2021 ASCO ANNUAL MEETING

PHASE II RANDOMIZED STUDY OF RAMUCIRUMAB PLUS PEMBROLIZUMAB VERSUS STANDARD OF CARE FOR ADVANCED NON-SMALL CELL LUNG CANCER PREVIOUSLY TREATED WITH A CHECKPOINT INHIBITOR—TOXICITY UPDATE (LUNG-MAP NON-MATCHED SUB-STUDY S1800A)

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rapid communications

Phase II Randomized Study of Ramucirumab and Pembrolizumab Versus Standard of Care in Advanced Non–Small-Cell Lung Cancer Previously Treated With Immunotherapy—Lung-MAP S1800A

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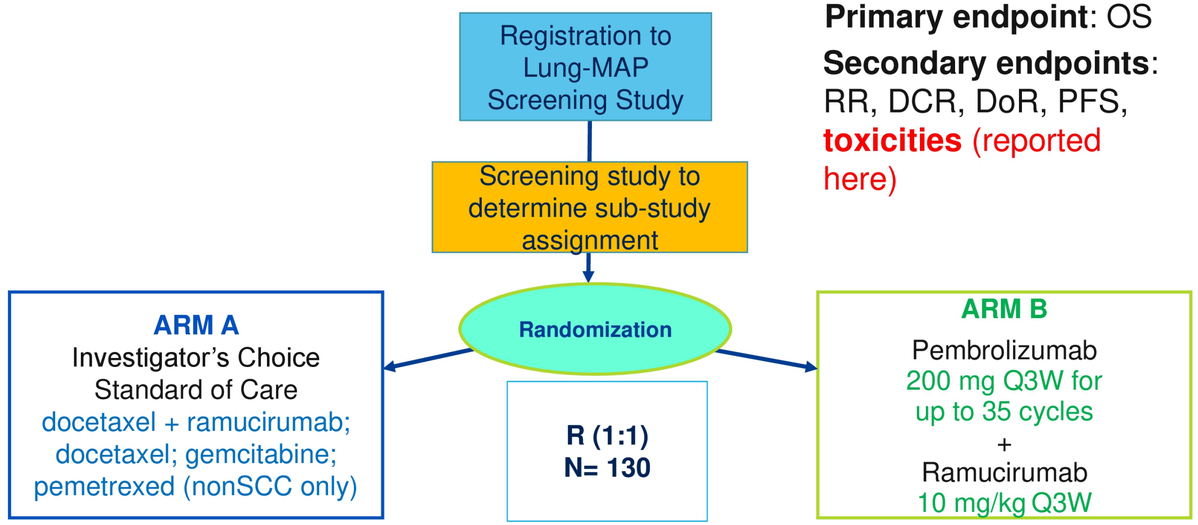
Background

- Therapeutic landscape in metastatic NSCLC includes immunotherapy agents in both treatment-naïve and previously treated patients
- Irrespective of histology
- Resistance to immunotherapy is a significant area of unmet need
- Vascular endothelial growth factor (VEGF) modulates tumor immune microenvironment
- Combination immune checkpoint and VEGF/VEGF receptor inhibition produce clinical benefit in multiple tumor types
- Lung-MAP is a master protocol for patients with stage IV, previously treated NSCLC
- Those not eligible for a biomarker-matched substudy, enrolled in S1800A

S1800A Schema



Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, **toxicities** (reported here)

Randomized phase II trial

- Main eligibility: 1) Previously received PD-1 or PD-L1 inhibitor therapy for at least 84 days and platinum-based doublet therapy; 2) ECOG 0-1
- Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care (SOC) arm

NCT03971474

Patient Characteristics

	SOC, docetaxel/ramucirumab (n = 45)	SOC, no ramucirumab (n = 23)	pembrolizumab/ramucirumab (n = 69)
Median age (years) (range)	62.8 (45.6-84.1)	69.8 (48.9-84.3)	66.4 (37.6-85.3)
Sex, n (%)			
Male	28 (62)	14 (61)	41 (59)
Female	17 (38)	9 (39)	28 (41)
PD-L1 status, n (%)			
<1%	18 (40)	8 (35)	29 (42)
≥1%	26 (58)	12 (52)	30 (43)
Unknown	1 (2)	3 (13)	10 (14)
Histology, n (%)			
Adenocarcinoma	27 (60)	12 (52)	36 (52)
Squamous cell carcinoma	18 (40)	10 (43)	28 (41)
Mixed	0	1 (4)	1 (1)
NSCLC NOS	0	0	4 (6)
Zubrod PS, n (%)			
0	6 (13)	3 (13)	23 (33)
1	39 (87)	20 (87)	46 (67)
Smoking history, n (%)			
Current	12 (27)	5 (23)	18 (29)
Former	29 (64)	15 (68)	39 (62)
Never	4 (9)	2 (9)	6 (10)

Standard of care (SOC); performance status (PS)

Safety summary (n = 131)

	SOC, docetaxel/ramucirumab (n = 44)	SOC*, no ramucirumab (n = 16)	pembrolizumab/ramucirumab (n = 69)
Any cause AE, n (%)	41 (93)	16 (100)	63 (91)
Grade 3-5 AE	27 (61)	9 (56)	24 (35)
Grade 5	3 (7)~	1 (6) sepsis	2 (3)+
Serious AE	15 (34)	4 (25)	6 (9)
AE leading to treatment withdrawal	10 (23)	1 (6)	5 (7)
Cardiac and thromboembolic events, n (%)	7 (16)	0 (0)	9 (13)
Cardiac			
Grade 1-2	3 (7)	0 (0)	6 (9)
Grade 3-5	1 (2) grade 4 only	0 (0)	2 (3)^
Thromboembolic			
Grade 1-2	1 (2)	0 (0)	0 (0)
Grade 3-5#	2 (5)#	0 (0)	1 (1)#

Standard of care (SOC); Adverse event (AE); *SOC chemotherapy: Docetaxel = 3 (19%), Gemcitabine = 12 (75%), Pemetrexed =1 (6%)
#grade 3 only; ~included 2 respiratory failure and sepsis; +included respiratory failure and cardiac arrest; ^included grade 3 sinus tachycardia and grade 5 cardiac arrest

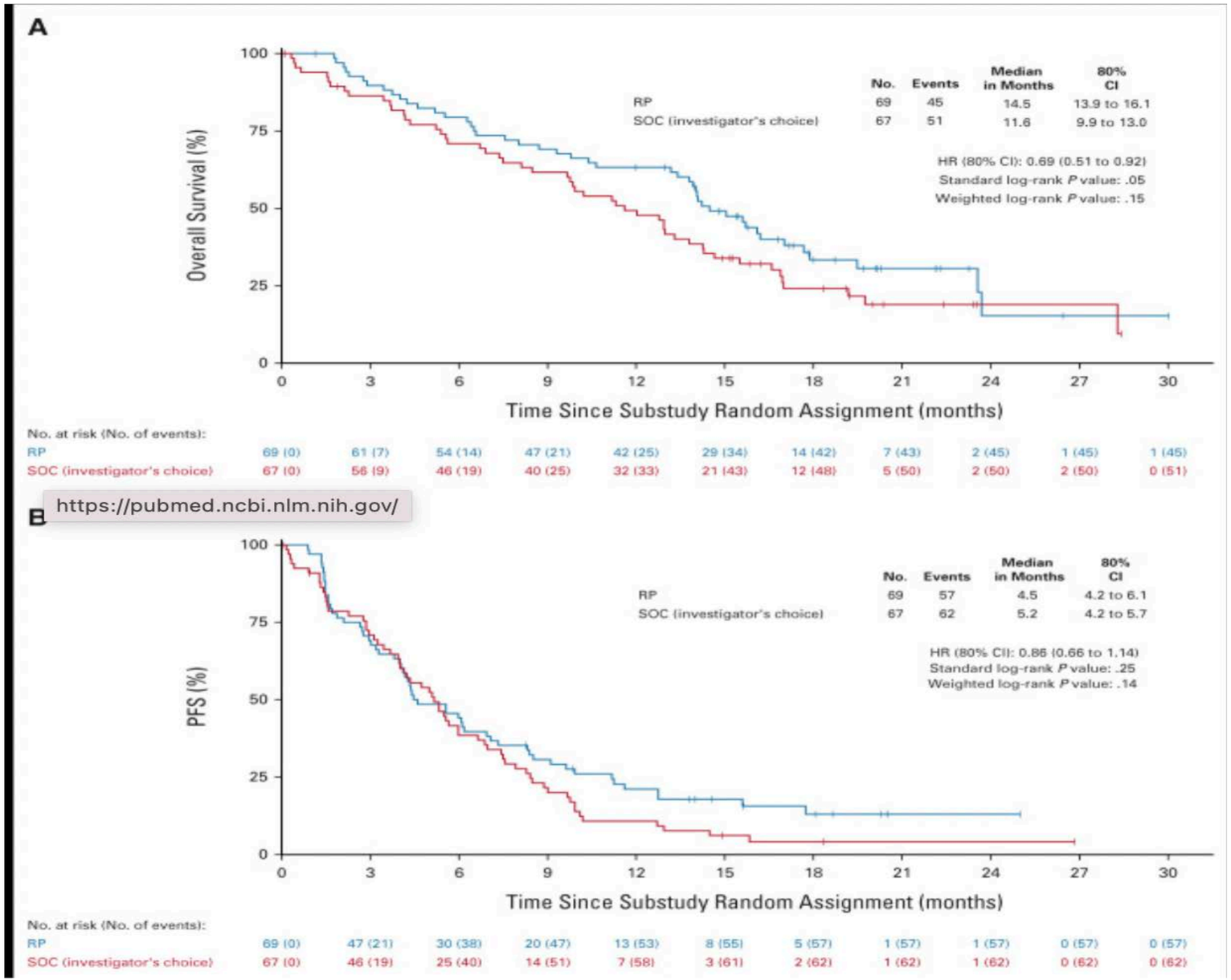
Most Common Adverse Events

	SOC, docetaxel/ramucirumab (n = 44)	SOC*, no ramucirumab (n = 16)	pembrolizumab/ramucirumab (n = 69)
Anemia grade, n (%)			
1	13 (30)	4 (25)	5 (7)
2	7 (16)	5 (31)	3 (4)
≥3#	4 (9) #	0 (0)	0 (0)
Diarrhea grade, n (%)			
1	15 (34)	0 (0)	13 (19)
2	3 (7)	2 (13)	2 (3)
≥3#	2 (5) #	0 (0)	0 (0)
Fatigue grade, n (%)			
1	9 (20)	2 (13)	17 (25)
2	17 (39)	4 (25)	6 (9)
≥3#	3 (7) #	1 (6) #	4 (6) #
Hypertension grade, n (%)			
1	1 (2)	0 (0)	1 (1)
2	7 (16)	0 (0)	10 (14)
≥3#	2 (5) #	0 (0)	8 (12) #
Proteinuria grade, n (%)			
1	7 (16)	0 (0)	9 (13)
2	3 (7)	0 (0)	11 (16)
≥3#	0 (0)	0 (0)	1 (1)
Lymphocyte count decreased grade, n (%)			
1	2 (5)	1 (6)	0 (0)
2	4 (9)	2 (13)	3 (4)
≥3	6 (14) #	4 (25); G3: 3 (19); G4: 1 (6)	3 (4) #
Neutrophil count decreased grade, n (%)			
1	5 (11)	1 (6)	1 (1)
2	1 (2)	0 (0)	1 (1)
≥3	14 (32); G3: 2 (5); G4: 12 (27)	6 (38); G3: 4 (25); G4: 2 (13)	2 (3) #
White blood cell decreased grade, n (%)			
1	2 (5)	3 (19)	7 (10)
2	4 (9)	1 (6)	0 (0)
≥3	12 (27); G3: 9 (20); G4: 3 (7)	5 (31); G3: 4 (25); G4: 1 (6)	1 (1) #
Hypothyroid grade, n (%)			
1	0 (0)	0 (0)	7 (10)
2	0 (0)	0 (0)	9 (13)
≥3	0 (0)	0 (0)	0 (0)

*SOC chemotherapy: Docetaxel = 3 (19%), Gemcitabine = 12 (75%), Pemetrexed =1 (6%)
#grade 3 only

standard of care (SOC); grade (G)

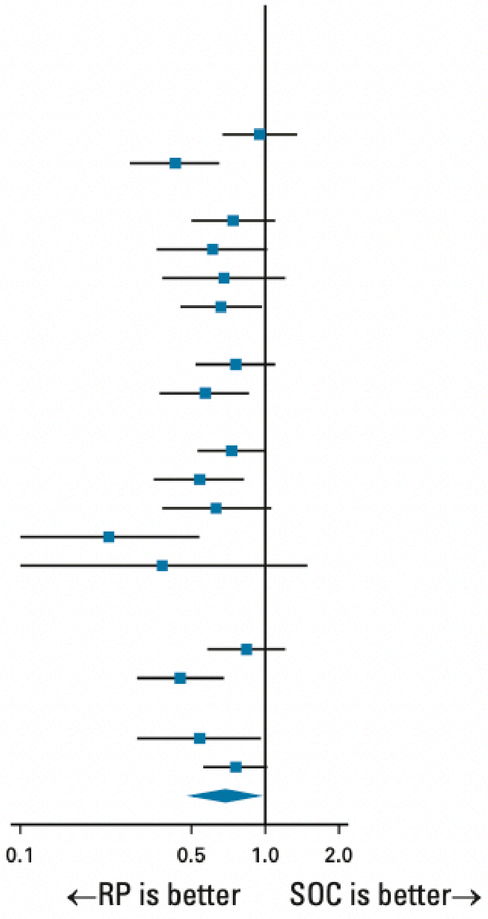
Survival Analysis



Subgroup Analysis

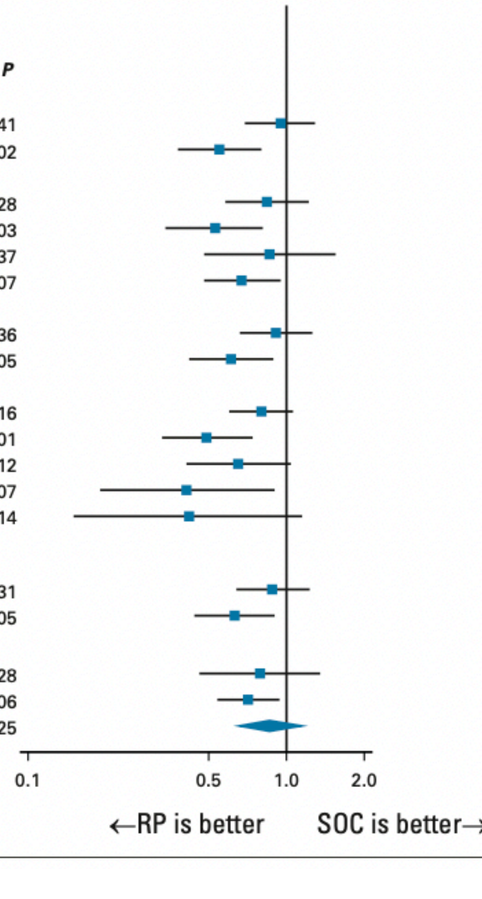
A

	RP Events/n	SOC Events/n	HR (80% CI)	*P*
Histology				
Nonsquamous	27/40	27/39	0.95 (0.67 to 1.35)	.43
Squamous/mixed	18/29	24/28	0.43 (0.28 to 0.65)	.005
PD-L1				
0	21/29	21/26	0.74 (0.50 to 1.10)	.16
1-49	11/21	15/22	0.61 (0.36 to 1.02)	.11
≥ 50	8/12	12/16	0.68 (0.38 to 1.21)	.20
≥ 1	19/33	27/38	0.66 (0.45 to 0.97)	.08
TMB				
< 10	23/32	28/38	0.76 (0.52 to 1.10)	.17
≥ 10	18/33	20/25	0.57 (0.37 to 0.86)	.04
Biomarker				
TP53	31/48	35/48	0.73 (0.53 to 1.00)	.10
CDKN2A	18/27	21/24	0.54 (0.35 to 0.82)	.03
KRAS	12/21	13/16	0.63 (0.38 to 1.06)	.13
STK11	4/7	10/10	0.23 (0.10 to 0.54)	.01
KEAP1	1/3	7/10	0.38 (0.10 to 1.49)	.18
Prior Treatment				
IO + Chemotherapy combination	20/32	32/42	0.84 (0.58 to 1.21)	.27
Chemotherapy→IO	25/36	18/23	0.45 (0.30 to 0.68)	.006
PS				
0	15/23	8/9	0.54 (0.30 to 0.96)	.08
1	30/46	43/58	0.76 (0.56 to 1.02)	.12
Overall	45/69	51/67	0.69 (0.51 to 0.92)	.05



B

	RP Events/n	SOC Events/n	HR (80% CI)	*P*
Histology				
Nonsquamous	34/40	34/39	0.95 (0.69 to 1.29)	.41
Squamous/mixed	23/29	28/28	0.55 (0.38 to 0.80)	.02
PD-L1				
0	27/29	25/26	0.84 (0.58 to 1.22)	.28
1-49	16/21	22/22	0.53 (0.34 to 0.81)	.03
≥ 50	8/12	12/16	0.86 (0.48 to 1.55)	.37
≥ 1	24/33	34/38	0.67 (0.48 to 0.95)	.07
TMB				
< 10	29/32	36/38	0.91 (0.66 to 1.26)	.36
≥ 10	24/33	23/25	0.61 (0.42 to 0.89)	.05
Biomarker				
TP53	39/48	43/48	0.80 (0.60 to 1.06)	.16
CDKN2A	22/27	24/24	0.49 (0.33 to 0.74)	.01
KRAS	16/21	15/16	0.65 (0.41 to 1.04)	.12
STK11	5/7	10/10	0.41 (0.19 to 0.90)	.07
KEAP1	2/3	10/10	0.42 (0.15 to 1.15)	.14
Prior Treatment				
IO + Chemotherapy Combination	26/32	40/42	0.88 (0.64 to 1.23)	.31
Chemotherapy→IO	31/36	21/23	0.63 (0.44 to 0.90)	.05
PS				
0	21/23	8/9	0.79 (0.46 to 1.35)	.28
1	36/46	54/58	0.71 (0.54 to 0.94)	.06
Overall	57/69	62/67	0.86 (0.66 to 1.14)	.25



Survival Analysis

- The median (80% CI) OS was 14.5 (13.9 to 16.1) months for RP and 11.6 (9.9 to 13.0) months for SOC.
- OS benefit for RP was seen in most subgroups.
- Investigator-assessed progression-free survival and response rates (22% RP v 28% SOC, one-sided P 5 .19) were similar between arms
- Grade 3 treatment-related adverse events occurred in 42% of patients in the RP group and 60% on SOC

Conclusions

- Most common AEs per arm
  - Pembrolizumab/ramucirumab—diarrhea (22%), fatigue (38%), hypertension (23%), hypothyroidism (22%), proteinuria (28%)
  - Docetaxel/ramucirumab—anemia (48%), diarrhea (41%) fatigue (61%), neutropenia (39%)
  - SOC chemotherapy alone—anemia (56%), fatigue (44%), leukopenia (56%), neutropenia (44%)
- Grade ≥ 3 treatment-related AEs occurred less frequently in patients who received pembrolizumab and ramucirumab compared to the SOC arms with or without ramucirumab
- Grade 3-5 cardiac and thromboembolic events were similar in patients who received ramucirumab with pembrolizumab or docetaxel
- Pembrolizumab and ramucirumab was generally well-tolerated
- [redacted]

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Conclusion

- This randomized phase II trial demonstrated significantly improved OS with RP compared with SOC in patients with advanced NSCLC previously treated with ICI and chemotherapy. The safety was consistent with known toxicities of both drugs. These data warrant further evaluation.