ENA 2024
EORTC NCI AACR
36th Symposium

Preliminary results from SEACRAFT-1: An open-label study of naporafenib with trametinib in patients with locally advanced unresectable or metastatic solid tumor malignancies with RAS Q61X mutations

Elisa Fontana[1], Alexander I. Spira[2], Meredith McKean[3], Jeeyun Lee[4], Nicole Chau[5], Eric Winquist[6], Ilhwan Kim[7], Sook Hee Hong[8], Brian Andrew Van Tine[9], Adewale Fawole[10], Robert Shoemaker[11], Yue Cui[11], Rebecca Sutton[11], Joyce Antal[11], Shannon R. Morris[11], David S. Hong[12]

[1]Sarah Cannon Research Institute, London, United Kingdom; [2]NEXT Oncology, Fairfax, VA, United States (US); [3]Sarah Cannon Research Institute, Nashville, TN, US; [4]Samsung Medical Center, Seoul, Republic of Korea; [5]BC Cancer Agency, Vancouver, British Columbia, Canada; [6]London Health Sciences Centre, London, Ontario, Canada; [7]Inje University Haeundae Paik Hospital, Busan, Republic of Korea; [8]The Catholic University of Korea, Seocho-Gu, Republic of Korea; [9]Washington University School of Medicine, St. Louis, MO, US; [10]Florida Cancer Specialists, St Petersburg, FL, US; [11]Erasca, Inc., San Diego, CA, US; [12]MD Anderson Cancer Center, Houston, TX, US

EORTC NIH NATIONAL CANCER INSTITUTE AACR American Association for Cancer Research

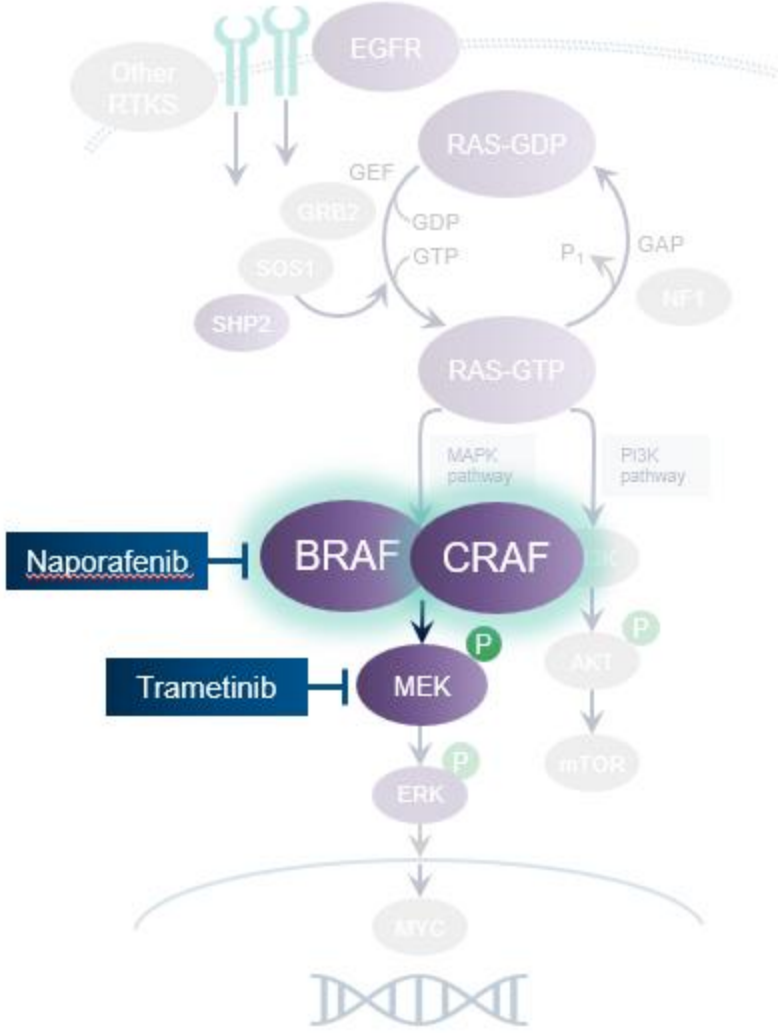
DISCLOSURES

❑ I have the following potential conflict(s) of interest to report

- Employee of Hospital Corporation of America (HCA) International
- Personal financial interest:
  - Repare Therapeutics, CARIS Life Science, Seagen, Sapience, BicycleTx Ltd, Erasca (conference attendance)
  - Astellas, Pfizer, BicycleTx Ltd, BMS (Advisory Board)
- Leadership role:
  - European Organisation for Research and Treatment of Cancer (EORTC), GITCG secretary (2021-2023)
  - ASCO Annual Meeting Scientific Programme Committee GI cancers, Colorectal and Anal Track (2024-2026)
- Funding to Institution:
  - Acerta Pharma, ADC Therapeutics, Amgen, Arcus Biosciences, Array BioPharma, Artios Pharma Ltd, Astellas Pharma Inc, Astex, Astra Zeneca, Basilea, Bayer, BeiGene, BicycleTx Ltd, BioNTech, Blueprint Medicines, Boehringer Ingelheim, Calithera Biosciences, Inc., Carrick Therapeutics, Casi Pharmaceuticals, Clovis Oncology, Inc, Crescendo Biologics Ltd., CytomX Therapeutics, Daiichi Sankyo, Deciphera, Eli Lilly, Ellipses, Erasca, Exelixis, F. Hoffmann-La Roche Ltd, Fore Biotherapeutics, G1 Therapeutics, Genentech, GSK, H3 Biomedicine Inc, Hutchinson MediPharma, Ignyta/Roche, Immunocore, Immunomedics, Inc., Incyte, Instil Bio, IOVANCE, Janssen, Jiangsu Hengrui, Kronos Bio, Lupin Limited, MacroGenics, Menarini, Merck KGaA, Mereo BioPharma, Merus, Millennium Pharmaceuticals, MSD, Nerviano Medical Sciences, Nurix Therapeautics Inc, Oncologie, Oxford Vacmedix, Pfizer, Plexxikon Inc., QED Therapeutics, Inc., Relay Therapeutics, Repare Therapeutics, Ribon Therapeutics, Roche, Sapience, Seagen, Servier, Stemline, Synthon Biopharmaceuticals, Taiho, Tesaro, Turning Point Therapeutics, Inc, PMVPharma, Takeda

Naporafenib and RAS Q61X Solid Tumors

- **Naporafenib** is a potent and selective inhibitor of BRAF and CRAF[1]
- Naporafenib synergizes with **trametinib**, which targets MEK, the immediate downstream node of RAF



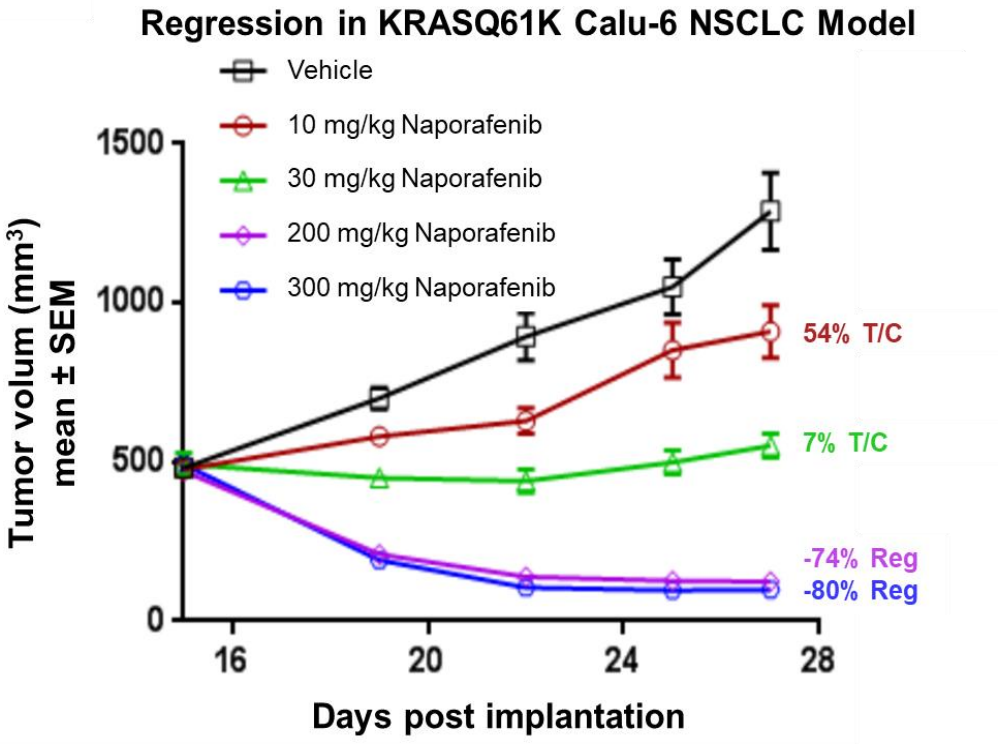
- Naporafenib does not result in paradoxical BRAF activation, a resistance mechanism observed with BRAF V600E inhibitors[1]
- RAS mutations at codon 61 (RAS Q61X), are generally thought to be the most MAPK pathway-activating mutations relative to those at codons 12 and 13, and are therefore thought to be the most oncogenic

[1]Monaco et al. (2021). *Clin Cancer Res* **27**, 2061-2073.

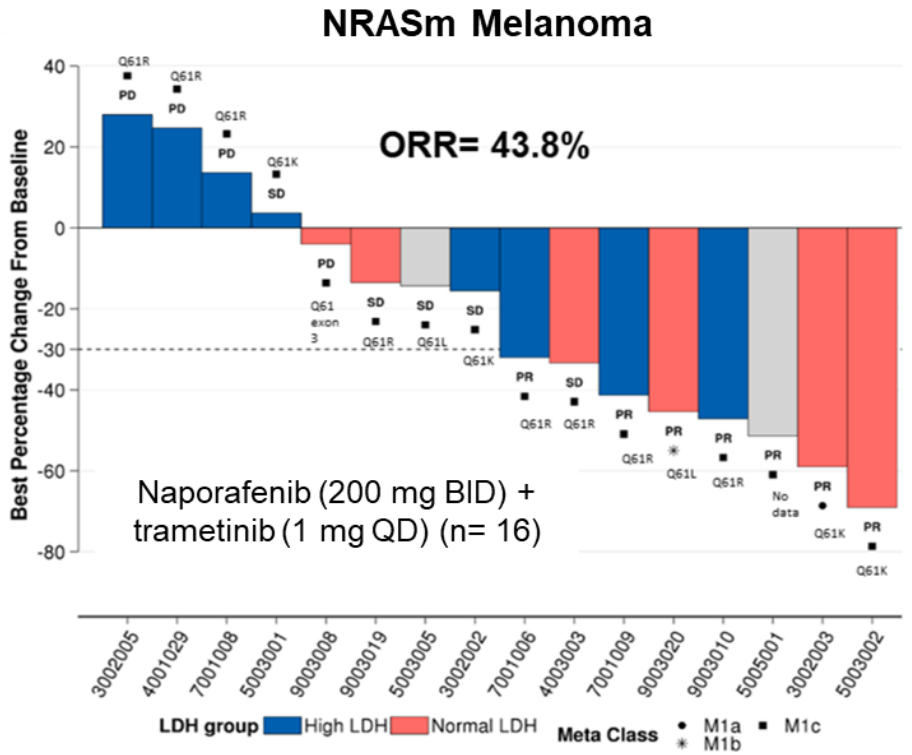
BRAF=B-Raf proto-oncogene; CRAF=C-Raf proto-oncogene; EGFR=epidermal growth factor receptor; ERK=Extracellular signal-regulated kinase; GDP=guanosine diphosphate; GTP=guanosine triphosphate; MEK=mitogen activated protein kinase kinase; mTOR=mechanistic target of rapamycin; RTK=receptor tyrosine kinase

ENA 2024
EORTC NCI AACR
36th Symposium

Pan-RAS codon Q61 Tumor Mutations May Be Predictive Biomarker of Response to Naporafenib + Trametinib



- Tumor regression was demonstrated with naporafenib in the KRAS Q61K Calu-6 NSCLC model



- In a phase Ib escalation/expansion study (CLXH254X2102), patients with *NRAS*-mutant melanoma showed promising clinical benefit with naporafenib + trametinib combination[1]
- 15 of 16 with NRAS Q61X mutation
- The most frequently reported adverse event (AE) was rash
- The most common grade 3-4 AEs that led to treatment discontinuation were rash and anemia[1]

[1]Filippo de Braud et al. (2023). *JCO* **41**, 2651-2660(2023).
BID=twice daily; LDH=lactate dehydrogenase; meta class=m-stage; NSCLC=non-small cell lung cancer; ORR=objective response rate; QD=daily; Reg=regression; SEM=standard error of the mean; T/C=tumor to control rate

ENA 2024
EORTC NCI AACR
36th Symposium

Skin Toxicity Reported in Previous Naporafenib + Trametinib Clinical Studies

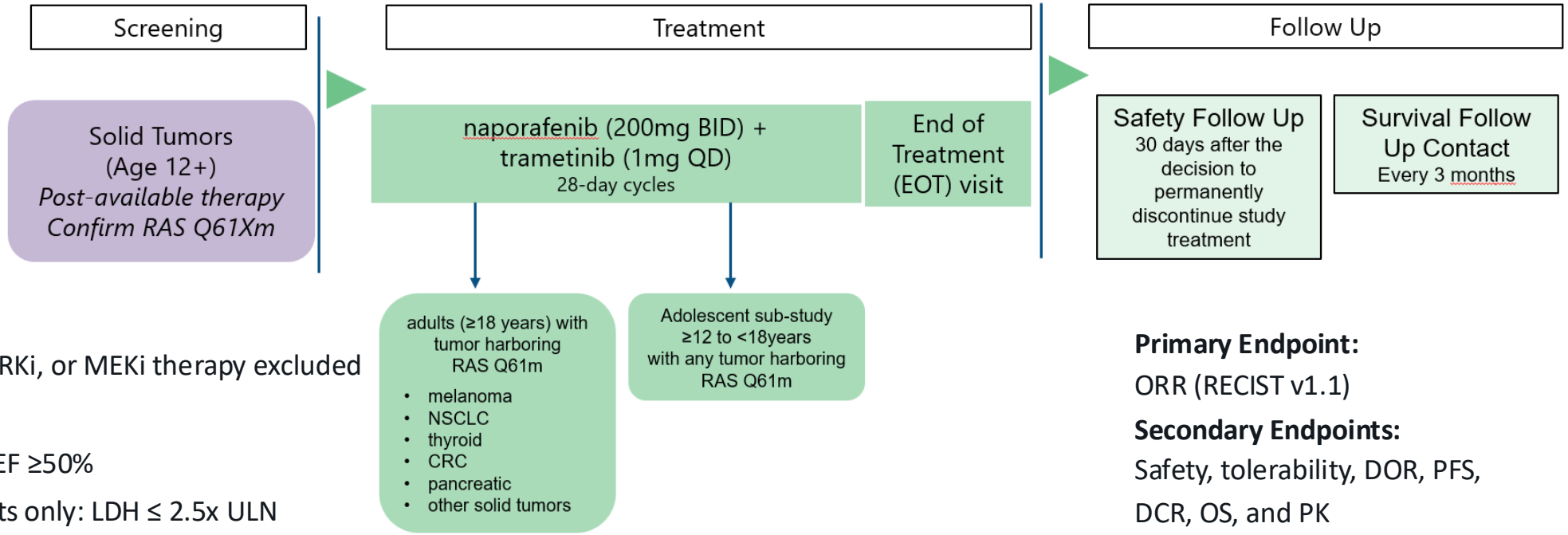
Naporafenib/Trametinib [200/1]	CLXH254X2102 [200/1]	CLXH254C12201 [200/1]
	N=54	N=30
Pts with dermatologic* toxicities, n(%)	49 (90.7)	26 (86.7)
Pts with G≥3 dermatologic* toxicities, n(%)	20 (37.0)	11 (36.7)
Pts with dermatitis acneiform, n(%)	17 (31.5)	9 (30.0)
Pts with G≥3 dermatitis acneiform, n(%)	4 (7.4)	1 (3.3)
Pts with rash, n(%)	23 (42.6)	11 (36.7)
Pts with G≥3 rash, n(%)	9 (16.7)	4 (13.3)
TEAE leading to permanent discontinuation of study treatment n(%)	10 (18.5)	6 (20.0)
	5/10 for skin tox TEAE	5/6 for skin tox TEAE
Median RDI, %	66.3 / 59.2	57.5 / 62.4

- Frequency of dermatologic toxicities increased, including high grade events, with naporafenib + trametinib compared to naporafenib monotherapy
- Primary prophylaxis for dermatologic toxicity (which was not mandatory) was introduced into prior trials by amendment late in the enrollment period for each study
- Majority of TEAE leading to permanent discontinuation were skin toxicities
- RDI of 200/1 dose suggests tolerability limitations

200/1 = 200 mg naporafenib BID (twice daily) + trametinib 1 mg QD (daily); G=CTCAE grade; Pts=patients; RDI=relative dose intensity; TEAE=treatment emergent adverse event
*"Dermatologic" includes MedDRA HLTs (rashes, eruptions and exanthems NEC; bullous conditions; dermatitis and eczema; exfoliative conditions) and the following PTs: dermatitis acneiform, drug eruption, drug reaction with eosinophilia and systemic symptoms, palmar-plantar erythrodysaesthesia, severe cutaneous adverse reaction, toxic skin eruption, photosensitivity reaction, skin fissures, pruritis
CLXH254C12201 DCO 30Dec2022; CLXH254X2102 DCO 04Aug2022

EORTC NIH NATIONAL CANCER INSTITUTE AACR American Association for Cancer Research

SEACRAFT-1 Study Design (NCT05907304)



Criteria:

Prior RASi, RAFi, ERKi, or MEKi therapy excluded

ECOG 0, 1, or 2

QTcF ≤450 and LVEF ≥50%

Melanoma patients only: LDH ≤ 2.5x ULN

Primary Endpoint:

ORR (RECIST v1.1)

Secondary Endpoints:

Safety, tolerability, DOR, PFS, DCR, OS, and PK

- Mandatory primary prophylaxis for management of skin toxicity
- As of 03 Sep 2024, 82 adult patients have been enrolled, 30 of whom have CRC or pancreatic cancer and whose data are not included in this presentation.

BID = twice daily; CRC = colorectal carcinoma; DCR=disease control rate; DOR=duration of response; ECOG=Eastern Cooperative Oncology Group; EOT = end of treatment; LDH=lactate dehydrogenase; LVEF=left ventricular ejection fraction; NSCLC = non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PK=pharmacokinetics; QD = once daily; ULN=upper limit normal; QTcF=corrected QT interval (Fridericia); RECIST=Response Evaluation Criteria in Solid Tumors

Demographics and Disposition

	Melanoma (N=14)	NSCLC (N=10)	Thyroid (N=10)	"other" (N=18)	All (N=52)
Sex, n(%)					
Male	8 (57.1)	4 (40.0)	7 (70.0)	13 (72.2)	32 (61.5)
Female	6 (42.9)	6 (60.0)	3 (30.0)	5 (27.8)	20 (38.5)
Median age at enrollment (years)	66.5	62.5	63.0	67.5	64.0
ECOG (screening), n(%)					
0	2 (14.3)	4 (40.0)	3 (30.0)	4 (22.2)	13 (25.0)
1	11 (78.6)	6 (60.0)	7 (70.0)	14 (77.8)	38 (73.1)
2	1 (7.1)	0	0	0	1 (1.9)
Median number of prior lines of systemic therapy	2.0	2.0	1.0	3.0	2.0
Prior lines of systemic therapy, n(%)					
1	5 (35.7)	2 (20.0)	4 (40.0)	1 (5.6)	12 (23.1)
2	3 (21.4)	3 (30.0)	1 (10.0)	7 (38.9)	14 (26.9)
≥3	5 (35.7)	4 (40.0)	1 (10.0)	10 (55.6)	20 (38.5)
Missing / not applicable*	1 (7.1)	1 (10.0)	4* (40.0)	0	6* (11.5)

ECOG=Eastern Cooperative Oncology Group; NSCLC=Non-small cell lung cancer;
*Systemic anti-cancer therapy was not administered to 4 patients with thyroid cancer who had only prior surgeries and radiotherapy.
Total excludes patients with CRC and pancreatic cancer; Source: Table 14.1.1, Table 14.1.2 (DCO 03Sep2024)
"Other" includes: Appendix, Ampulla of vater, Cholangiocarcinoma (n=4), Common bile duct, Duodenal, GOJ adenocarcinoma, Leiomyosarcoma, Neuroendocrine (rectum), Ovarian, Peripheral nerve sheath tumor, Prostate, Rhabdomyosarcoma, Salivary gland, Small intestine, Urothelial

- Baseline LDH reported for 13 of 14 melanoma patients: 42.9% with LDH ≤ULN, 21.4% with LDH >ULN and ≤2x ULN, and 28.6% with LDH >2x ULN
- Majority of RAS mutations were NRAS Q61R (35%), KRAS Q61H (23%), and NRAS Q61K (15%)
- As of 03 Sep 2024, 24 (46.2%) patients have discontinued study treatment, primarily due to disease progression (28.8%)
- 1 patient (1.9%) discontinued treatment for an unrelated AE
- Treatment was ongoing in 28 (53.8%) of patients as of the data cut-off date

ENA 2024
EORTC NCI AACR
36th Symposium

Mandatory Primary Prophylaxis in SEACRAFT-1 Improved Tolerability

Primary Prophylaxis Regimen

- Oral antibiotic (e.g., doxycycline, minocycline, oxytetracycline)
  - Start 1-3 days prior to first dose study treatment
  - Mandatory for first 8 weeks (daily)
  - If no symptoms of dermatologic toxicity are reported in this period, antibiotic prophylaxis can be discontinued with close evaluation
  - At first appearance of dermatologic toxicity during study treatment, the antibiotic should be restarted and continued daily administration for 4 weeks. If the dermatologic reaction resolves after 4 weeks, discontinue antibiotics with close monitoring for the reappearance of any dermatologic reactions.
- Prophylactic topical low-potency corticosteroids

With mandatory primary prophylaxis in SEACRAFT-1:

- Decreased overall and Grade ≥3 frequency of dermatologic toxicities (including dermatitis acneiform and rash)
- No patient has permanently discontinued naporafenib (or trametinib) due to dermatologic toxicity TEAE
- Improved relative dose intensity (RDI)

	CLXH254X2102 [200/1]	CLXH254C12201 [200/1]	SEACRAFT-1 [200/1]
	N=54	N=30	N=52
Pts with dermatologic* toxicities, n(%)	49 (90.7)	26 (86.7)	38 (73.1)
Pts with G≥3 dermatologic* toxicities, n(%)	20 (37.0)	11 (36.7)	6 (11.5)
Pts with dermatitis acneiform, n(%)	17 (31.5)	9 (30.0)	11 (21.2)
Pts with G≥3 dermatitis acneiform, n(%)	4 (7.4)	1 (3.3)	1 (1.9)
Pts with rash, n(%)	23 (42.6)	11 (36.7)	22 (42.3)
Pts with G≥3 rash, n(%)	9 (16.7)	4 (13.3)	3 (5.8)
TEAE leading to permanent discontinuation of study treatment n(%)	10 (18.5)	6 (20.0)	5 (9.6)
	5/10 for skin tox TEAE	5/6 for skin tox TEAE	0 for skin tox TEAE
Median RDI, % [naporafenib / trametinib]	66.3 / 59.2	57.5 / 62.4	98.5 /100

200/1 = 200mg naporafenib BID + trametinib 1mg QD; G=CTCAE grade; Pts=patients; RDI=relative dose intensity; TEAE=treatment emergent adverse event

*"Dermatologic" includes MedDRA HLTs (rashes, eruptions and exanthems NEC; bullous conditions; dermatitis and eczema; exfoliative conditions) and the following PTs: dermatitis acneiform, drug eruption, drug reaction with eosinophilia and systemic symptoms, palmar-plantar erythrodysaesthesia, severe cutaneous adverse reaction, toxic skin eruption, photosensitivity reaction, skin fissures, pruritis

Data cut offs- CLXH254C12201 30Dec2022; CLXH254X2102 04Aug2022; SEACRAFT-1 03Sep2024

ENA 2024
EORTC NCI AACR
36th Symposium

Naporafenib + Trametinib is Safe and Tolerable

TRAE Occurring in ≥5% patients	All Patients(N=52)	
Preferred Term [n(%)]	**All Grades**	**≥Grade 3**
Patients with at least 1 TRAE	44 (84.6)	15 (28.8)
Rash	21 (40.4)	3 (5.8)
Dermatitis acneiform	11 (21.2)	1 (1.9)
Constipation	9 (17.3)	0
Diarrhea	8 (15.4)	2 (3.8)
Stomatitis	8 (15.4)	2 (3.8)
Fatigue	8 (15.4)	1 (1.9)
Rash maculo-papular	7 (13.5)	2 (3.8)
Nausea	7 (13.5)	1 (1.9)
AST increased	7 (13.5)	1 (1.9)
Pruritis	6 (11.5)	0
ALT increased	5 (9.6)	2 (3.8)
Pyrexia	4 (7.7)	1 (1.9)
Decreased appetite	4 (7.7)	0
Myalgia, vomiting (each)	3 (5.8)	1 (1.9)
Anaemia, Arthralgia, Dry Mouth, Oedema Peripheral, Paronychia (each)	3 (5.8)	0

ALT=alanine aminotransferase ; AST=aspartate aminotransferase; PK=Pharmacokinetics; TRAE=Treatment-related adverse event.
Table above: Source: Table 14.3.1.3 (DCO 03Sep2024),Safety data excludes patients with CRC and pancreatic cancer; Table to right: Source: Table 14.3.1.1 (DCO 03Sep2024)

- Toxicities were generally low grade and manageable
- 1 Grade 5 TEAE was reported
- PK profiles were similar to those from previous clinical trials
- No apparent drug-drug interactions have been identified between naporafenib and trametinib

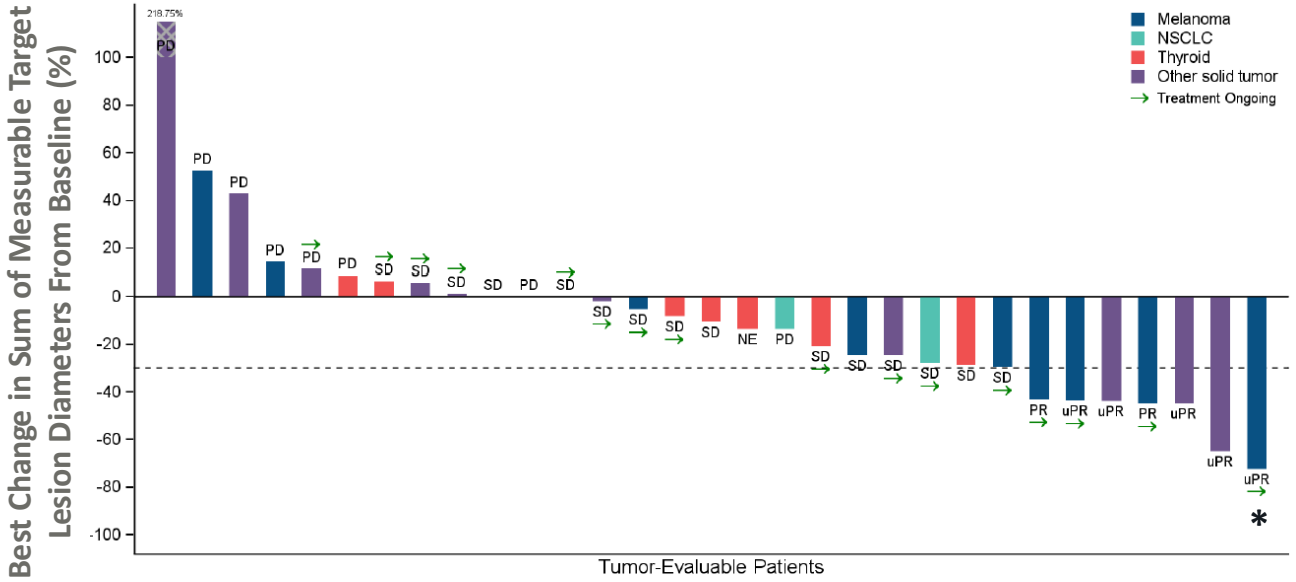
AE Category Patients experiencing at least one [n(%)]	**All (N=52)**
AE leading to d/c naporafenib	4 (7.7)
Naporafenib-related	1 (1.9)[a]
AE leading to napo dose reduction	7 (13.5)[b]
Naporafenib-related	6 (11.5)
AE leading to d/c trametinib	5 (9.6)
Trametinib-related	2 (3.8)[a]
AE leading to trametinib dose reduction	6 (11.5)
Trametinib-related	5 (9.6)

[a] Grade 3 worsening nausea (permanent discontinuation of both study drugs), Grade 2 LVEF decreased (permanent discontinuation of trametinib)
[b] TEAE leading to dose reduction: diarrhea, pyrexia, rash, follicular eczema, peripheral oedema, immune thrombocytopenia, rash pustular, urticaria, vomiting

Preliminary Efficacy Across Tumor Types

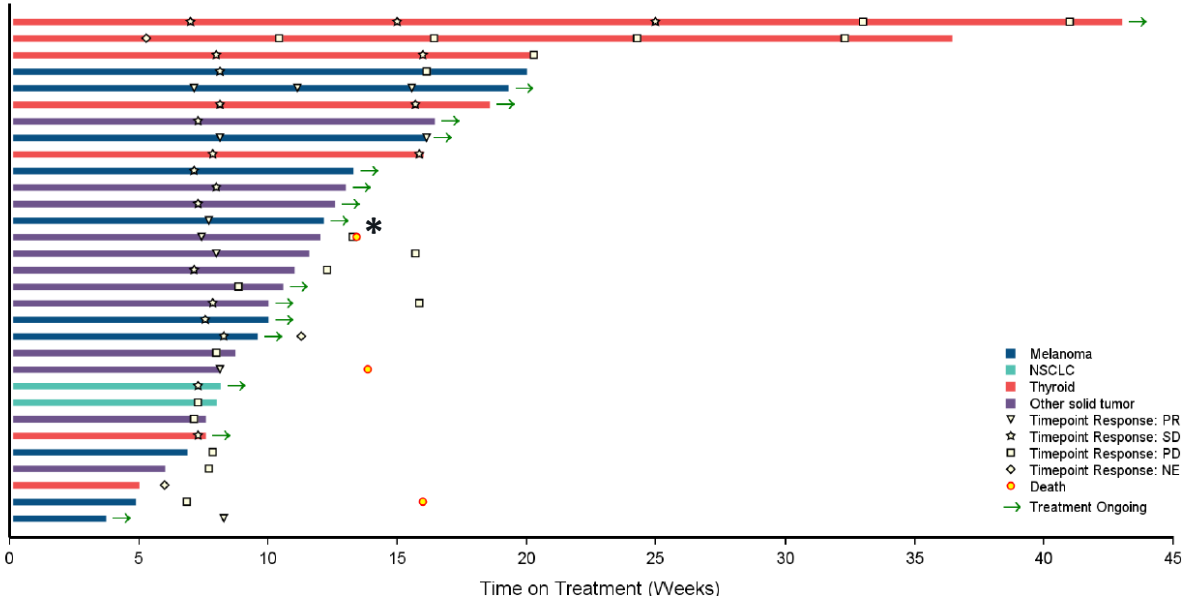
Efficacy-evaluable[1] RAS Q61X solid tumor patients (N=31)

naporafenib + trametinib (200/1)[2]



Efficacy-evaluable[1] RAS Q61X solid tumor patients (N=31)

naporafenib + trametinib (200/1)[2]



- 23% (7/31) response rate (3 PRs, 4 uPRs)
- 71% (22/31) disease control rate (CR+PR+SD)
- mDOR not reported as data were immature as of the DCO date

DA=disease assessment (q8weeks); NSCLC=Non-small cell lung cancer; PD=progressive disease; PR=partial response; SD=stable disease; uPR= unconfirmed PR

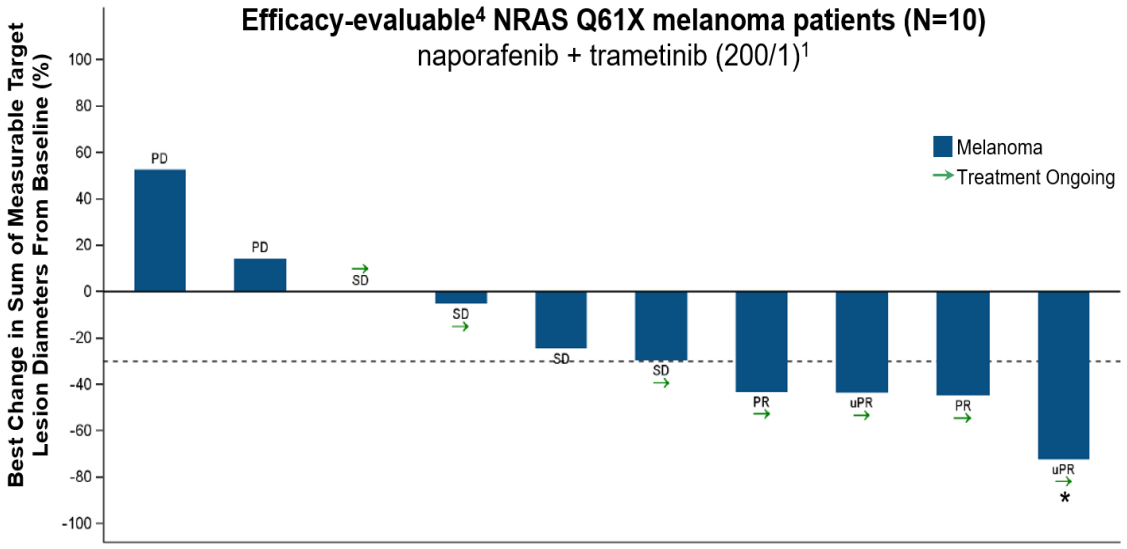
[1] Defined as patients who received at least one dose of study drug, had measurable disease at baseline per RECIST, and had at least one post-baseline response assessment

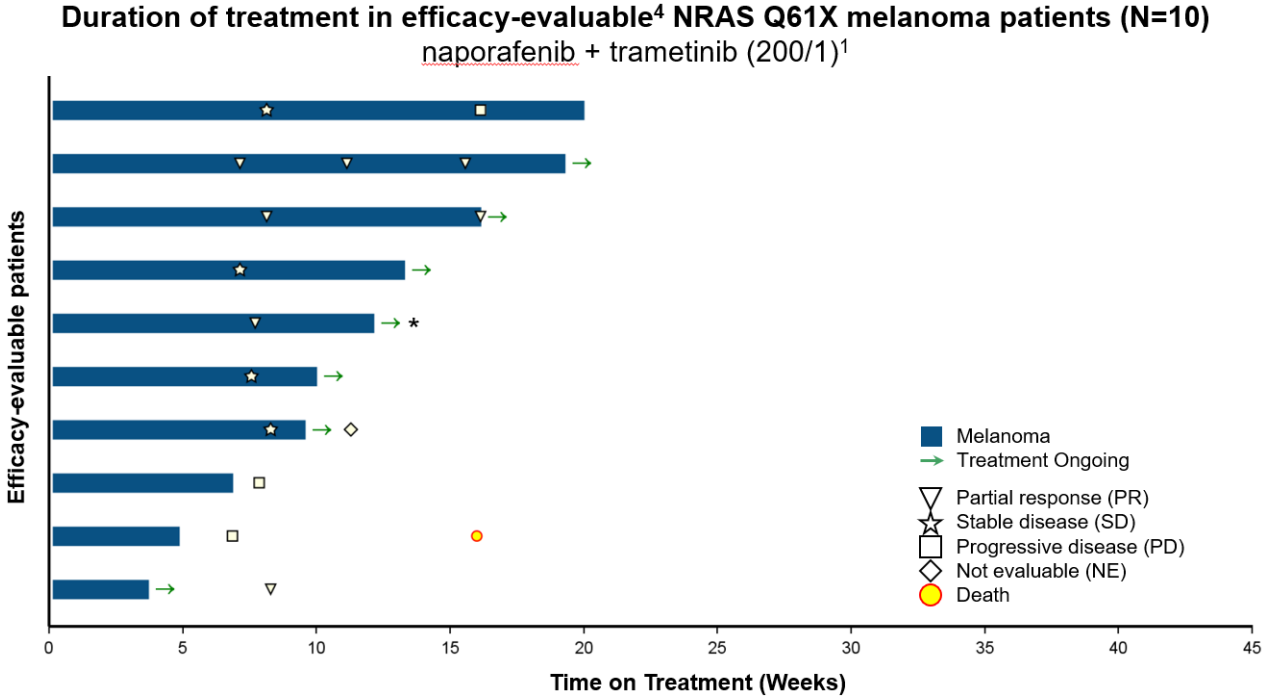
[2] naporafenib 200 mg BID + trametinib 1 mg QD (BID: twice daily; QD: once daily)

* Patient response was confirmed after DCO

Source: Fig 14.2.1.2a and Fig 14.2.2.2a; excludes CRC and pancreatic patients (DCO 05Sep2024)

Promising Efficacy Observed in SEACRAFT-1 Melanoma Cohort





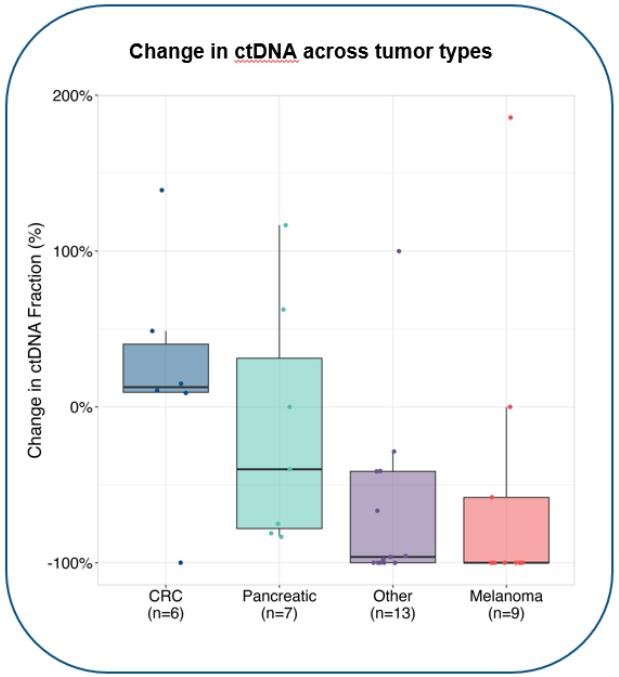
- 40% (4/10) response rate (3 confirmed PR, 1 uPR[2])
- 80% (8/10) disease control rate[3]
- Response observed in patient with mucosal melanoma, a population which had not been enrolled in previous studies

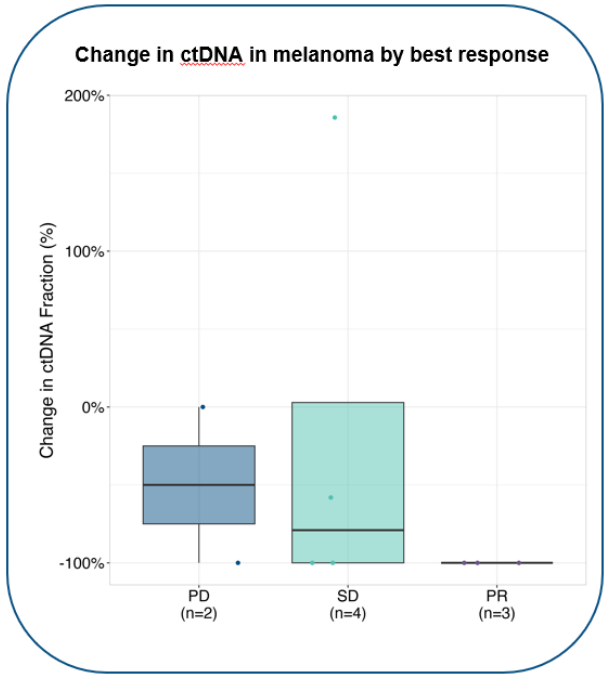
- 70% (7/10) of patients remain on treatment as of data cutoff, including all confirmed and unconfirmed responders

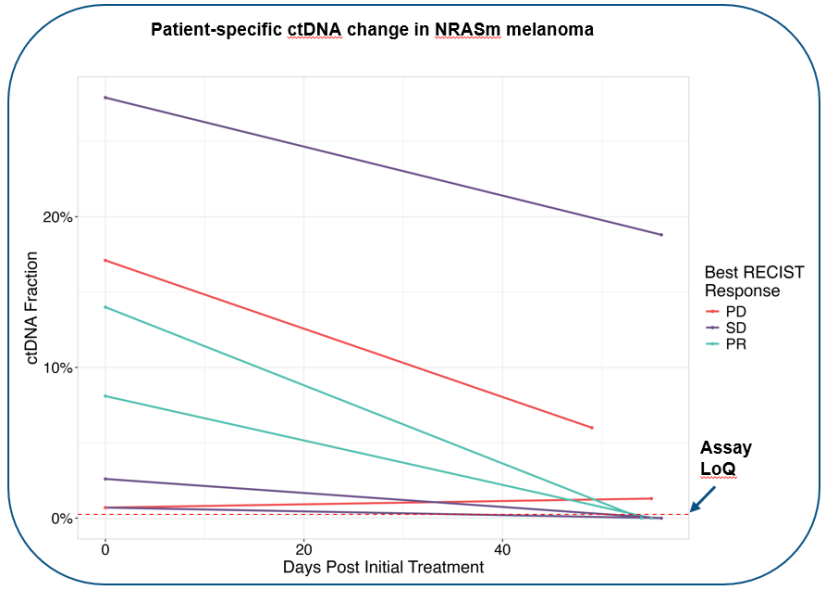
Data cutoff (DCO) 05Sep2024
* Patient response was confirmed after DCO
[1] naporafenib 200 mg BID + trametinib 1 mg QD (BID: twice daily; QD: once daily)
[2] Melanoma patient with uPR continuing study treatment with next scan pending;
[3] Disease control rate (DCR) = CR + PR + SD; uPR is included
[4] Defined as patients who received at least one dose of study drug, had measurable disease at baseline per RECIST, and had at least one post-baseline response assessment
NRASm: NRAS mutated; PR: partial response; uPR: unconfirmed partial response; PD: progressive disease: SD: stable disease

EORTC NIH NATIONAL CANCER INSTITUTE AACR American Association for Cancer Research

Decrease in ctDNA Correlates With RECIST Response







ctDNA=circulating DNA; LoQ=limit of quantification; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease

- Across all tumor types, ctDNA was undetectable at the majority of timepoints where tumor shrinkage was observed by imaging
- Greatest decreases in ctDNA at C2D1 were observed in melanoma relative to other solid tumors
- 14 melanoma patients enrolled: 13 patients with NRAS Q61X mutation, 1 patient with HRAS Q61R mutation
- The 10 efficacy evaluable melanoma patients had tumors with NRAS Q61R (n=6), Q61L (n=2), or Q61K (n=2) mutations
  - 1 of 10 efficacy evaluable patients not evaluated for ctDNA
- Within NRAS Q61X melanoma, patients with a best response of PR showed greatest decreases in ctDNA at C2D1
- In NRAS Q61X melanoma patients, PRs and SDs correlated with undetectable ctDNA at tumor imaging timepoints

CONCLUSIONS

- Naporafenib + trametinib is a safe and tolerable regimen with clinically relevant activity in patients with melanoma
  - The addition of mandatory primary prophylaxis for skin toxicity resulted in a more tolerable regimen compared with prior studies using ≥Grade 3 TEAEs, discontinuation of study drug for TEAEs, and relative dose intensity as surrogates for tolerability
  - Efficacy signal was reproduced in patients with melanoma harboring RAS Q61X mutation, including a patient with mucosal melanoma, which was a population not enrolled in prior studies
  - In other tumor types, transient responses per RECIST and decreases in target lesions were seen but durability was limited
  - Decreases in ctDNA appear to correlate with RECIST response

- These results support the continued development of naporafenib + trametinib for the treatment of patients with NRASm melanoma in SEACRAFT-2 [NCT06346067]

ENA 2024
EORTC NCI AACR
36th Symposium

On behalf of the SEACRAFT-1 Study Team,

Canada

Verspeeten Family Cancer Centre, London Health Sciences Centre (Eric Winquist MD)

BC Cancer Agency - Vancouver (Nicole Chau MD)

USA

MD Anderson Cancer Center (David Hong MD)

SCRI Oncology Partners (Meredith McKean MD)

NEXT Oncology VA (Alexander Spria MD)

UC San Francisco (Adil Daud MD)

Univ Wisconsin Hospitals and Clinics (Dustin Deming MD)

FL Cancer Specialists North (Adewale Fawole MD)

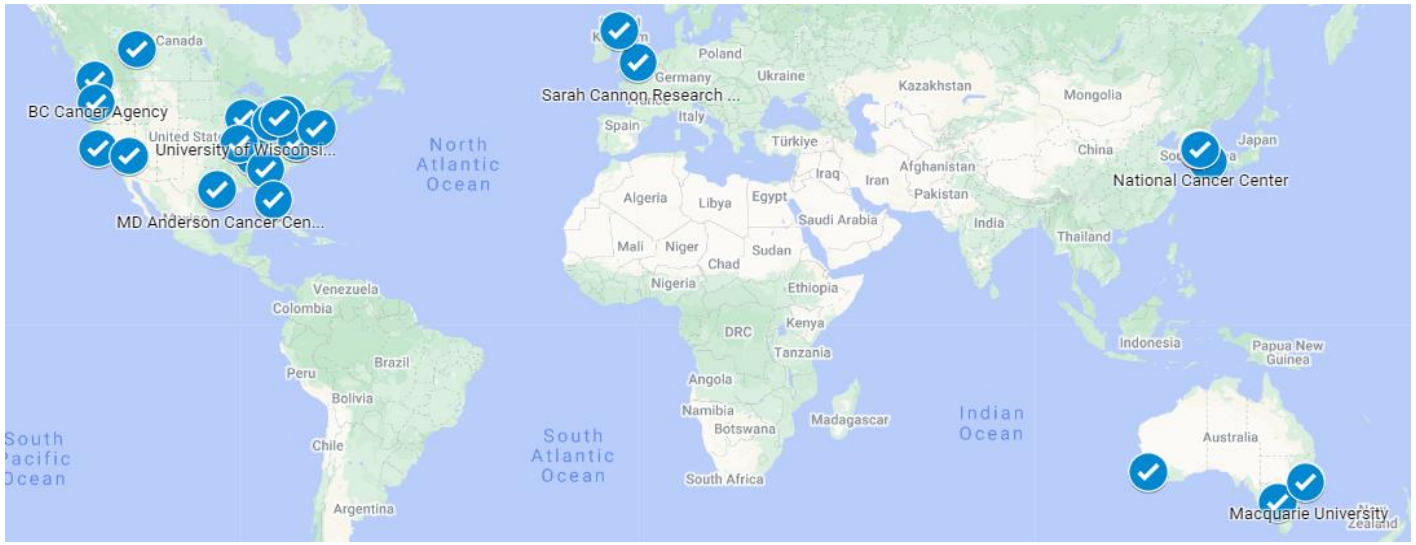
FL Cancer Specialists & Research Institute (Judy Wang MD)

Washington Univ School of Medicine (Brian Van Tine MD)

Comprehensive Cancer Centers of Nevada (Kyaw Thein MD)

Winship Cancer Institute, Emory Univ (Olumide Gbolahan MD)

Oregon Health & Science University (Shivaani Kummar MD)



United Kingdom

SCRI UK (Elisa Fontana MD)

Australia

Linear Clinical Research Ltd (Michael Millward MD)

Prince of Wales Hospital (Melvin Chin MD)

Republic of Korea

Samsung Medical Center (Jeeyun Lee MD)

Inje University Haeundae Park Hospital (Ilhwan Kim MD)

National Cancer Center (Young Joo Lee MD)

Catholic University of Korea, St. Mary's Hospital (Sook Hee Hong MD)

Seoul National University Hospital (Tae Min Kim MD)

Seoul National University Bundang Hospital (Keun Wook Lee MD)

THANK YOU to the patients, their families, and caregivers for participating in SEACRAFT-1