IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Updates in Management of Unresectable Locally Advanced NSCLC

Ana I. Velazquez, MD MSc
University of California, San Francisco
USA

DISCLOSURES

Company	Relationship(s)
Astra Zeneca	Consultant
Corbus Pharmaceuticals	Stock

Locally Advanced NSCLC

- 20% of NSCLC at diagnosis
- Heterogeneous group
- Treatment consists of multimodality therapy and is influenced by potential of surgical resection

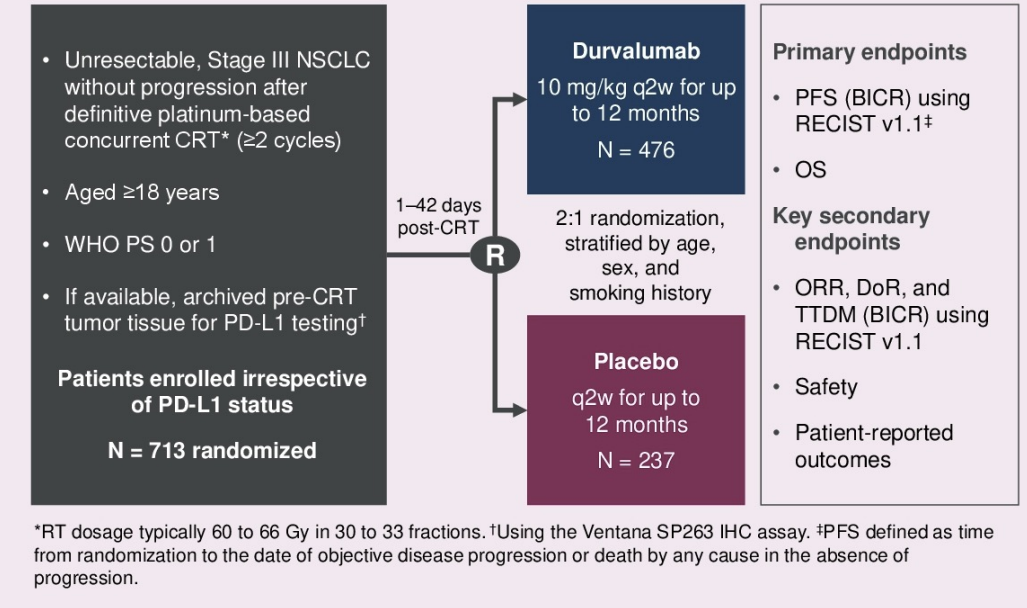
8th Edition AJCC/UICC Stage

T/M	Subgroup	N0	N1	N2	N3
T1	T1a T1b T1c	IA1 IA2 IA3	IIB IIB IIB	IIIA IIIA IIIA	IIIB IIIB IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a M1b	IVA IVA	IVA IVA	IVA IVA	IVA IVA
	M1c	IVB	IVB	IVB	IVB

Goldstraw. J Thorac Oncol. 2016;11:39.

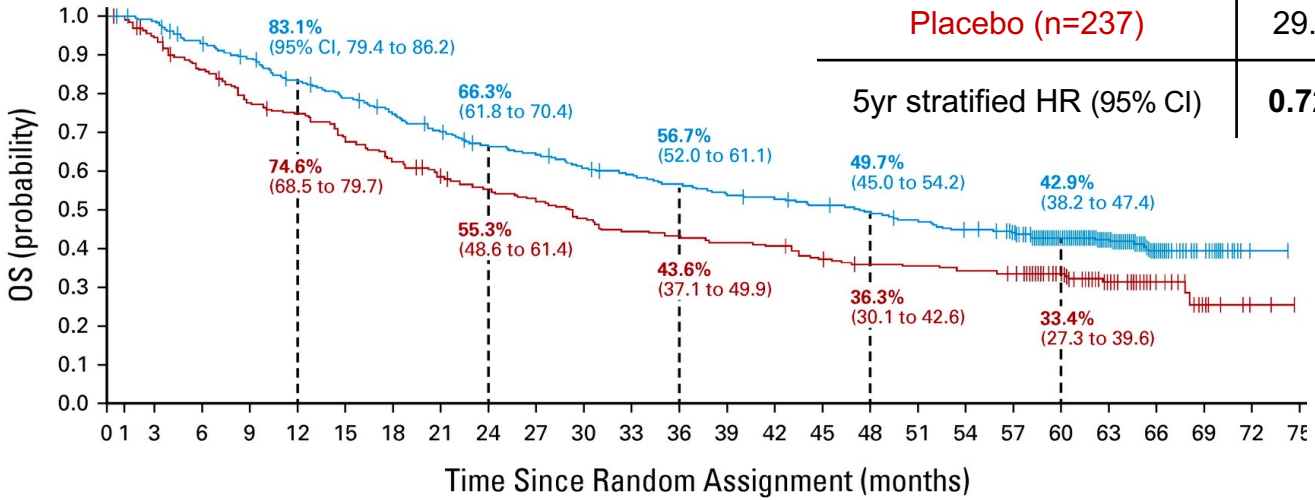
Current Standard of Care: PACIFIC

- In February 2018, FDA approved durvalumab for treatment of unresectable stage III NSCLC without disease progression following concurrent CRT.



PACIFIC: 5-year outcomes

	Median OS, mo (95% CI)	Median PFS, mo (95% CI)
Durvalumab (n=476)	**47.5** (38.1 – 52.9)	**16.9** (13.0-23.9)
Placebo (n=237)	29.1 (22.1– 35.1)	5.6 (4.8-7.7)
5yr stratified HR (95% CI)	**0.72 (0.59 – 0.89)**	**0.55 (0.45-0.68)**



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

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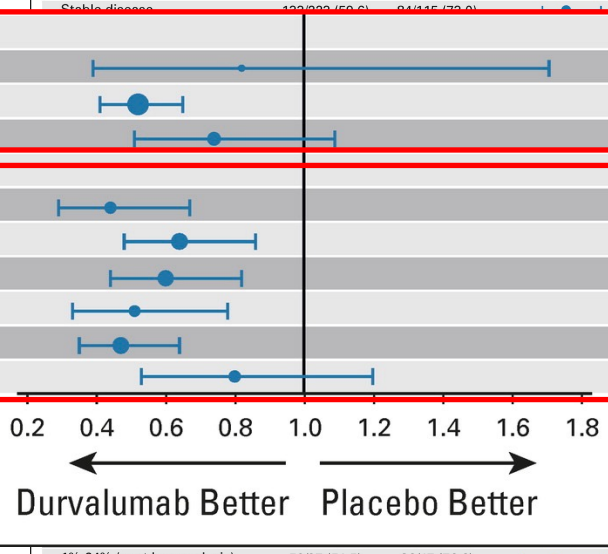
PACIFIC: 5-year outcomes

Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	268/476 (56.3)	175/237 (73.8)	0.58 (0.48 to 0.70)
Sex			
Male	192/334 (57.5)	122/166 (73.5)	0.61 (0.48 to 0.76)
Female	76/142 (53.5)	53/71 (74.6)	0.52 (0.36 to 0.74)
Age at random assignment			
< 65 years	140/261 (53.6)	100/130 (76.9)	0.46 (0.36 to 0.60)
≥ 65 years	128/215 (59.5)	75/107 (70.1)	0.76 (0.57 to 1.01)
Smoking status			
Smoker	246/433 (56.8)	158/216 (73.1)	0.61 (0.50 to 0.75)
Nonsmoker	22/43 (51.2)	17/21 (81.0)	0.33 (0.17 to 0.63)
NSCLC disease stage			
IIIA	132/252 (52.4)	95/125 (76.0)	0.53 (0.40 to 0.69)
IIIB	130/212 (61.3)	77/107 (72.0)	0.64 (0.48 to 0.85)
Tumor histologic type			
Squamous	138/224 (61.6)	74/102 (72.5)	0.71 (0.54 to 0.94)
All other	130/252 (51.6)	101/135 (74.8)	0.48 (0.37 to 0.63)
Best response to prior treatment			
Complete response	5/9 (55.6)	4/7 (57.1)	Not calculated[a]
Partial response	126/237 (53.2)	85/112 (75.9)	0.56 (0.43 to 0.74)
Stable disease	133/233 (57.1)	84/115 (73.0)	0.57 (0.44 to 0.76)
EGFR or ALK aberration status			
Positive[d]	21/29 (72.4)	11/14 (78.6)	0.82 (0.39 to 1.71)
Negative	169/317 (53.3)	124/165 (75.2)	0.52 (0.41 to 0.65)
Unknown	78/130 (60.0)	40/58 (69.0)	0.74 (0.51 to 1.09)
PD-L1 expression level			
≥ 25%	61/115 (53.0)	33/44 (75.0)	0.44 (0.29 to 0.67)
< 25%	105/187 (56.1)	77/105 (73.3)	0.64 (0.48 to 0.86)
Unknown	102/174 (58.6)	65/88 (73.9)	0.60 (0.44 to 0.82)
1%-24% (post hoc analysis)	50/97 (51.5)	36/47 (76.6)	0.51 (0.33 to 0.78)
≥ 1% (post hoc analysis)	111/212 (52.4)	69/91 (75.8)	0.47 (0.35 to 0.64)
< 1% (post hoc analysis)	55/90 (61.1)	41/58 (70.7)	0.80 (0.53 to 1.20)



1%-24% (post hoc analysis) 50/97 (51.5) 36/47 (76.6) 0.51 (0.33 to 0.78)
≥ 1% (post hoc analysis) 111/212 (52.4) 69/91 (75.8) 0.47 (0.35 to 0.64)
< 1% (post hoc analysis) 55/90 (61.1) 41/58 (70.7) 0.80 (0.53 to 1.20)
0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8
Durvalumab Better Placebo Better

Spigel DR, et al. JCO. 40, no. 12 : 1301-1311.

Unresectable Stage III NSCLC

- Concurrent CRT with platinum doublet chemotherapy followed by durvalumab for 1 year.

Unanswered questions:

- How can we improve outcomes? Novel combinations? Concurrent IO + CRT? Dual CPI?
- How does molecular testing affect management?
- How does PD-L1 impact our management?
  - In the US, durvalumab is approved irrespective of PD-L1 expression
  - In the EU, durvalumab is only approved in PD-L1+ population

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Sugemalimab vs placebo after concurrent or sequential chemoradiotherapy in patients with unresectable stage III NSCLC (GEMSTONE-301): final progression-free survival analysis of a phase 3 study

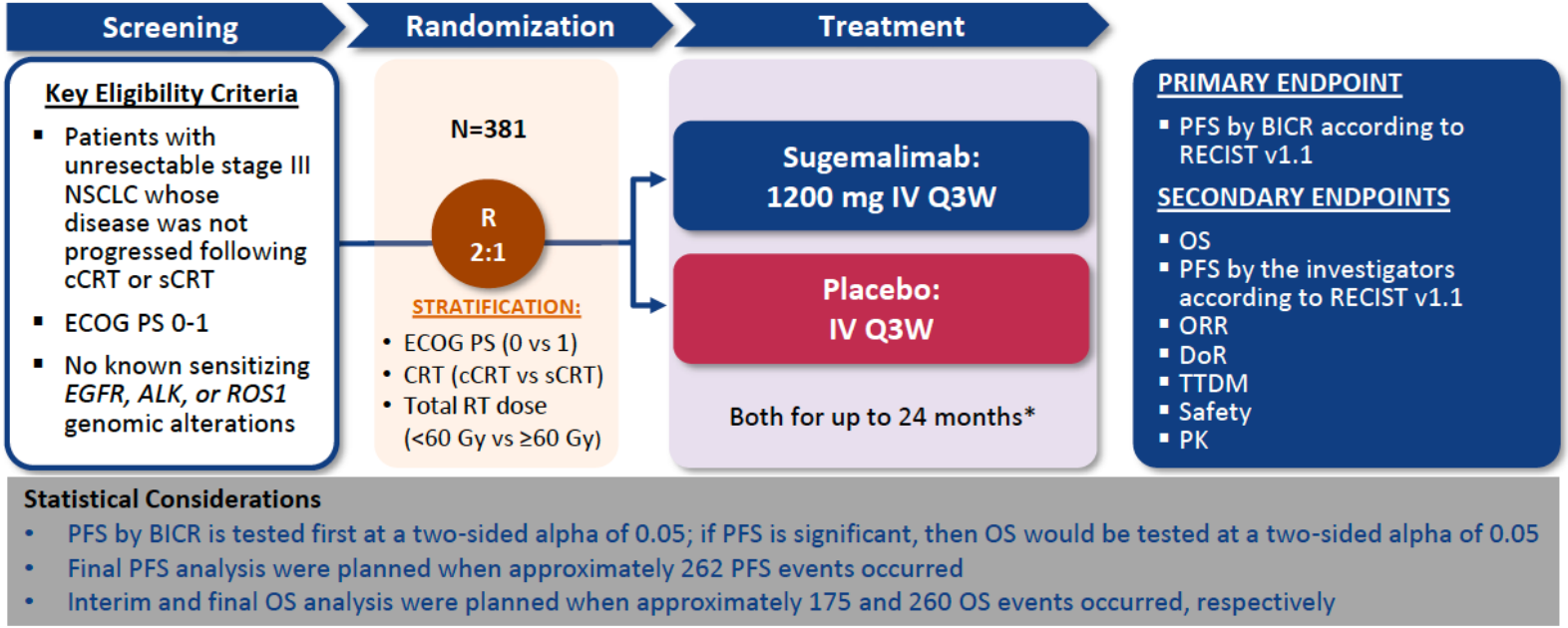
Presenter: Yi-Long Wu

Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, China

Yi-Long Wu[1], Qing Zhou[1], Ming Chen[2,3], Ou Jiang[4], Yi Pan[1], Desheng Hu[5], Qin Lin[6], Gang Wu[7], Jiuwei Cui[8], Jianhua Chang[9,10], Yufeng Cheng[11], Cheng Huang[12], Anwen Liu[13], Nong Yang[14], Youling Gong[15], Chuan Zhu[16], Zhiyong Ma[17], Jian Fang[18], Gongyan Chen[19], Jun Zhao[18], Anhui Shi[18], Yingcheng Lin[20], Guanghui Li[21], Yunpeng Liu[22], Dong Wang[23], Rong Wu[24], Xinhua Xu[25], Jianhua Shi[26], Zhihua Liu[27], Rumei Chen[28], Qiang Wang[28], Mengmeng Qin[28], Yiding Ma[28], Jingru Wang[28], Jason Yang[28]

[1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; [2]The Cancer Hospital of the University of Chinese Academy of Sciences, Hangzhou, China; [3]Sun Yat-sen University Cancer Centre, Guangzhou, China; [4]The Second People's Hospital of Neijiang, Neijiang, China; [5]Hubei Cancer Hospital, Wuhan, China; [6]The First Affiliated Hospital of Xiamen University, Xiamen, China; [7] Cancer Centre, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [8]The First Hospital of Jilin University, Changchun, China; [9]Fudan University Cancer Centre, Shanghai, China; [10]Cancer Hospital, Chinese Academy of Medical Sciences, Shenzhen Centre, Shenzhen, China; [11]Qilu Hospital of Shandong University, Jinan, China ; [12]Fujian Medical University, Fujian Provincial Cancer Hospital, Fuzhou, China; [13]The Second Affiliated Hospital of Nanchang University, Nanchang, China ; [14]Hunan Cancer Hospital, Changsha, China; [15]West China Hospital of Sichuan University, Chengdu, China; [16]Chongqing University Three Gorges Hospital, Chongqing, China; [17]The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [18]Beijing Cancer Hospital, Beijing, China; [19]Harbin Medical University Cancer Hospital, Harbin, China; [20]Cancer Hospital of Shantou University Medical College, Shantou, China; [21]Xinqiao Hospital of Army Medical University, Chongqing, China; [22]The First Hospital of China Medical University, Shenyang, China; [23]Army Medical Centre of PLA, Chongqing, China; [24]Shengjing Hospital of China Medical University, Shenyang, China; [25]The First College of Clinical Medical Science, China Three Gorges University, Yichang Central People's Hospital, Yichang, China; [26]Linyi Cancer Hospital, Linyi, China; [27]Jiangxi Cancer Hospital, Nanchang, China; [28]CStone Pharmaceuticals Suzhou, Shanghai, China

GEMSTONE-301: Study Design



Statistical Considerations

- PFS by BICR 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
- Final PFS analysis were planned when approximately 262 PFS events occurred
- Interim and final OS analysis were planned when approximately 175 and 260 OS events occurred, respectively

DoR: duration of response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; Q3W: once every 3 weeks; TTDM: Time to death or distant metastasis

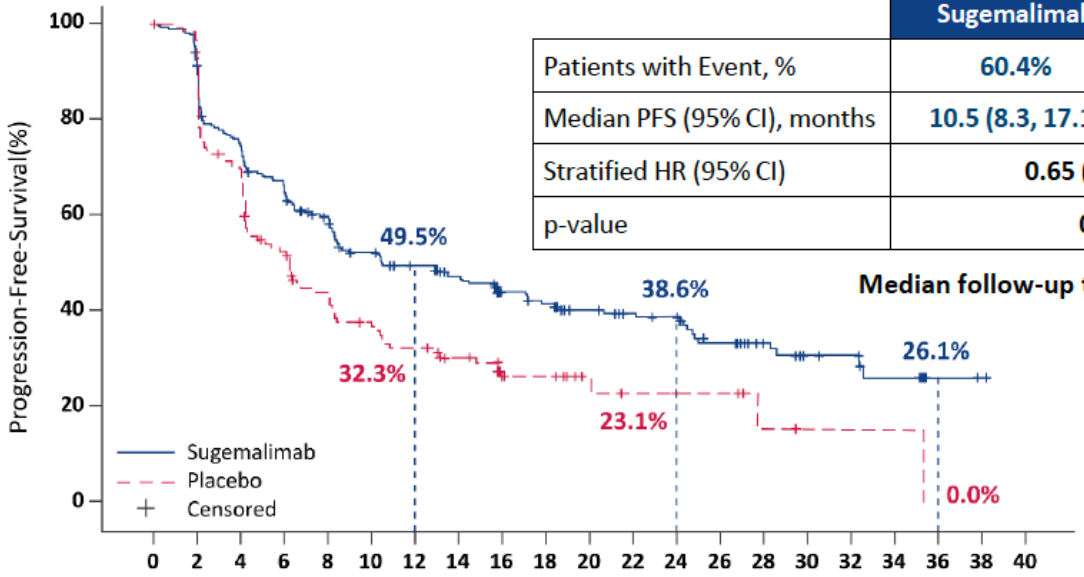
*At the discretion of the study investigator, patients without progression and with tolerance for Sugemalimab after 24 months of treatment may continue to receive the treatment.

GEMSTONE-301: Baseline Characteristics

	Sugemalimab (n=255)	Placebo (n=126)
Age, Median (range), years	61.0 (46,78)	60.0 (42,73)
Sex, Male/Female, n (%)	236 (92.5%)/19 (7.5%)	115 (91.3%)/11 (8.7%)
Baseline ECOG PS, 0/1, n (%)	78 (30.6%)/177 (69.4%)	38 (30.2%)/88 (69.8%)
Smoking Status, Never/Former or current, n (%)	42 (16.5%)/213 (83.5%)	16 (12.7%)/110 (87.3%)
Disease Stage#, IIIA/IIIB/IIIC, n (%)	74 (29.0%)/146 (57.3%)/33 (12.9%)	32 (25.4%)/65 (51.6%)/28 (22.2%)
Histology Type*, Squamous/Non-squamous, n (%)	177 (69.4%)/76 (29.8%)	89 (70.6%)/37 (29.4%)
CRT Type, sCRT/cCRT, n (%)	86 (33.7%)/169 (66.3%)	41 (32.5%)/85 (67.5%)
Radiotherapy Dose, < 60 Gy/≥ 60 Gy, n (%)	43 (16.9%)/212 (83.1%)	21 (16.7%) /105 (83.3%)
Best Response to CRT, CR/PR/SD, n (%)	4 (1.6%)/172 (67.5%)/79 (31.0%)	2 (1.6%)/77 (61.1%)/47 (37.3%)
Prior Platinum Treatment, Cisplatin/Carboplatin/Nedaplatin, n (%)	130 (51.0%)/82 (32.2%)/56 (22.0%)	61 (48.4%)/47 (37.3%)/20 (15.9%)
Time from Last Radiation to Randomization, ≤ 14 days/> 14 days, n (%)	47 (18.4%)/208 (81.6%)	24 (19.0%)/102 (81.0%)
Time from Last Radiation to Randomization, ≤ 25 days/> 25 days, n (%)	121 (47.5%)/134 (52.5%)	77 (61.1%)/49 (38.9%)

GEMSTONE-301: PFS

	Sugemalimab	Placebo
Patients with Event, %	60.4%	71.4%
Median PFS (95% CI), months	10.5 (8.3, 17.1)	6.2 (4.2, 8.1)
Stratified HR (95% CI)	0.65 (0.50, 0.84)	
p-value	0.0012	



Median follow-up time *27.1* vs *23.5* months

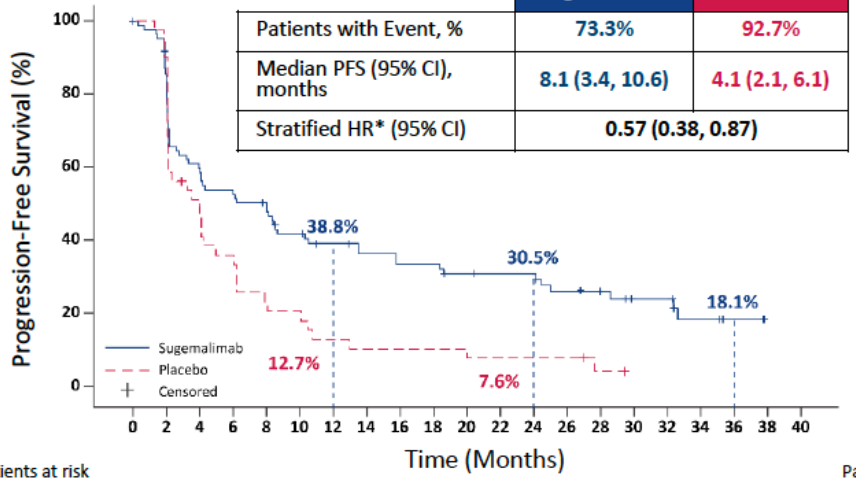
Patients at risk

Sugemalimab	255	233	188	167	142	121	111	92	71	65	56	51	49	37	26	17	16	11	3	1	0
Placebo	126	118	86	63	50	41	36	26	18	13	8	6	5	5	2	1	1	1	0	0	0

GEMSTONE-301: PFS by CRT Type

sCRT

	Sugemalimab	Placebo
Patients with Event, %	73.3%	92.7%
Median PFS (95% CI), months	8.1 (3.4, 10.6)	4.1 (2.1, 6.1)
Stratified HR* (95% CI)	0.57 (0.38, 0.87)	



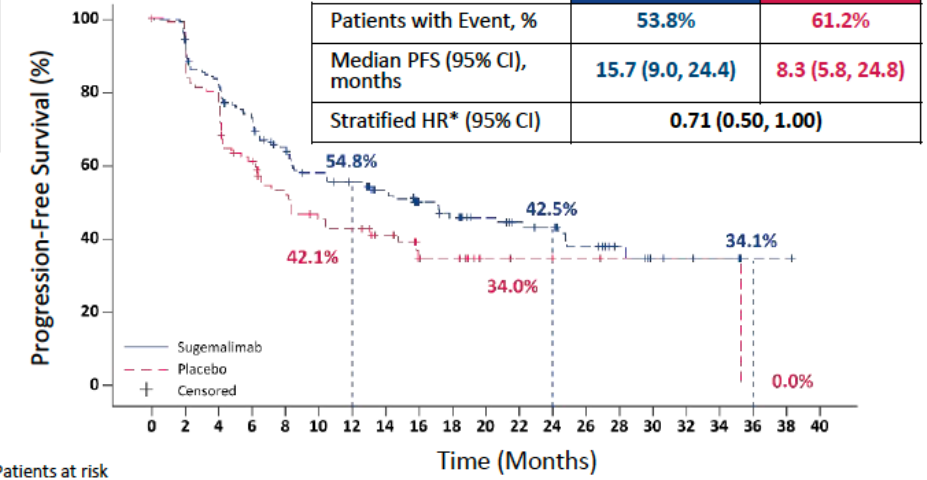
Patients at risk

Sugemalimab	86	73	50	45	41	33	29	26	24	24	21	20	20	16	14	10	10	6	2	0	0
Placebo	41	37	20	14	10	8	5	4	4	4	4	3	3	3	1	0	0	0	0	0	0

- Median follow-up: ***30.6*** vs ***27.8*** months
- Median time from start date of CRT to randomization: ***156.5*** vs ***168.0*** days

cCRT

	Sugemalimab	Placebo
Patients with Event, %	53.8%	61.2%
Median PFS (95% CI), months	15.7 (9.0, 24.4)	8.3 (5.8, 24.8)
Stratified HR* (95% CI)	0.71 (0.50, 1.00)	

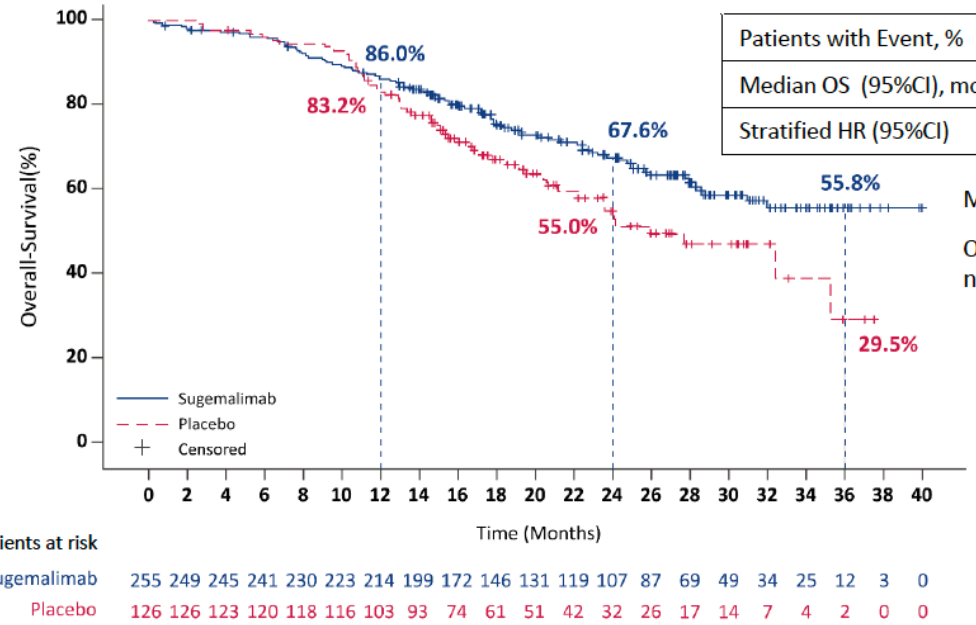


Patients at risk

Sugemalimab	169	160	138	122	101	88	82	66	47	41	35	31	29	21	12	7	6	5	1	1	0
Placebo	85	81	66	49	40	33	31	22	14	9	4	3	2	2	1	1	1	1	0	0	0

- Median follow-up: ***22.4*** vs ***20.0*** months
- Median time from start date of CRT to randomization: ***72.0*** vs ***69.0*** days

GEMSTONE-301: OS



	Sugemalimab	Placebo
Patients with Event, %	33.3%	42.9%
Median OS (95%CI), months	NR (31.0, NR)	25.9 (21.2, NR)
Stratified HR (95%CI)	0.69 (0.49, 0.97)	

Median follow-up time ***27.1*** vs ***23.5*** months

OS data were immature at the data cutoff date, no formal analysis was performed

OS by CRT type:

- **sCRT: HR 0.60 (0.34,1.05)**
- **cCRT: HR 0.75 (0.48, 1.15)**

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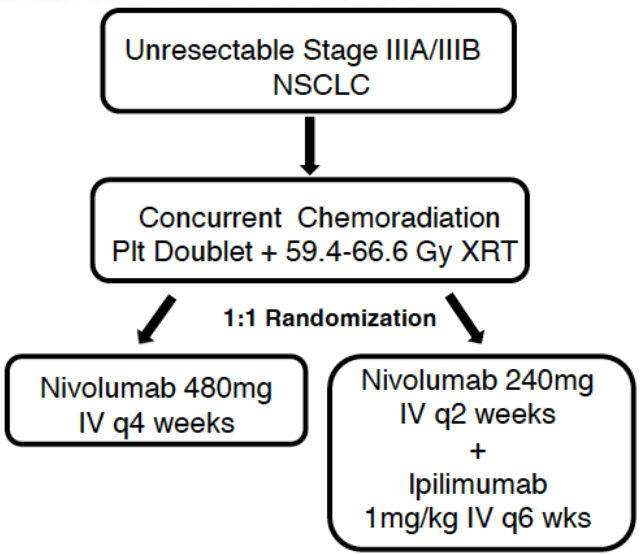
Phase II Study of Consolidation Immunotherapy with Nivolumab and Ipilimumab or Nivolumab alone following Concurrent Chemoradiation for Unresectable Stage IIIA/IIIB NSCLC

Nasser Hanna, MD
Indiana University Simon Comprehensive Cancer Center
United States

Study Design

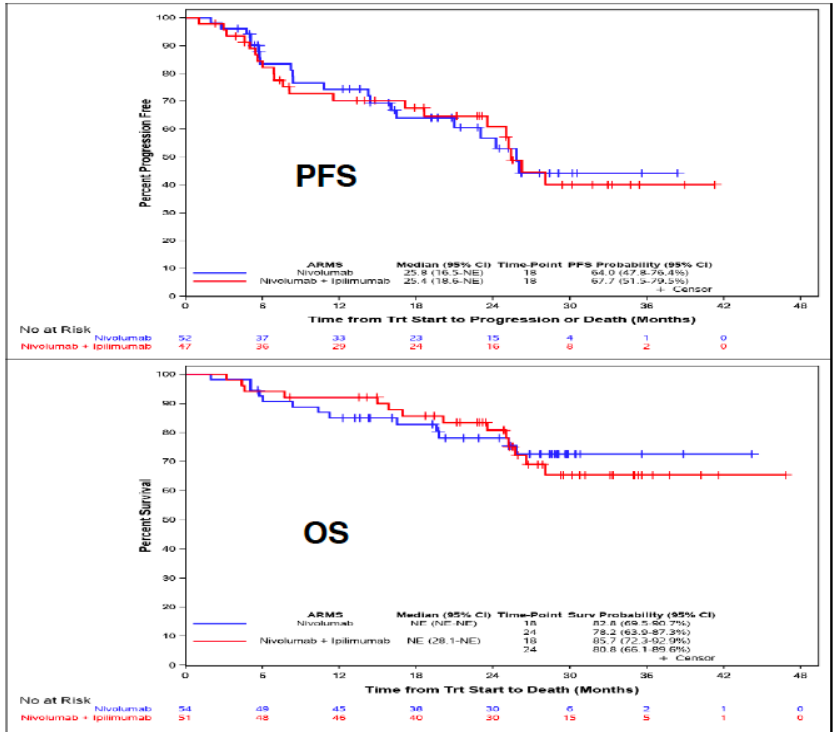


- Multi-center, open label randomized phase II trial
- **Duration of immunotherapy was 6 months in both arms**
- Nivolumab arm compared to historical control of CCRT alone
- Nivolumab/Ipilimumab arm compared to historical control of CCRT -> Durvalumab

Study Population

	Nivolumab Alone (N=54)	Nivo/Ipi (N=51)
Median Age, yrs (range)	65 (44-82)	63 (41-83)
Gender, n (%)		
Male	24 (44.4)	29 (56.9)
Race, n (%)		
White	2 (77.8)	30 (58.8)
Black/African-American	10 (18.5)	16 (31.4)
Other/Unknown	2 (3.7)	5 (9.8)
ECOG PS, n (%)		
0	18 (33.3)	27 (52.9)
Stage, n (%)		
IIIA	30 (55.6)	29 (56.9)
Histology, n (%)		
Non-Squamous	31 (57.4)	28 (54.9)
Chemotherapy Regimen, n (%)		
Carboplatin/Paclitaxel	36 (66.7)	37 (72.5)
Cisplatin/Pemetrexed	8 (14.8)	3 (5.9)
Cisplatin/Etoposide	7 (13)	7 (13.7)
Carboplatin/Pemetrexed	3 (5.6)	4 (7.8)
Completed 100% of Planned Tx	38 (70.4)	23 (45.1)

Results



	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	28.5 (2-44.2)	29.4 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	64.0 (53.8-72.6)	67.7 (57.6-75.9)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (23.0-NR)	25.4 (25.0-NR)
Overall Survival		
18- Month (95% CI)	82.8 (69.5-90.7)	85.7 (72.3-92.9)
24- Month (95% CI)	78.2 (63.9-87.3)	80.8 (66.1-89.6)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

Adverse Events

	Nivolumab Alone (N=54)	Nivolumab/Ipilimumab (N=51)
Any Treatment-Related AE (TRAE), n (%)	39 (72.2)	41 (80.4)
Any Grade ≥3 AE, n (%)*	21 (38.9)	27 (52.9)
Any Grade ≥3 TRAE, n (%)	10 (18.5)	14 (27.5)
TRAE Occurring in ≥ 10% Pts, n (%)		
Fatigue	17 (31.5)	16 (31.4)
Dyspnea	8 (14.8)	10 (19.6)
Rash	9 (16.7)	8 (15.7)
Hypothyroidism	7 (13)	8 (15.7)
Diarrhea	4 (7.4)	10 (19.6)
Pruritus	5 (9.3)	9 (17.7)
Arthralgia	2 (3.7)	6 (11.8)
Nausea	2 (3.7)	6 (11.8)
Pneumonitis		
Grade ≥2	12 (22.2)	16 (31.4)
Grade 3 (no Gr 4/5 pneumonitis)	5 (9.3)	9 (17.6)
Median time to Gr ≥2 Pneum, mo. (range)	11.9 (4.1-36.6)	7.3 (1.3-36.9)

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Phase II Study of Durvalumab Plus Concurrent Radiotherapy in Unresectable Locally Advanced NSCLC DOLPHIN Study (WJOG11619L)

Motoko Tachihara[1], Kayoko Tsujino[2], Mototsugu Shimokawa[3],Takeaki Ishihara[4], Hidetoshi Hayashi[5], Yuki Sato[6], Takayasu Kurata[7], Shunichi Sugawara[8], Yoshimasa Shiraishi[9], Shunsuke Teraoka[10], Koichi Azuma[11], Haruko Daga[12], Masafumi Yamaguchi[13], Takeshi Kodaira[14], Miyako Satouchi[15], Nobuyuki Yamamoto[10], Kazuhiko Nakagawa[5]

[1]Division of Respiratory Medicine, Kobe University Graduate School of Medicine, Kobe, Japan. [2]Department of Radiation Oncology, Hyogo Cancer Center, Akashi, Japan.[3]Department of Biostatistics, Yamaguchi University Graduate School of Medicine Yamaguchi, Ube, Japan. [4]Division of Radiation Oncology, Kobe University Graduate School of Medicine, Kobe, Japan. [5]Department of Medical Oncology, Kindai University, Osakasayama, Japan. [6]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan. [7]Department of Thoracic Oncology, Kansai Medical University Hospital, Hirakata, Japan. [8]Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan. [9]Research Institute for Diseases of the Chest, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan.[10]Internal Medicine III, Wakayama Medical University, Wakayama, Japan.[11]Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan.[12]Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan.[13]Department of Thoracic Oncology , National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan.[14]Departments of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi.[15]Department of Thoracic Oncology, Hyogo Cancer Center, Akashi, Japan.

DOLPHIN: Study Design

Multi-center, Single arm, Investigator Initiated, phase II trial (JapicCTI-194840)

Primary registration

Key Eligibility Criteria

- **Suspected** unresectable stage III or postoperative recurrent NSCLC
- ECOG PS 0 or 1

- Sep 2019- Nov 2020
- 12 institutions in Japan

Secondary registration

Key Eligibility Criteria

- **Confirmed** unresectable stage III or postoperative recurrent NSCLC
- Can be treated according to radiation protocol
- PD-L1≥1% (SP263)

n=35

Treatment

Radiation therapy (60Gy) plus durvalumab (10 mg/kg, Q2w)

for up to 1 year until PD or unacceptable toxicity

Tumor evaluation by CT scan **Q8W**

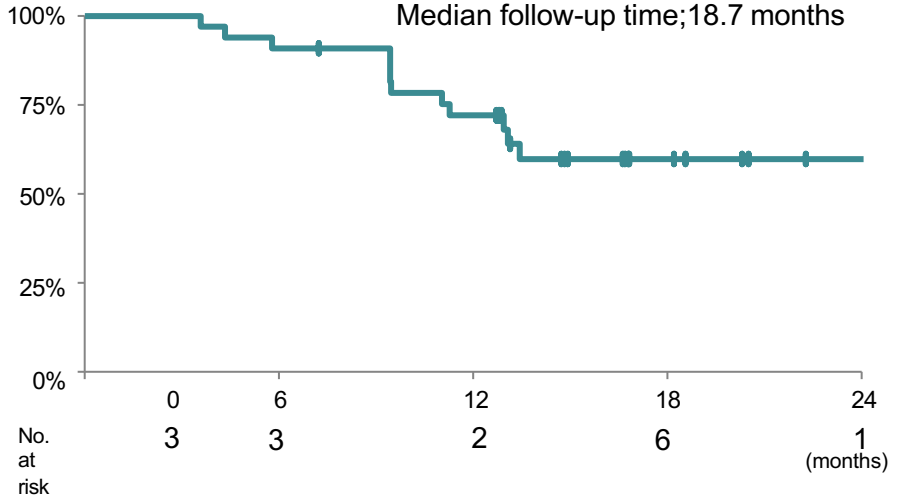
Sample size calculated
threshold of the 12-month PFS rate ; **28%**
expected rate ; **50%**
α=0.05(one-sided) and power 0.8

Primary endpoint:12-month PFS rate (assessed by independent central review)
Secondary endpoints:PFS, OS, objective response rate, disease control rate, treatment completion rate, time to death or distant metastasis, and safety

DOLPHIN: PFS by ICR

Characteristics, median(range), n(%)		n=35
Age		72(44-83)
Sex	male(%)	31 (88.6)
Smoking history	never	1 (2.9)
	former	16 (45.7)
	current	18 (51.4)
Pathology	adenocarcinoma	19 (54.3)
	Squamous cell carcinoma	15 (42.9)
	NOS	1 (2.9)
Stage	post-operative recurrence	9 (25.7)
	IIIA	16 (45.7)
	IIIB	7 (20.0)
	IIIC	3 (8.6)
ECOG PS	0/1	19/16 (54.3/45.7)
TPS (SP263)		60(1-100)
Radiation	3D-CRT	24 (70.6)

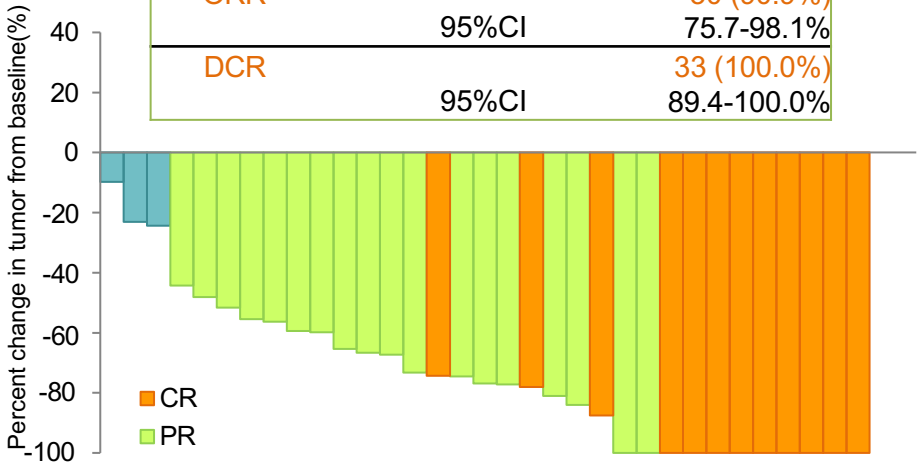
12-month PFS rate by ICR



12-month PFS rate	90%CI (%)	95%CI(%)
72.1%	59.1-85.1	56.1-87.6

DOLPHIN: Response Rate by ICR

Confirmed ORR	n=33
CR	12 (36.4%)
PR	18 (54.5%)
SD	3 (9.1%)
PD	0 (0.0%)
ORR	30 (90.9%)
95%CI	75.7-98.1%
DCR	33 (100.0%)
95%CI	89.4-100.0%



Safety

	n(%)
Any grade AEs	34 (100)
Grade 3/4	16 (47.1)
Grade 5	2 (5.9)
Leading to discontinuation of durvalumab	6 (17.6)
Leading to discontinuation of RT	0 (0.0)
Any grade treatment-related AEs	30 (88.2)
SAEs	13 (38.2)
Severe immune-mediated AEs	10 (29.4)

Pneumonitis or Radiation Pneumonitis	n(%)
Any grade	21 (61.8)
Grade 3/4	4 (11.8)
Grade 5	0 (0.0)
Leading to discontinuation of durvalumab	2 (5.9)
Leading to discontinuation of RT	0 (0.0)

Take Home Points:

- **Multidisciplinary discussion is key**
- **Obtain molecular testing in ALL NSCLC**
- Unresectable NSCLC without actionable mutations: PACIFIC remains standard
    - Concurrent CRT with platinum doublet chemotherapy → durvalumab for 1 yr.
- Addition of Ipilimumab -> increase % pneumonitis

Remaining Questions:

- How can we improve outcomes?
  - Novel combinations?
  - Concurrent IO + CRT?
  -Induction (chemo)-immunotherapy?
- Role of durvalumab in patients with PD-L1 negative tumors?
- Length of consolidation immunotherapy?
- Can we de-escalate chemotherapy in unresectable disease?
- Role of targeted therapies in unresectable NSCLC with oncogenic alterations?
  - Role of EGFR TKIs in the post-ADAURA era?

Thank you!

Questions?