[Abstract ID 676P] - ATHENA - A multicenter Phase II trial of atezolizumab (A) and bevacizumab (B) in patients (pts) with recurrent or metastatic squamous-cell carcinoma of the head and neck (R/M HNSCC): the HPV negative cohort.

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
imCORE

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ABSTRACT

BACKGROUND - The standard therapy for R/M HNSCC includes anti-PD1. The combination A + B could be synergistic according to encouraging antitumor activity and safety in various tumor types and approval for hepatocellular carcinoma.

METHODS - This imCORE network investigator-initiated, multi-center, single arm, phase 2 trial evaluated the combination of A (1200 mg) + B (15 mg/kg), given intravenously every 3 weeks, after progression on platinum-based chemotherapy in R/M HNSCC pts naïve for anti-PD1.

The primary endpoint was objective response rate as per RECIST V1.1 after 18 weeks of treatment (ORR$_{18W}$). The trial used an adaptive Simon 2-stage design. In the HPV negative cohort, we hypothesized that excluding an ORR$_{18W}$ ≤15% (null hypothesis) while targeting an ORR$_{18W}$ ≥30% (relevant hypothesis, power 80%) or ≥35% (high hypothesis, power 90%) would be an optimal approach.

At the end of the stage I, if less than 5 objective response were reported in the first 27 evaluable patients, the study will be closed for futility. Secondary endpoints included: disease control rate as per RECIST V1.1 after 18 weeks (DCR$_{18W}$), progression free survival (PFS), overall survival (OS) and adverse events (AE).
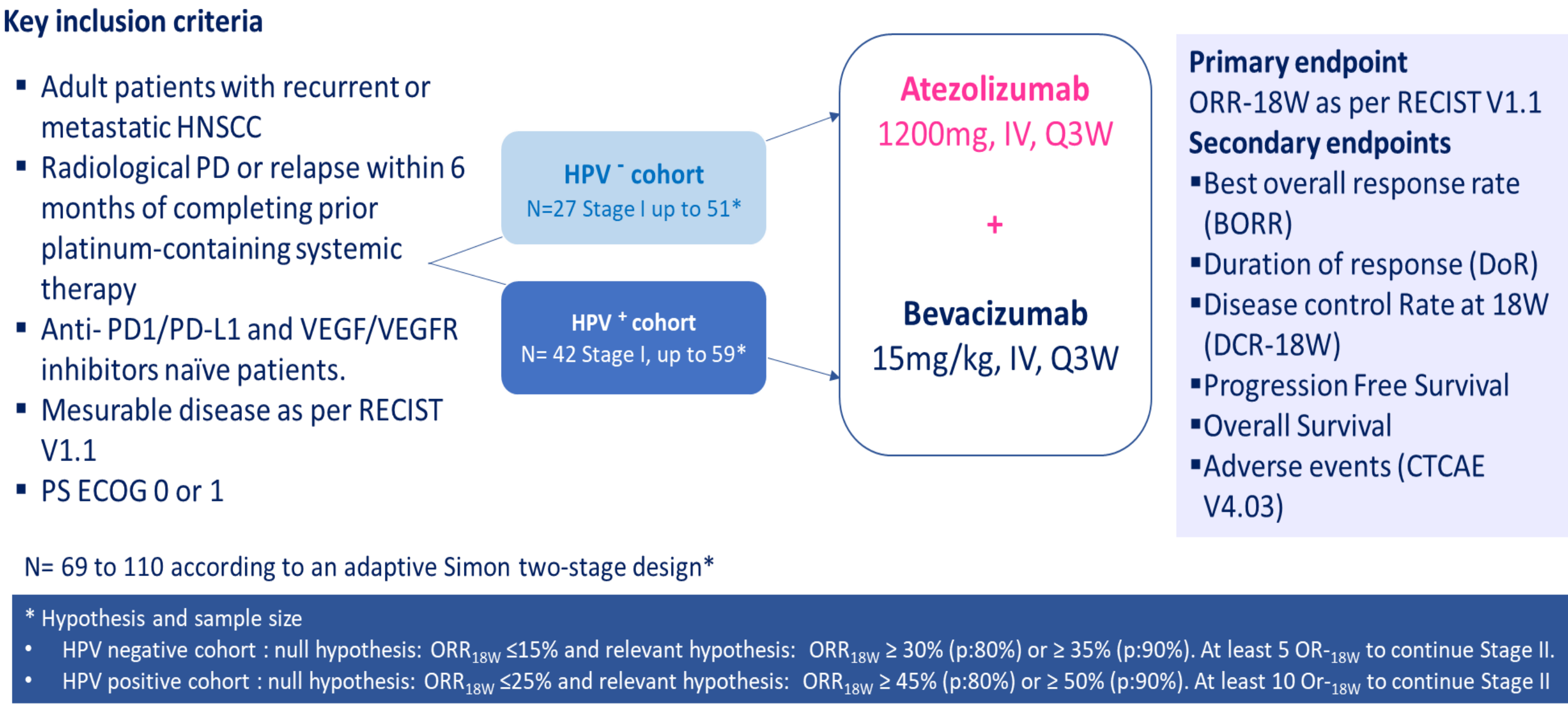
RESULTS - A total of 30 pts (24 males, median age: 64.0 years [range:39.0-77.0]) were enrolled in the HPV negative cohort. Among the 28 pts evaluable for primary endpoint, the ORR$_{18W}$ was 3.6% (1 /28, unilateral 95% lower confidence limit: 0.2%). The DCR-18W was 17.9% (95%CI: 6.1-36.9). With a median follow-up of 75.1 weeks (range: 2.9-100.9), the median PFS and OS were 6.2 (95%CI: 5.7 - 12.7) and 41.1 weeks (95%CI: 28.4 - 80.4), respectively.

Main AE (≥ 10%, all grades) related to A were thyroid disorders, diarrhea, fatigue, transaminase increase, arthralgia and pruritus. Main AE (≥ 10%, all grades) related to B were fatigue, proteinuria and hypertension. Eleven pts (36.7 %) experienced at least one Grade ≥3 related AE and 13.3% at least one SAE related to study drugs including one sudden death.

CONCLUSION - Based on the first stage of this study, the efficacy of A+B is limited in HPV negative RM-HNSCC and does not warrant further investigation.

STUDY OVERVIEW

This multicenter, open-label, phase II proof-of-concept study was conducted according to an adaptive Simon two-stage design.

Key inclusion criteria
- Adult patients with recurrent or metastatic HNSCC
- Radiological PD or relapse within 6 months of completing prior platinum-containing systemic therapy
- Anti- PD1/PD-L1 and VEGF/VEGFR inhibitors naïve patients.
- Measurable disease as per RECIST V1.1
- PS ECOG 0 or 1

HPV ⁻ cohort N=27 Stage I up to 51*
HPV ⁺ cohort N= 42 Stage I, up to 59*

Atezolizumab 1200mg, IV, Q3W
+
Bevacizumab 15mg/kg, IV, Q3W

Primary endpoint
ORR-18W as per RECIST V1.1
Secondary endpoints
- Best overall response rate (BORR)
- Duration of response (DoR)
- Disease control Rate at 18W (DCR-18W)
- Progression Free Survival
- Overall Survival
- Adverse events (CTCAE V4.03)

N= 69 to 110 according to an adaptive Simon two-stage design*

* Hypothesis and sample size
- HPV negative cohort : null hypothesis: ORR$_{18W}$ ≤15% and relevant hypothesis: ORR$_{18W}$ ≥ 30% (p:80%) or ≥ 35% (p:90%). At least 5 OR-$_{18W}$ to continue Stage II.
- HPV positive cohort : null hypothesis: ORR$_{18W}$ ≤25% and relevant hypothesis: ORR$_{18W}$ ≥ 45% (p:80%) or ≥ 50% (p:90%). At least 10 Or-$_{18W}$ to continue Stage II

BASELINE CHARACTERISTICS

From May 2019 to November 2021, 30 R/M HNSCC patients were enrolled and treated with at least one dose of both study drugs (80% men, median age: 64 years [39-77], PS ECOG 1: 66.7%).

At inclusion, all patients, except 1, had stage IV HNSCC. Median delay between the last progression/relapse to inclusion was 1.1 month [0.1-1.6]. Main metastatic site was lung (63.3%). All patients were enrolled after 1 or 2 lines of prior treatment in the advanced/metastatic setting including a platinum-based therapy except 1 in violation to eligibility criteria.

Primary tumor site	
Hypopharynx	5 (16.7%)
Larynx	2 (6.7%)
Oral cavity	11 (36.7%)
Oropharynx	12 (40.0%)
Histological type	
Well differentiated squamous carcinoma	15 (50.0%)
Moderately differentiated squamous carcinoma	8 (26.7%)
Poorly differentiated squamous carcinoma	7 (23.3%)
AJCC stage at initial diagnosis*	
I-II	6 (20.0%)
III - IV	23 (76.6%)
Metastases at initial diagnosis*	
M0	26 (86.7%)
M1	3 (10.0%)
N metastatic sites at inclusion	
0	8 (26.7%)
1-2	17 (56.7%)
> 2	5 (16.6%)
N prior lines before inclusion**	
1	27 (90%)
2	1 (3.3%)
3	1 (3.3%)

*Missing data n = 1 ; ** 1 patient was enrolled with no prior systemic line in metastatic setting*

EFFICACY ENDPOINTS

Among the 30 patients enrolled and treated, median number of cycle for atezolizumab and bevacizumab was 3 [1-24]. At time of the analysis, all patients had discontinued both study treatments, mainly for progression.

Among the 28 patients evaluable* at the end of Stage I : the ORR-18W was 3.6% (1 patient with PR). According to the Simon 2-stage design, the HPV negative cohort was closed for futility.
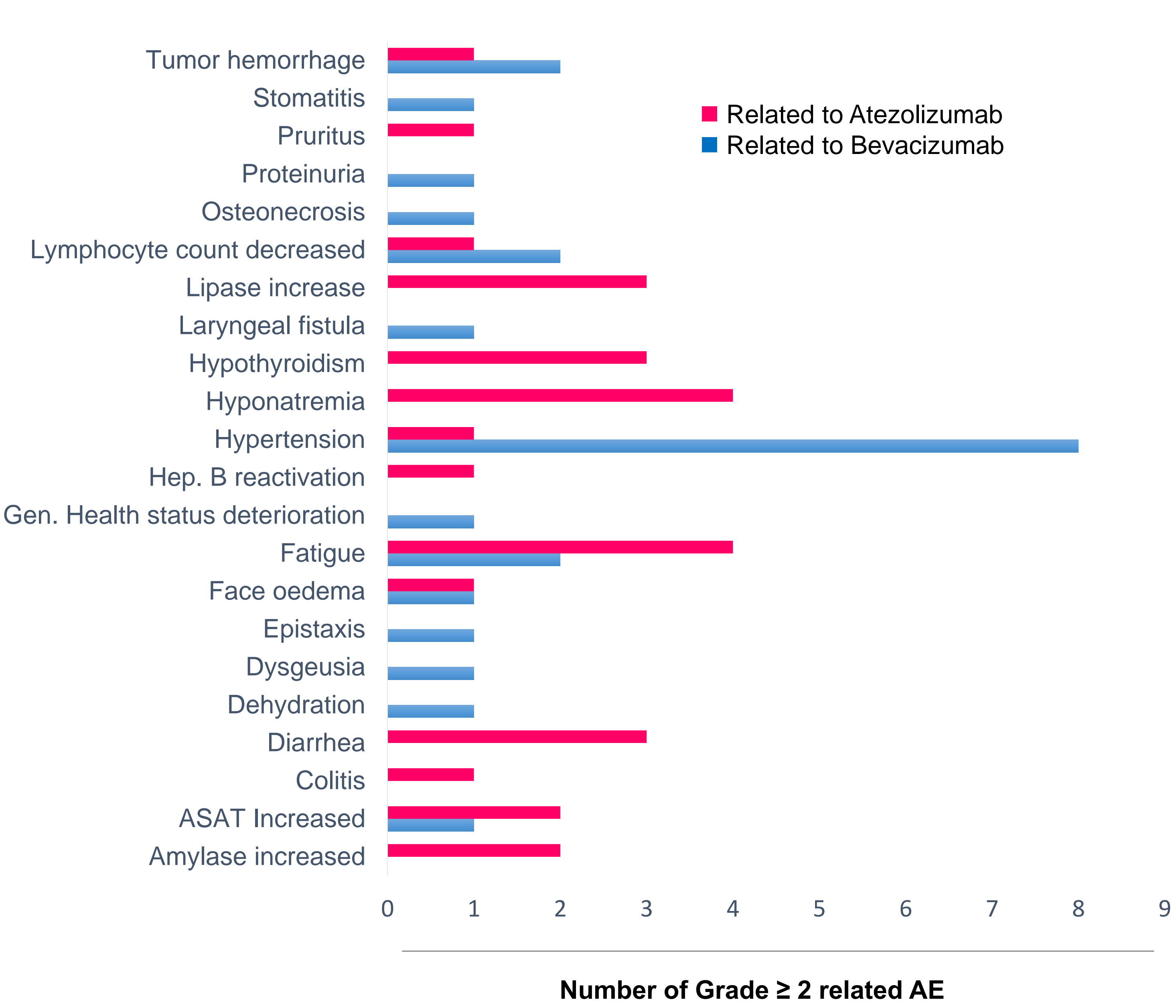
10 patients had SD and 3 patients reached PR as best response.

ORR-18W, N (%) [unilateral 95% lower CL]	1 (3.6%) [0.2%]	
DoR, weeks PR [Patient 01-002]	45.6	
BORR N (%)		
▪ PD	15 (50%)	
▪ SD	10 (33.3%)	
▪ PR	3 (10%)	
DCR-18W, N (%) [95% lower and upper CL]	5 (17.9%) [6.1% - 36.9%]	
Median PFS, weeks [95% CI]	6.2 [5.7-12.7]	
Median OS, weeks [95% CI]	41.1 [28.4-80.4]	

* 2 patients were non evaluable for ORR-18W : one patient had withdrawn his consent and one patient discontinued before Week 18 both study treatments due to lipase increase not allowing study treatments continuation per protocol.

SAFETY ENDPOINTS

All patients experienced at least one AE. According to the investigators, 22 patients (73.3%) had at least one event related to atezolizumab, and 19 patients (63.3%) had at least one event related to bevacizumab. Grade ≥ 2 AE related to study drugs are presented in the Figure below.

Tumor hemorrhage, Stomatitis, Pruritus, Proteinuria, Osteonecrosis, Lymphocyte count decreased, Lipase increase, Laryngeal fistula, Hypothyroidism, Hyponatremia, Hypertension, Hep. B reactivation, Gen. Health status deterioration, Fatigue, Face oedema, Epistaxis, Dysgeusia, Dehydration, Diarrhea, Colitis, ASAT Increased, Amylase increased

Related to Atezolizumab
Related to Bevacizumab

Number of Grade ≥ 2 related AE

Among the 10 patients (33.3%) with at least one SAE, 7 patients had at least one SAE related to the study drugs according to the Sponsor (Grade 4 general health deterioration, Grade 4 hyponatremia with a Grade 3 tumor haemorrhage, Grade 3 colitis and a fatal case of tumor haemorrhage with pharyngeal fistula, one case of sudden death, a Grade 3 pneumonia, a Grade 3 sepsis).

The fatal tumor haemorrhage was a toxic death reported in a 65-year male with pharyngeal fistula related to study treatment. The sudden death was related to cardiovascular origin, favorized by smoking history and cervical irradiation. It was possibly related to study drugs for the Sponsor and reported as a SUSAR.

CONCLUSION

- Based on the first stage of this study, the efficacy of atezolizumab + bevacizumab is limited in HPV negative RM-HNSCC and does not warrant further investigation. Median OS was similar to OS reported for other immunotherapies after failure of platinum-based treatment.
- HPV positive cohort (N=3) was closed for enrolment in March 2022 due to very low accrual.
- Translational research on pre and on-treatment tumor biopsies, blood samples and stool samples is ongoing.