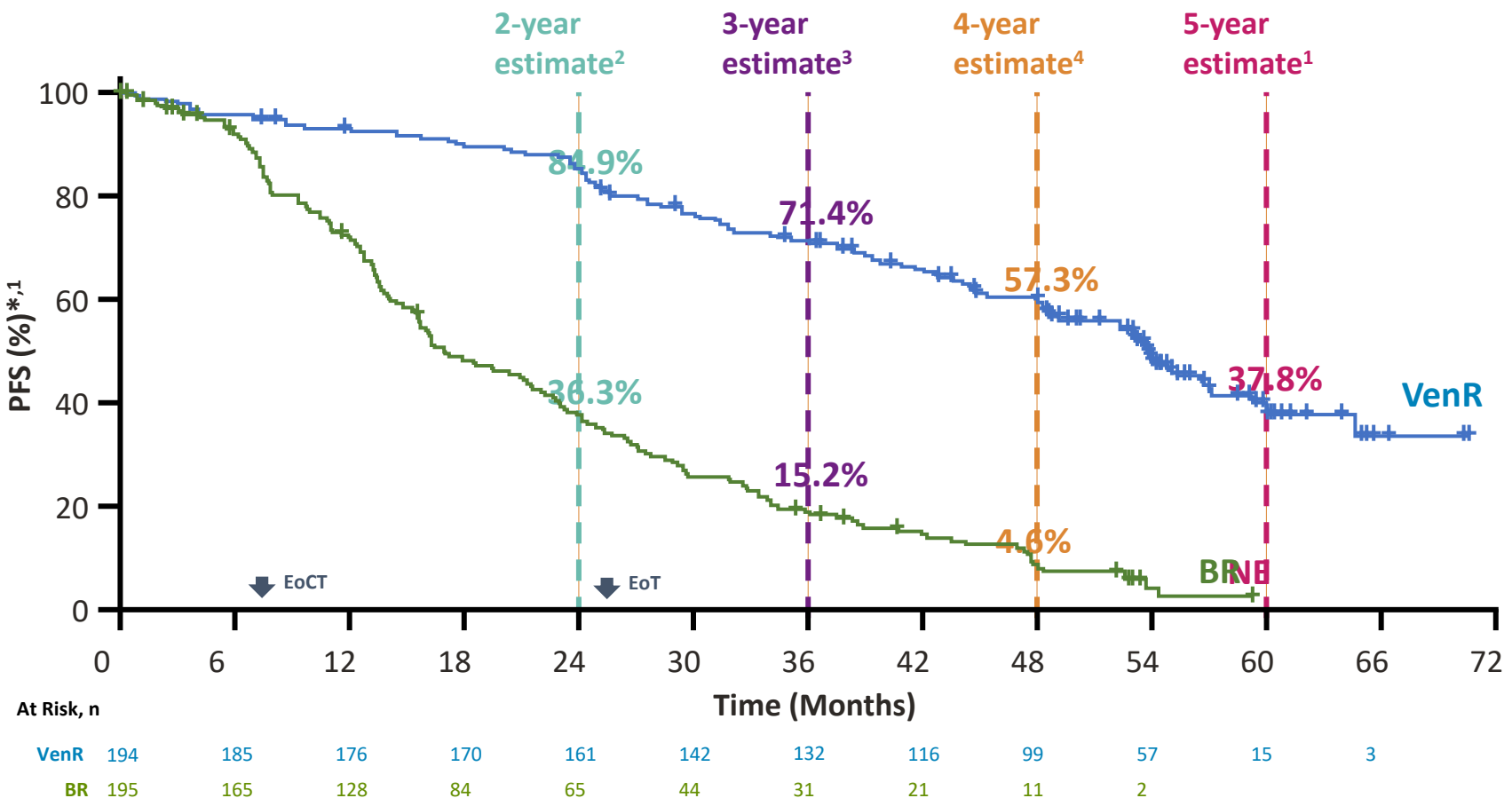
Key Secondary Endpoints:

- IRC-assessed PFS
- PFS in patients with del(17p) (IRC- and INV-assessed)
- ORR (CR, CRi, nPR, PR) (IRC- and INV-assessed) at EoCT
- OS, rates of MRD clearance, DoR, EFS, TTNT

- * Rituximab: 375 mg/m^2 C1D1 and 500 mg/m^2 D1C2–6; † Bendamustine: 70 mg/m^2 days 1 and 2 of each cycle; ‡ Or until PD or unacceptable toxicity; § Or end of study.

Seymour JF, *et al. N Engl J Med* 2018

Progression Free Survival

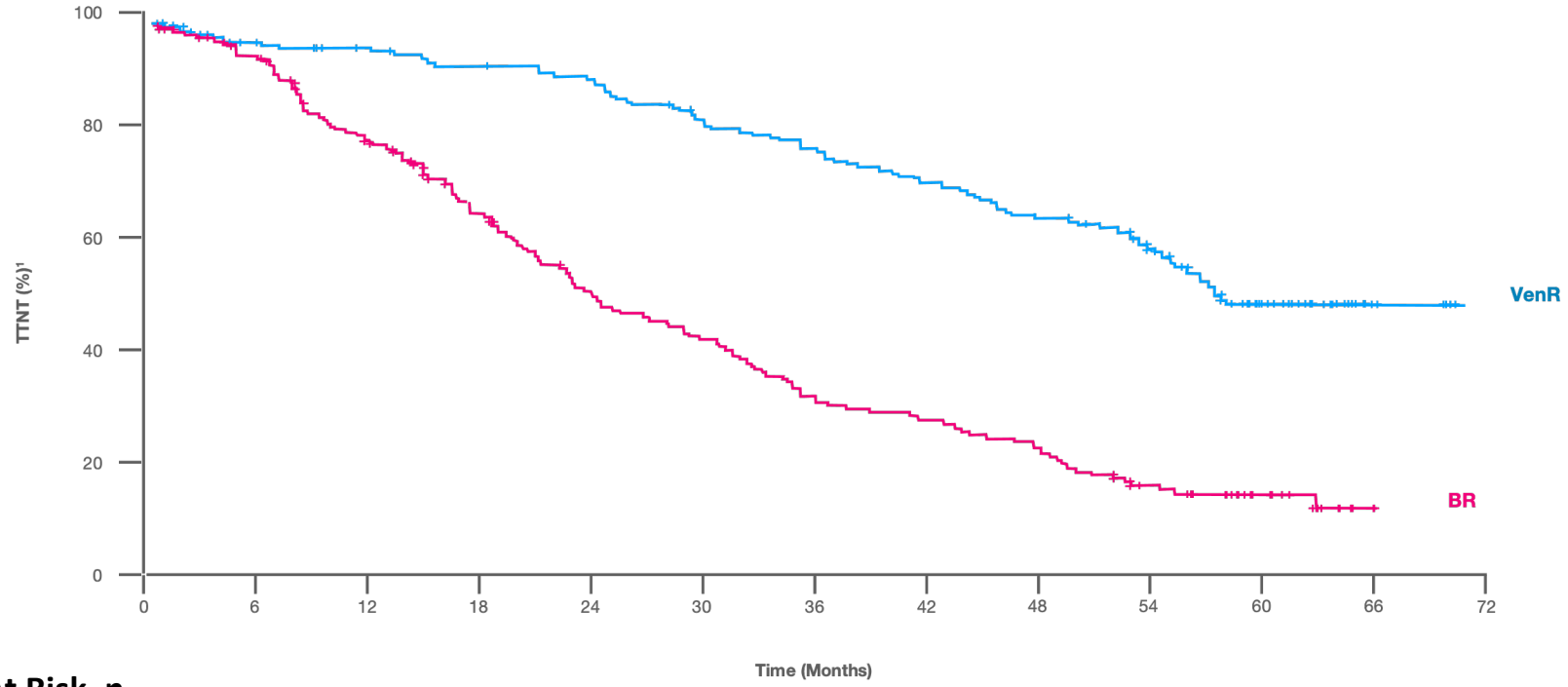


Analysis	HR (95% CI)
Primary[2]	0.17 (0.11–0.25)
3-year[3]	0.16 (0.12–0.23)
4-year[4]	0.19 (0.14–0.25)
5-year[1]	0.19 (0.15–0.26)

The PFS benefit with VenR vs BR was maintained from the primary analysis through the 5-year analysis, with an 81% reduction in the risk of PD/death with VenR vs BR 3 years after EoT

Seymour JF, *et al. N Engl J Med* 2018; Kater et al . Kater AP, *et al. J Clin Oncol* 2020; 34:4042–4054

Time to next anti CLL treatment



	VenR (n=193)	BR (n=195)
Received subsequent Tx following PD, n/N (%)[1]	67/87 (77.0)	123/148 (83.1)
Median TTNT, months (95% CI)[1]	57.8 (55.1–NE)	23.9 (20.7–29.5)
HR (95% CI), p-value	0.26 (0.20–0.35)[1] p<0.001*,[2]	

At Risk, n

VenR	193†	183	179	173	166	150	141	131	119	93	38	7
BR	195	168	139	112	83	71	52	47	37	23	9	1

The risk of starting a new anti-CLL line of treatment (or death from any cause) was reduced by 74% with VenR vs BR

- **TTNT was defined as time from initiation of BR/VenR to next anti-CLL treatment or death (whichever occurs first), as such N shows total events for subsequent anti-CLL treatment and death from any cause.**

* p-values are descriptive only; † 1 patient omitted due to invalid date for commencement of follow-up therapy.

Harrup RA, *et al.* ASH 2020; Poster 3139; 2. Harrup RA, *et al.* ASH 2020; Abstract 3139.

Arruolato nello studio a marzo 2015

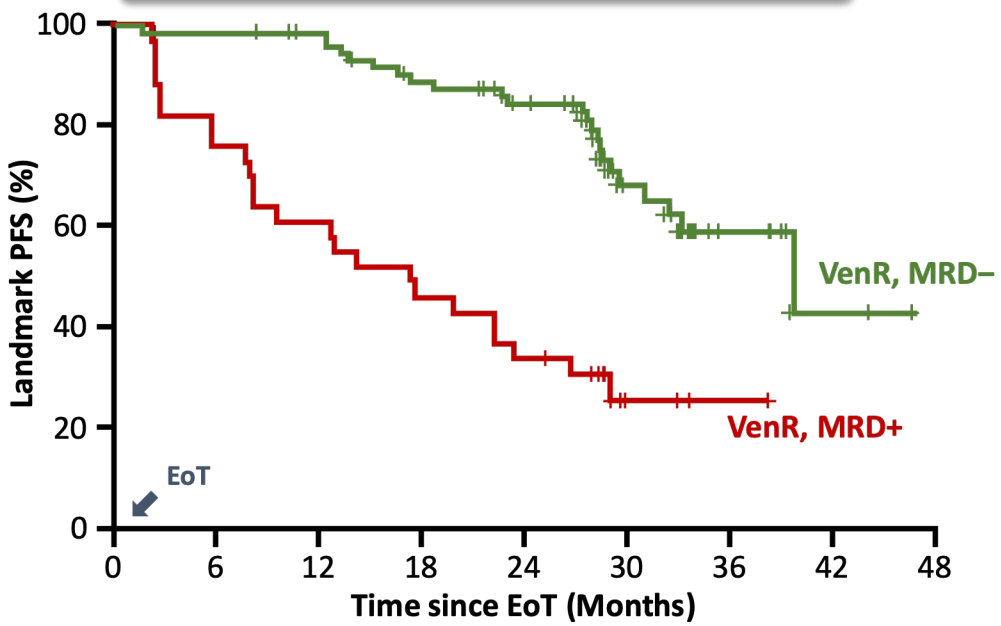
- CLL attiva per anemia, linfocitosi e linfoadenomegalie progressive
- FISH: del11q,del 13q,
- IGHV: unmutaded
- TP53: wt
- Randomizzato a VR

Marzo 2015- marzo 2017

- Inizia terapia
- Non effetti collaterali
- Completa rump up senza TLS
- TC dopo 6 mesi: linfoadenomegalie<15 mm, milza 12,5 cm
- Termina terapia a marzo 2017
- CR con mrd detectabile
- Non AE significativi
- Solo ipogamma in terapia sostitutiva non eventi infettivi

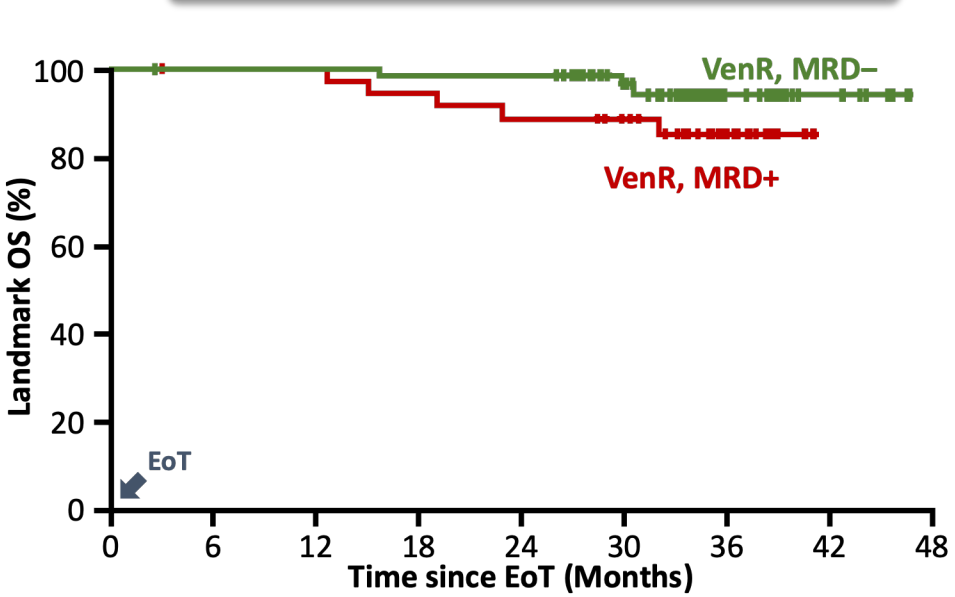
PFS and OS according to PB MRD Status at EoT

PFS[1]



PFS estimate	2 years after EoT	3 years after EoT
VenR MRD– (n=83)	85.4%	61.3%
VenR MRD+ (n=35)	37.1%	29.2%

OS[2]



OS estimate	2 years after EoT[1]	3 years after EoT[2]
VenR MRD– (n=83)	98.8%	95.3%
VenR MRD+ (n=35)	88.6%	85.0%

PB MRD– at EoT was associated with improved outcomes post-EoT, in VenR patients who reached EoT without PD

Kater AP, *et al.* ASH 2020, Oral presentation 125

Giugno 2018

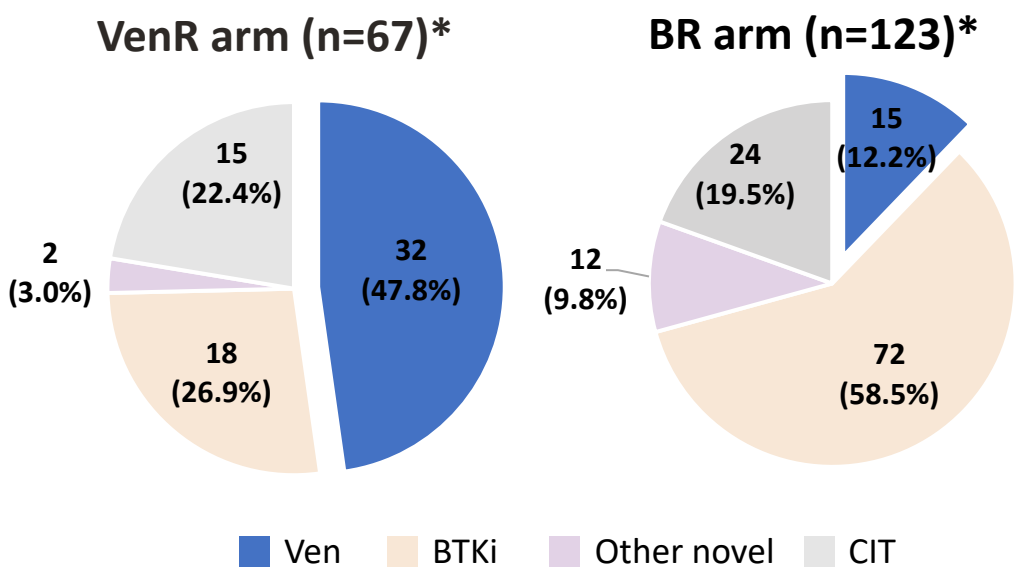
- Il paziente sta bene, in terapia con immunoglobuline sc
- Nuovo emocromo:
  - Hb 15,1 g/dl, Plt 263x10^9/L, ALC 15,9x10^9/L
- TC collo torace e addome: multiple linfoadenomegalie al collo, mediastiniche, ascellari, mesenteriche, dimensioni massime 35 mm, milza 12 cm

Cosa fare?

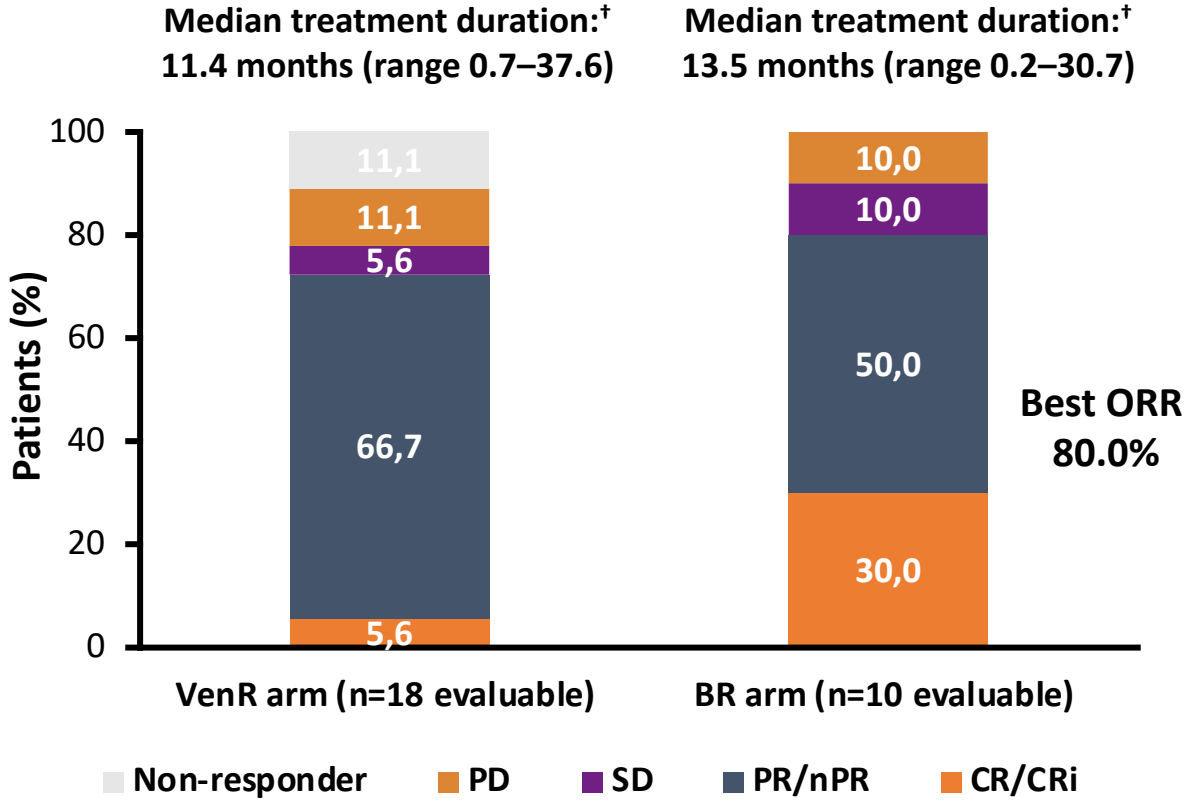
- Continuare W&W
- Ripetere FISH e TP53
- Iniziare una terapia per la recidiva
  - Inibitori di BTK
  - Ripetere venetoclax

Venetoclax post Venetoclax-rituximab

Subsequent Therapy



Best ORR to Subsequent Ven-Based Therapy†



Best ORR to Ven-based regimen as next therapy after PD was 72.2% and 80.0% in patients previously treated with VenR or BR, respectively

Harrup RA, *et al.* ASH 2020; Poster 3139.

Giugno 2018

- Prescritto venetoclax off label
- FISH: delezione del 11q, delezione 13q
- Completato rump up senza complicanze
- Miglior risposta CR
- Non è stato effettuato un immunofenotipo
- No Aes
- Continua immunoglobuline sc

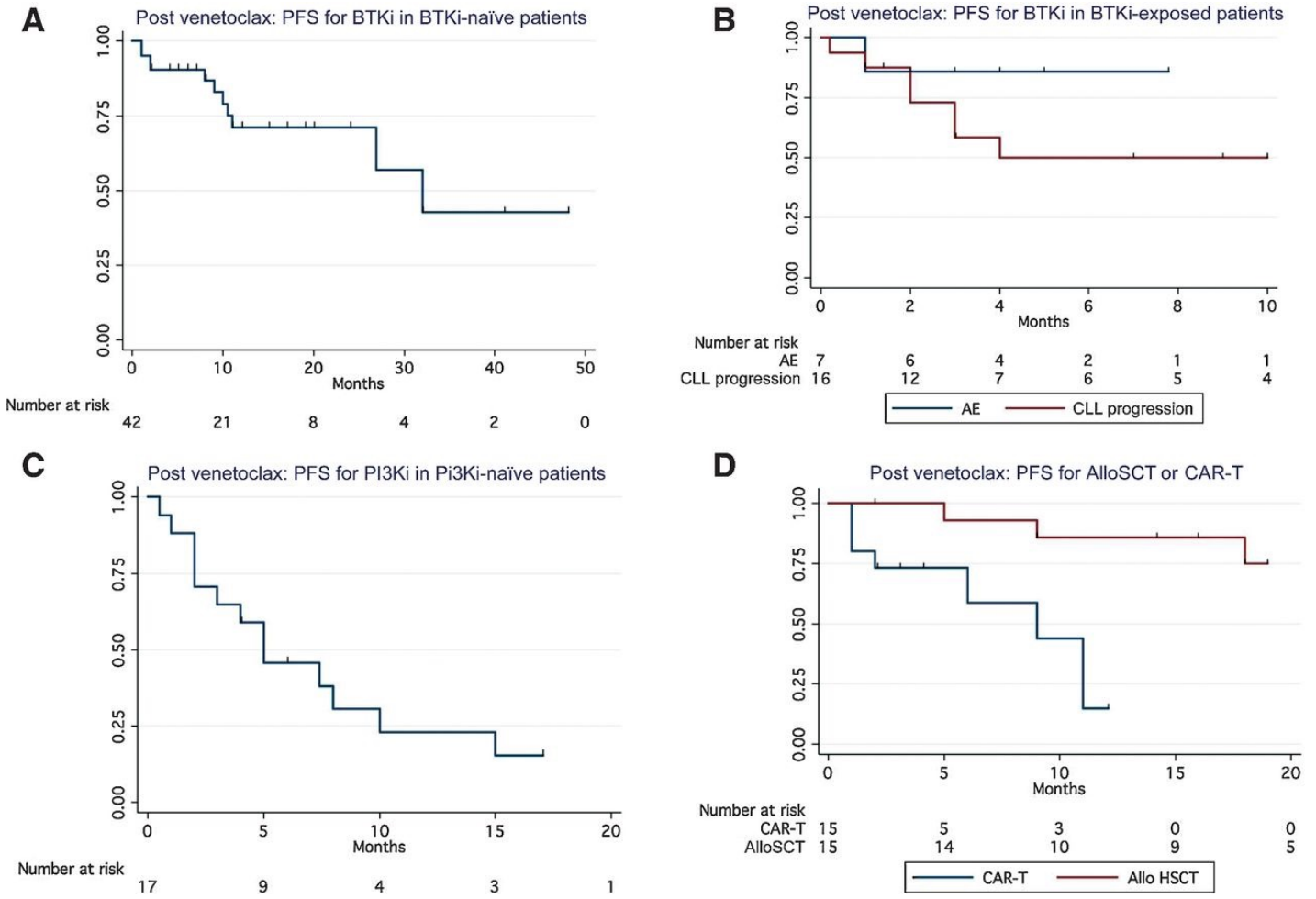
Recidiva

- Dicembre 2020
  - Incremento della linfocitosi (ALC 19,45x10^9/L)non citopenie e comparsa di linfoadenomegalie max 3 cm a livello del collo, 5 cm ascellari, milza palpabile
  - Non sintomi sistemici
- Gennaio 2021
  - ALC 46x10^9/L, hb 12,8 g/dl, plt 160x10^9/L
- Eo multiple linfoadenomegalie 4 cm al collo e 6 cm ascellari, milza palpabile
- Effettua TC: milza 13,5 cm, linfoadenomegalie diffuse le più grandi mediastiniche 60x32 mm, addominali 45x28 mm, ascellari 45x23 mm, LC 46x34 mm

Che terapia fare dopo venetoclax?

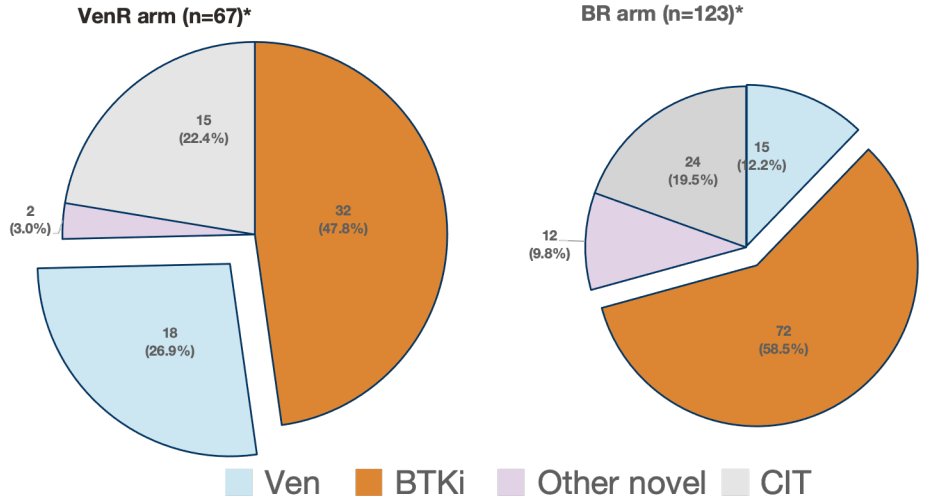
- Ibrutinib ?
- Rituximab idelalisib?
- Chemio immunoterapia?
- Protocolli sperimentali?
- Trapianto allogenico?

Terapie post venetoclax



BTKi post Venetoclax-rituximab

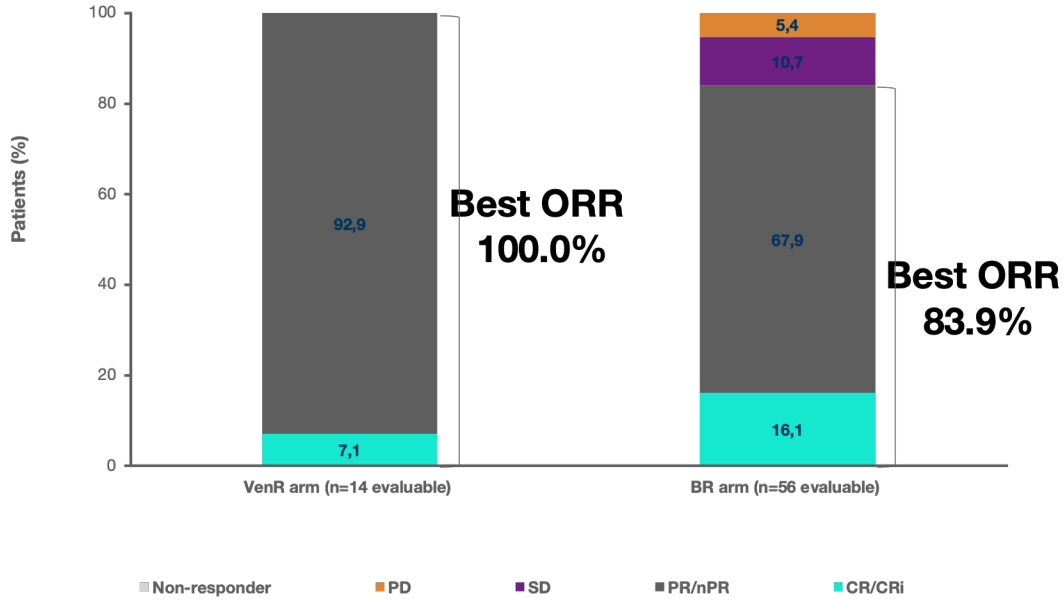
Subsequent Therapy



Best ORR to Subsequent BTKi-Based Therapy†

Median treatment duration:† 21.9 months (range 5.6–59.2)

Median treatment duration:† 26.6 months (range 0–50.4)



Best ORR to BTKi-based regimen as next therapy after PD was 100.0% and 83.9% in patients previously treated with VenR or BR, respectively

* Patients treated; † Calculated among patients with evaluable responses (i.e. reported by the investigators prior to discontinuation/initiation of subsequent line of therapy;
responses in patients who were treated for insufficient time to have their response assessed, or those who had no response assessments, were considered unevaluable).

Harrup RA, *et al.* ASH 2020; Poster 3139.

Gennaio 2021

- Inizia Ibrutinib 420 mg die
- Aveva ripetuto fish del11q,del 13q, tp53 wt
- Ha lamentato lievi crampi g1 trattati con acqua tonica

Oggi

- Paziente in Remissione completa
- A marzo 2022 ricoverato per polmonite da covid che ha necessitato alti flussi
- Aveva effettuato tre dosi di vaccino a mRNA
- Sta bene, svolge una vita normale

Conclusioni

- Il paziente ha effettuato un totale di 5 anni e 9 mesi di venetoclax (2 anni murano, 1 anno e 3 mesi libero, 2 anni e 6 mesi in continuativo)
- Il ritrattamento funziona anche nei pazienti non in risposta profonda
- Il sequencing inverso è una valida alternativa anche in pratica clinica

Grazie per l'attenzione...