# Emerging and current treatments of AL amyloidosis and Waldenstrom Macroglobulinemia

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# Venetoclax-Targeted Therapy in t(11;14) AL Amyloidosis Patients After Frontline Daratumumab + CyBorD

## Background

- Treatment of AL amyloidosis relies mainly on chemotherapy aimed at suppressing the underlying secreting plasma cell clone
- Organ responses and survival are greatly influenced by the degree of hematological response evaluated by the decrease in sFLC
- Although DARA combination therapy is approved for treating AL amyloidosis in the frontline setting, some patients will still not achieve a CR or will eventually relapse
- VEN has shown activity in MM cell lines with t(11;14), partly because of greater BCL-2 codependence of such clones
- VEN should provide a novel targeted therapy in AL amyloidosis, as 50-60% of patients have a t(11;14)

## Methods

- Retrospective study of 9 patients with AL amyloidosis from the French Amyloidosis Network
  - Received VEN for consolidation (n=3) or for biological progressive disease (n=6) after DARA+CyBorD frontline therapy
  - Should have received ≥1 cycle of VEN-containing regimen to be analyzed
- Responses were reviewed using current criteria for CR (serum and urine negative immunofixation and normal involved FLC) and for VGPR (dFLC <40 mg/L)

- **Baseline Characteristics and Previous Therapies**

| Characteristics | All patients (n=9) |
|---|---|
| **Age, median, years (IQR)** | 67 (61-71) |
| **Male, n (%)** | 5 (56) |
| **Light chain only: n (%)** | 6 (67) |
| **Lambda light chain: n (%)** | 5 (56) |
| **Kappa at diagnosis: median, mg/L (IQR)** | 29.50 (13.75-544.00) |
| **Lambda at diagnosis: median, mg/L (IQR)** | 135.00 (10.15-385.00) |
| **dFLC at diagnosis: median, mg/L (IQR)** | 255.00 (80.60-1059.75) |
| **dFLC>180, n (%)** | 6 (67) |
| **Plasma cells: median % (IQR)** | 14 (11-24) |
| **<5%/>10%/>20%, n** | 1/4/4 |
| **5MM, n (%)** | 8 (89) |
| **t(11;14) n (%)** | 9 (100) |
| **1q gain** | 1 (11) |
| **EOCG performance status: n (%)** | |
| **0/1** | 2 (22) / 3 (33) |
| **2** | 4 (45) |
| **Involved organs: median, n (IQR)** | 2 (1-3) |
| **Kidney, n (%)** | 5 (56) |
| **Heart, n (%)** | 6 (67) |
| **Nerve, n (%)** | 0 |
| **Gastrointestinal tract, n (%)** | 1 (11) |
| **Liver, n (%)** | 2 (22) |
| **Soft tissue, n (%)** | 2 (22) |
| **MAYO staging** | |
| **I** | 2 |
| **II** | 1 |
| **III** | 4 |
| **IV** | 2 |

AL=amyloid light chain; CyBorD=cyclophosphamide + bortezomib + dexamethasone; sFLC=serum-free light chain; DARA=daratumumab; CR=complete response; VEN=venetoclax; BCL-2=B-cell lymphoma 2; VGPR=very good partial response; dFLC=differential free light chain.

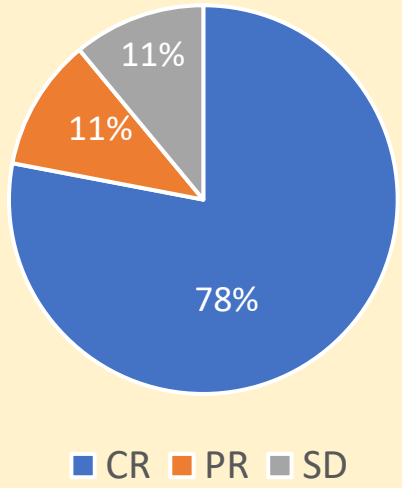
Roussel M, et al. Abstract 4531. ASH 2022.

# Venetoclax-Targeted Therapy in t(11;14) AL Amyloidosis Patients After Frontline Daratumumab + CyBorD

- **Results**

- Median time from diagnosis to VEN therapy: 6.0 months (IQR: 2.5-7.5)
- Median time on therapy: 7.0 months (IQR: 3.0-9.5)
- At data cut-off (06/2022), 6 patients had discontinued therapy because of a CR (n=5) and/or GI tract toxicity (n=4)
- Median time to CR: 1 month (IQR: 1-3)

**Hematologic Response Rate**




- Consolidation patients
  - All achieved a CR in 1 month (IQR: 1-3) with the addition of VEN to DARA+CyBorD
- Progressive/relapsed patients
  - 4 (67%) achieved a CR, 1 was in stable disease, and 1 reached a PR and progressed to end-stage renal disease
- DARA R/R patients
  - Reached a CR with VEN±BOR

| Treatment | CR, % [dFLC <10 mg/L] |
|---|---|
| VEN alone (n=1) | 50 |
| VEN+DEXA (n=1) | 50 |
| VEN+BOR (n=2) | 100 |
| VEN+DARA+BOR (n=5) | 80 |

**Conclusion:** In AL amyloidosis, VEN can be used in combination with DARA±BOR as consolidation or relapsed therapy after frontline DARA+CyBorD, even in refractory patients, with an expected favorable safety profile.

DEX=dexamethasone; BOR=bortezomib; IQR=interquartile range; PR=partial response.

Roussel M, et al. Abstract 4531. ASH 2022.

# Survival Benefit of Birtamimab in Mayo Stage IV AL Amyloidosis in the Phase 3 VITAL Study Consistent After Adjustment for Key Baseline Variables

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[2]The Hospital of the University of Pennsylvania, Philadelphia, PA; [3]Tufts Medical Center, Boston, MA; [4]National and Kapodistrian University of Athens, Athens, Greece; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Fred Hutchinson Cancer Center, Seattle, WA; [7]Univeristy of Washington, Seattle, WA; [8]Stanford Cancer Institute, Stanford, CA; [9]Boston University School of Medicine, Boston, MA; [10]Universitätsklinikum Heidelberg, Heidelberg, Germany; [11]Royal Free Hospital, London, UK; [12]Karmanos Cancer Institute, Detroit, MI; [13]University of Pavia, Pavia, Italy; [14]Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy; [15]Prothena Biosciences Inc, South San Francisco, CA

# There Is an Urgent Need for Therapies That Improve Survival in Patients With Advanced AL Amyloidosis

- **Amyloid light chain (AL) amyloidosis is a rare, progressive, and typically fatal disorder caused by an underlying plasma cell dyscrasia**
- **Misfolded kappa (κ) and lambda (λ) immunoglobulin light chain proteins[1,2] form aggregates that can cause cellular toxicity and form amyloid fibrils that deposit in tissues, causing organ dysfunction that is the hallmark of advanced AL amyloidosis[3]**
- **Using the validated 2012 Mayo Clinic Staging System, Stage IV patients have the highest risk for early death (median survival from diagnosis of 5.8 months)[4]**

**Survival by Mayo 2012 Stage**

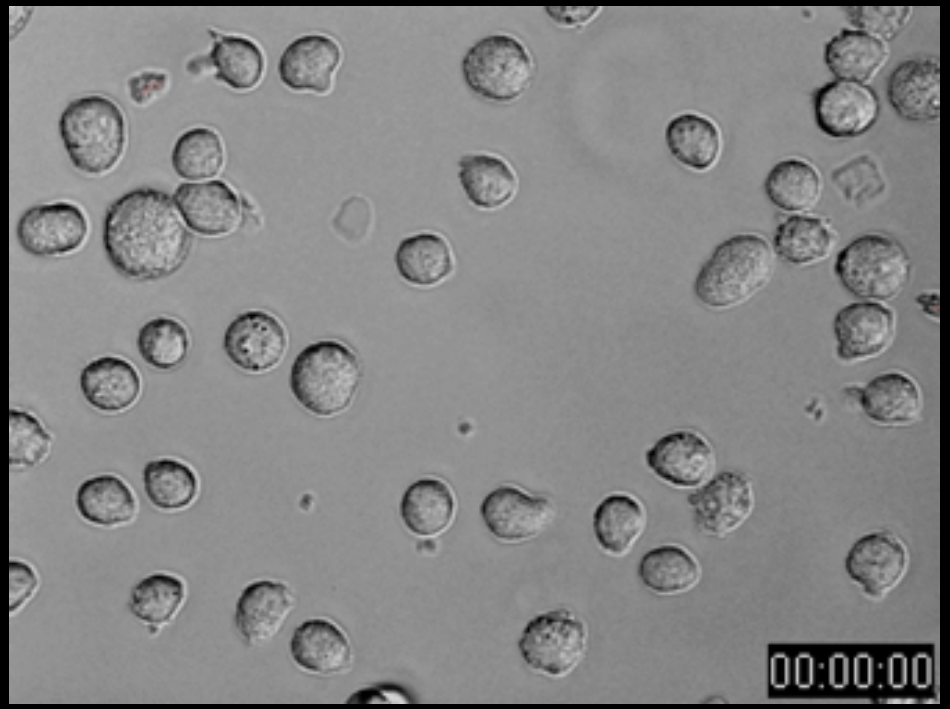
N=810 patients with AL amyloidosis[4]

| Mayo 2012 Stage | Median OS, Months (95% CI) | 5-Year Survival Rate (%) |
|---|---|---|
| I | 94.1 (64–154) | 59 |
| II | 40.3 (24–59) | 42 |
| III | 14.0 (11–18) | 20 |
| **IV** | **5.8 (5–7)** | **14** |

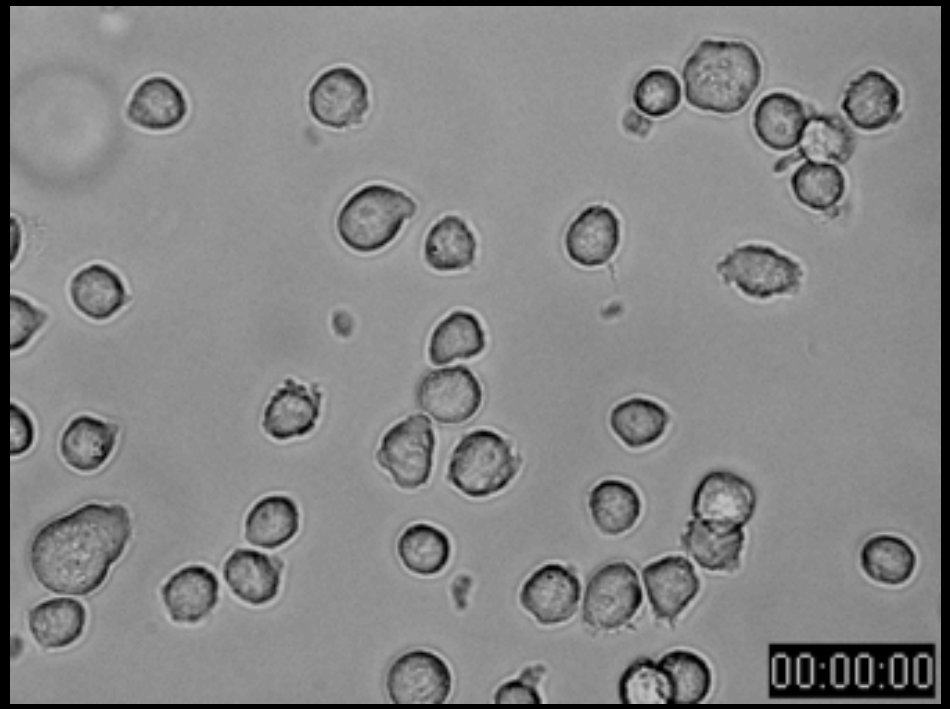
**Current treatments target plasma cells to decrease production of immunoglobulin light chains and have not yet demonstrated a survival benefit in patients with advanced AL amyloidosis[5–7]**

# Birtamimab Is an Investigational Humanized IgG1 mAb that Binds Both κ and λ Immunoglobulin Light Chain Isoforms[1]

**Isotype Control mAb[2]**




**m-Birtamimab[2*]**




**Birtamimab:**

- **neutralizes and disaggregates circulating soluble, toxic light chain aggregates[1]**
- **depletes insoluble AL amyloid deposits by inducing macrophages to clear amyloid via phagocytosis[1,3†]**

# VITAL: Phase 3 Multicenter, Double-Blind, Placebo-Controlled RCT in Newly Diagnosed Treatment-Naïve AL Amyloidosis Patients[1,2]

**Key Inclusion Criteria**
- ≥18 years old
- Confirmed diagnosis of AL amyloidosis
- Newly diagnosed and treatment naïve
- Cardiac involvement
  - NT-proBNP ≥650 pg/mL and ≤8500 pg/mL

**Key Exclusion Criteria**
- Non-AL amyloidosis or MM
- NT-proBNP >8500 pg/mL
- Plans to undergo ASCT or receipt of prior anti-PCD therapy

Screening → 1:1 Randomization (N=260)

**Birtamimab**
(24 mg/kg IV) + SoC*
n=130

Infusion every 28 days for 42 months

**Placebo**
(normal saline IV) + SoC*
n=130

→ End of study/early treatment discontinuation visit† → Open-label extension study

Interim futility analysis performed in April 2018 resulted in early study termination

**Stratification criteria:**
- 6MWT (<300 m vs ≥300 m)
- Mayo Stage (I/II vs III/IV)
- Renal Stage (I vs II/III)

**Primary endpoint:**
Time to all-cause mortality (ACM) or cardiac hospitalization (CH)

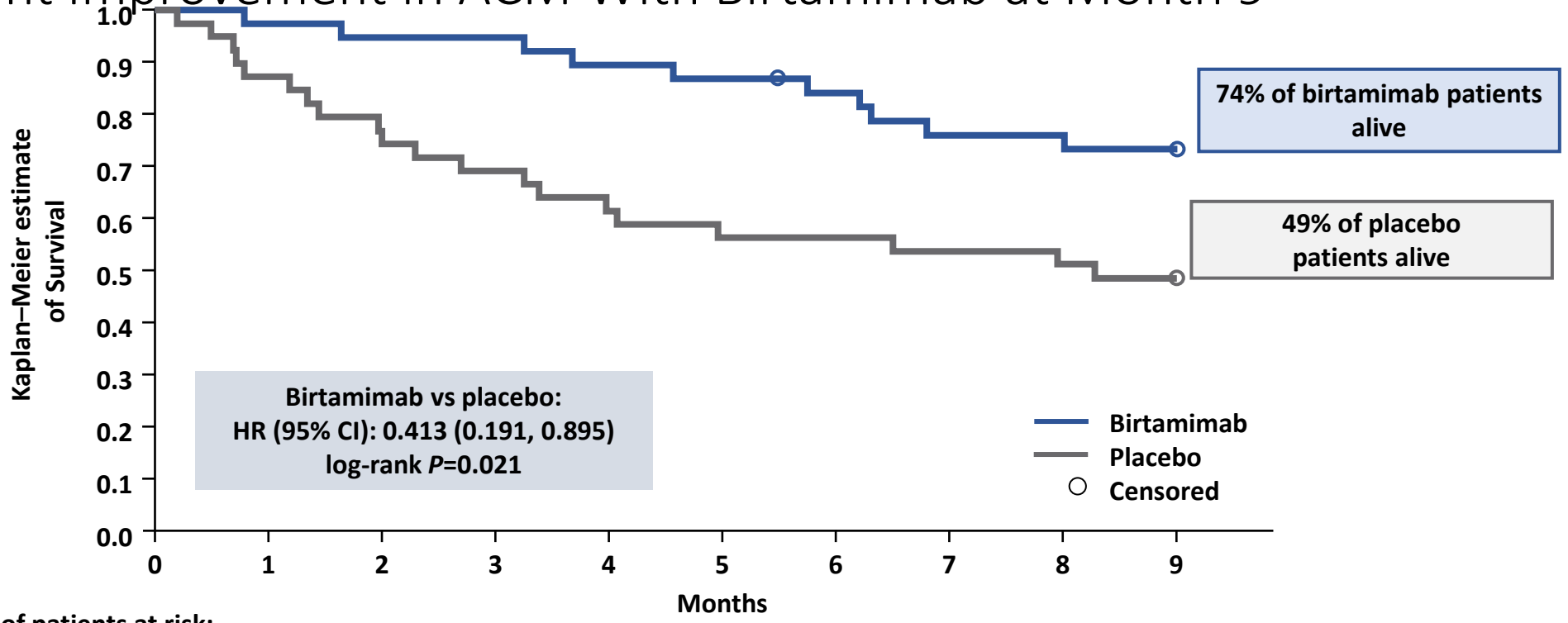
**Key secondary endpoints:**
- Change from baseline to month 9 in 6MWT distance
- Change from baseline to month 9 in the SF-36v2 PCS

**Safety**

**Post hoc analyses:**
- Time to ACM in Mayo Stage IV patients at month 9†
- Sensitivity analyses of time to ACM in Mayo Stage IV patients adjusted for baseline characteristics

**The primary composite endpoint of time to ACM or CH in the overall population (n=260) favored birtamimab over placebo, but the difference was not statistically significant (HR=0.826 [95% CI: 0.574, 1.189]; log-rank *P*=0.303)**

# Post Hoc Analyses in Mayo Stage IV Patients (n=77) Showed Significant Improvement in ACM With Birtamimab at Month 9*

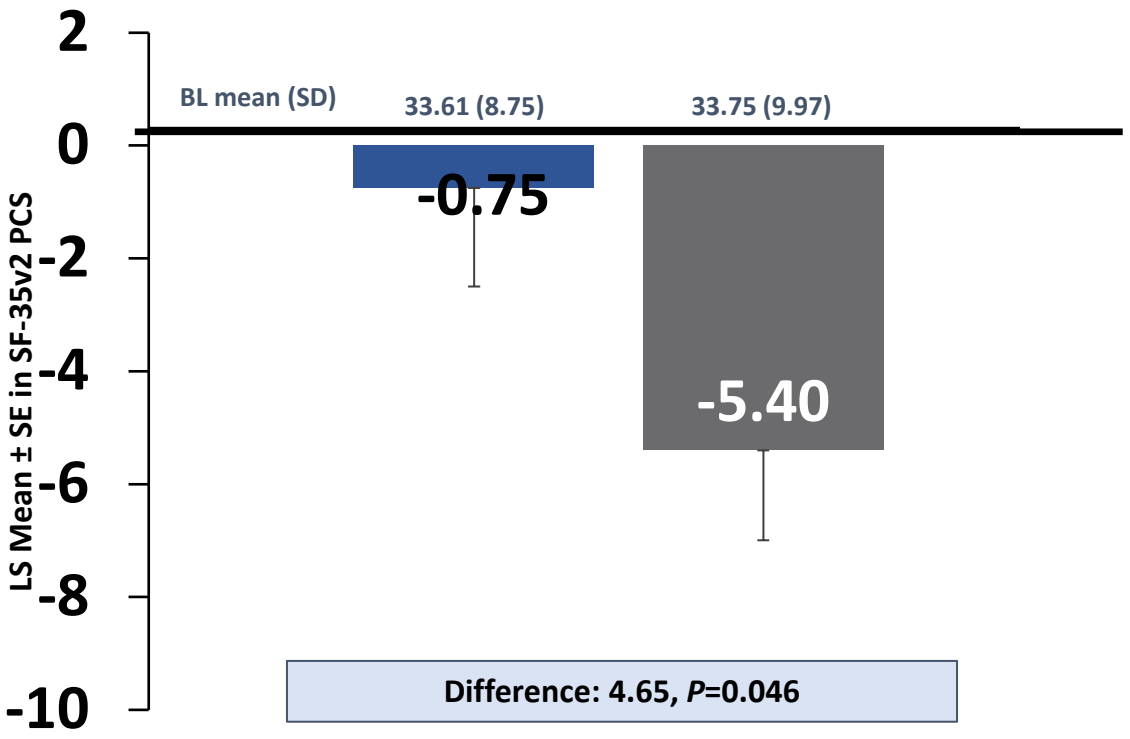



| No. of patients at risk: | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Birtamimab | 38 | 37 | 36 | 36 | 34 | 33 | 31 | 28 | 28 | 27 |
| Placebo | 39 | 34 | 30 | 27 | 24 | 22 | 22 | 21 | 20 | 19 |

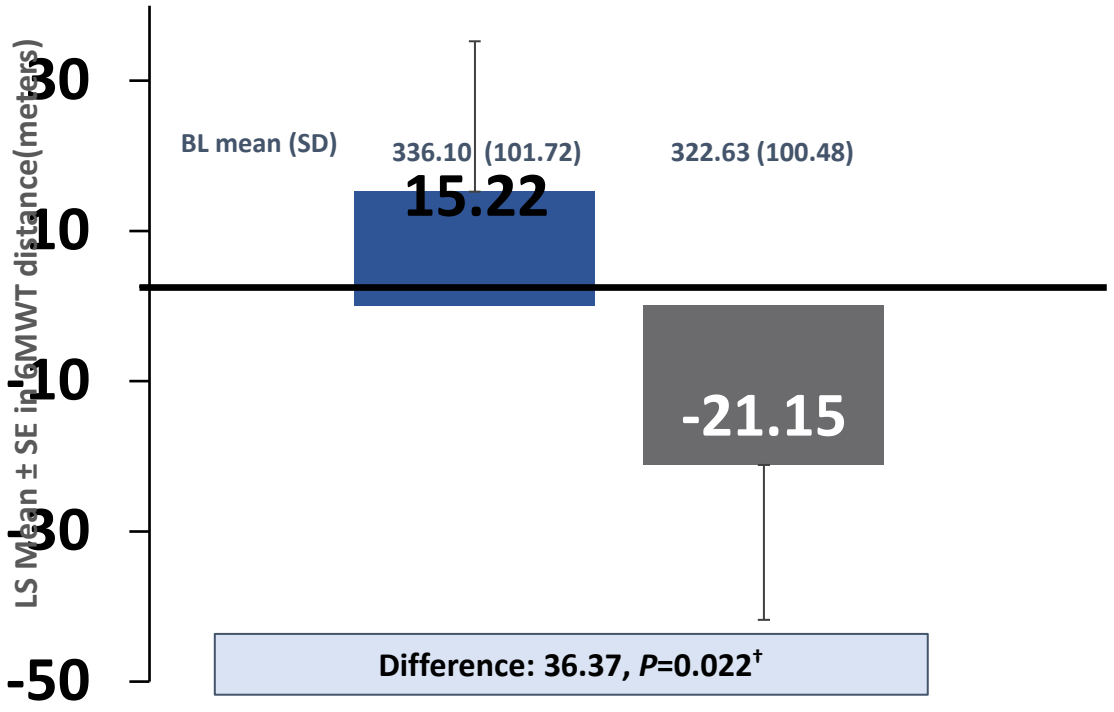
**Survival curves separated early between the two treatment arms; at month 9, 74% of Mayo Stage IV patients treated with birtamimab and 49% of those given placebo survived**

# In Mayo Stage IV Patients, Birtamimab Was Associated With Less Deterioration in Quality of Life and Improved 6MWT Distance At Month 9

## SF-36v2 PCS Change from Baseline at Month 9*




## 6MWT Distance Change from Baseline at Month 9*



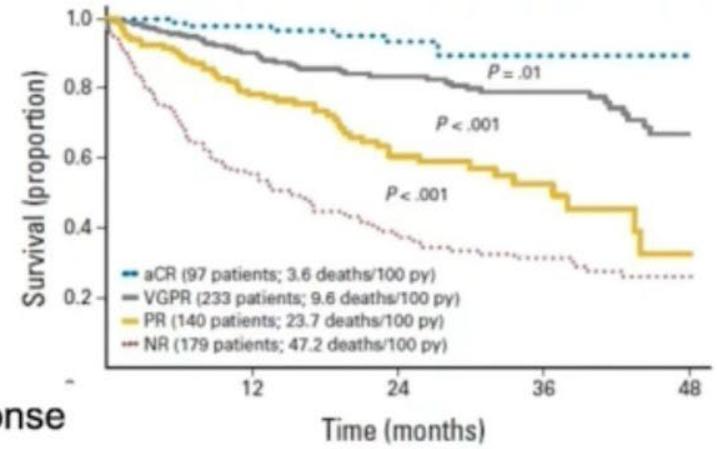

Birtamimab + SoC (n=38)  Placebo + SoC (n=39)

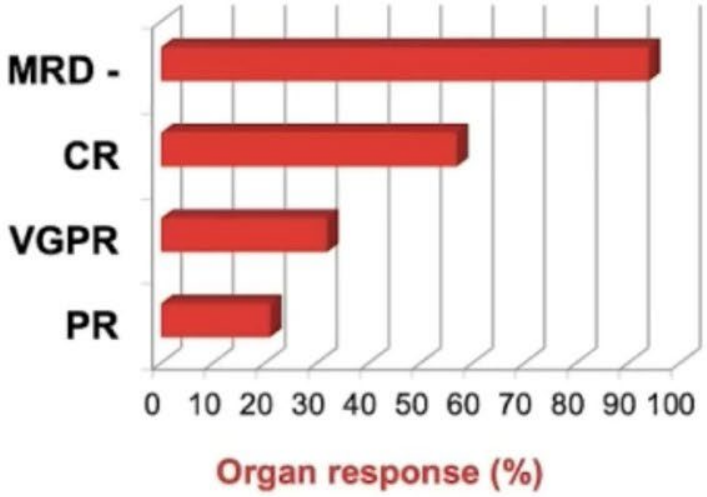
# VITAL Conclusions in Mayo Stage IV Patients

- **Post hoc analysis of Mayo Stage IV patients showed a significant improvement in time to all-cause mortality at month 9**
  - **At month 9, 74% of patients treated with birtamimab survived versus 49% of those given placebo**
- **The survival benefit of birtamimab in VITAL was consistent across all key baseline variables in Mayo Stage IV patients, reinforcing the strength of the survival data in these patients at high risk of early mortality**
- **Treatment with birtamimab in Mayo Stage IV patients was also associated with significantly less deterioration in QoL and improved cardiac functioning***
- **Birtamimab was generally safe and well tolerated in the overall patient population and in Mayo Stage IV patients in this study**

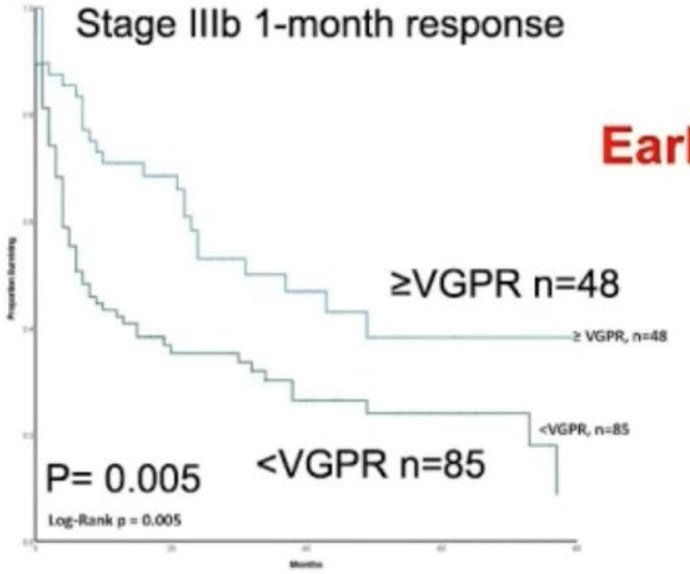
# AL amyloidosis – response assessment based on graded FLC reduction

| Criteria | Definition | HR (95%CI) | P |
|---|---|---|---|
| CR | Negative s & u IFE + normal. FLCR | reference | - |
| VGPR | dFLC <40 mg/L | 2.67 (1.26-5.66) | 0.01 |
| PR | dFLC decrease >50% | 6.24 (2.96-16.15) | <0.001 |
| NR | All other patients | 12.34 (6.03-25.35) | <0.001 |




Palladini et al, *BCJ 2021*




Ravichandran et al, *BCJ 2021*

**Early and deep HR is vital**

**aim at:**

**PR by 1 month**

**VGPR by 2 months**

**OR by 3/6 months**

**MRD- if CR & no OR**

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# Staging of AL amyloidosis

## Cardiac staging

The heart is the single most important predictor of survival

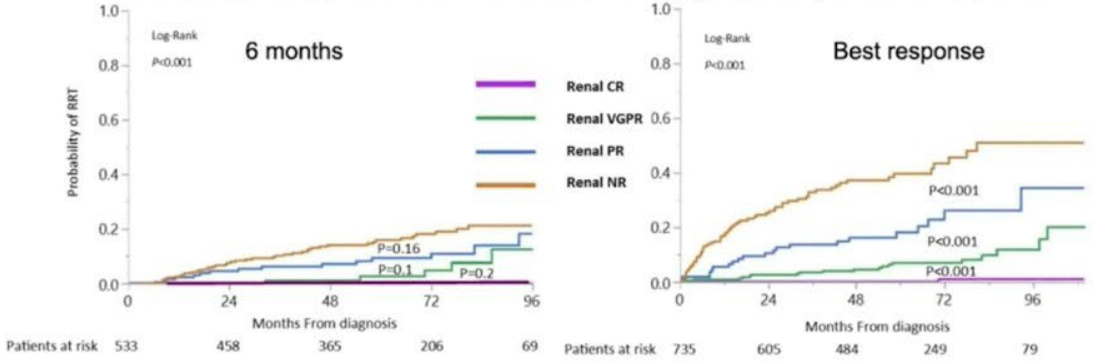
## Renal staging

Predicts the risk for progression to ESRD

## Graded renal response assessment

- **Renal complete response (renCR):** 24-h proteinuria ≤200 mg/24-h
- **Renal very good partial response (renVGPR):** >60% reduction in 24-h proteinuria
- **Renal PR (renPR):** 31-60% reduction
- **Renal NR (renNR):** ≤30% reduction.

- Response was assessed compared to baseline at:
  - Fixed time points (6, 12 and 24 months from therapy initiation) and best response




Muchtar et al, *ASH 2021 abstr. # 2721*

## Graded cardiac response assessment

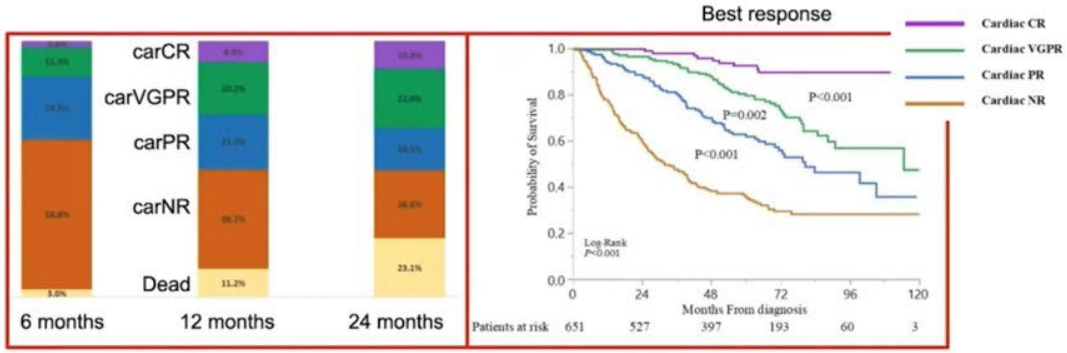
- **Cardiac complete response (carCR):** nadir NT-proBNP≤350 pg/mL or BNP≤80 pg/mL)
- **Cardiac very good partial response (carVGPR):** >60% reduction in NT-proBNP/BNP from baseline)
- **Cardiac PR (carPR):** 31-60% reduction
- **Cardiac NR:** ≤30% reduction

esponse was assessed compared to baseline at:

- Fixed time points (6, 12 and 24 months from therapy initiation) and best response

ıe primary outcome was overall survival based on depth of cardiac response

## Graded cardiac response assessment




Muchtar et al, *ASH 2021 abstr. #2720*





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# Efficacy and Safety of Daratumumab Monotherapy in Newly Diagnosed Patients with Stage 3B Light Chain Amyloidosis: A Phase 2 Study by the European Myeloma Network

Efstathios Kastritis[1], Monique C. Minnema[2], Meletios A. Dimopoulos[1], Giampaolo Merlini[3], Foteini Theodorakakou[1], Despina Fotiou[1], Antoine Huart[4], Karim Belhadj[5], Sreeja Varghese[6], Kyriaki Manousou[6], Pieter Sonneveld[7], Giovanni Palladini[3]

[1]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; [2]Department of Hematology, University Medical Center Utrecht, Utrecht, Netherlands; [3]Amyloidosis Research and Treatment Center, University of Pavia, Pavia, Italy; [4]Department of Nephrology and Transplantation, Rangueil University Hospital, Toulouse; [5]Lymphoid Malignancies Unit, Henri Mondor Hospital, Créteil, France; [6]Health Data Specialists, Dublin, Ireland; [7]Erasmus MC Cancer Institute, Rotterdam, Netherlands

# Introduction

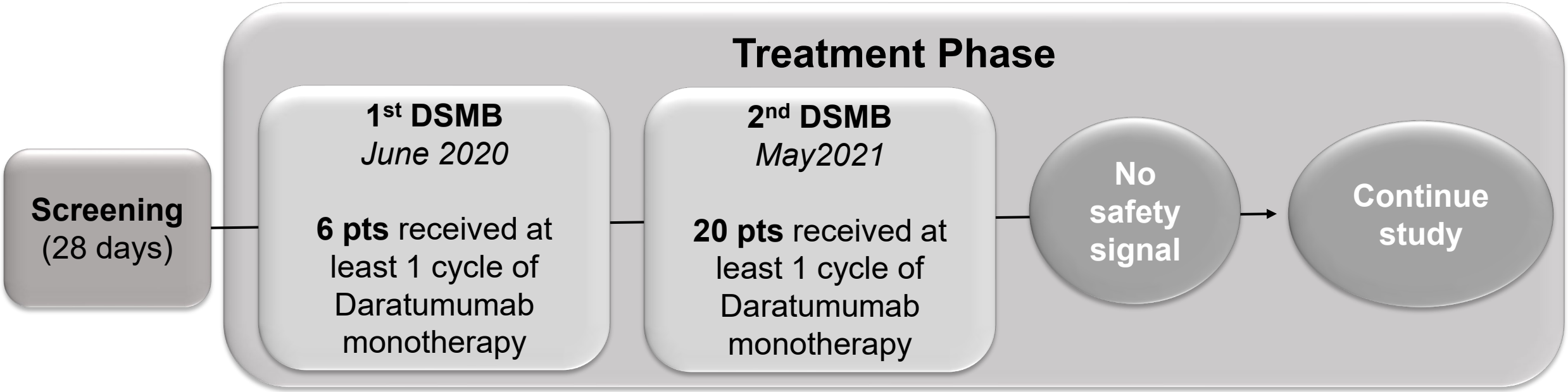
- Early death remains a frequent complication particularly for patients with advanced cardiac involvement due to AL amyloidosis such as those with Mayo stage 3B disease- a patient population with historical median OS of 4.5 months and median 6-months rate of 43.3%[1].

- Daratumumab, an IgGκ monoclonal anti-CD38 antibody, has proven effective and tolerable in pts with AL amyloidosis, either alone or in combination with D-VCd.
- D-VCd is now an approved therapy for patients with AL amyloidosis, but patients with Mayo stage 3B disease were excluded from enrolment in ANDROMEDA.

- This study evaluates the ***efficacy and safety of daratumumab monotherapy in newly diagnosed stage 3B AL amyloidosis pts***.

1: CSR Report; A Retrospective Observational Multicenter Study on the Management and Outcome of Patients with Systemic AL Amyloidosis in Europe, Table 29 Post-2010, June 2021 .
Median OS, Median Overall Survival; CI, Confidence Interval; IgGk, Immunoglobulin class G heavy chains and kappa light chains; anti-CD38, anti-cluster of differentiation 38; D-VCd, Daratumumab, Velcade, Cyclophosphamide, dexamethasone;

# Study Design (2)

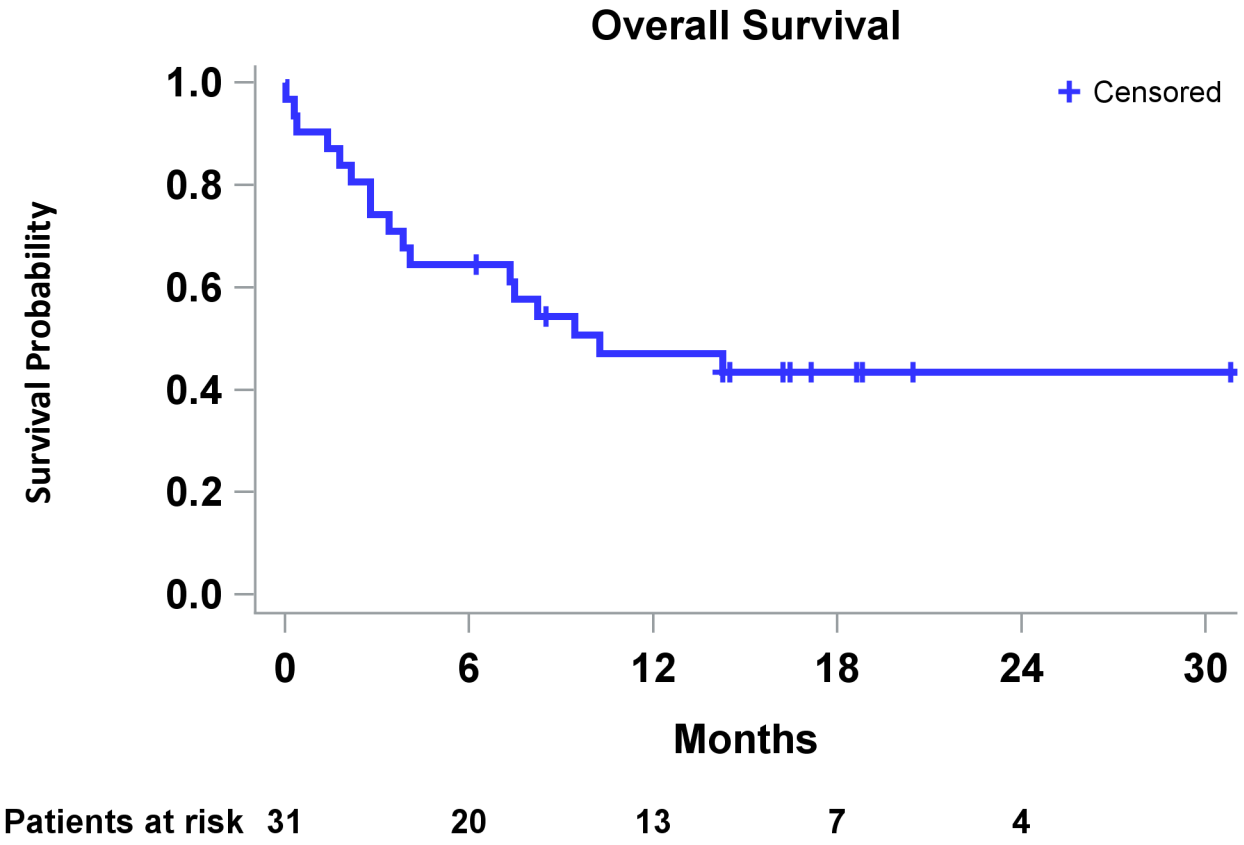



**2 DSMB meetings performed, and no safety signal found.**
**The board recommended for the study to continue unmodified.**

# Baseline characteristics

| | | | |
|---|---|---|---|
| **Age** in years, median (range) | 68.0 (45.0−84.0) | **NT-proBNP in pg/mL**, median (range) | 14,916.0 (8,816.0−72,522.0) |
| **Gender**, n (%) | | **hsTnT** in pg/mL, median (range) | 138.9 (59.8−692.0) |
| Male | 18 (58.1) | | |
| Female | 13 (41.9) | **dFLC** in mg/L, median (range) | 452 (49-2823) |
| **ECOG PS**, n (%) | | **Number of organ involved other than heart**, median (range) | 2.0 (0.0−5.0) |
| 1 | 10 (32.3) | | |
| 2 | 18 (58.1) | | |
| 3 | 3 (9.7) | **Most commonly affected organs** other than heart, n (%) | |
| **NYHA**, n (%) | | | |
| II | 11 (35.5) | Kidneys | 15 (48.4) |
| IIIA | 20 (64.5) | Peripheral Nervous system | 12 (38.7) |

# Primary endpoint: Overall Survival

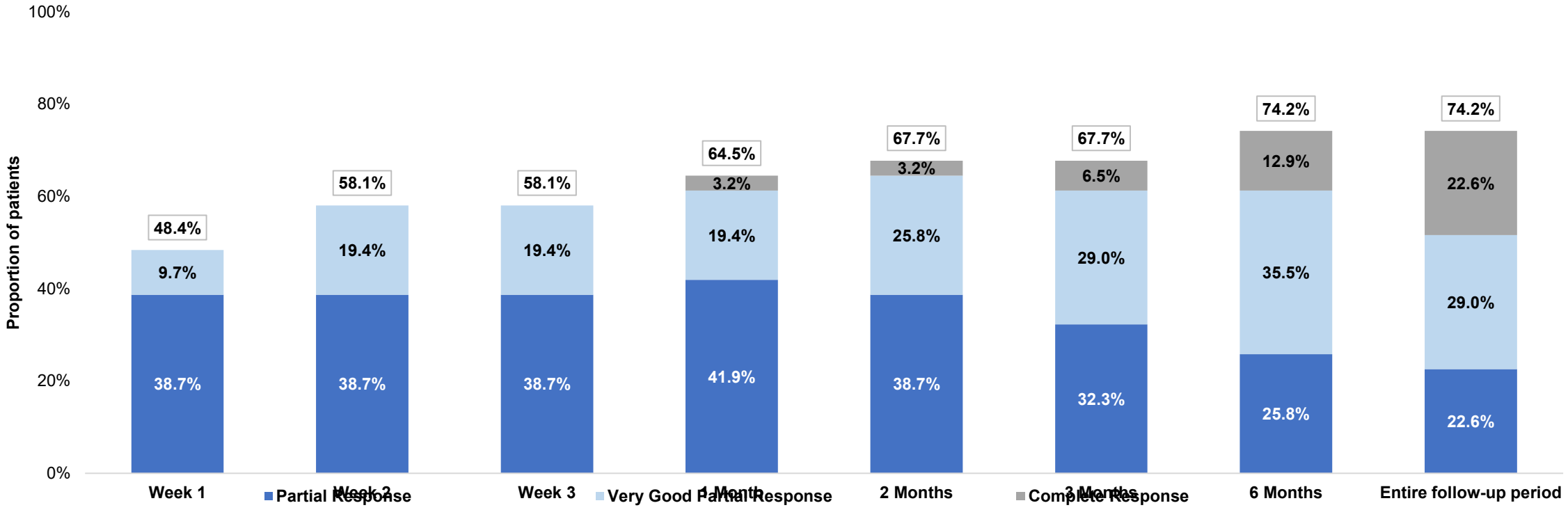



**6-month OS rate**: 64.5%
**12-month OS rate**: 47.1%

**Median and 6-months OS with daratumumab monotherapy is longer than the historical median and 6-months OS in this high-risk patient population**

# Secondary endpoint: Hematologic Reponses

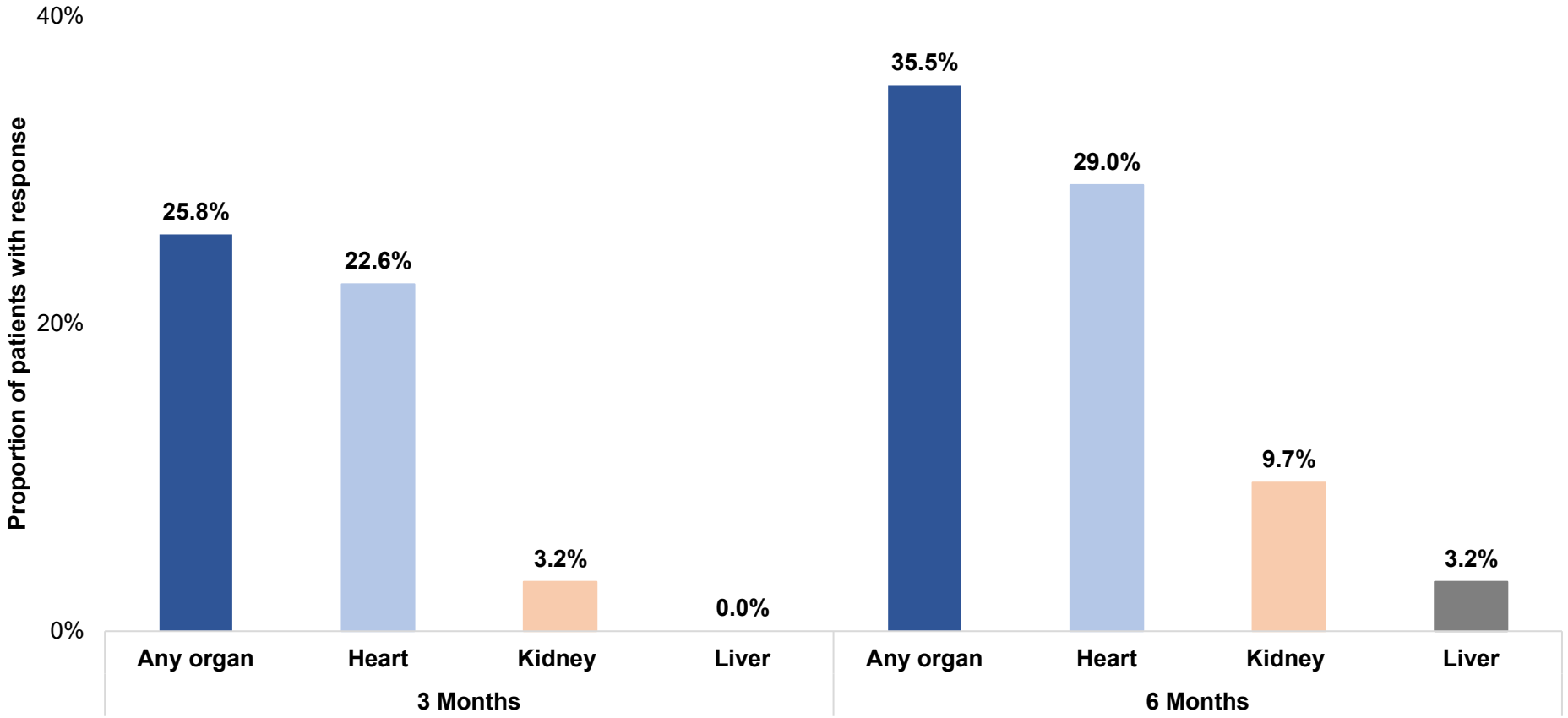
**Time to first response (PR or better)**, median (range): **7 (6−125) days**
**Time to at least VGPR**, median (range): **1.8 (0.2−7.3) months**




**Overall, more than 50% of the patient population achieved a VGPR or better response**

*Note: all proportions are calculated over the ITT population (31 patients); best responses observed until each timepoint are presented*

# Secondary endpoint Organ responses




**Daratumumab monotherapy can induce clinically meaningful cardiac responses in these patients with very advanced cardiac disease**

# Conclusion

- In this high risk (stage 3B) patient population, daratumumab monotherapy demonstrates activity with clinically meaningful rates of hematologic and cardiac responses with no new safety signals.

- Compared to historic controls, early mortality is reduced and the median OS of stage 3B pts exceeds 10 months suggesting that novel treatments can help change the course of AL Amyloidosis even in pts at advanced stages of the disease.

## EHA-ISA Guidelines for Stem Cell Transplantation in AL Amyloidosis

### Eligibility Criteria

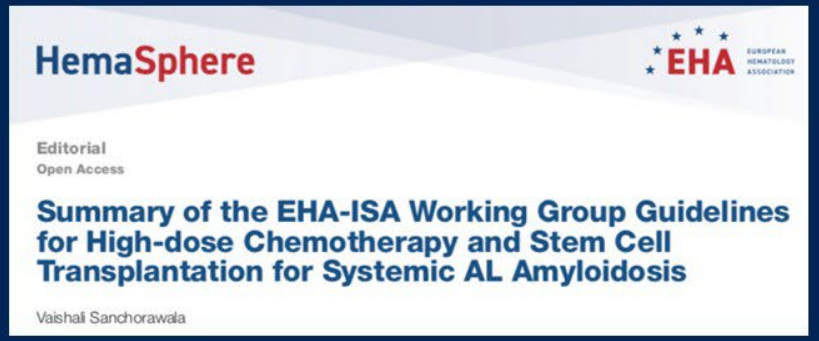
- Age >18 and <70 years
- At least one vital organ involvement
- Left ventricular ejection fraction ≥40% and NYHA class <III
- Oxygen saturation ≥95% on room air and DLCO >50%
- Supine systolic blood pressure ≥90 mm Hg
- ECOG performance status score ≤2
- Direct Bilirubin <2 mg/dL
- NTproBNP <5000 pg/mL
- Troponin I <0.1 ng/mL, Troponin T <0.06 ng/mL, hs-Troponin T <75 ng/mL

### Induction Therapy

- Consider if bone marrow plasmacytosis >10%
- Bortezomib based regimen 2-4 cycles
- Defer SCT if hematologic CR achieved with induction therapy

### Stem Cell Mobilization and Collection

- G-CSF at 10-16 mcg/kg/day (single or split dose)
- Plerixafor on demand or planned
- Avoid cyclophosphamide




### Risk-Adapted Melphalan Dosing

| | MEL 200[a] | MEL 200 vs non-SCT regimens[b] | MEL 140 |
|---|---|---|---|
| Age (years) | ≤65 | 66-70 | |
| Cardiac stage | I | II | |
| eGFR (mL/min/m²) | >50 | 30-50 | ≤30[c] |

[a] *must meet **all** criteria*
[b] *multidisciplinary discussion recommended*
[c] *increased risk of AKI and ESRD during the peri-SCT period; may consider if on a stable chronic dialysis schedule*

Sanchorawala V, Boccadoro M, Gertz MA, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. *Amyloid* 2021:1–7.





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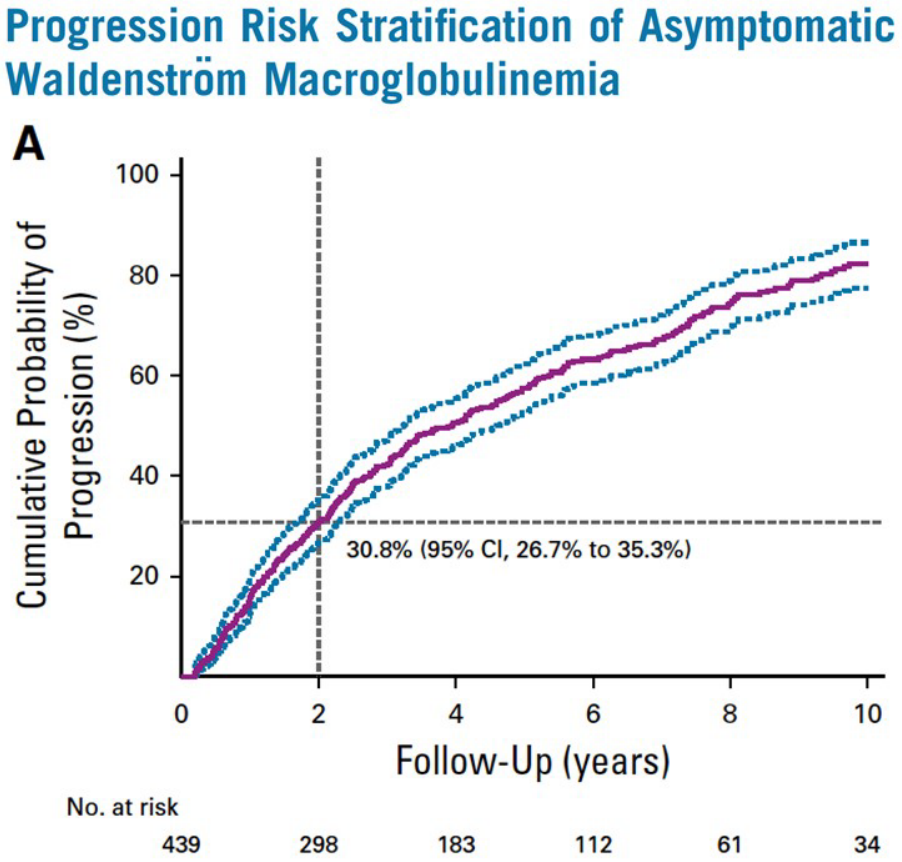
# Why not treat everybody at diagnosis?

- WM is incurable
- Treatment promotes resistance
- Treatment comes with toxicity
- No evidence that treating early prolongs survival
- WM patients enjoy decades of life

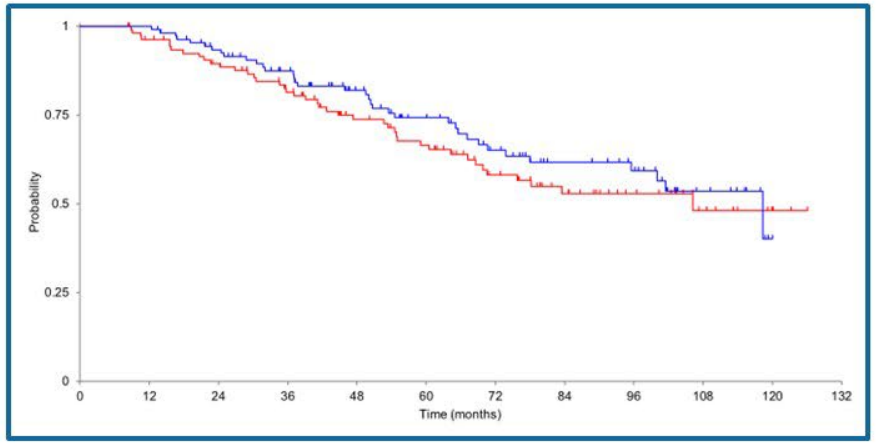


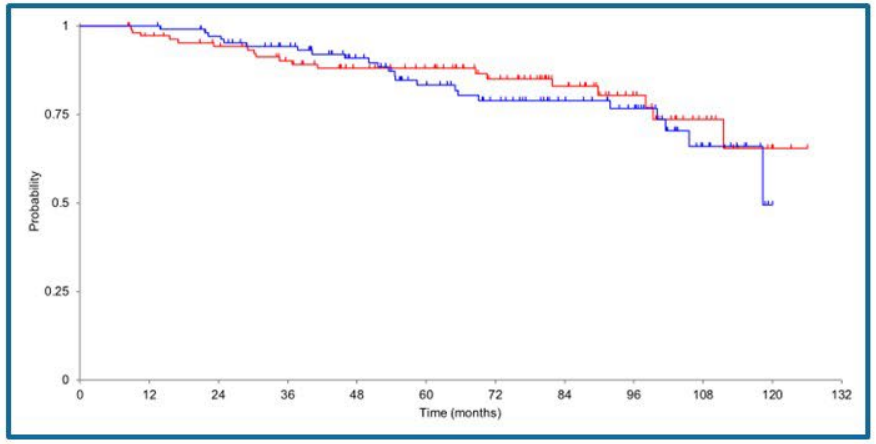

Bustoros et al. JCO 2019

# Two years Rituximab maintenance versus observation after first line treatment with Bendamustine plus Rituximab in patients with Waldenström Macroglobulinemia

| | All | R + | R- |
|---|---|---|---|
| Total (n) | 218 | 109 | 109 |
| Age (median) | 66 | 67 | 65 |
| Hemoglobin <11 g/dl | 149 (68%) | 70 (64%) | 79 (72%) |
| IgM g/l (median) | 32.7 | 32.7 | 31.3 |
| $\beta_2$-Microglobulin | 3.5 | 3.3 | 3.7 |
| B-symptoms | 75 (34%) | 43 (39%) | 32 (29%) |

Rummel et al. ASH 2019



# Bendamustine Rituximab (BR) versus Ibrutinib as Primary Therapy for Waldenström Macroglobulinemia: An International Collaborative Study

| | BR (n=123) | Ibrutinib (n=123) |
|---|---|---|
| CR | 20% | 2% |
| VGPR | 30% | 31% |
| PR | 42% | 50% |
| MR | 2% | 11% |
| 4-y PFS | 72% | 78% |
| 4-Y OS | 95% | 86% |

**Figure 1: Progression-free survival**

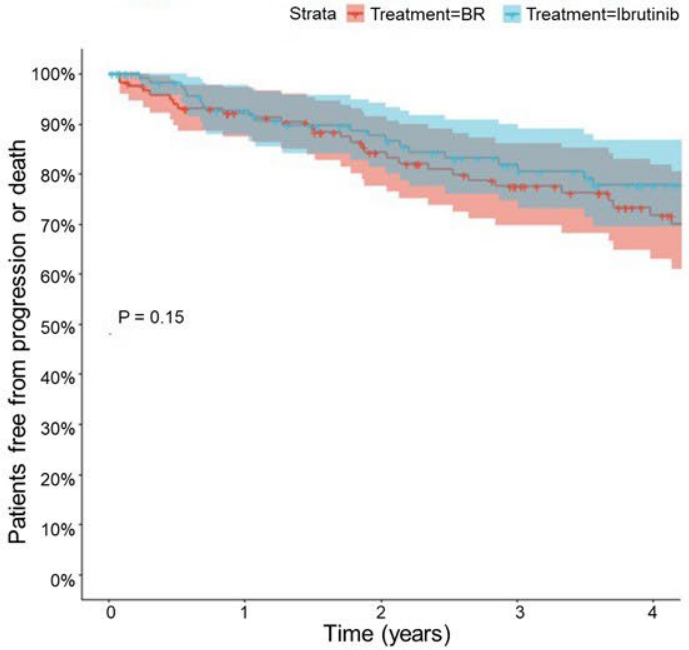
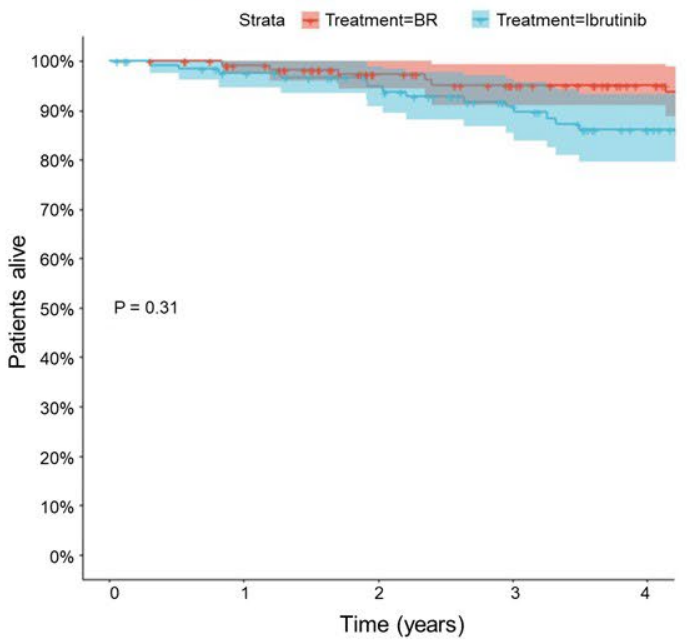



**Figure 2: Overall survival**




Abeykoon et al. ASCO 2022: 7566

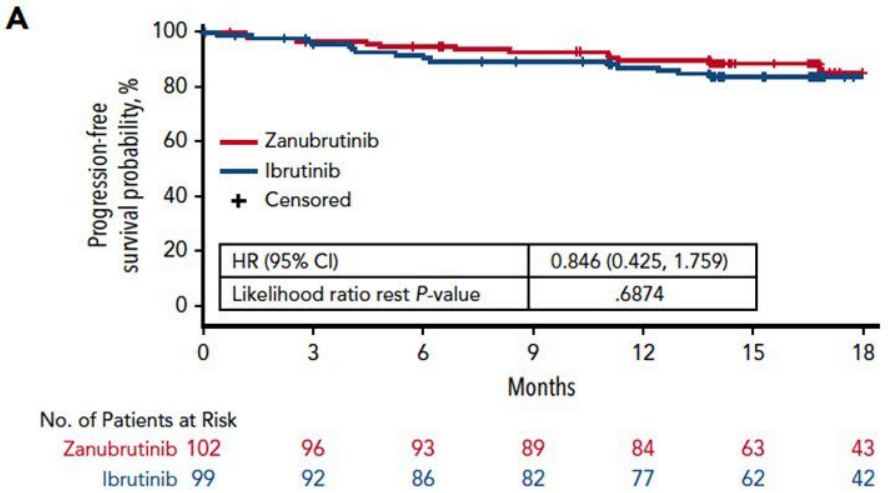
Phase III
TN/RR

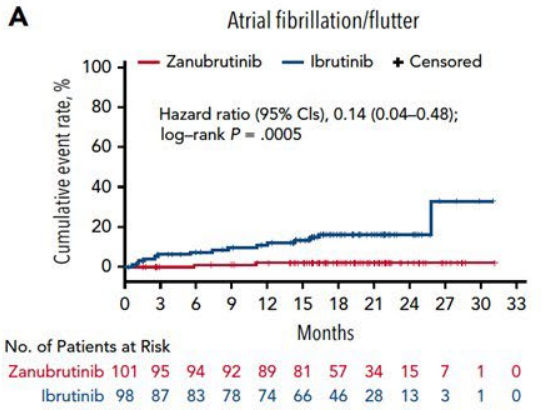
FDA

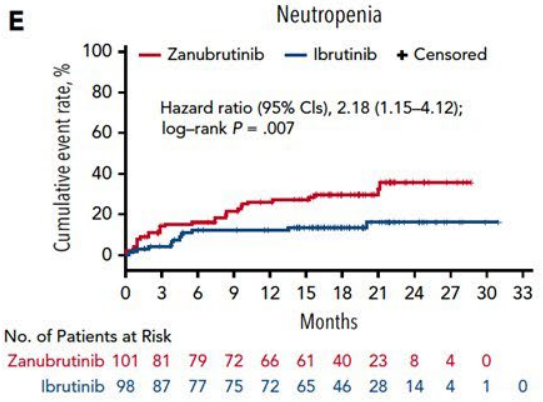
# A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study

| | Ibrutinib (n=99) | Zanubrutinib (n=102) |
|---|---|---|
| CR | 0 (0) | 0 (0) |
| VGPR | 19 (19) | 29 (28) |
| PR | 58 (59) | 50 (49) |
| MR | 15 (15) | 17 (17) |
| SD | 3 (3) | 3 (3) |
| PD | 2 (2) | 2 (2) |

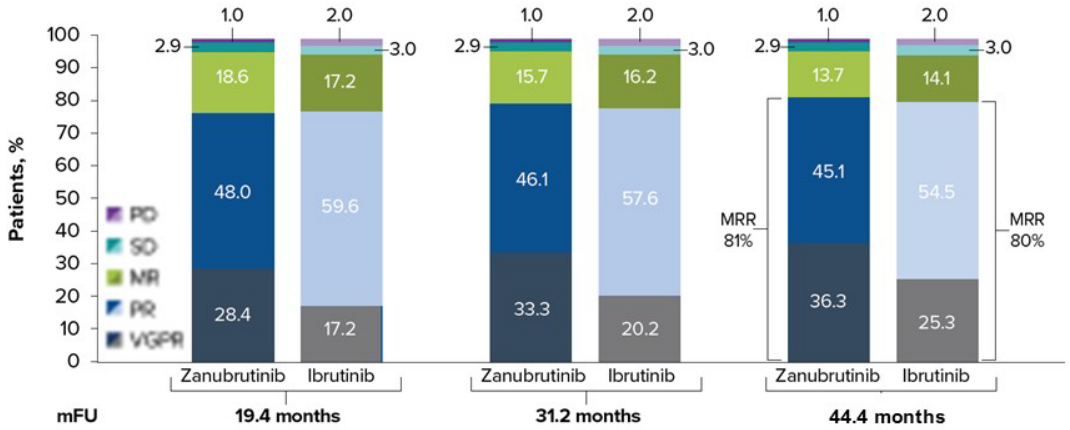
Tam et al. Blood 2020

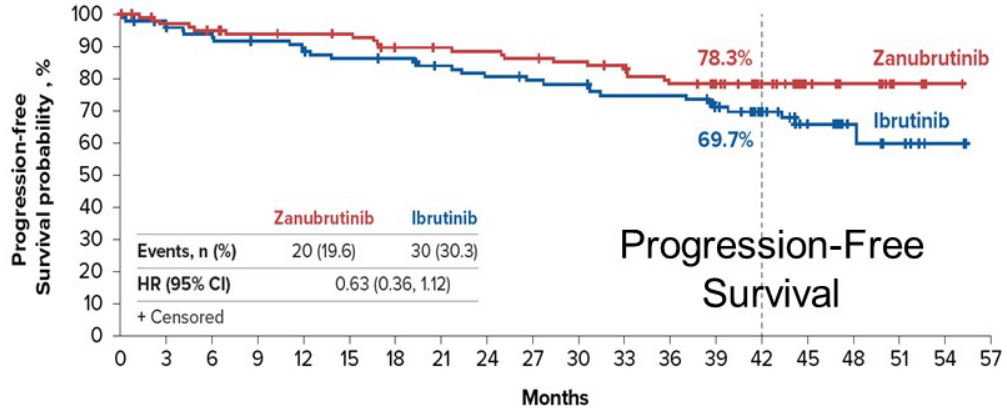


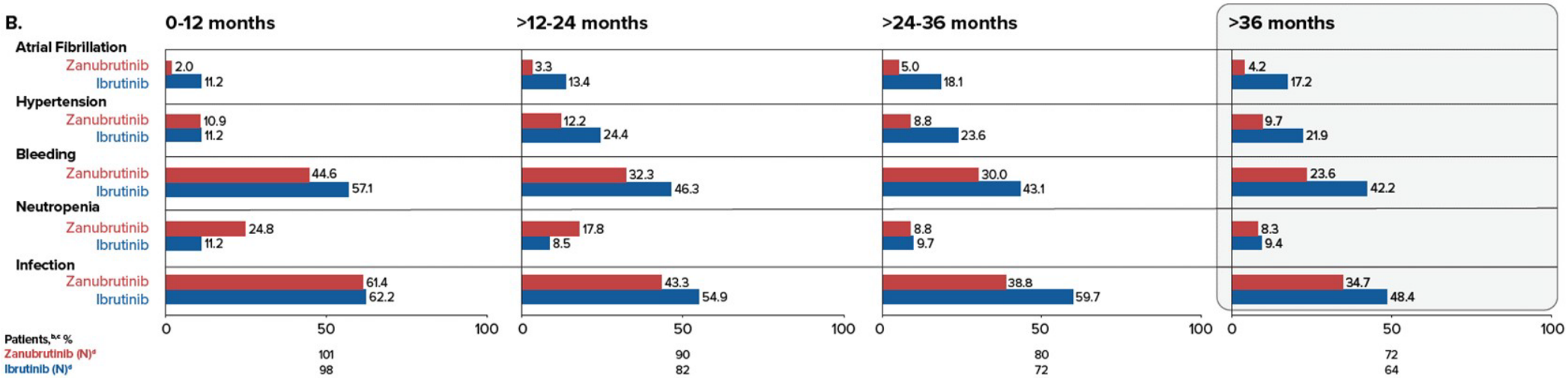



# ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia



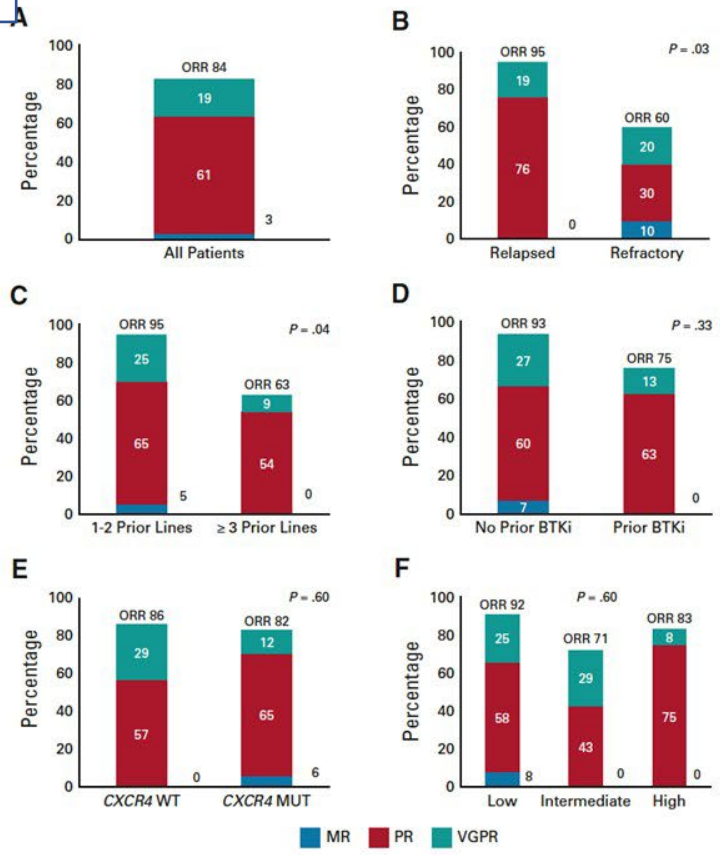



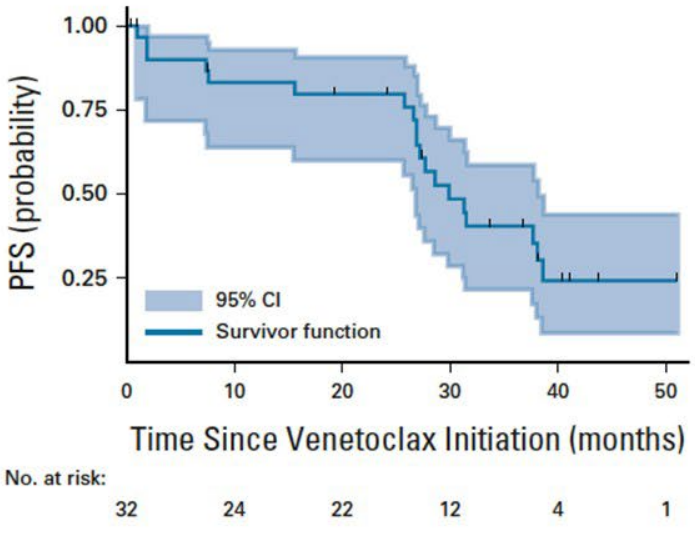



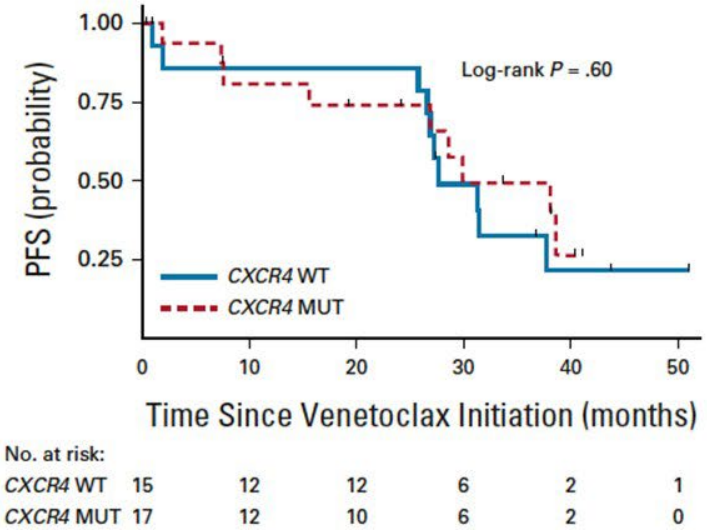

Tam et al. ASCO 2022: 7521

Phase II
RR
NCCN

# Venetoclax in Previously Treated Waldenström Macroglobulinemia




Castillo et al. J Clin Oncol 2022