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# NC318, a Siglec-15 antibody, shows early evidence of disease control in subjects with Siglec-15 positive advanced or metastatic solid tumors in Phase 1 & 2 studies

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# DISCLOSURE

- Elaine Shum
  - Consulting: AstraZeneca, Boehringer Ingelheim, Genentech (Roche)
- Omid Hamid
  - Consulting/Advisory Boards: Aduro, Akeso, Amgen, Beigene, Bioatla, BMS, Genentech (Roche), GSK, Immunocore, Idera, Incyte, Janssen, Merck, NextCure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Tempus, Zelluna.
  - Speaker Bureau: BMS, Novartis, Pfizer, Sanofi/Regeneron.
  - Contracted Research (For Institution): Arcus, Aduro, Akeso, Amgen, Bioatla, BMS, CytomX, Exelixis, Genentech (Roche), GSK, Immunocore, Idera, Incyte, Iovance, Merck, Moderna, Merck-Serono, NextCure, Novartis, Pfizer, Sanofi/Regeneron, Seattle Genetics, Torque, Zelluna.
- Employees of NextCure Inc.
  - Han Myint, Jahangheer S. Shaik, Qinjie Zhou, Emilia A. Barbu, Aaron Morawski, Hasan Abukharma, Linda N. Liu, Megan Nelson, Stephanie Zeidan, Zachary Cusumano.
- Employees of Generable Inc.
  - Eric Novik, Daniel Lee.

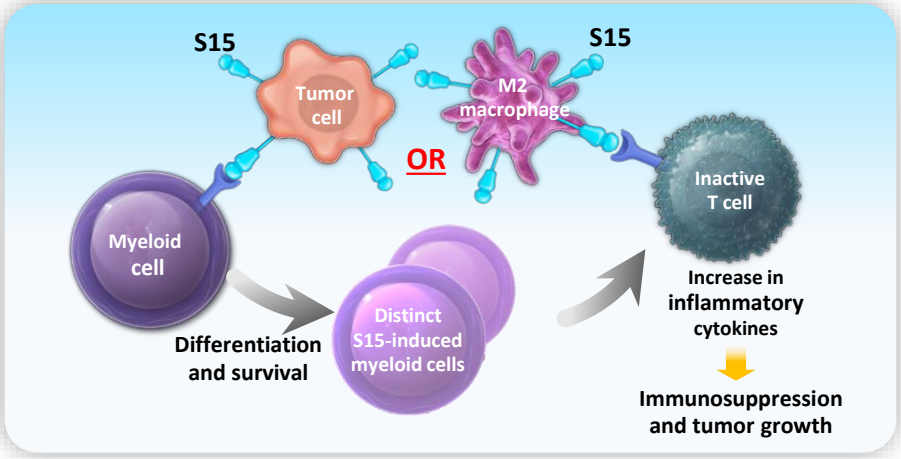
# INTRODUCTION

- Siglec-15 (S15) is a member of the Siglec family (**S**ialic acid binding **I**mmuno**g**lobulin **Lec**tins), a distinct subgroup of immunoglobulin (**Ig**) superfamily proteins involved in the discrimination of self and non-self immune regulation[1].
- S15 is an immune suppressor upregulated on various cancer cells and tumor-infiltrating myeloid cells. Its expression is non-overlapping with PD-L1. S15 leads to immunosuppression in the tumor microenvironment (TME)[2].
- NC318 is a first-in-class humanized IgG1κ monoclonal antibody that blocks S15-mediated immune suppression, providing opportunities to overcome anti-PD-1/PD-L1 therapy resistant tumors.
- Phase 1 data was previously presented[3]. Here we will update the combined data of Phase 1 (n=49) and Phase 2 (n=47) from NC318-01 study.

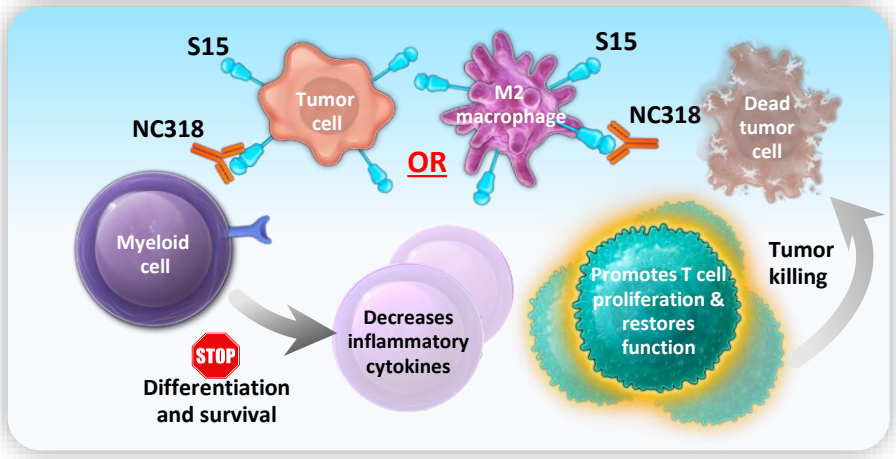
[1]Macauley et al., *Nat Rev Immunol* (2014). [2]Wang et al., *Nat Med* (2019). [3]Tolcher et al., *SITC* (2019).

# NC318: MECHANISM OF ACTION

## S15 is Immunosuppressive in the Tumor Microenvironment




## NC318 Blocks Immunosuppressive Activity Induced by S15



# NC318 PHASE 1 & 2 STUDY DESIGN

## Key Inclusion Criteria

- Men and women aged 18 or older
- ECOG performance status 0 to 1
- Refractory/intolerant to standard of care with no limit to the number of prior treatment regimens
- Measurable disease per RECIST v1.1
- Subjects with advanced or metastatic low PD-L1 (TPS <50%) expressing malignancies

## Key Exclusion Criteria

- Inadequate hematologic, renal and hepatic function
- Active autoimmune disease
- History of interstitial lung disease or active noninfectious pneumonitis
- Active infection requiring systemic therapy

## Phase 1 Dose Escalation

8 mg (n=4)
↓
24 mg (n=4)
↓
80 mg (n=10)
↓
240 mg (n=12)
↓
400 mg (n=11)
↓
800 mg (n=4)
↓
1600 mg (n=4)

## Phase 2 Dose Expansion

**400 mg (n=47)**

| | |
|---|---|
| Lung | Head & Neck |
| Breast | Ovarian |

## Study Design

- **Phase 1: 3 + 3 Design**
  - Subjects dosed every 2 weeks
  - 28-day DLT period
  - Safety expansion enrolled additional subjects for biopsies
- **Phase 2: Simon two-stage design**
  - Subjects dosed every 2 weeks at 400 mg
  - Subjects with advanced or metastatic low PD-L1 (TPS <50%) expressing malignancies
  - Screening and on treatment biopsies

**Primary Endpoint**

- Safety and tolerability

**Secondary Endpoints**

- Assessment of PK
- Assessment of antitumor activity/efficacy

**Exploratory Endpoints**

- Immunogenicity, defined as the occurrence of anti-drug antibodies (ADA) to NC318
- Biomarker changes of NC318 in peripheral blood and tumor tissue

**Tumor assessments**

- RECIST v1.1 and modified RECIST v1.1

# NC318 PHASE 1 & 2 DEMOGRAPHICS

| Demographic Information | Phase 1 (n=49) | Phase 2 (n=47) |
|---|---|---|
| Age | | |
| • Median | 62 | 65 |
| • Range | (32 – 78) | (36 – 86) |
| Gender, n (%) | | |
| • Female | 28 (57%) | 30 (64%) |
| • Male | 21 (43%) | 17 (36%) |
| Number of subjects with prior immunotherapy, n (%) | 32 (65%) | 33 (70%) |
| **Tumor Diagnoses** | | |
| • Lung (NSCLC; SCLC) | 14 (13; 1) | 21 (20; 1) |
| • Head & Neck | 2 | 4 |
| • Breast | 4 | 7 |
| • Ovarian | 7 | 12 |
| • Other | 22[1] | 3[2] |

[1]Other Cancer diagnoses in Phase 1 include Bladder Cancer, CRC, Esophageal Cancer, Endometrial, Gastric Cancer (Stomach), Hepatocellular Carcinoma, Pancreatic Cancer, Leiomyosarcoma, Melanoma, Merkel cell carcinoma, Prostate Cancer, and SCC/Basaloid. [2]Other Cancer diagnoses in Phase 2 include Bladder Cancer and Prostate Cancer.

# INCIDENCE OF TREATMENT-RELATED ADVERSE EVENTS ≥ 5%

| Adverse Event[1,2], n (%) | Phase 1 (n=49) | | Phase 2 (n=47) | |
|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| Amylase Increased | 4 (8.2) | 1 | 0 | 0 |
| Diarrhea | 8 (16.3) | 0 | N/A | N/A |
| Fatigue | 4 (8.2) | 0 | 4 (8.5) | 0 |
| Headache | 3 (6.1) | 0 | 0 | 0 |
| Infusion Related Reaction | 5 (10.2) | 0 | 9 (19.1) | 1 |
| Lipase Increase | 4 (8.2) | 3 | 0 | 0 |
| Muscular Weakness | 4 (8.2) | 1 | 0 | 0 |
| Pruritus | 8 (16.3) | 0 | 4 (8.5) | 0 |
| Chills | N/A | N/A | 4 (8.5) | 0 |
| Influenza-like Illness | N/A | N/A | 3 (6.4) | 0 |
| Nausea | N/A | N/A | 3 (6.4) | 0 |

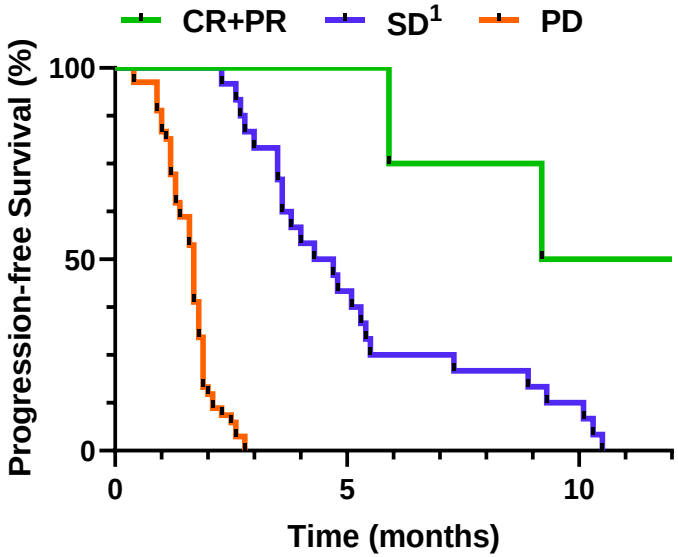
[1]Treatment Related AEs are determined by the investigator for those adverse events deemed as possibly, probably, or definitely-related to NC318.
[2]Pneumonitis: 2 cases (1 subject with grade 1 and another with grade 3) in Phase 1 only (not reaching 5% cut off threshold). N/A: Not Applicable is used in cases where incidence of event terms occurred <5% among subjects enrolled in study Phase. The data extract date is as of 18AUG2021.

# NC318 SHOWED EARLY EVIDENCE OF DISEASE CONTROL IN THE ABSENCE OF S15 SELECTION

| Tumor Diagnoses[1] | Complete Response (CR) (n=1) | Partial Response (PR) (n=3) | Stable Disease (SD) (n=28) | Disease Control (DC) (n=32; 37%) | Progressive Disease (PD) (n=54) | Total Efficacy Evaluable Subjects (n=86)[3] | mPFS[4] in Disease Control (5.0 months) |
|---|---|---|---|---|---|---|---|
| **Lung** | 1 | 1 | 13 | 15 (45%) | 18 | 33 | 5.2 months[5] |
| **Head & Neck** | 0 | 1 | 0 | 1 (20%) | 4 | 5 | N/A |
| **Breast** | 0 | 1 | 3 | 4 (40%) | 6 | 10 | 4.8 months |
| **Ovarian** | 0 | 0 | 4 | 4 (24%) | 13 | 17 | 4.0 months[6] |
| **Other** | 0 | 0 | 8[2] | 8 (38%) | 13 | 21 | 5.1 months |

[1]CLIA validated S15 staining was not available at the time to select subjects. [2]SD 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). [3]Total 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). [4]mPFS: median of progression-free survival in months. [5]3 SD subjects were censored for PFS analysis. [6]1 SD subject censored 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.

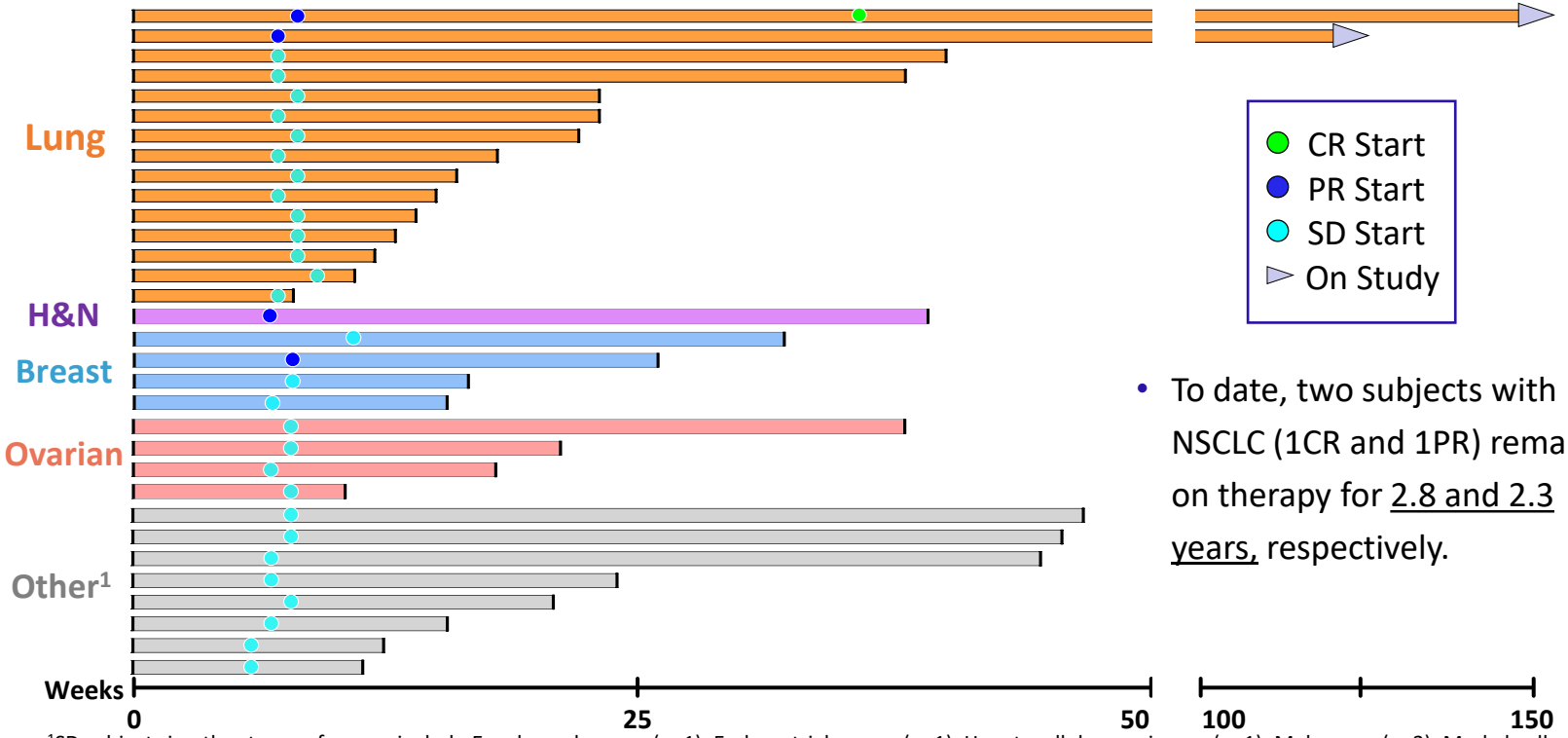
# PROGRESSION-FREE SURVIVAL (PFS) IN SUBJECTS WITH PREVIOUSLY TREATED ADVANCED SOLID TUMORS




[1]4 SD subjects were censored for PFS analysis.

- Median PFS of subjects across all tumor types in Disease Control (DC; CR+PR+SD) was 5.0 months.
- Median PFS of subjects from each group is as follows:
  - CR+PR: 18.3 months
  - SD: 4.5 months
  - PD: 1.7 months

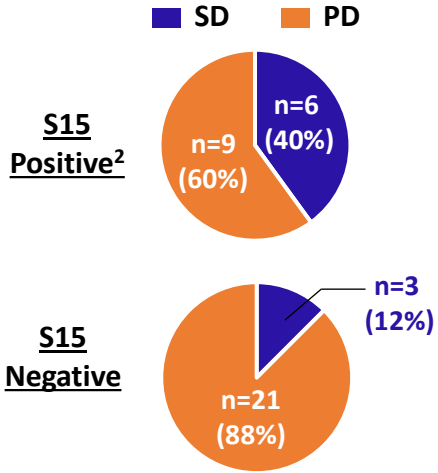
# TIME TO & DURATION OF DISEASE CONTROL IN SUBJECTS WITH PREVIOUSLY TREATED ADVANCED SOLID TUMORS

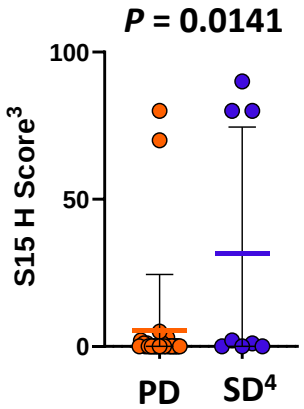



- To date, two subjects with NSCLC (1CR and 1PR) remain on therapy for 2.8 and 2.3 years, respectively.

[1]SD 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).

# RETROSPECTIVE ANALYSIS OF BIOPSIES: SELECTING S15+ SUBJECTS MIGHT HAVE PREDICTED BETTER DISEASE CONTROL

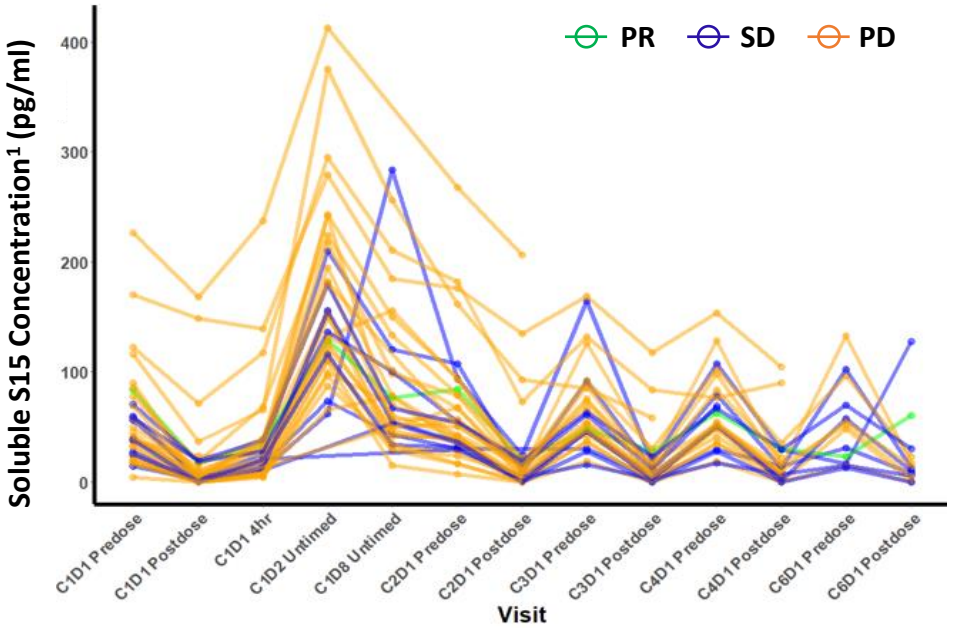



- 40% of S15+ subjects (H score ≥ 1) achieved stable disease (SD), whereas 12% of S15- subjects achieved SD.
- S15 H score was significantly higher amongst SD subjects compared to PD subjects.
- S15+ subjects with stable disease exhibited mPFS of 4.8 months.

[1]CLIA validated S15 staining is available now to select subjects. [2]S15 positivity is defined as S15 IHC with a H score ≥ 1 on the plasma membrane of tumor cells. [3]H score is calculated by summing the percentage of S15 positive tumor cells multiplied by the intensity on a four-point semi-quantitative scale (0, 1+, 2+, 3+) on the plasma membrane. [4]In total, S15 H scores from 30 PD subjects and 8 SD subjects were subjected to statistical analysis. 1 additional SD subject (H score = 160) was not included in the analysis..

# SOLUBLE S15 LEVEL MAY SERVE AS A MARKER FOR NC318 ACTIVITY

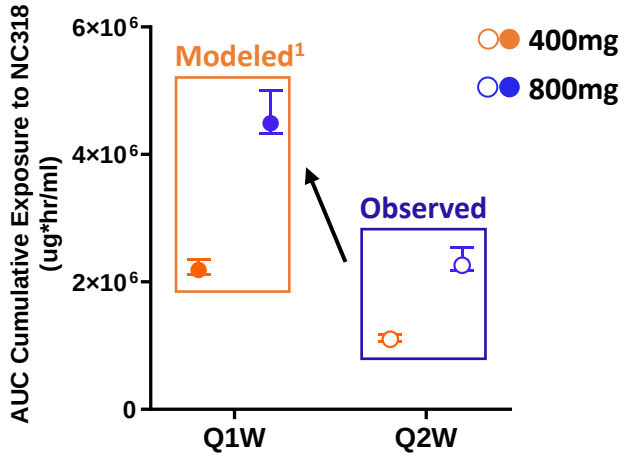



[1]Soluble S15 from subjects in phase 2 only.

- Patients treated with NC318 had soluble form of Siglec-15 (sS15) present in their serum.
  - After NC318 infusion, sS15 increased several fold compared to the baseline.
- Progressive disease was seen with a higher fold increase post-infusion (24 hour).
- Progressive disease may also correlate with a higher baseline sS15 level.

# INCREASING THE DOSE OF NC318 TO 800 mg Q1W MAY INCREASE DRUG EXPOSURE ~ 10-FOLD COMPARED TO 400 mg Q2W

**NC318 Area Under the Curve (AUC) by Dosing Schedule**




[1]Modeled AUC was estimated based on a 75kg subject.

- PK/PD modeling showed that NC318 at 800 mg Q1W would result in approximately 10-fold increase in drug exposure than that achieved with 400 mg Q2W.
- Increasing drug exposure may enhance overall drug activity.

# CONCLUSION & DISCUSSION

- NC318 showed early evidence of clinical benefit in subjects with advanced or metastatic solid tumors in Phase 1 (with escalating dose) & Phase 2 studies (at 400 mg Q2W).
  - To date, 2 subjects with NSCLC remain on therapy for 2.8 and 2.3 years, respectively.
  - 13 out of 33 subjects with lung cancers had stable disease (SD), with a disease control rate (CR,PR and SD) of 45% (15/33) and a median PFS of 5.2 months.
  - Disease control rate across all tumor diagnoses was 37% with a median PFS of 5.0 months.
- Retrospective analysis showed that 40% of S15 positive subjects (H score ≥ 1) achieved stable disease, whereas 12% of S15 negative subjects achieved stable disease.
  - S15 positive subjects with stable disease exhibited median PFS of 4.8 months.
- PK/PD modeling showed that NC318 at 800 mg Q1W would result in approximately 10-fold increase in drug exposure than with 400 mg Q2W.
  - Use of soluble s15 assay for patient selection/monitoring is being explored with further studies.
- New schedule of 800 mg Q1W and selecting patients for S15 score of H ≥ 1 has been implemented into ongoing studies in NSCLC, Head & Neck cancer and Breast cancer.

# ACKNOWLEDGMENT


- We would like to dedicate this presentation to all the brave patients. Without whom, this study and the data we have generated would not have been possible.