Nivolumab combined with brentuximab vedotin for relapsed/refractory mediastinal gray zone lymphoma: Primary efficacy and safety analysis of the phase 2 CheckMate 436 study

Armando Santoro,[1] Alison J. Moskowitz,[2] Silvia Ferrari,[3] Carmelo Carlo-Stella,[1] Michelle A. Fanale,[4] Stephen Francis,[5] Mariana Sacchi,[5] Kerry J. Savage[6]

[1]Humanitas Clinical and Research Center IRCCS, Humanitas University, Milano, Italy; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [4]Seattle Genetics, Bothell, WA, USA; [5]Bristol Myers Squibb, Princeton, NJ, USA; [6]Department of Medical Oncology, BC Cancer, Vancouver, BC, Canada

Disclosures

Kerry J. Savage

- Consultancy
  - AbbVie, AstraZeneca, Bristol Myers Squibb, Gilead, Merck, Seattle Genetics, Servier
- Research funding
  - Roche (institutional)
- Honoraria
  - AbbVie, AstraZeneca, Bristol Myers Squibb, Gilead, Merck, Seattle Genetics
- Steering committee
  - BeiGene

Introduction

- Mediastinal gray zone lymphoma is **an extremely rare form of NHL** with a predominance in young men,[1] and with features intermediate between nodular sclerosis cHL and PMBL[2,3]
- Compared with PMBL, patients with MGZL have inferior survival outcomes after conventional chemotherapy[4]
  - Five-year EFS rates were 62% in MGZL versus 93% in PMBL
  - Five-year OS rates were 74% in MGZL versus 97% in PMBL
- Nivolumab + BV has shown high ORR in adult patients with R/R PMBL and R/R cHL

Nivolumab + BV	ORR, %	CR rate, %
R/R PMBL (CheckMate 436)[5]	73	37
R/R cHL[6]	85	67

- **In this analysis, the efficacy and safety of nivolumab + BV was evaluated in a separate MGZL cohort in CheckMate 436**

BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CR, complete response; EFS, event-free survival; MGZL, mediastinal gray zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PMBL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory.

1. Quintanilla-Martinez L, Fend F. *Haematologica* 2011;96:496–499; 2. Eberle FC, et al. *Haematologica* 2011;96:558–566; 3. Melani C, et al. *N Engl J Med* 2017;377:89–91; 4. Wilson WH, et al. *Blood* 2014;124:1563–1569; 5. Zinzani PL, et al. *J Clin Oncol* 2019;37:3081–3089; 6. Moskowitz AJ, et al. Oral presentation at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition; December 7–10, 2019; Orlando, FL, USA. Abstract 238.

CheckMate 436 MGZL cohort study design

Key inclusion criteria

- Aged ≥ 18 years
- ECOG PS 0 or 1
- CD30 expression of ≥ 1% in the tumor or tumor-infiltrating lymphocytes
- Measurable MGZL disease
- R/R disease after
  - High-dose chemotherapy + auto-HCT
    or
    ≥ 2 prior multi-agent chemotherapy if auto-HCT ineligible

n = 10[a]

Treatment

Nivolumab
240 mg IV, Q3W[b]
+
BV
1.8 mg/kg[c] IV, Q3W[d]

Cycles are 21 days until disease progression or unacceptable toxicity

Endpoints

- **Primary**: Investigator-assessed ORR, safety
- **Secondary**: CR rate, OS, duration of response, PFS

Assessments

- Tumor assessment per Lugano 2014[e,f]
- Safety evaluated continuously

Follow-up

- Disease progression, safety, OS

[a]Based on historical data, a sample size of 10 patients was chosen with the null hypothesis that the true ORR was ≤ 10%, to be rejected if 5 or more responses were observed based on an 80% CI; [b]Day 8 of Cycle 1, then Day 1 of every cycle thereafter; [c]Prespecified dose modifications allowed; [d]Day 1 of every cycle. [e]PET/CT on week 6, 12, then Q9W for the subsequent 4 tumor assessment timepoints, and Q12W after the first year; [f]CR is defined as Deauville score 1–3.
Auto-HCT, autologous hematopoietic cell transplantation; PET, positron emission tomography; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks.

Baseline characteristics and patient disposition

	MGZL (n = 10)
Age, median (range), years	35 (25–72)
> 65 years	1[a] (10)
Male sex	6 (60)
ECOG PS	
0–1	9 (90)
≥ 2	1 (10)
Refractory disease[b]	7 (70)
Median number of prior systemic cancer therapies (range)	2 (1–3)[c]
Prior auto-HCT	0
Time from completion of most recent prior systemic therapy to study treatment	
< 3 months	8 (80)
3–6 months	1 (10)
> 6 months	1 (10)

- Patients received a median (range) of 7 (5–26) doses of nivolumab and 7 (1–29) doses of BV
- At database lock[d] all patients had discontinued treatment due to disease progression (n = 5), maximum clinical benefit (n = 3; all achieved CR and proceeded to allo-HCT), allo-HCT (n = 1), and auto-HCT (n = 1)

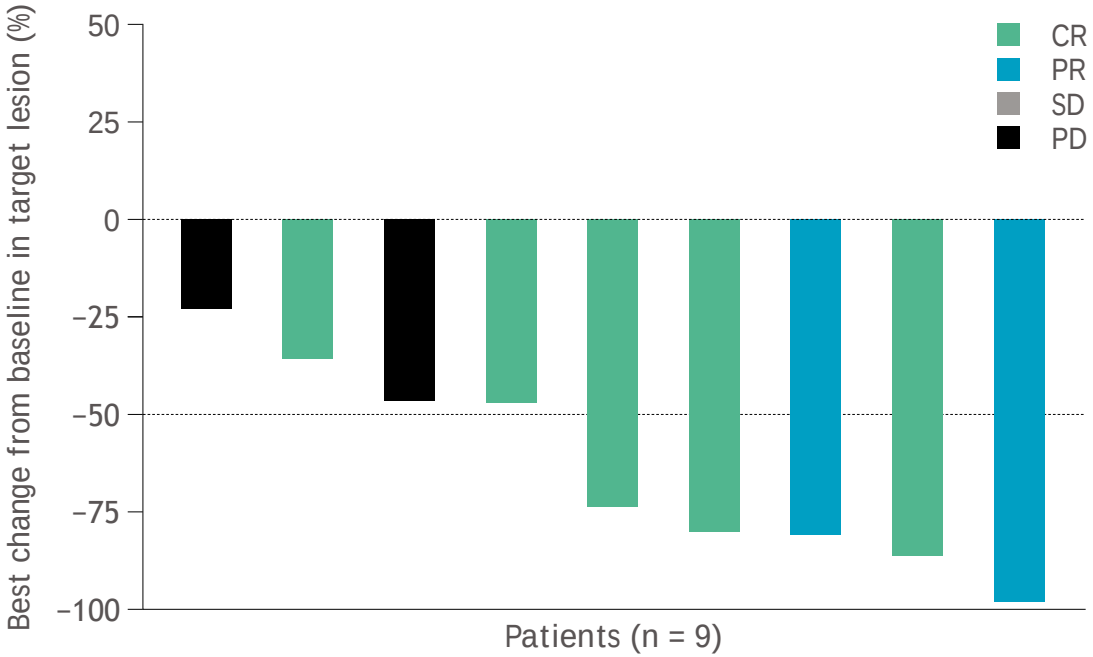
Data are n (%) unless stated otherwise. [a]Patient was 72 years old; [b]No CR following frontline therapy and no CR/PR to any salvage therapy; [c]One patient received 2 prior regimens but reported as having unknown lines of therapy; [d]8 months after the last patient received the first treatment.

Allo-HCT, allogenic hematopoietic cell transplantation; PR, partial response.

Best overall response and tumor reduction, investigator-assessed

	MGZL (n = 10)
ORR	7 (70)
80% CI, %	45–88
CR	5 (50)
PR	2 (20)
SD	0
PD	2 (20)
Death prior to disease assessment	1 (10)

Data are n (%) unless stated otherwise.

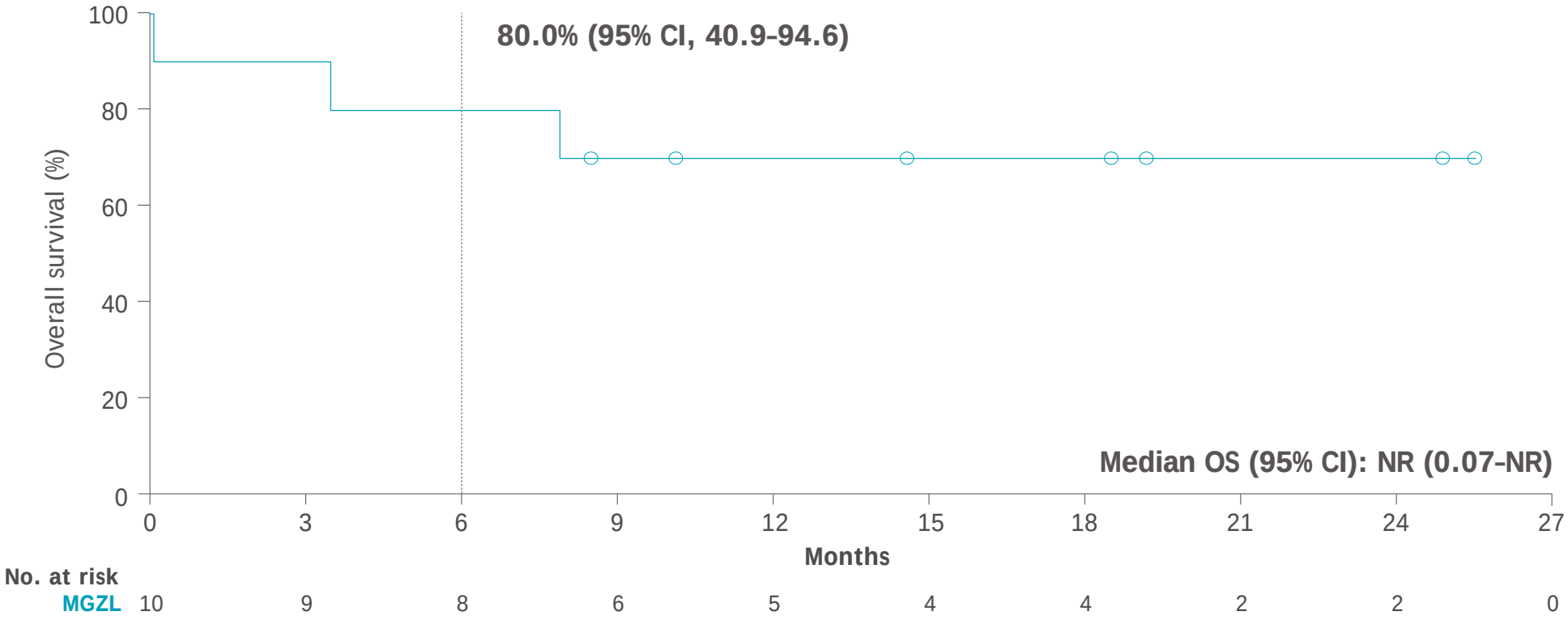


- Median follow-up (range) was 12.4 months (0.1–25.5)
- Time to CR was 1.2–4.8 months and the duration of CR was 1.5+ to 3.2+ months before patients were censored for subsequent therapy
- All patients who achieved CR were bridged to hematopoietic cell transplantation (4 allo- and 1 auto-HCT) and censored (all were alive at database lock)

For tumor reduction, response evaluable patients are those with target lesion(s) assessed at baseline and with all baseline target lesion(s) assessed at ≥ 1 on-study timepoint. Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy.

PD, progressive disease; SD, stable disease.

Overall survival



- Duration of response and PFS could not be estimated reliably due to earlier censoring of patients who received subsequent therapies

Median follow-up (range): 12.4 months (0.1–25.5).

NR, not reached.

Safety

n (%)	MGZL (n = 10)	
	Any grade	Grade 3
Any TRAEs	9 (90)	3[a] (30)
TRAEs occurring in ≥ 2 patients		
Neutropenia	3 (30)	1 (10)
Paresthesia	3 (30)	0
Thrombocytopenia	2 (20)	1 (10)
Anemia	2 (20)	0
Peripheral sensory neuropathy	2 (20)	0
Serious TRAEs		
Febrile neutropenia	1 (10)	1 (10)

- No grade 4 toxicity was observed
- There were 3 deaths, all due to disease progression
- Infusion-related reaction occurred in 1 patient (grade 1)
- Only 1 patient had an immune-mediated AE (grade 2 maculo-papular rash) which resolved without systemic steroids

[a]Grade 3 neutropenia, grade 3 thrombocytopenia, and grade 3 febrile neutropenia (n = 1 each).

AE, adverse event; TRAE, treatment-related adverse event.

Summary

- Nivolumab + BV demonstrated a high investigator-assessed ORR of 70%, with a 50% CR rate, and a short time to CR (1.2–4.8 months) in patients with R/R MGZL
  - These findings were consistent with those reported with nivolumab + BV in R/R PMBL[1] and R/R cHL[2,3]
- Safety profile was tolerable and was consistent with previous reports[1–3]
- The regimen may represent a potential option for bridging to stem cell transplant in patients with chemotherapy-refractory disease

1. Zinzani PL, et al. *J Clin Oncol* 2019;37:3081–3089; 2. Herrara A, et al. *Blood* 2018;131:1183–1194; 3. Moskowitz AJ, et al. Oral presentation at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition; December 7–10, 2019; Orlando, FL, USA. Abstract 238.

Acknowledgments

- The patients and families who are making the study possible
- The clinical study teams who participated in the trial
- Study drugs provided by Bristol Myers Squibb (Princeton, NJ, USA) and Seattle Genetics, Inc. (Bothell, WA, USA)
- This study was supported by Bristol Myers Squibb, in collaboration with Seattle Genetics
- All authors contributed to and approved the presentation; professional medical writing and editorial assistance were provided by Jane Cheung, Caudex, funded by Bristol Myers Squibb
- For questions please visit: www.globalbmsmedinfo.com