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GEMSTONE-301: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Sugemalimab in Patients With Unresectable Stage III Non-Small Cell Lung Cancer Without Progression After Concurrent or Sequential Chemoradiotherapy

Yi-Long Wu[1], Qing Zhou[1], Ming Chen[2], Ou Jiang[3], Desheng Hu[4], Qin Lin[5], Gang Wu[6], Jiuwei Cui[7], Jianhua Chang[8], Yufeng Cheng[9], Cheng Huang[10], Anwen Liu[11], Na Cui[12], Jingru Wang[12], Qiang Wang[12], Mengmeng Qin[12], Ran Zhang[12], Jason Yang[12]

[1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, and Guangdong Academy of Medical Sciences, Guangzhou, China; [2]Zhejiang Cancer Hospital, Hangzhou, China; [3]The Second People's Hospital of Neijiang, Neijiang, China; [4]Hubei Cancer Hospital, Wuhan, China; [5]The First Affiliated Hospital of Xiamen University, Xiamen, China; [6]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [7]The First Hospital of Jilin University, Changchun, China; [8]Fudan University Shanghai Cancer Center, Shanghai, China; [9]Qilu Hospital of Shandong University, Jinan, China; [10]Fujian Medical University - Fujian Provincial Cancer Hospital, Fuzhou, China; [11]The Second Affiliated Hospital of Nanchang University, Nanchang, China; [12]CStone Pharmaceuticals (Su Zhou), Shanghai, China

DECLARATION OF INTERESTS

Y.-L.W. reports advisory services for AstraZeneca, Boehringer Ingelheim, Novartis, Takeda; personal fees from AstraZeneca, Beigene, Boehringer Ingelheim, BMS, Eli Lilly, MSD, Pfizer, Roche, Sanofi; grants from AstraZeneca, Boehringer Ingelheim, BMS, Hengrui, and Roche, outside the submitted work.

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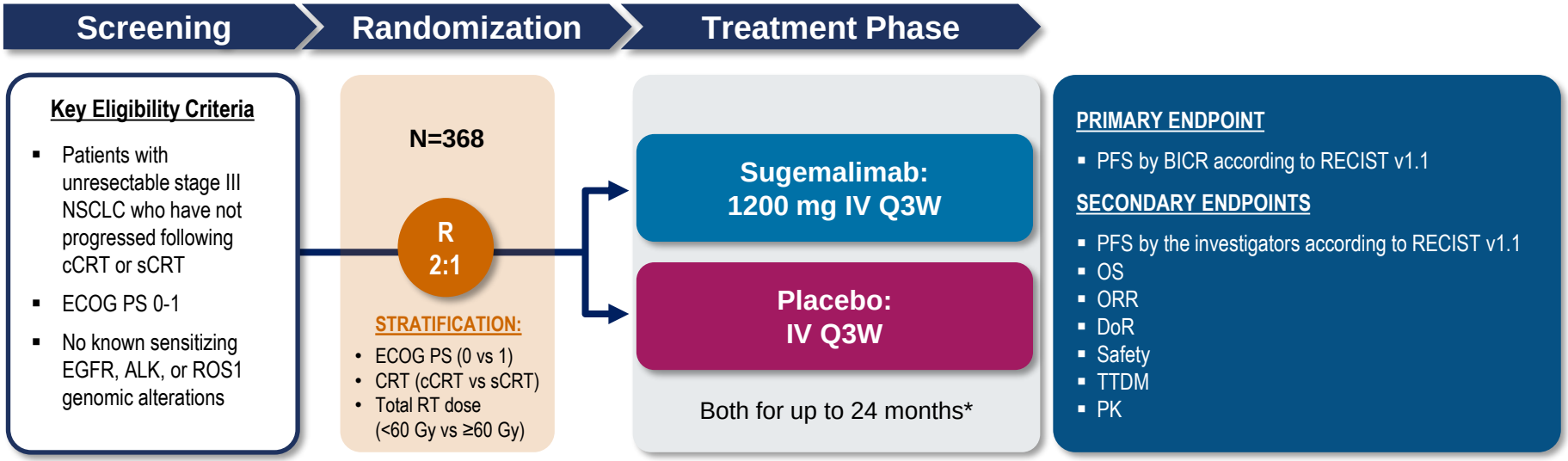
All other authors declare no competing interests.

Introduction

- Patients with stage III NSCLC represent a heterogeneous population. For those with unresectable disease, concurrent chemoradiotherapy (cCRT) followed by an immune checkpoint inhibitor is the standard of care[1,2]
- However, cCRT is associated with significant toxicity and treatment-related mortality[3,4]
  - Patient comorbidities and lack of access to cCRT in certain areas often limit its use in the real-world setting
  - Observational data indicate a 30-55% utilization rate for cCRT globally[5-8]
- Sequential CRT (sCRT) is a widely used alternative in a large subset of patients who cannot tolerate or access cCRT; thus, there remains a high unmet need to improve outcomes for patients without disease progression following sCRT
- Sugemalimab is a full-length, fully human immunoglobulin G4 (s228p) monoclonal antibody that targets PD-L1
  - Sugemalimab plus chemotherapy demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared with chemotherapy in patients with metastatic NSCLC (GEMSTONE-302 study)
- GEMSTONE-301 (NCT03728556) is a randomized, phase 3 trial comparing sugemalimab with placebo as a consolidation treatment in patients with unresectable stage III NSCLC without progression after cCRT or sCRT
  - This is the first phase 3 trial evaluating an anti–PD-1/PD-L1 agent in both populations in this setting

1. Melosky B, et al. *Lung Cancer* 2019;134:259–67. **2.** Antonia SJ, et al. *N Engl J Med* 2017;377:1919–29. **3.** Aupérin A, et al. *J Clin Oncol* 2010;28:2181–90. **4.** Palma DA, et al. *Int J Radiat Oncol Biol Phys* 2013;85:444–50. **5.** Jazieh AR, et al. *J Thorac Oncol* 2021 May 26 [Online ahead of print]. **6.** Conibear J. *Br J Cancer* 2020;123(suppl 1):10–17. **7.** Zhang T, et al. *J Thorac Dis* 2020;12:4347–56. **8.** Vyfhuis MA, et al. *Clin Lung Cancer* 2019;20:248–57.

GEMSTONE-301 Study Design



Statistical Considerations

- PFS is tested first at a two-sided alpha of 0.05; if PFS is significant, then OS would be tested at a two-sided alpha of 0.05
- Interim and final PFS analysis were planned when approximately 194 and 262 PFS events occurred, respectively. O'Brien-Fleming method was used to control the type I error
- Interim and final OS analysis were planned when approximately 175 and 260 OS events occurred, respectively.

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*First dose administered within 1–42 days after cCRT or sCRT (including at least 2 cycles of platinum-based chemotherapy) was completed.
BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous administration; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RT, radiotherapy; sCRT, sequential chemoradiotherapy; TTDM, time to death/distant metastasis

GEMSTONE-301 VS PACIFIC

	GEMSTONE-301	PACIFIC[1]
Patient area	China	Non-China
Prior CRT	cCRT or sCRT	cCRT only
Treatment period	24 months*	12 months
EGFR/ALK/ROS1	Exclude EGFR/ALK/ROS1+	Not exclude EGFR/ALK/ROS1+
Disease Stage	IIIA: 29%	IIIA: 53%
Histology	SCC:69%	SCC:46%

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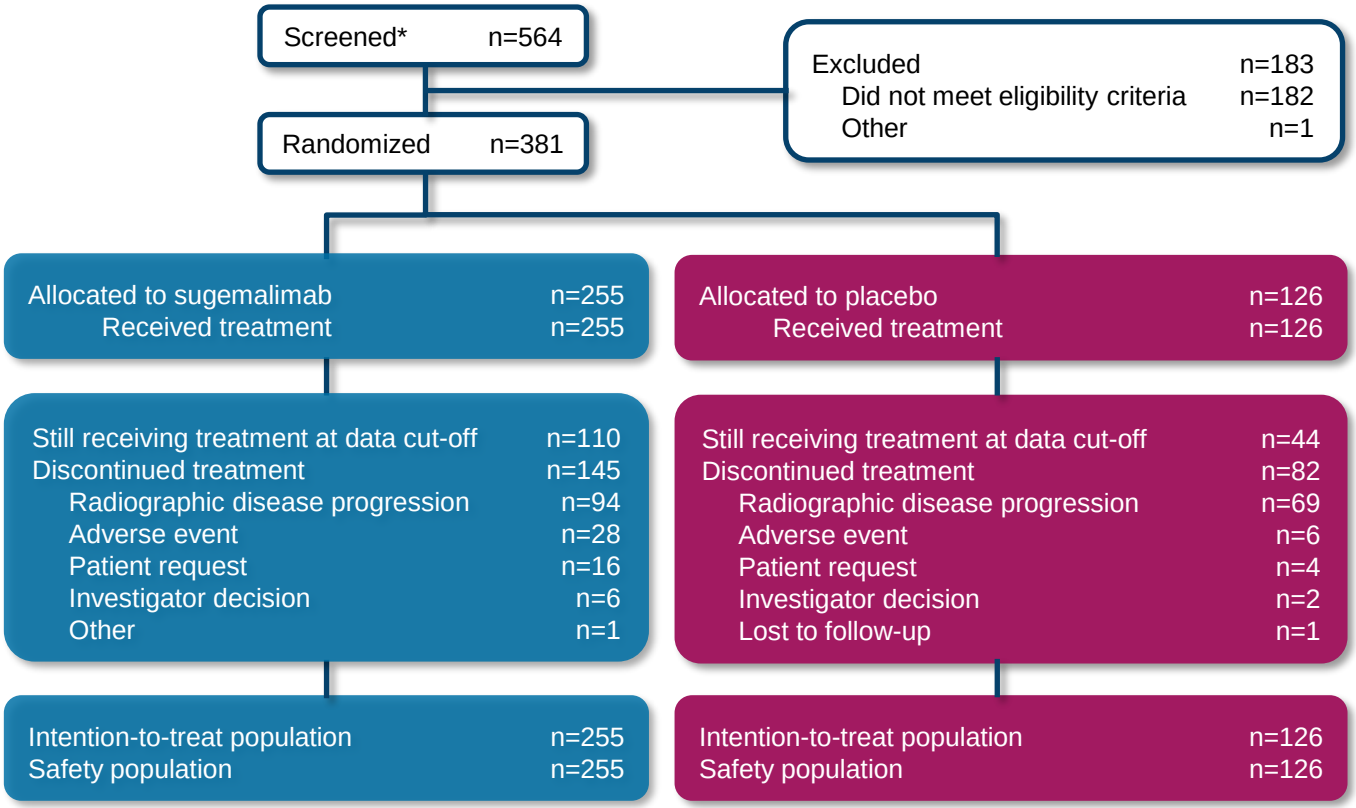
*if subject can benefit from sugemalimab, treatment period can extend
SCC, Squamous cell carcinoma
[1]Antonia SJ, et al. N Engl J Med 2017;377:1919–29

Patient Disposition



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*Between October 2018 and December 2020, 564 patients were screened at 50 sites in China.

Data cutoff date: March 8, 2021

Baseline Characteristics

	Sugemalimab (N=255)	Placebo (N=126)
Sex		
Male	93%	91%
Female	7%	9%
Age, years – median (range)	61 (46–78)	60 (42–73)
Age ≥65 years	29%	25%
Smoking history		
Never	16%	13%
Former or current	84%	87%
ECOG performance status		
0	31%	30%
1	69%	70%
Radiotherapy dose		
<60 Gy	17%	16%
≥60 Gy	83%	84%

	Sugemalimab (N=255)	Placebo (N=126)
Pathologic type*		
Squamous cell carcinoma	69%	68%
Nonsquamous cell carcinoma	30%	32%
CRT type		
Sequential	34%	33%
Concurrent	66%	67%
Disease stage#		
IIIA	29%	25%
IIIB	57%	52%
IIIC	13%	22%
Best response to CRT		
Complete response	2%	2%
Partial response	67%	61%
Stable disease	31%	37%

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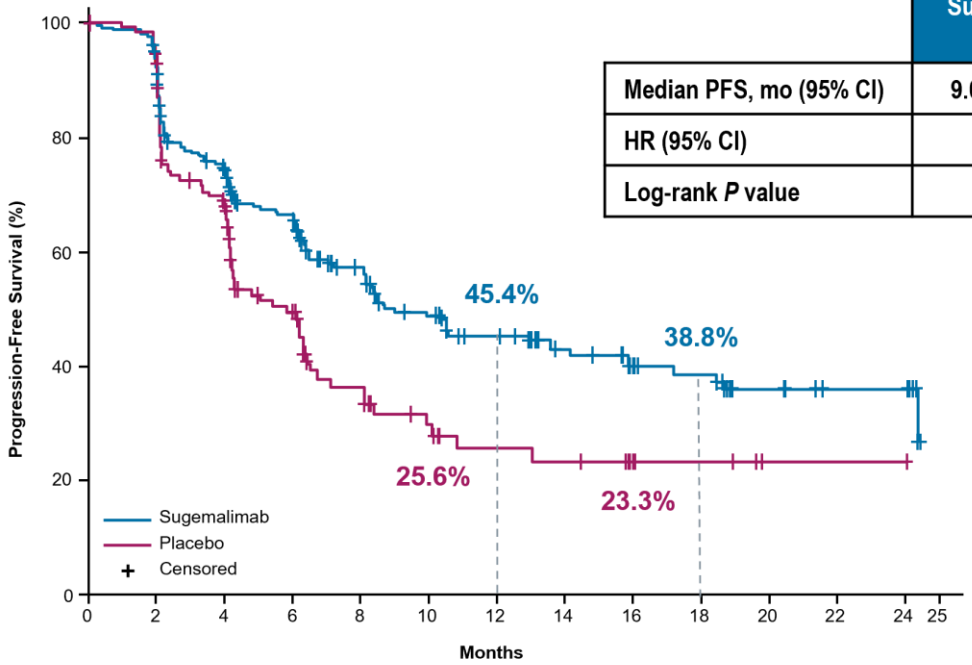
*Two patients in the sugemalimab group had NSCLC not otherwise specified and NSCLC poorly differentiated carcinoma.
#Staged according to the International Association for the Study of Lung Cancer [IASLC] classification, version 8.

Data cutoff date: March 8, 2021

PFS by BICR

	Sugemalimab (N=255)	Placebo (N=126)
Median PFS, mo (95% CI)	9.0 (8.1–14.1)	5.8 (4.2–6.6)
HR (95% CI)	0.64 (0.48–0.85)	
Log-rank *P* value	0.0026	



Patients at Risk

Sugemalimab	255	225	162	130	96	76	63	48	35	30	20	11	11	0
Placebo	126	115	77	46	25	16	11	10	6	4	1	1	1	0

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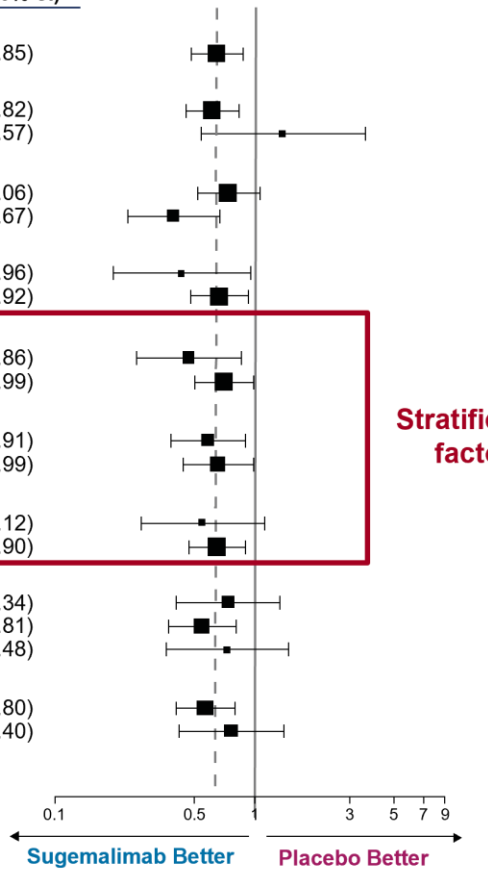
Interim PFS analysis (reviewed by iDMC) with median follow-up of 14 months; observed 197 PFS events with two-sided alpha of 0.0195

Data cutoff date: March 8, 2021

Subgroup Analyses of PFS

	Sugemalimab No. patients	Placebo No. patients	Hazard Ratio (95% CI)*
All patients	255	126	**0.64** (0.48–0.85)
Sex			
Male	236	115	**0.61** (0.45–0.82)
Female	19	11	**1.40** (0.55–3.57)
Age			
<65 years	182	94	**0.75** (0.52–1.06)
≥65 years	73	32	**0.40** (0.23–0.67)
Smoking history			
Never	42	16	**0.44** (0.20–0.96)
Former or current	213	110	**0.67** (0.49–0.92)
ECOG PS			
0	78	38	**0.47** (0.26–0.86)
1	177	88	**0.71** (0.51–0.99)
CRT type			
Sequential	86	41	**0.59** (0.39–0.91)
Concurrent	169	85	**0.66** (0.44–0.99)
Radiotherapy dose			
<60 Gy	43	20	**0.55** (0.27–1.12)
≥60 Gy	212	106	**0.66** (0.48–0.90)
Cancer stage# before CRT			
Stage IIIA	74	32	**0.74** (0.41–1.34)
Stage IIIB	146	65	**0.55** (0.37–0.81)
Stage IIIC	33	28	**0.73** (0.36–1.48)
Pathologic type			
Squamous cell carcinoma	177	86	**0.57** (0.41–0.80)
Nonsquamous cell carcinoma	76	40	**0.77** (0.42–1.40)



Stratification factors

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*Stratified for all patients, unstratified for the subgroups.
#Staged according to the IASLC classification, version 8.

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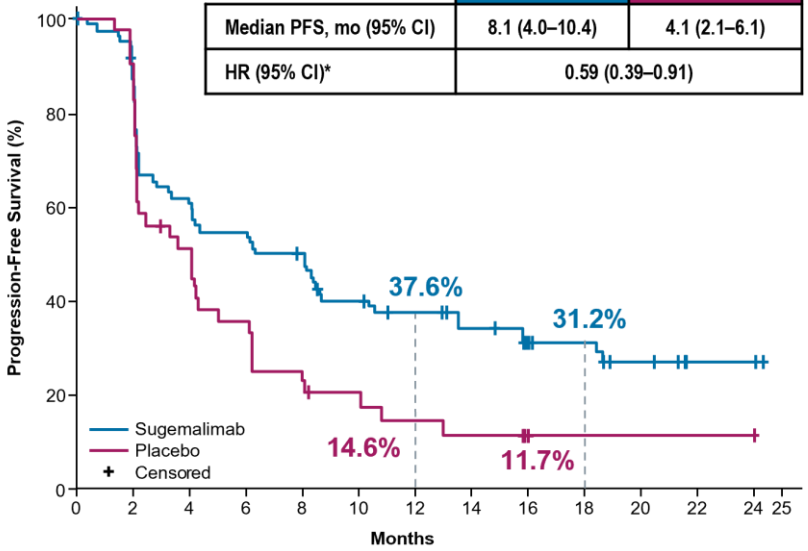
PFS by CRT Type

Sequential CRT

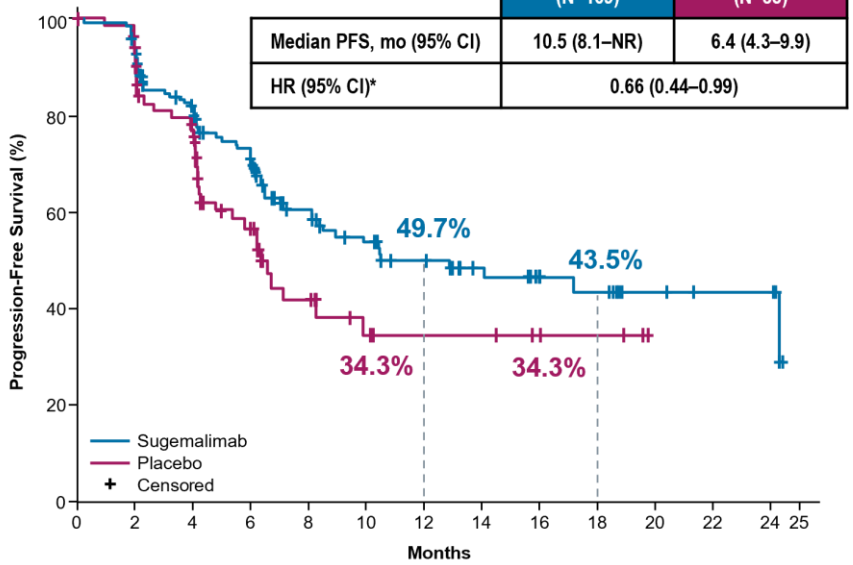
	Sugemalimab (N=86)	Placebo (N=41)
Median PFS, mo (95% CI)	8.1 (4.0–10.4)	4.1 (2.1–6.1)
HR (95% CI)*	0.59 (0.39–0.91)	



Patients at Risk														
Sugemalimab	86	73	51	46	41	32	28	22	17	15	11	6	6	0
Placebo	41	37	20	14	10	7	5	4	2	1	1	1	1	0

Concurrent CRT

	Sugemalimab (N=169)	Placebo (N=85)
Median PFS, mo (95% CI)	10.5 (8.1–NR)	6.4 (4.3–9.9)
HR (95% CI)*	0.66 (0.44–0.99)	



Patients at Risk														
Sugemalimab	169	152	111	84	55	44	35	26	18	15	9	5	5	0
Placebo	85	78	57	32	15	9	6	6	4	3	0	0	0	0

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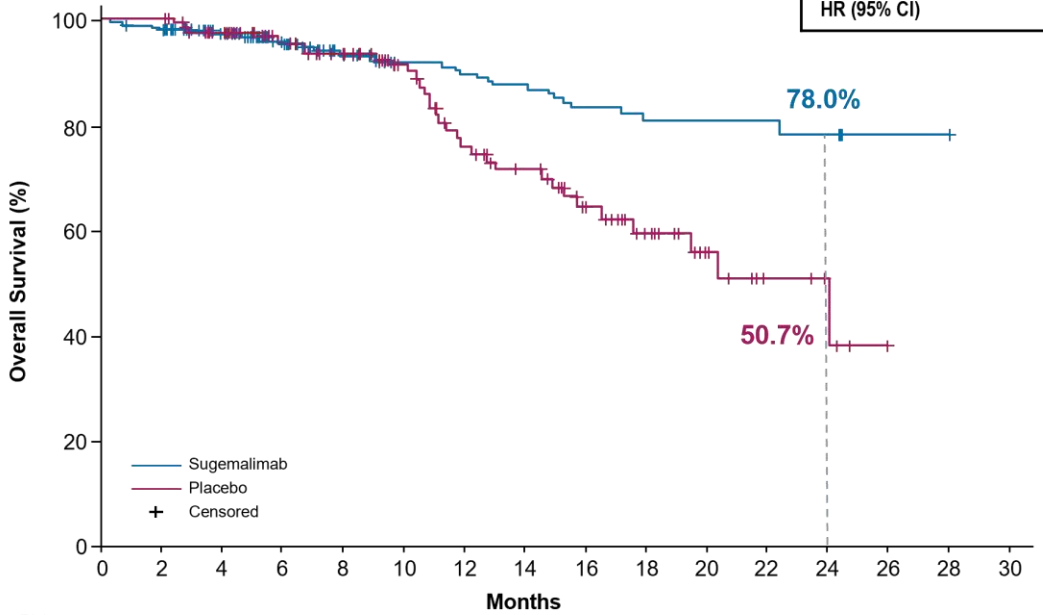
*Unstratified HR.

Data cutoff date: March 8, 2021

Preliminary Analysis of OS*

	Sugemalimab (N=255)	Placebo (N=126)
No. events (%)	32 (12.5)	32 (25.4)
Median OS, mo (95% CI)	NR	24.1 (16.5–NR)
HR (95% CI)	0.44 (0.27–0.73)	

NR, not reached.



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*OS data were immature at the data cutoff date.

Data cutoff date: March 8, 2021

Treatment Emergent Adverse Events

	Sugemalimab (N=255)	Placebo (N=126)
Treatment Emergent Adverse Events (TEAE)	246 (96.5%)	116 (92.1%)
Grade 3-5 TEAE	62 (24.3%)	30 (23.8%)
Treatment-related TEAE (TRAE)	193 (75.7%)	73 (57.9%)
Grade 3-5 TRAE	26 (10.2%)	7 (5.6%)
Immune-related adverse events (irAE)	109 (42.7%)	17 (13.5%)
Grade 3-5 irAE	12 (4.7%)	1 (0.8%)
Infusion-related reaction	1 (0.4%)	2 (1.6%)
TEAE leading to drug permanently discontinued	29 (11.4%)	6 (4.8%)
TEAE leading to treatment cycle delay	82 (32.2%)	31 (24.6%)
TEAE leading to death	10 (3.9%)	3 (2.4%)

TEAE, treatment-emergent adverse event.
*Adverse events of special interest were sponsor-assessed immune-related adverse events, which were defined based on a list of preferred categories of terms specified by the sponsor.

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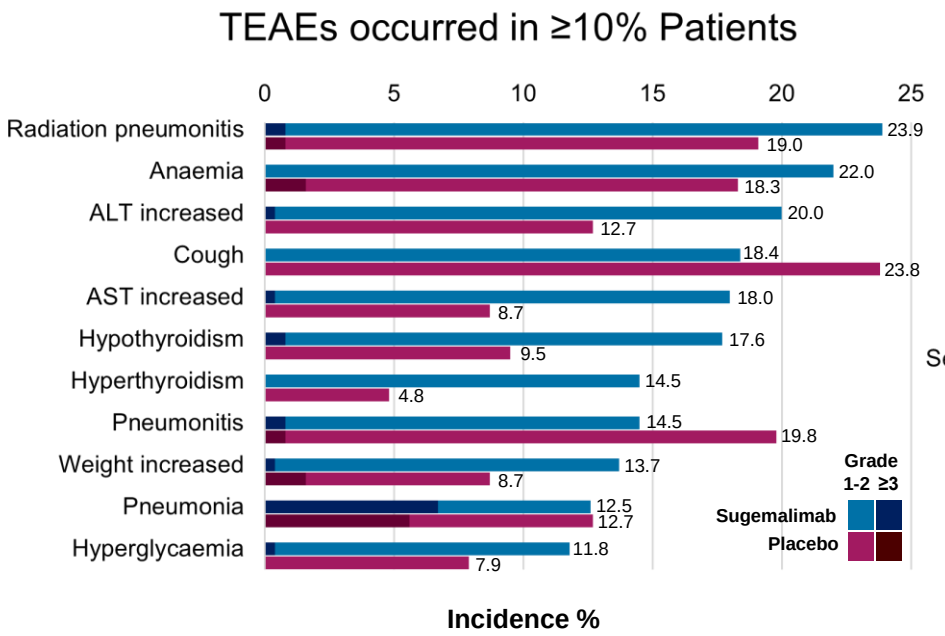
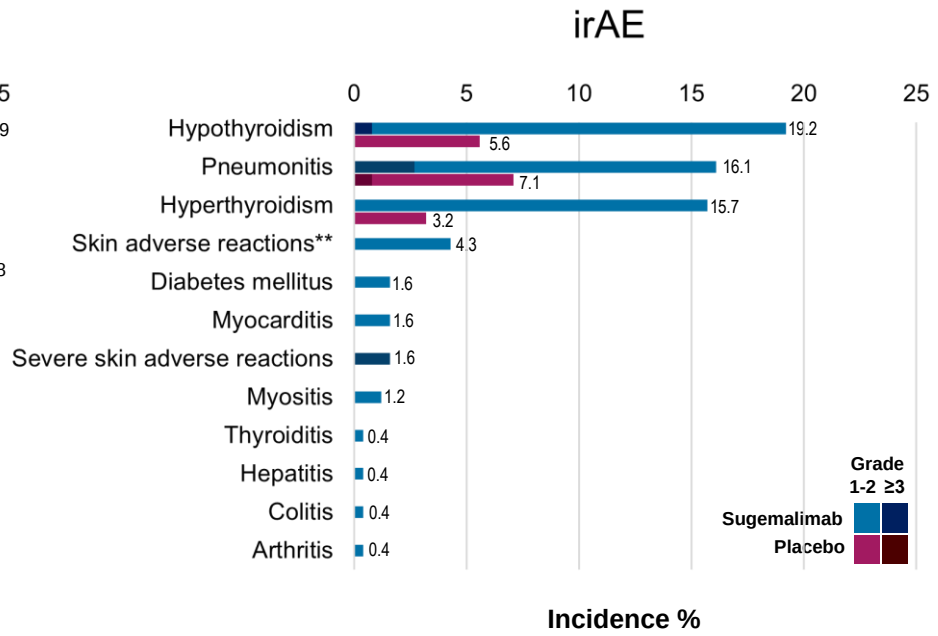
TEAEs and irAEs





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ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; TEAE, treatment-emergent adverse event.
*Adverse events of special interest were sponsor-assessed immune-related adverse events, which were defined based on a list of preferred categories of terms specified by the sponsor. **Excluding severe events.

Data cutoff date: March 8, 2021

Summary/Conclusions

- At this pre-planned interim analysis, a statistically significant and clinically meaningful improvement in PFS was observed with sugemalimab vs. placebo among patients with unresectable stage III NSCLC who had not progressed following cCRT or sCRT
  - BICR assessed mPFS: 9.0 vs 5.8 months, stratified HR= 0.64
  - sCRT subgroup mPFS: 8.1 vs 4.1 months, unstratified HR=0.59
  - cCRT subgroup mPFS: 10.5 vs 6.4 months, unstratified HR=0.66

- OS data were immature, but an encouraging trend for a survival benefit with sugemalimab vs. placebo was observed. Follow-up of the patients is ongoing
  - mOS: NR vs 24.1 months, stratified HR=0.44

- Sugemalimab had a well-tolerated safety profile and no new safety signals were observed, consistent with the safety profile previously reported for sugemalimab monotherapy in NSCLC

- The results of the GEMSTONE-301 study suggest that sugemalimab is an effective consolidation therapy for patients with unresectable stage III NSCLC who have not progressed following cCRT or sCRT

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GEMSTONE-301 Study Investigators

Yi-Long Wu
Qing Zhou
Ming Chen
Ou Jiang
Yi Pan
Desheng Hu
Qin Lin
Gang Wu
Jiuwei Cui
Jianhua Chang
Yufeng Cheng
Cheng Huang
Anwen Liu
Nong Yang
Youling Gong
Chuan Zhu
Zhiyong Ma
Jian Fang
Gongyan Chen
Jun Zhao
Anhui Shi
Yingcheng Lin
Guanghui Li
Yunpeng Liu
Dong Wang
Rong Wu
Xinhua Xu
Jianhua Shi
Zhihua Liu
Xingya Li
Conghua Xie
Ying Cheng
Kejing Ying
Jifeng Feng
Kaihua Lu
Bing Xia
Hongqing Zhuang
Yong Song
Nan Bi
Qi Li
Zhijie Pan
Baolin Qu
Wenxue Zhang
Xiaolong Cao
Zhendong Chen
Junfang Tang
Yueyin Pan
Guoping Sun
Xiaoyan Lin
Lin Li
Shundong Cang
Hong Shen
Jun Liang