



A phase II study of NC318 alone or in combination with Pembrolizumab in patients with advanced NSCLC

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ARTICLES

<https://doi.org/10.1038/s41591-019-0374-x>
nature
medicineSiglec-15 as an immune suppressor and potential
target for normalization cancer immunotherapy

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NATURE MEDICINE

ARTICLES

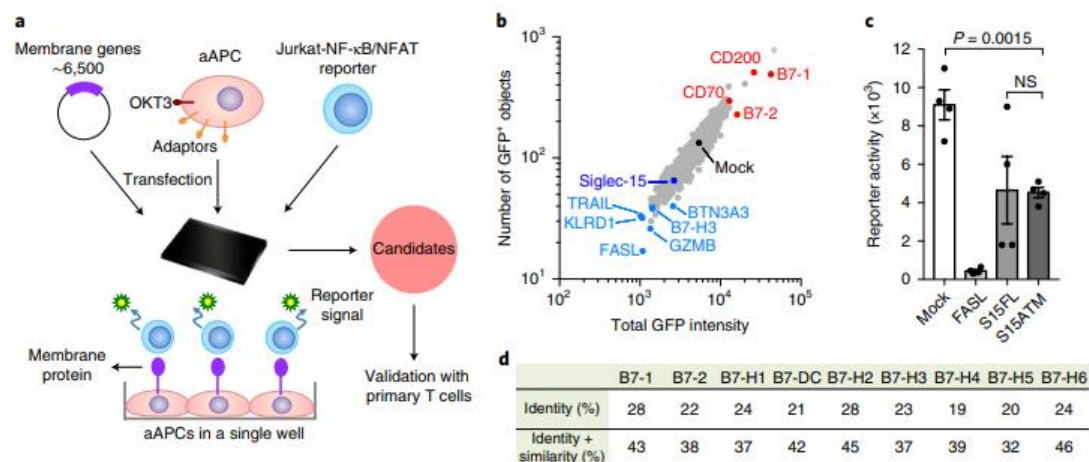


Fig. 1 | Identification of Siglec-15 as a T cell suppressive molecule in the TCAA. a, Schematic representation of TCAA for rapid screening of cell surface

NATURE MEDICINE

ARTICLES

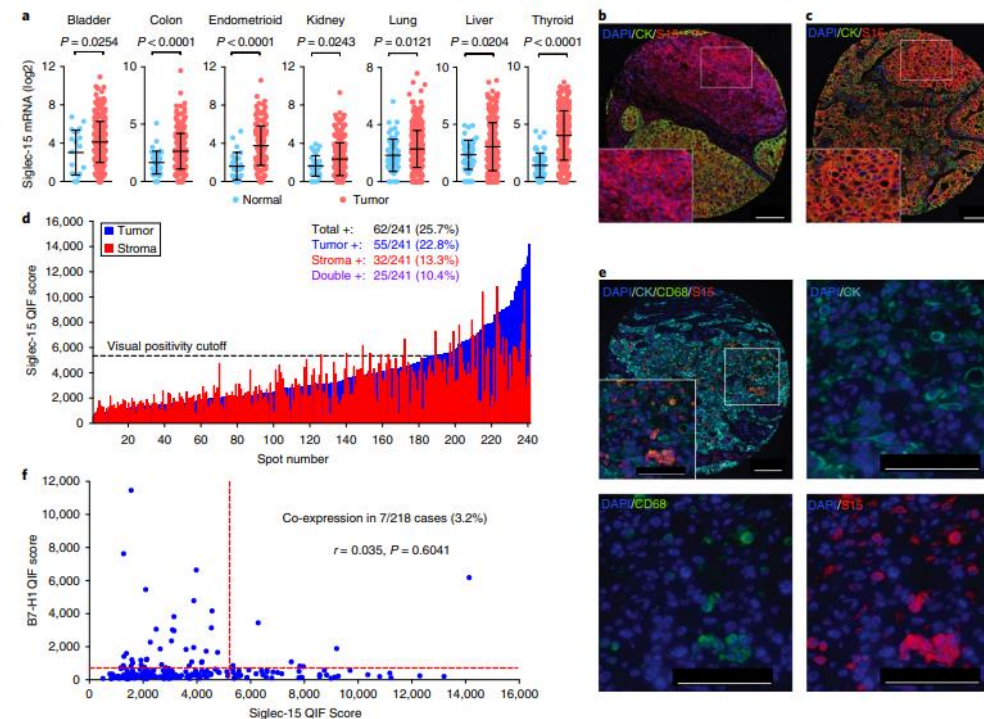


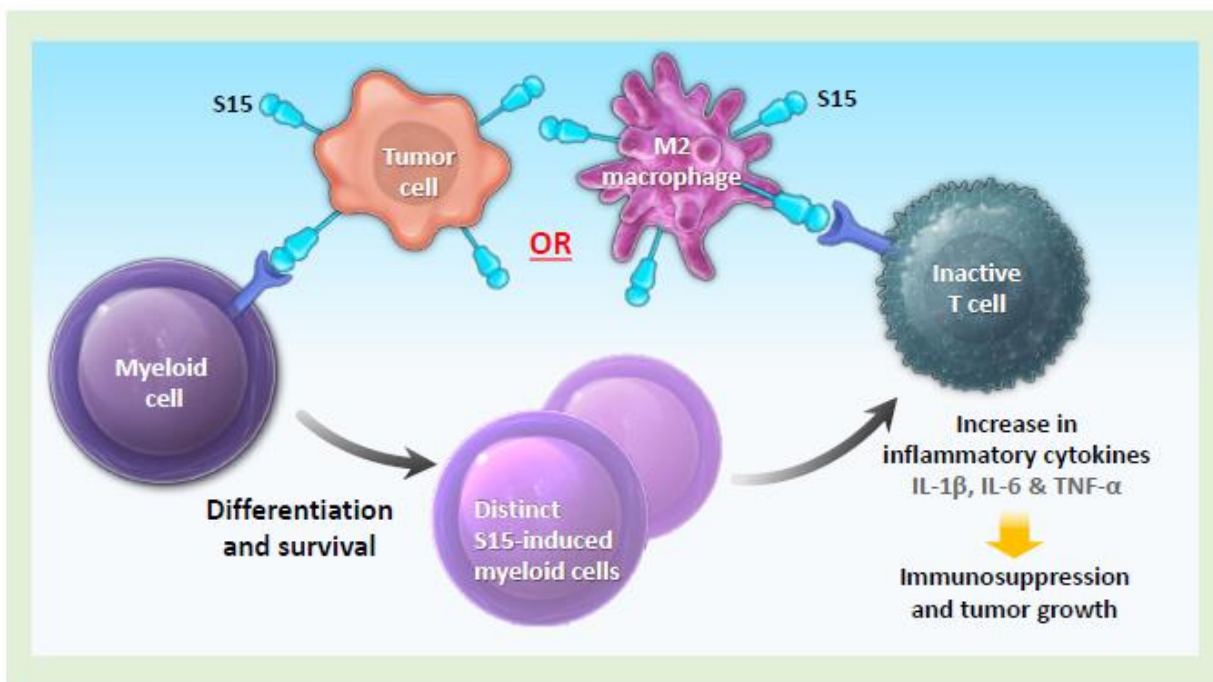
Fig. 4 | Siglec-15 is abundant in human cancers. a, The mRNA expression levels of Siglec-15 in human cancers versus corresponding normal tissues by

Wang et al, Nat Med 2019

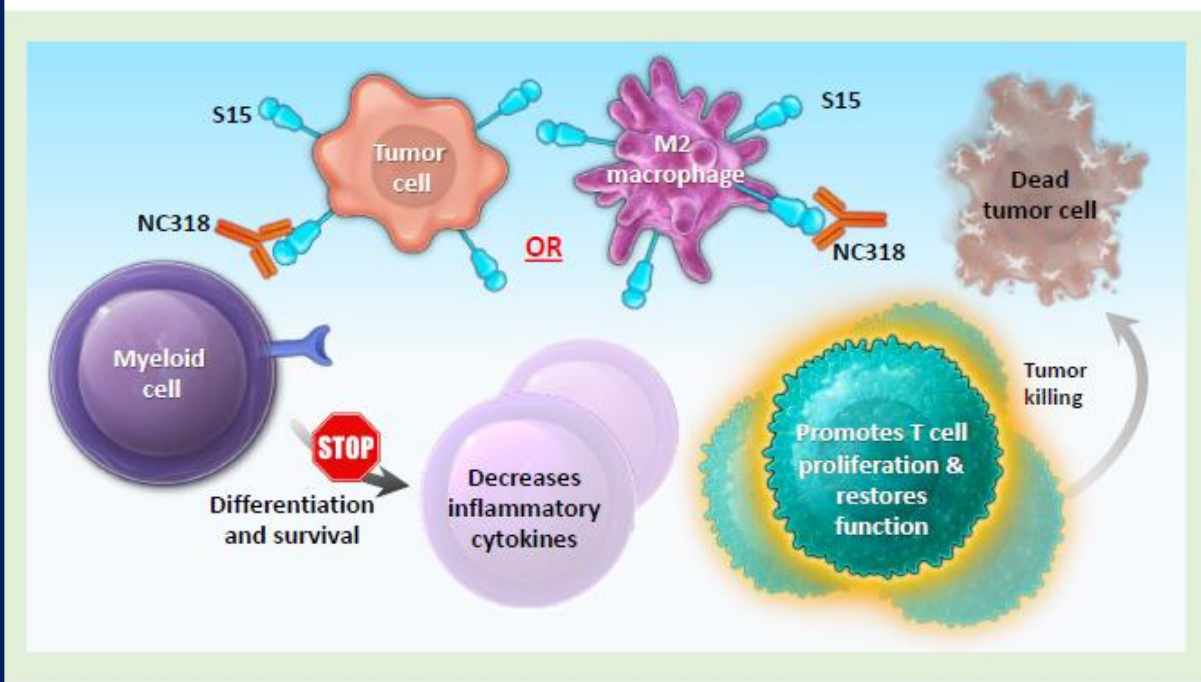




S15 is Immunosuppressive in the Tumor Microenvironment



NC318 Blocks Immunosuppressive Activity Induced by S15



NC318: MECHANISM OF ACTION





NC318 Phase 1/ 2: Analysis in All Patients: Early Evidence of Disease Control Without S15 Selection in Ph1 & Ph2

Cancer Types	Responses n=32	Disease Control (CR+PR+SD) n=32 (37%)	Progressive Disease (n=54)	Total Evaluable Subjects (n=86) ²	mPFS in Disease Control (5.0 months)
Lung	1 CR, 1 PR, 13 SD	15 (45%)	18	33	5.2 ³
H&N	1 PR	1 (20%)	4	5	N/A
Breast	1 PR, 3 SD	4 (40%)	6	10	4.8
Ovarian	4 SD	4 (24%)	13	17	4.0 ⁴
Other ¹	8 SD	8 (38%)	13	21	5.1

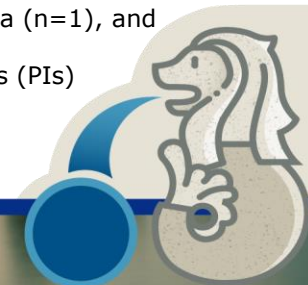
¹SD subjects in other types of cancer include Esophageal Cancer (n=1), Endometrial Cancer (n=1), Hepatocellular Carcinoma (n=1), Melanoma (n=3), Merkel cell carcinoma (n=1), and SCC/Basaloid (n=1)

²Total of 96 subjects were treated with 10 subjects determined as non-evaluable (NE) for efficacy based on RECIST v1.1 and or clinical evaluations by principal investigators (PIs)

³3 SD subjects were censored for PFS analysis

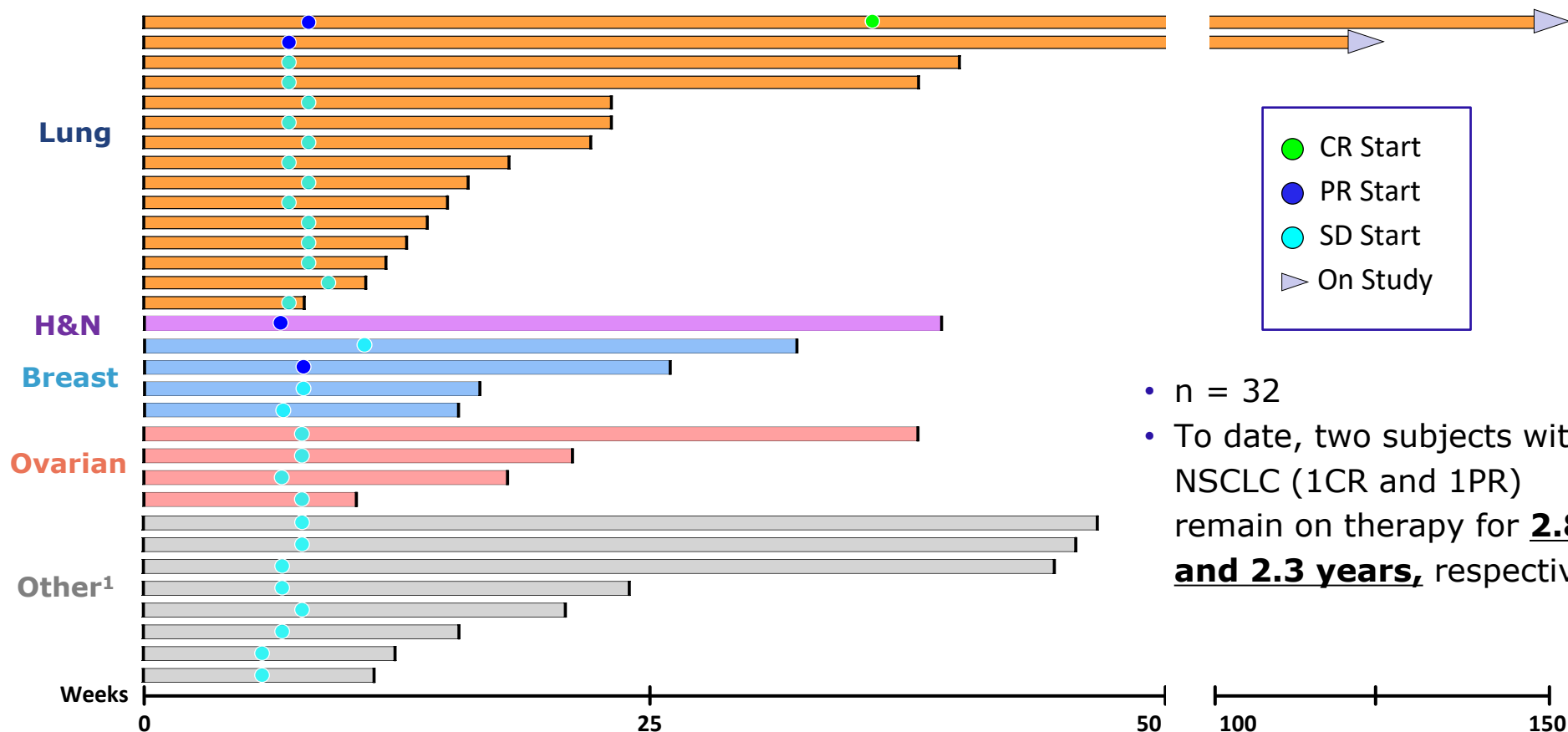
⁴1 SD subject lost to follow up for PFS analysis

N/A: Not Applicable is used where sample size is less than 3 for median analysis. The data extract date is as of 18AUG2021





Time to & Duration of Disease Control



- $n = 32$
- To date, two subjects with NSCLC (1CR and 1PR) remain on therapy for **2.8** and **2.3 years**, respectively.

¹SD subjects in other types of cancer include Esophageal cancer (n=1), Endometrial cancer (n=1), Hepatocellular carcinoma (n=1), Melanoma (n=3), Merkel cell carcinoma (n=1), and SCC/Basaloid (n=1).

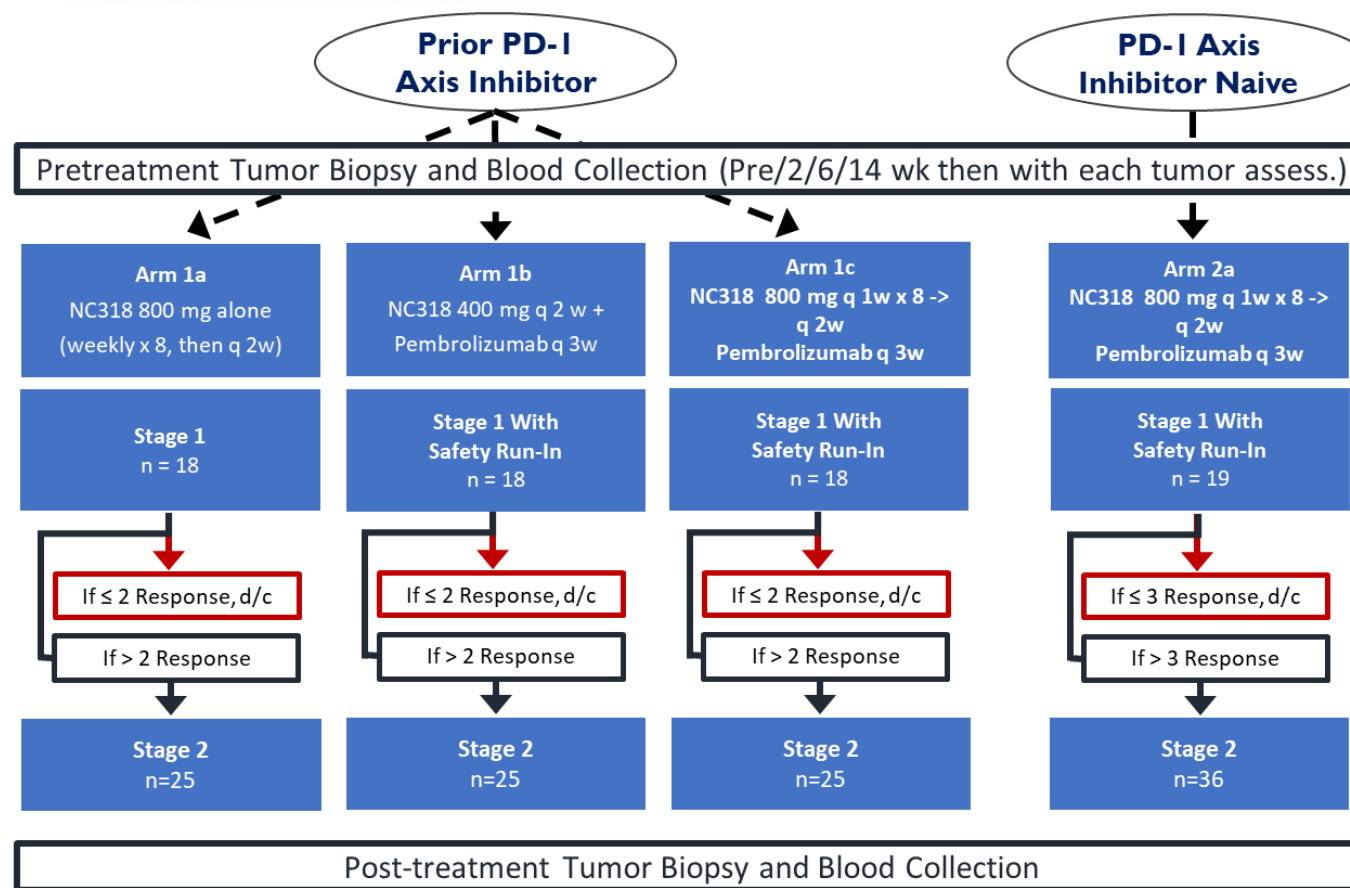




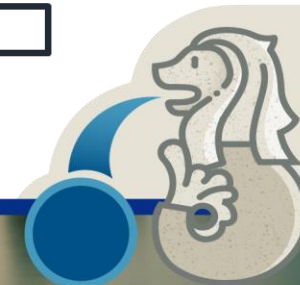
TRIAL SCHEMA

NC318 dose will be determined by Ph I trial
Pembrolizumab 200 mg

- Advanced NSCLC
- ECOG 0-1
- Willing/able to undergo tumor biopsy
- ARM 1a, 1b and 1c:
Progression on PD-I axis Inhibitor (+/- chemo)
- ARM 2a: No prior PD-I axis Inhibitor or NC318; tumor PD-L1 < 50%
- No symptomatic or untreated CNS metastases



- Patients treated on arm 1a will be allowed to receive combination therapy with NC318 and pembrolizumab (same dose and schedule as arms 1c and 2a) at the time of progression, after a mandatory tumor biopsy





BASELINE CHARACTERISTICS	Arm 1a n=11	Arm 1b n=18		Arm 1a n=11	Arm 1b n=18
Age			PDL1 on Tumor Cells, n (%)		
Median	67	67	<1	6 (55)	7 (39)
Range	50, 82	51, 80	1 to 49	1 (9)	3 (17)
Gender, n (%)			≥ 50	0	1 (6)
Female	5 (45)	8 (44)	Unknown	4 (36)	7 (39)
Male	6 (55)	10 (56)	PDL1 on Immune Cells, n (%)		
Race, n (%)			<1	6 (55)	7 (39)
White	8 (73)	17 (94)	≥ 1	1 (9)	4 (22)
Black	1 (9)	1 (6)	Unknown	4 (36)	7 (39)
Unknown	2 (18)	-	SIGLEC 15		
Ethnicity, n (%)			1, Tumor Cell staining	0	1 (6)
Hispanic	1 (9)	1 (6)	2, Immune Cell staining $\geq 10\%$	3 (27)	5 (28)
Non Hispanic	9 (82)	17 (94)	3, No staining	4 (36)	5 (28)
Unknown	1 (9)	-	Unknown	4 (36)	7 (39)
Smoking History, n (%)					
< 1 pack year	2 (18)	3 (17)	Select Molecular Alterations	n/N tested (%)	
1-10 pack year	0	3 (17)	<i>KRAS</i>	4/9 (44)	5/18 (28)
> 10 pack year	9 (82)	12 (67)	<i>STK11</i>	2/9 (22)	2/18 (11)
Histology, n (%)			<i>PIK3CA</i>	1/9 (11)	2/18 (11)
Squamous	4 (36)	4 (22)	<i>PTEN</i>	1/9 (11)	1/18 (6)
Adenocarcinoma	6 (55)	13 (72)	<i>SMARC</i>	2/9 (22)	2/18 (11)
Sarcomatoid	1 (9)	1 (6)			

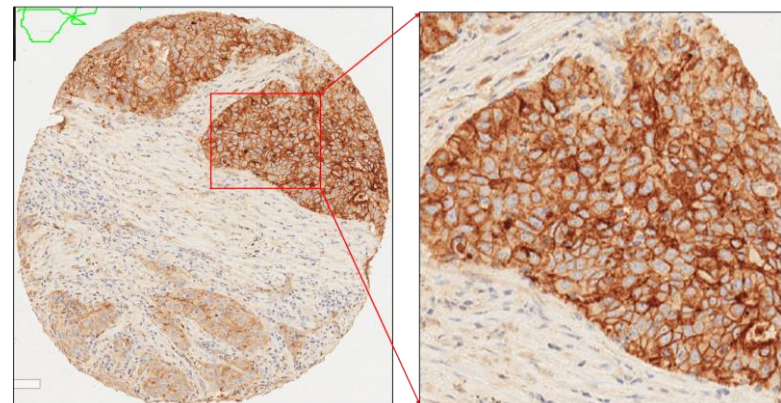


Scoring Criteria for S15 with 1F7

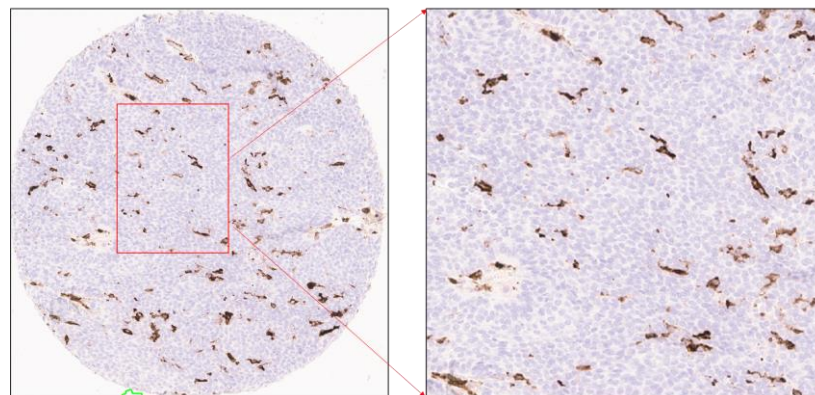
Proposed Categories

1. Category 1: Tumor cell staining (but not granular apical) (in at least 10% of cells)
2. Category 2: Immune cell staining (in at least 10% of cells)
3. Category 3: No evidence of any staining

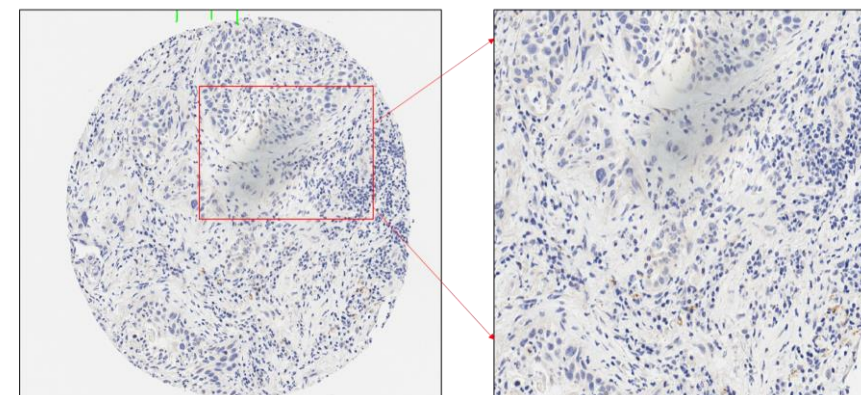
Category 1



Category 2



Category 3





EFFICACY

	Arm 1a Mono (n=11)	Arm 1b Combo (n=18)
ORR, n (%)	1 (9)	2 (11)
Best overall response, n (%)		
Partial response	1 (9)	2 (11)
Stable disease	2 (18)	6 (33)
Stable disease > 6 mos.	0	2* (11)
Progressive disease	8 (73)	9 (50%, includes 1 pt with PR by irRC)
DCB (PR/CR or SD > 6 mos. by RECIST and/or irRC), n (%)	1 (9)	5 (28)
PFS		1.7 mos
OS		6.9 mos

* Ongoing SD at 21.6 and 7.6 months respectively with tumor regression

SAFETY

- **Arm 1A (NC318 800 mg weekly)**
 - 3/ 11 pts experienced grade 3 (G3)+ TRAEs
 - G3 transverse myelitis (1)
 - G3 NC318 infusion reaction (rxn) (1)
 - G3 rash (1)
 - 2 pts discontinued (d/c) trial therapy due to TRAEs [G3 transverse myelitis & G3 NC318 infusion rxn]
- **Arm 1b (NC318 400 mg q 2 weeks with pembrolizumab)**
 - 3/ 18 pts experienced G3+ TRAEs
 - G3 pneumonitis (1)
 - G3 NC318 infusion rxn (2)
 - 5 pts d/c trial therapy due to TRAEs [G3 pneumonitis (1), G2 pericarditis (1), G2 psoriasis (1) and G3 NC318 infusion rxn (2)]
- **NC318 infusion rxn in 7 patients** (3 G3, 4 G2), six receiving NC318/ pembrolizumab and one, NC318 alone
 - No additional infusion rxn since increasing NC318 infusion time from 30 minutes to 60 minutes, with primary prophylaxis consisting of diphenhydramine, acetaminophen and famotidine (Dec 2022).





Pre- Treatment Trial Biopsy S15 IHC (only available for 20 pts, including 2 screen failures)

- Category 1 (tumor cell staining): 5% (n= 1)
- Category 2 (immune cell staining): 50% (n= 10)
- Category 3 (no staining): 45% (n= 9)
- No clear correlation with clinical benefit

ARM 1a	PDL1 (IC) Immune Cell	PDL1 (TC) Tumor Cell	S15	Best Response	Tumor Change
008	0	0	3	SD conf. (c)	+1
019	> 1	1 to 49	2	PD	+ 44
021	0	0	2	SD c	0
025	0	0	2	PD	+ 11
029	0	0	3	PD	+29
031	0	0	3	PD	+ 4
032	0	0	3	PR	- 40

ARM 1b	PDL1 IC	PDL1 TC	S15	Best Response	Tumor Change
001	0	0	2	PD RECIST PR irRC	- 100
002	> 1	1 to 49	2	PD	+ 34
003	0	0	3	SD uc	ND
004	0	0	2	PD	- 4
006	> 1	1 to 49	3	PD	+ 17
013	> 1	1 to 49	2	SD uc	- 1
015	> 1	≥ 50	2	PD	+ 24
016	0	0	1	PD	+ 29
026	0	0	3	SD c	- 6
033	0	0	3	PR	- 37
034	0	0	3	PD	ND



Patients with Clinical Benefit

Pt	Pk Yr	Histo	Mut	Prior Line	Prior RT	Prior IO, PFS (months, m)	PDL1 TC/ IC	S15 Cat.	Prior IO To 1 st Trial Tx	Trial Best Resp (Δ Target Lesion), PFS	1 st to last Tx (m)	Reason for Tx d/c	OS (m)	
001	11	Squam	-	3	Y	Consol. IO, 3.6 <i>Durvalumab</i>	0/ 0	2	10.4 m	PD but irRCPR (- 100), 12.8 m	6.3	Tox Pericarditis	20.1	1 b C O M B O
010	29	Adeno	PIK3CA KDR	1	N	ChemIO.12.3 <i>Cb/P/ Pembro</i>	-	-	1.3 m	SD (- 27%) 19.6+ m	15.8	Tx Complete	NR 21.6+	
017	10	Squam	PIK3CA HRAS	1	N	ChemIO, 1.4 <i>Cb/P/ Pembro</i>	-	-	1.4 m	PR (- 58%) 4.7 m	4.4	PD	6.1	
026	23	Adeno	PTEN ATM	1	N	ChemIO, 27.3 <i>Cb/P/ Pembro</i>	0/ 0	3	5.5 m	SD (- 6), 7.6+ m	6	Tox Inf. Rxn	NR 7.6+	
033	30	Adeno	KRAS Q61H	2	Y	Consol. IO, 3 <i>Durvalumab</i>	0/ 0	3	15.6 m	PR (- 37%) 7.4+ m	Ongoing	-	NR 9.2+	
032	0	Adeno	PTEN TP53	1	N	ChemIO, 3 <i>Cb/P/ Pembro</i>	0/ 0	3	1.4 m	PR (- 40%), 6.2 m	3.8	Tox/ PD	NR 9.5+	1 a

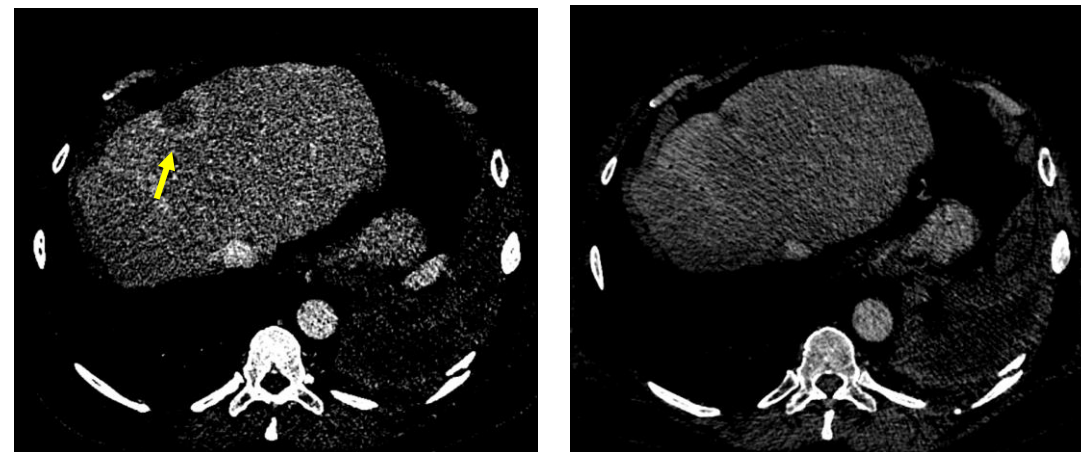
- **Pt 001:** Regression in liver/ lung/ adrenal. PD 6.4 m after last trial tx (held for question of pneumonitis), PD in lung, ? liver; **Pt 010:** Ongoing SD, 19.6 m (- 27% target lesions, lung). Completed Tx (1st to last dose, 15.8 m); **Pt 017:** Regression of subcut mets; PD in lung, bone, subcut. mets; **Pt 026:** Regression in neck/ thoracic LNs; Patient withdrew from follow up after infusion rxn; **Pt 033:** Ongoing response in adrenal, thoracic LN; **Pt 032:** Response in lung/ liver, med LN; PD in lung after 3 mos hold of therapy (held for diverticulitis with microperforation)

Patients with PR by RECIST/irRC

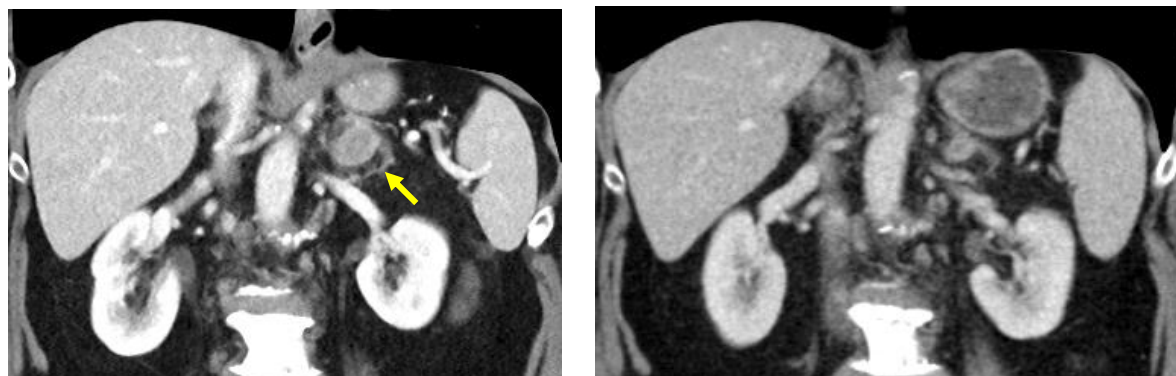
Pt 017: NC318 + Pembrolizumab



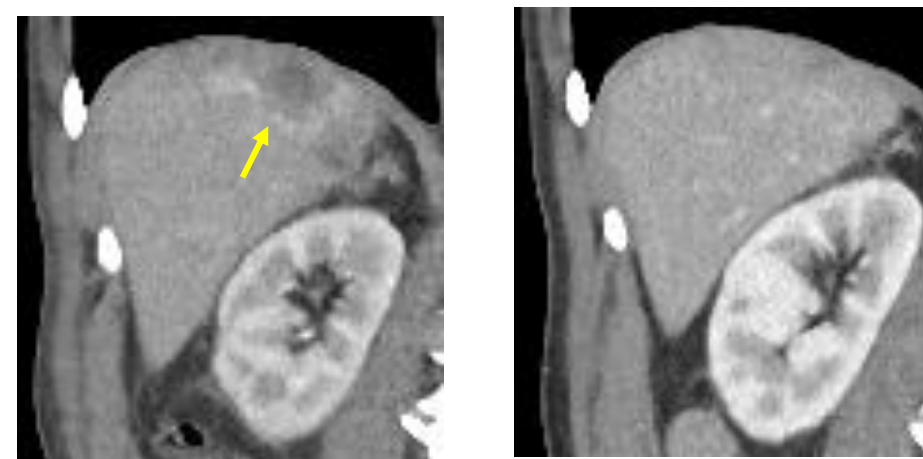
Pt 032: NC318 Monotherapy



Pt 033: NC318 + Pembrolizumab



Pt 001: NC318 + Pembrolizumab





CONCLUSIONS/ NEXT STEPS:

- Combination of NC318 400 mg q 2 weeks and Pembrolizumab 200 mg q 3 weeks (arm 1b) active in advanced PD1 axis inhibitor refractory NSCLC
 - **28% of patients had durable clinical benefit (5/18) with 3 responses by RECIST/irRC and 2 ongoing stable disease at 21.6 months and 7.6 months respectively**
 - Current SIGLEC-15 IHC assay does not predict responsiveness
 - Benefit seen in patients with PD-L1 negative tumors
- Accrual to NC318 800 mg weekly with Pembrolizumab 200 mg q 3 weeks (arm 1c) ongoing
- Accrual to NC318 800 mg alone weekly (arm 1a) ongoing
- Additional Biomarker/ Pharmacodynamic Studies: Tumor and Blood
 - Mandatory pre treatment tumor biopsy (and option on/ post treatment biopsy)
 - Blood: pre- and 2/6/14 wks after initiating trial (and with each subsequent imaging)
 - Ongoing analysis: Tumor, RNA seq; Serial blood, CyTOF

