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Daiichi-Sankyo

WCLC 2019 Highlights
DAIICHI SANKYO CO., LTD

September 10, 2019, 7:00-8:30pm (EDT)

Antoine Yver, MD, MSc
Global Head R&D Oncology

Forward-Looking Statements

Management strategies and plans, financial forecasts, future projections and policies, and R&D information that Daiichi Sankyo discloses in this material are all classified as Daiichi Sankyo's future prospects. These forward looking statements were determined by Daiichi Sankyo based on information obtained as of today with certain assumptions, premises and future forecasts, and thus, there are various inherent risks as well as uncertainties involved. As such, please note that actual results of Daiichi Sankyo may diverge materially from Daiichi Sankyo's outlook or the content of this material. Furthermore, there is no assurance that any forward-looking statements in this material will be realized. Regardless of the actual results or facts, Daiichi Sankyo is not obliged and does not have in its policy the duty to update the content of this material from the date of this material onward.

Compounds under discussion are investigational agents and are not approved by the FDA or any other regulatory agency worldwide as a treatment for indications under investigation. Efficacy and safety have not been established in areas under investigation. There are no guarantee that these compounds will become commercially available in indications under investigation.

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Today's Agenda

- **DS-1062: data update / what it means for Daiichi Sankyo**
- **U3-1402: data update / what it means for Daiichi Sankyo**
- **Recent Milestones**
- **Upcoming Events**

Today's Agenda

DS-1062: data update / what it means for Daiichi Sankyo

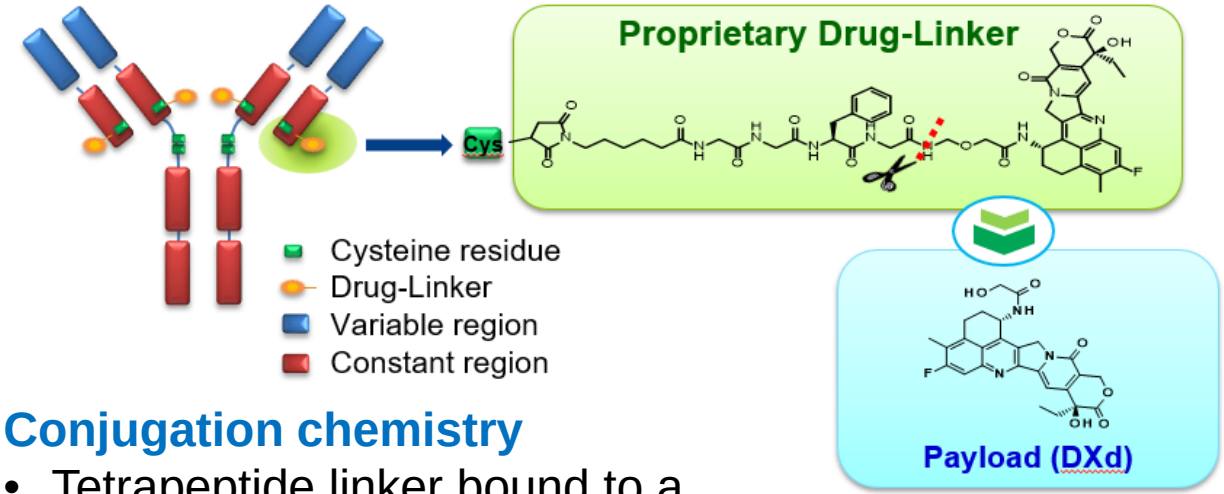
U3-1402: data update / what it means for Daiichi Sankyo

Recent Milestones

Upcoming Events

DS-1062: Background

DS-1062 structure: TROP2-targeting antibody-drug conjugate[1] with a novel topoisomerase I inhibitor (DXd)[2,3]

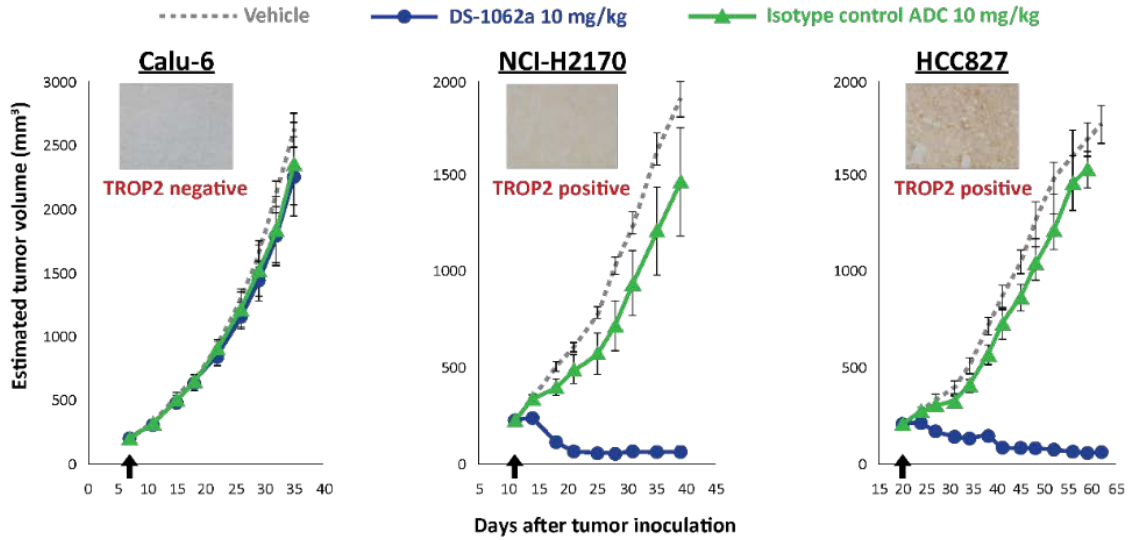


Conjugation chemistry

- Tetrapeptide linker bound to a cysteine residue of the antibody
- DS-1062 is a selective DAR4 conjugate

DAR, drug-to-antibody ratio; DXd, exatecan derivative; TROP2, trophoblast cell-surface antigen.

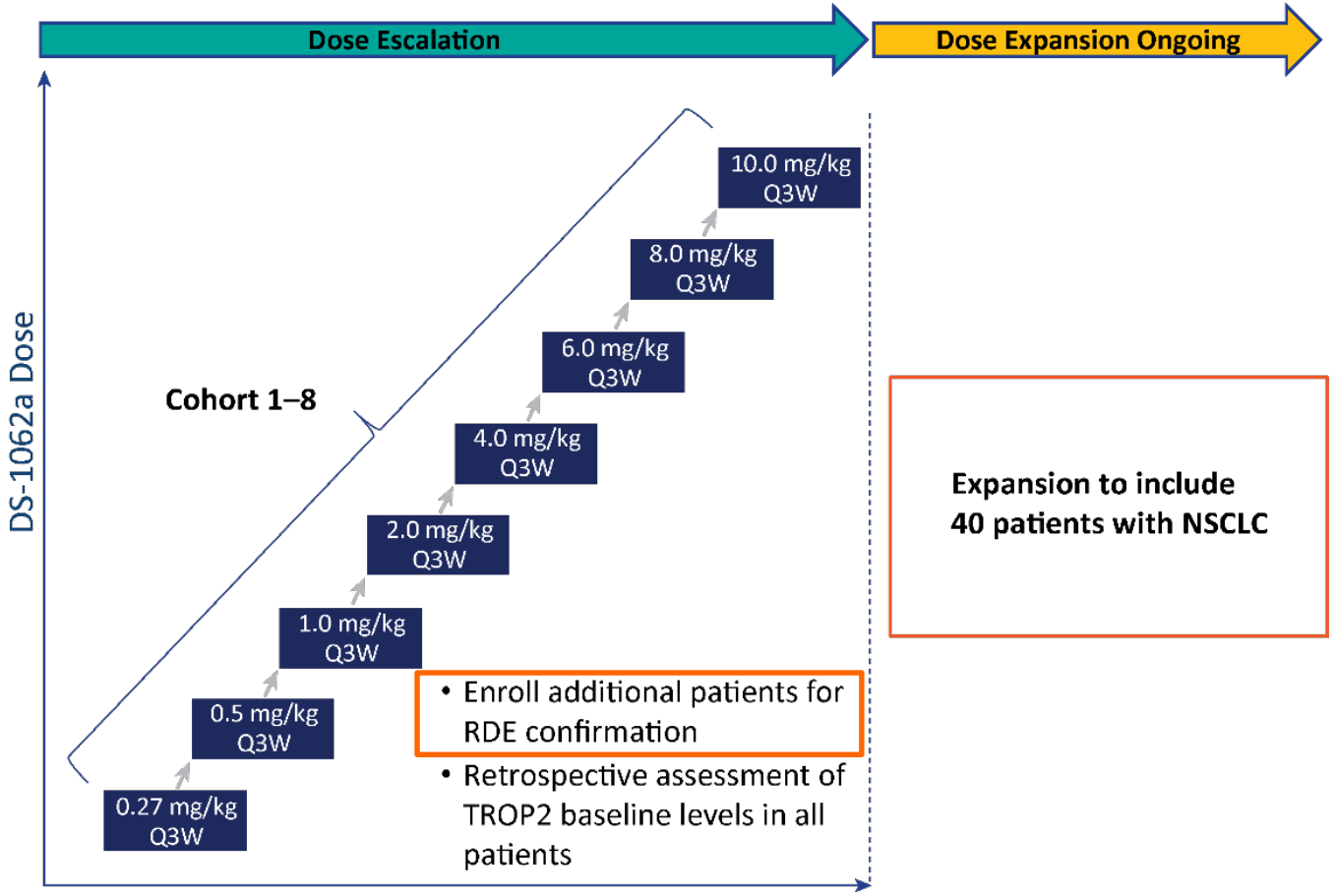
DS-1062 Antitumor activity in lung cancer xenograft mouse models: Stronger antitumor activity in TROP2-positive tumors[1,4]



1. Okajima D, et al. 22nd JFCR-ISCC 2017. Poster P6.
2. Nakada T, et al. *Bioorg Med Chem Lett*. 2016;26:1542–5.
3. Nakada T. et al. *Chem Pharm Bull*. 2019;67:173–85.
4. Okajima D, et al. ASCO 2018. Abstract e24206.

Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: Phase 1 Study Design (NCT03401385)



- Ongoing first-in-human, US and Japan dose escalation and expansion phase 1 study of DS-1062 in unselected pts with unresectable advanced NSCLC relapsed/refractory to SOC
  - Male (57.7%)
  - Stage IV disease (88.5%)
  - Adenocarcinoma histology (73.1%)
  - ECOG PS 1 (80.8%)
  - Failed prior immune checkpoint inhibitors (86.5%)

DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; Pt, patient; Q3W, every 3 weeks; RDE, recommended dose for expansion; SOC, standard of care; TROP2, trophoblast cell-surface antigen 2.

Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: Safety

TEAEs, regardless of causality, (in ≥10% of pts), n (%) (N=52)					
	All Grades	Grade ≥3		All grades	Grade ≥3
Any TEAE	48 (92.3)	22 (42.3)	Constipation	7 (13.5)	0
Fatigue	19 (36.5)	2 (3.8)	Cough	7 (13.5)	0
Nausea	19 (36.5)	0	Diarrhea	7 (13.5)	0
Alopecia	15 (28.8)	0	ALT increased	6 (11.5)	0
Decreased appetite	14 (26.9)	0	Weight decreased	6 (11.5)	0
Anemia	12 (23.1)	0	Dehydration	5 (9.6)	0
Stomatitis/mucosal inflammation	12 (23.1)	2 (3.8)	Dyspnea	5 (9.6)	1 (1.9)
Vomiting	12 (23.1)	0	Headache	5 (9.6)	0
Infusion related reaction	11 (21.2)	0	Pain	5 (9.6)	1 (1.9)
Rash	8 (15.4)	0			

Data cut-off: July 3, 2019.

- DLT reached at 10.0 mg/kg;[a] MTD at 8.0 mg/kg is also RDE, median exposure duration was 10.6 (range 3.0–43.1) weeks
- Serious TEAEs occurred in 14 (26.9%) pts and death in 3 (5.8%) pts; no deaths were related to study drug
- TEAEs associated with dose reduction,[b] interruption, or discontinuation[c] in 5 (9.6%), 5 (9.6%), and 2 (3.8%) pts, respectively
- One pt (1.9%) with disease progression treated with the 6.0 mg/kg dose developed a pulmonary adverse event of special interest of respiratory failure (grade 5), adjudicated as not an ILD
  - Including cases post-data cutoff, 4 not-yet adjudicated possible ILD reports were observed (1 grade 2 pneumonitis [6.0 mg/kg], 1 grade 2 organized pneumonia [8.0 mg/kg], 1 grade 2 pneumonitis [8.0 mg/kg], and 1 grade 5 [respiratory failure in a pt with disease progression; 8.0 mg/kg])

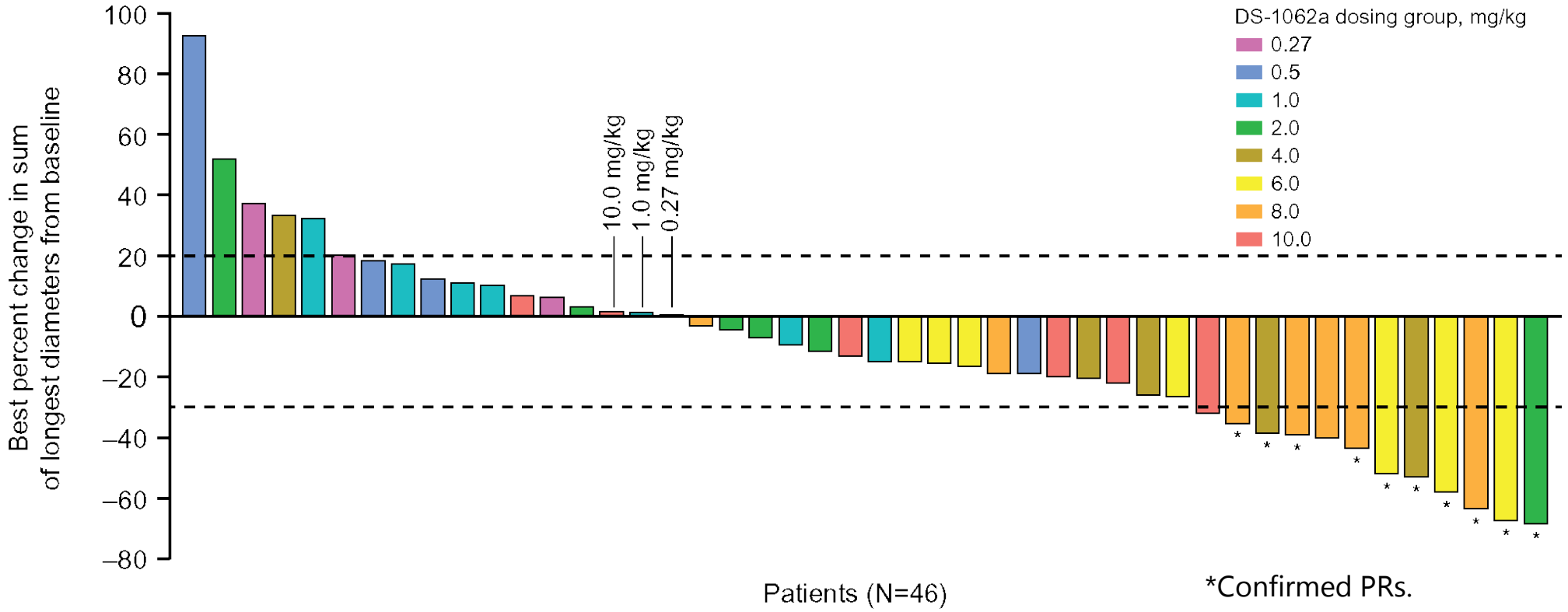
[a]2 DLTs occurred at the 10.0 mg/kg dose; 1 pt with mucosal inflammation and another pt with stomatitis. One DLT occurred at the 6.0 mg/kg dose in a pt with rash maculopapular.
[b]The most frequent TEAE leading to dose reduction was mucosal inflammation (2 pts [3.8%], 10.0 mg/kg group).
[c]TEAEs leading to drug discontinuation (1 pt each) were pleural effusion (0.27 mg/kg) and pain (2.0 mg/kg).

ALT, alanine aminotransferase; DLT, dose-limiting toxicity; ILD, interstitial lung disease; MTD, maximum tolerated dose; PD, progressive disease; Pt, patient; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event.

Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: Tumor Response

- **12 PRs (10 confirmed; 2 too early to confirm) across all doses in dose escalation**
  - **At the 8-mg/kg dose there were 5/7 PRs and 2/7 SDs, and 6/7 pts are ongoing**



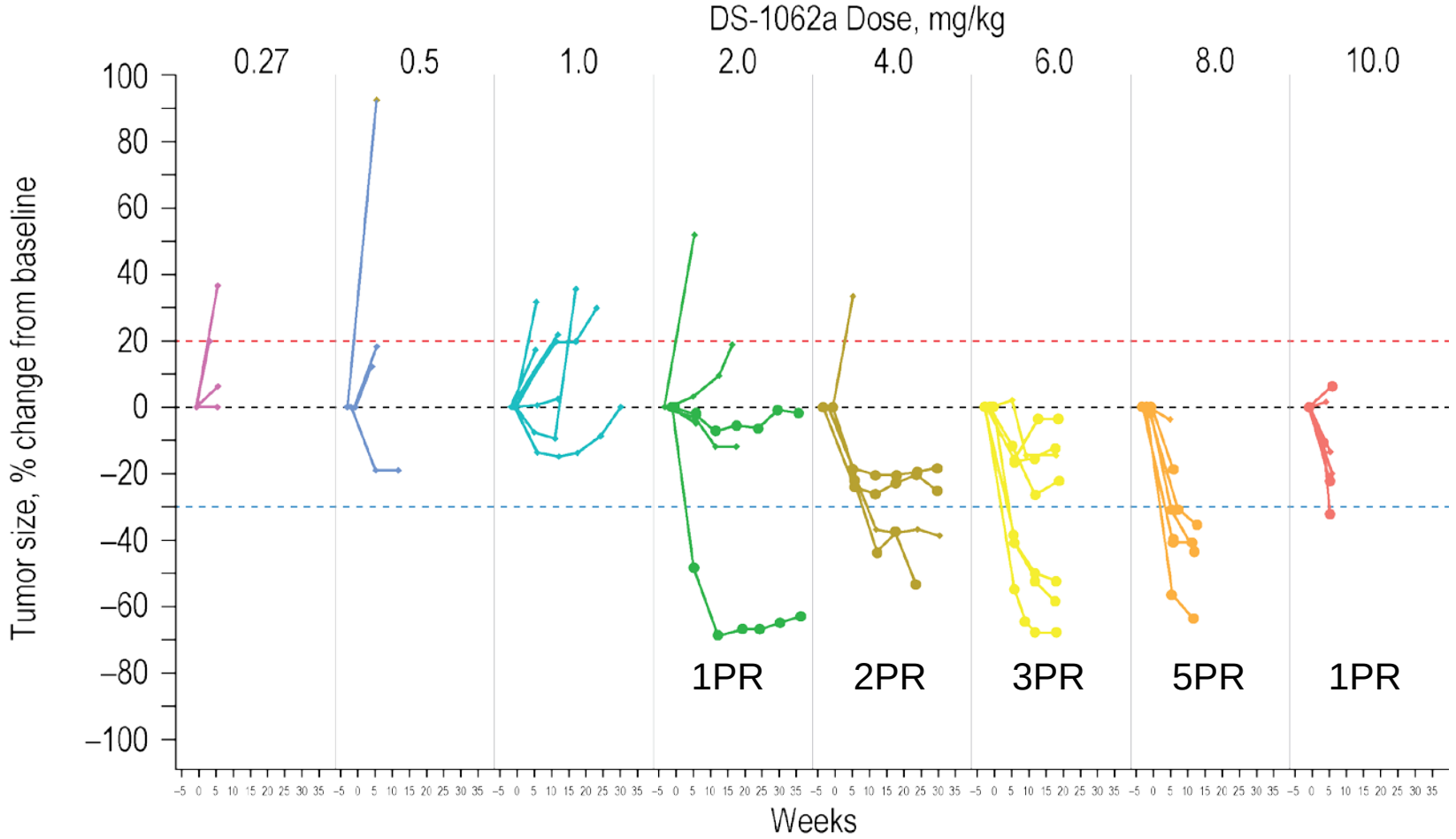
Data cut-off: July 3, 2019.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor, HER2; human epidermal growth factor receptor 2; PD, progressive disease; PR, partial response; Pt, patient; SD, stable disease.

Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: Tumor Response

Clear dose-effect on frequency of response



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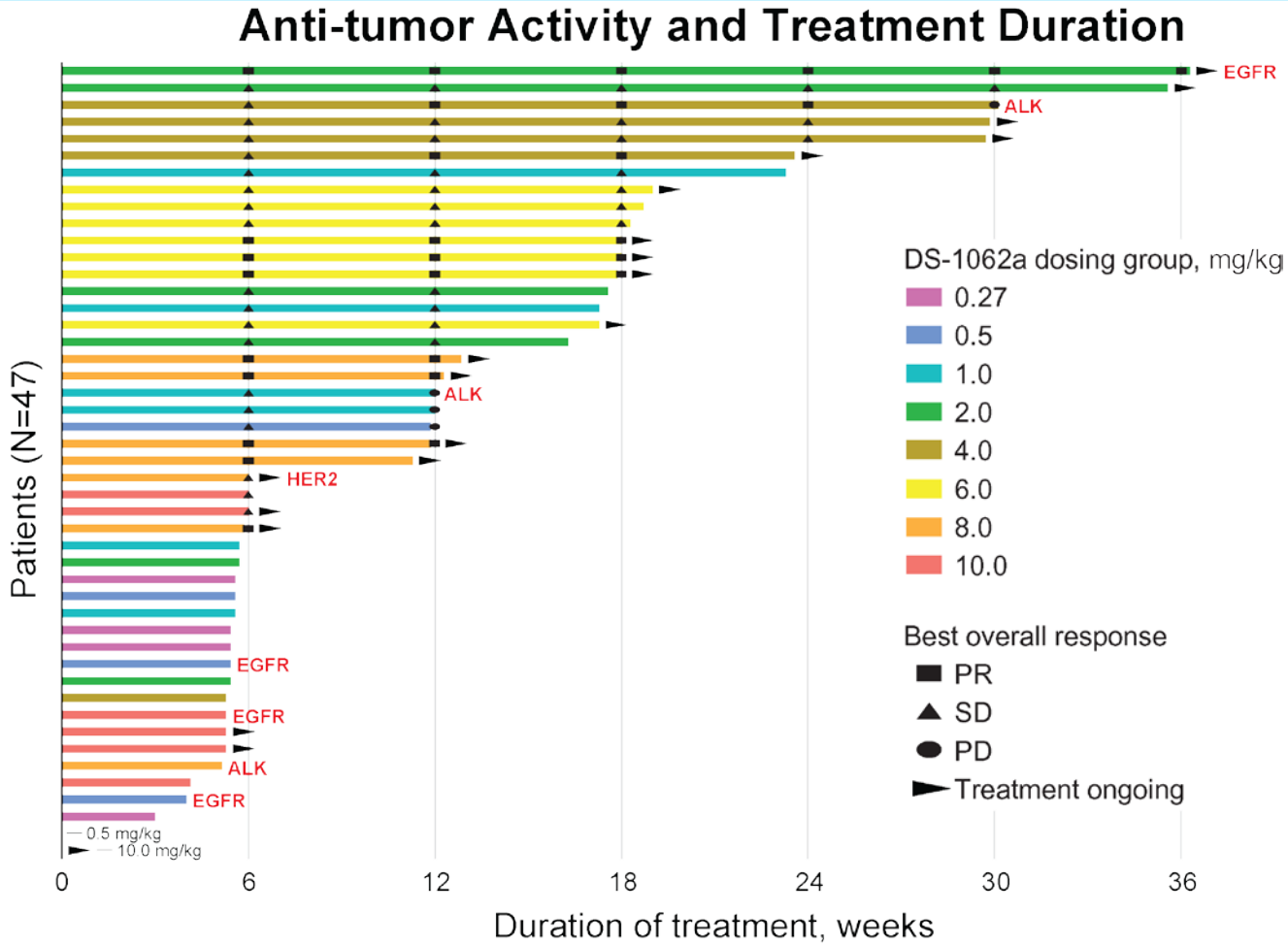
Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: Tumor Response

Durable responses seen at multiple dose levels



Data cut-off: July 3, 2019.

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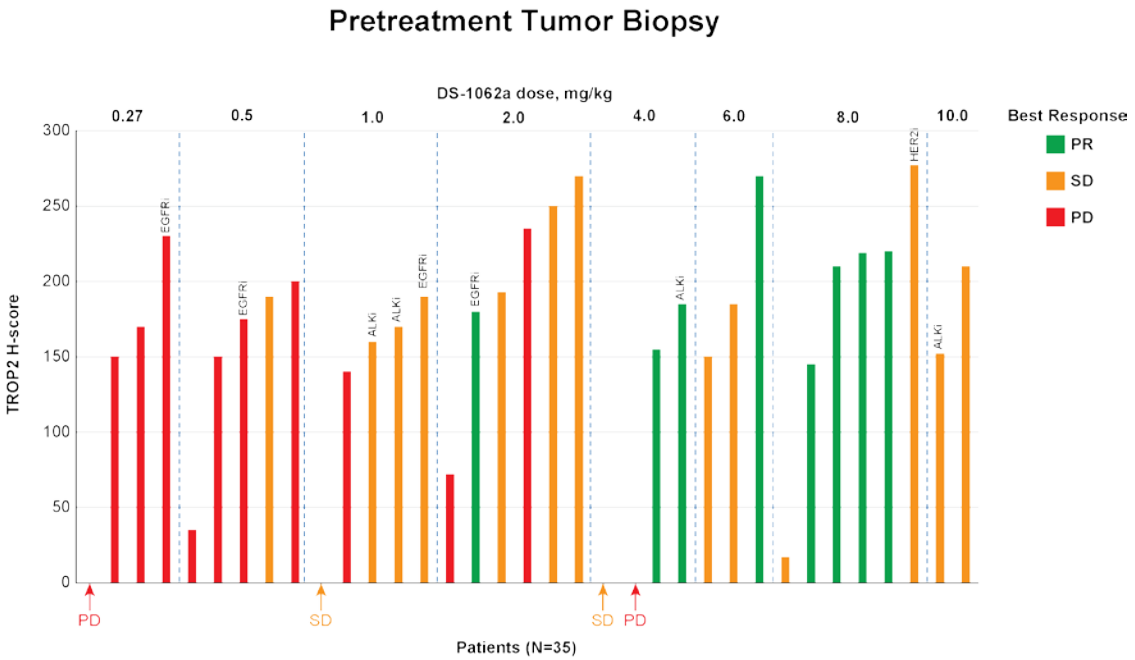
Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

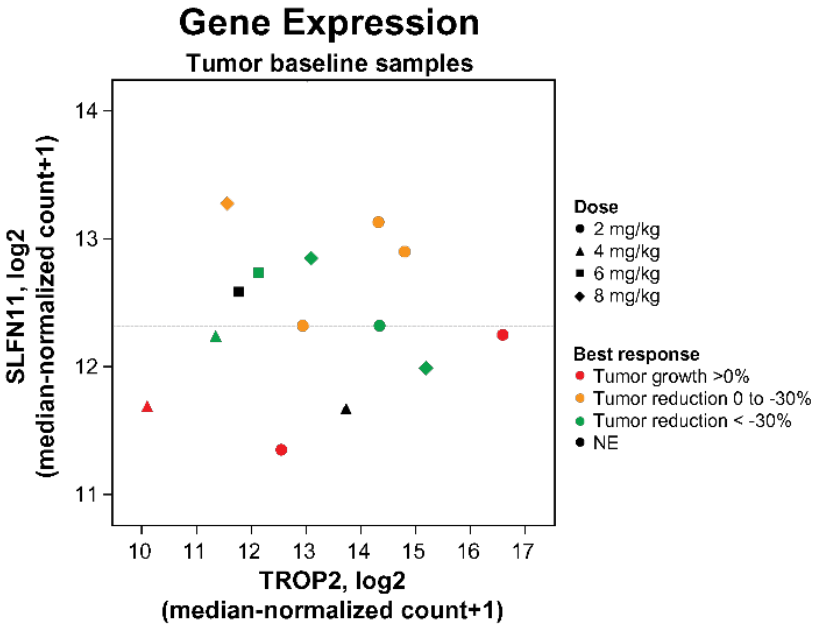
DS-1062: Biomarkers / Genomics

TROP2 IHC score: tended to be higher in pts with PR

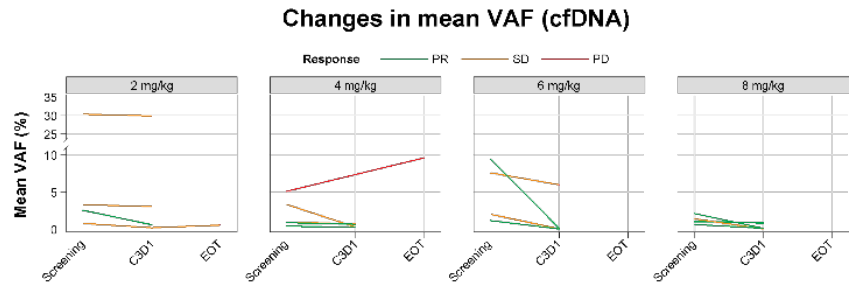


Prior TKI treatment (ALKi; EGFRi; HER2i) shown above bars;
the other 26 pts received prior I/O
6/8 pts with PR had an H score > median (vs 8/15 with SD and 4/12 with PD).

Data cut-off: July 3, 2019.



TROP2 and SLFN11 gene expression trended higher in pts with tumor reduction



DS-1062 reduced cfDNA in pts with SD and PR

ALKi, anaplastic lymphoma kinase inhibitor; BL, baseline; C3D1, cycle 3, day 1; cfDNA, circulating free DNA; EGFRi, epidermal growth factor receptor inhibitor; EOT, end of treatment; HER2i; human epidermal growth factor receptor 2 inhibitor; IHC, immunohistochemistry; H-score, "histo" score; I/O, immuno-oncology; NE, non-evaluable; PD, progressive disease; PR, partial response; Pt, patient; SD, stable disease; SLFN11, Schlafen family member 11, TROP2, trophoblast cell-surface antigen 2; VAF, variant allele fraction.

Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: Summary

- DS-1062 is well tolerated in doses up to 8.0 mg/kg
- 8.0 mg/kg dose defined as MTD and RDE
- Dose effect on anti-tumor activity observed over 2.0–8.0 mg/kg
- 12 PRs (10 confirmed, 2 too early) observed during dose escalation in heavily pretreated unselected NSCLC pts relapsed from or having progressed on standard of care, including immune checkpoint inhibitors
- This study is currently in dose expansion
  - 10 of 40 pts enrolled in dose expansion
  - 35 pts ongoing as of August 20, 2019

MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PR, partial response; Pt, patient; RDE, recommended dose for expansion.

Source: Heist-R *et al.*, Abstract #MA25.10, WCLC 2019

DS-1062: What It Means for Daiichi Sankyo?

DS-1062 appears to have the characteristics of a “drug-to-be”

- Clear activity, dose effect, durability and tolerability

DXd portability further established, added technology of **site-selective DAR4 conjugation** validated

Driven by emergent NSCLC Data, **Differentiation vs IMMU-132** appears credible

Fast-to-market US path emerging in NSCLC

Today's Agenda

DS-1062: data update / what it means for Daiichi Sankyo

U3-1402: data update / what it means for Daiichi Sankyo

Recent Milestones

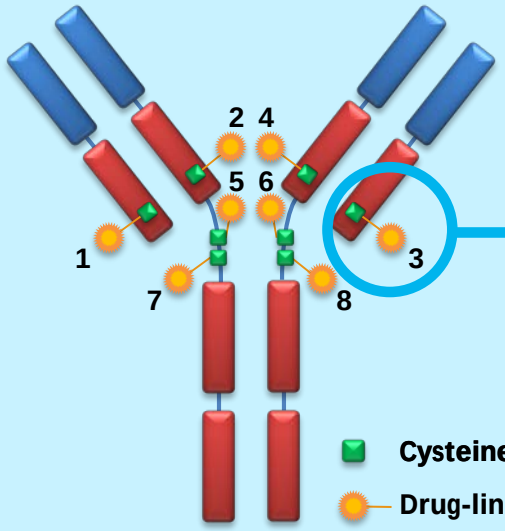
Upcoming Events

U3-1402: Anti-HER3 ADC

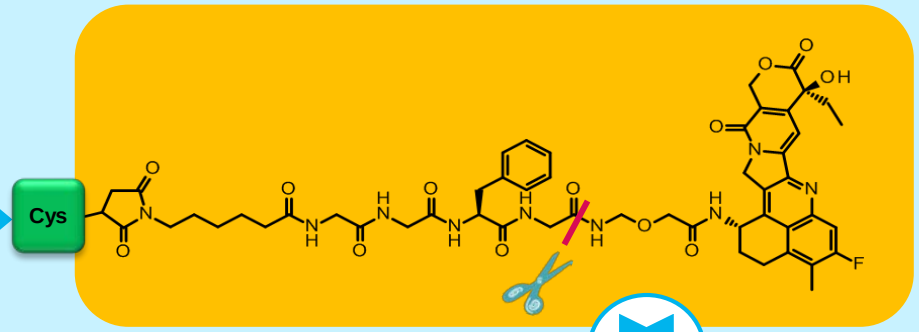
U3-1402 Design Features

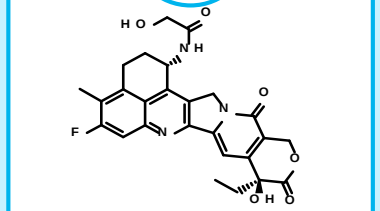
- Payload MOA: Topo I inhibitor
- High potency of payload
- High drug-to-antibody ratio (~8:1)
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Bystander effect

Anti-HER3 antibody



Proprietary drug-linker and payload





Payload (DXd)
Exatecan derivative

Topoisomerase I inhibitor

Conjugation chemistry

The drug-linker is conjugated to the antibody via cysteine residues

Potential first-in-class drug

U3-1402: Phase 1 Dose Escalation Study Design

Eligibility Criteria

- **Metastatic/unresectable *EGFR*-mutant NSCLC and:**
  - o T790M-negative after progression on erlotinib, gefitinib, or afatinib; *OR*
  - o Progressed on osimertinib
- **Stable brain metastases allowed**
- **Pretreatment tumor tissue (after progression on TKIs) was required for retrospective analysis of HER3 expression**

U3-1402 Dose Escalation (N = 30)

Received ≥ 1 dose of U3-1402 IV Q3W

- **6.4 mg/kg (n = 5)**
- **5.6 mg/kg (n = 12)**
- **4.8 mg/kg (n = 9)**
- **3.2 mg/kg (n = 4)**

Patient Disposition[a]

- **Ongoing**, n = 17
- **Discontinued**, n = 13
  - o Progressive disease: 9
  - o Consent withdrawal: 2
  - o Clinical progression: 1
  - o AE: 1

Objectives	Primary: Safety and tolerability of U3-1402 and RDE determination	Secondary: Antitumor activity of U3-1402	Exploratory: Biomarkers of U3-1402 antitumor activity

A phase 1 study of U3-1402 in NSCLC (NCT03260491). [a]Data cutoff of May 3, 2019.
AE, adverse event; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IV, intravenously; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RDE, recommended dose for expansion; TKI, tyrosine kinase receptor.

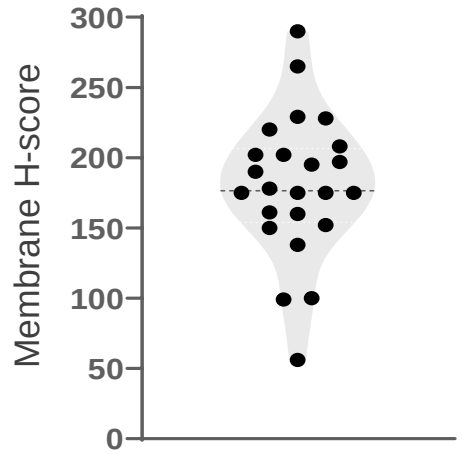
Source: Yu-H *et al.*, Abstract #MA21.06, WCLC 2019

U3-1402: Baseline Demographics of Patients

Baseline Characteristics	N = 30
Median age, years (range)	63 (44–80)
Female, n (%)	20 (67)
Race, n (%)	
White	18 (60)
Asian	8 (27)
African American	1 (3)
Other	3 (10)
ECOG performance status, n (%)	
0	12 (40)
1	18 (60)

Disease Characteristics	N = 30
Tumor stage (IV), n (%)	30 (100)
Prior therapy, n (%)	
EGFR TKI	30 (100)
Osimertinib	28 (93)
Chemotherapy	15 (50)
History of CNS metastases, n (%)	15 (50)
***EGFR* mutation, n (%)**	
Ex19del	17 (57)
L858R	12 (40)
L861Q	1 (3)

HER3 Expression	
Evaluable patients[a], n	25
Membrane H-score[b], median (range) (composite score of 0–300)	183 (56–290)



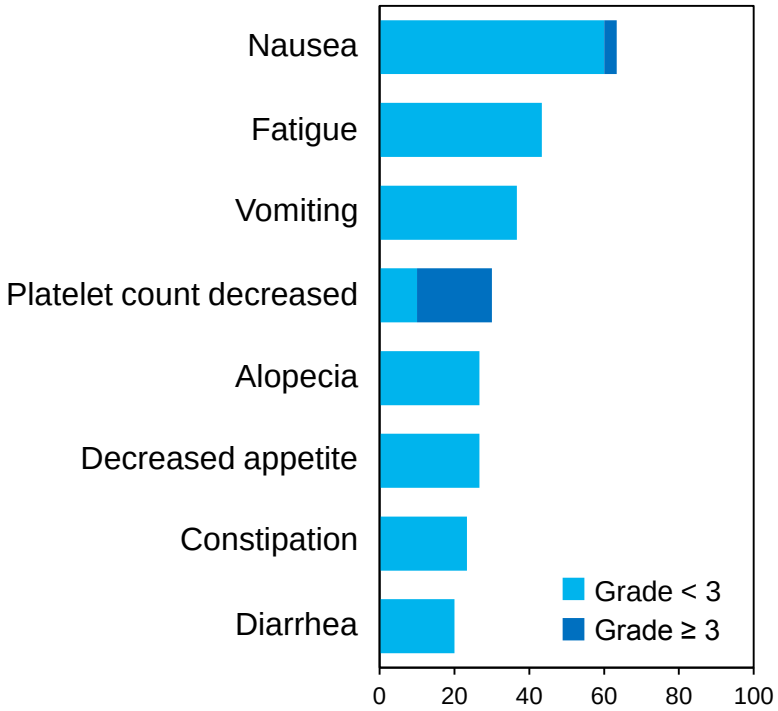
A phase 1 study of U3-1402 in NSCLC (NCT03260491). [a]Includes patients with tumor samples that have completed retrospective analysis. [b]Membrane H-score is a composite of percentage of positively staining cells and intensity of individual cell staining; for patients with multiple H-scores, the highest number was used.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; TKI, tyrosine kinase receptor.

Source: Yu-H *et al.*, Abstract #MA21.06, WCLC 2019

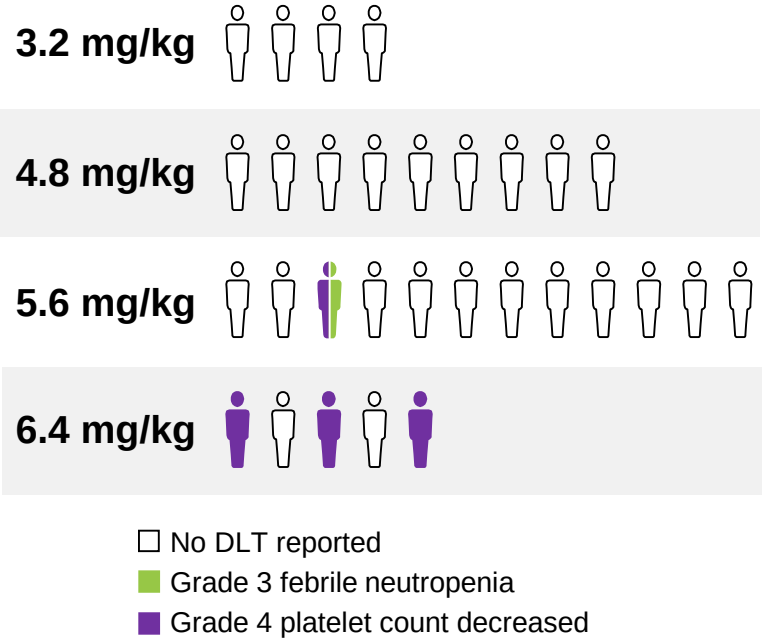
U3-1402: Safety in Dose Escalation[a]

TEAEs & AESI, n (%)	N = 30
TEAEs regardless of causality	29 (97)
Drug-related	28 (93)
Treatment-emergent SAEs regardless of causality	9 (30)
Drug-related	4 (13)
TEAEs associated with drug withdrawal/discontinuation	1 (3)
TEAEs associated with dose reduction	7 (23)
TEAEs associated with dose interruption	7 (23)
TEAEs associated with death	0
AESI	
Interstitial lung disease	0

TEAEs in ≥ 20% of Patients[b]



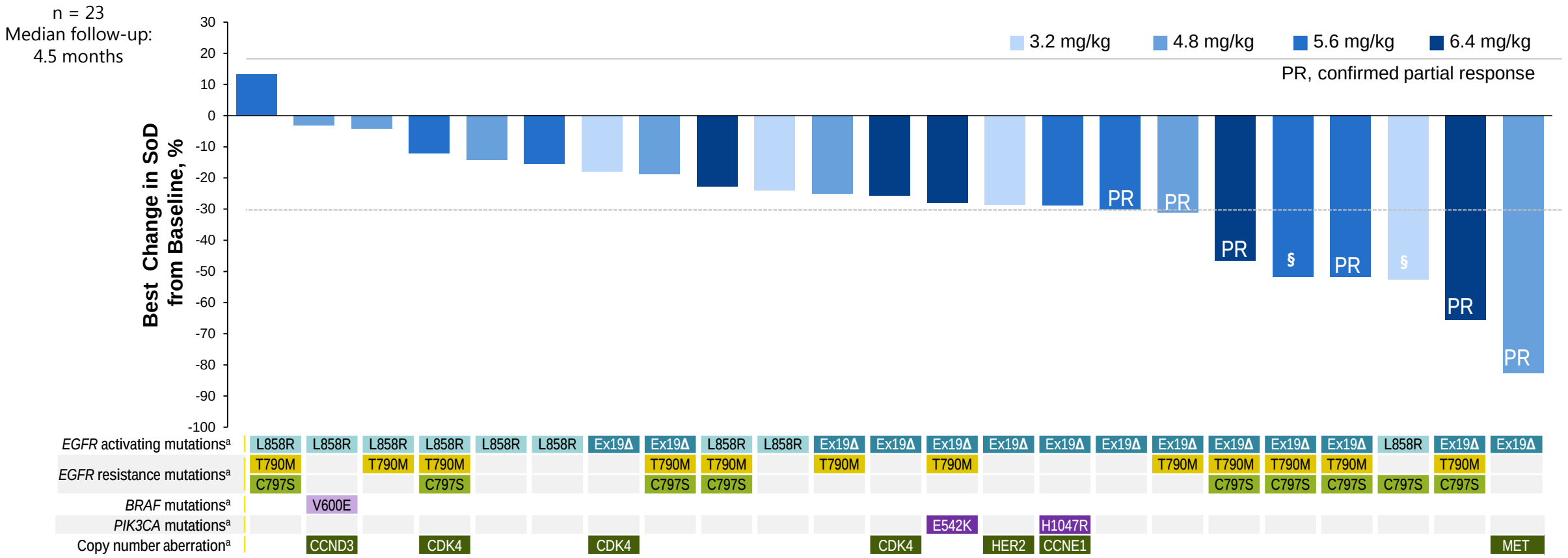
Dose-Limiting Toxicities (N = 30)



A phase 1 study of U3-1402 in NSCLC (NCT03260491). [a]Safety analysis set included all patients who received at least 1 dose of U3-1402. [b]For TEAEs in < 20% of patients, there were 15 grade 3 events: hypoxia and troponin increased, n = 2 each; alanine aminotransferase increased, anemia, confusional state, dyspnea, embolism, febrile neutropenia, hypokalemia, musculoskeletal chest pain, nausea, pleural effusion, psychiatric disorders, n = 1 each.
AESI, adverse event of special interest; DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Yu-H *et al.*, Abstract #MA21.06, WCLC 2019

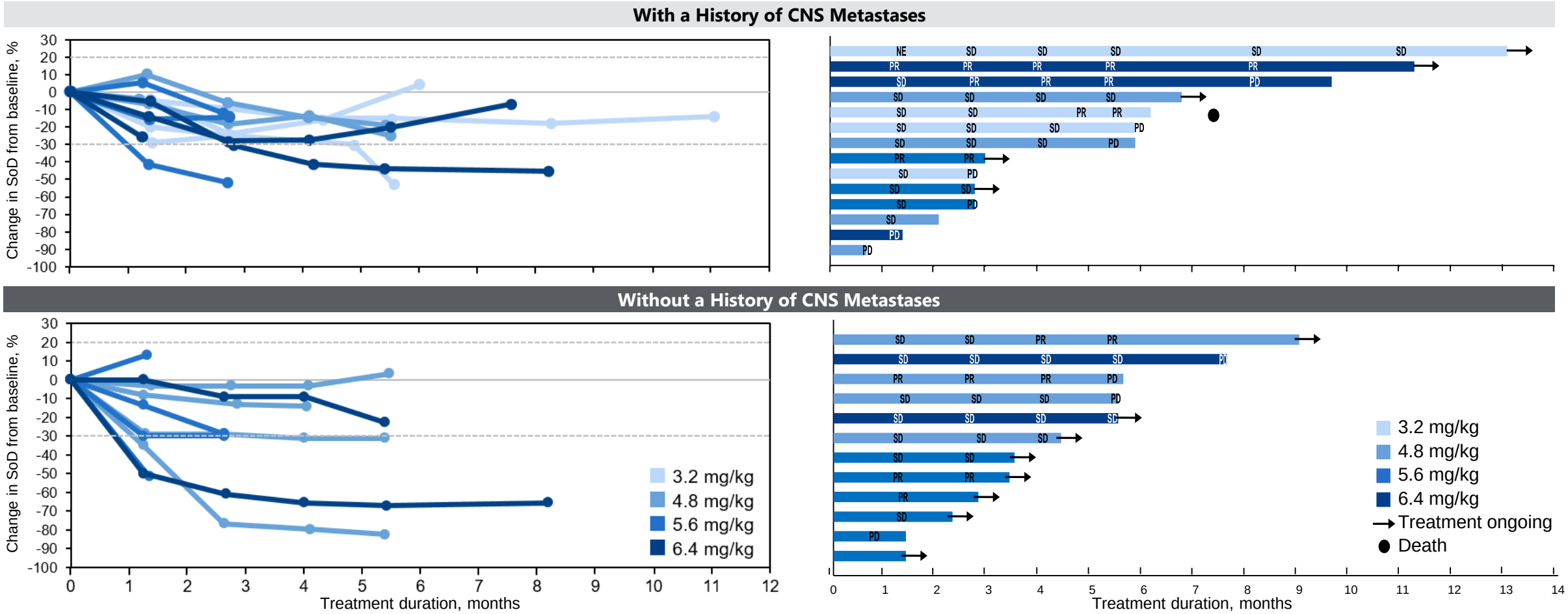
U3-1402: Antitumor Activity Across Diverse EGFR TKI Resistance Mechanisms



A phase 1 study of U3-1402 in NSCLC (NCT03260491). §2 patients had ≥ 30% reduction in SoD, which were not considered confirmed PRs; 1 experienced transient tumor size reduction and 1 had not yet been confirmed at data cutoff. [a]Performed centrally using Oncomine™ Comprehensive Assay v3 from formalin-fixed, paraffin-embedded tumor tissue. Results from local testing are included for patients where tissue was unavailable for central analysis. Additional mutations detected from cfDNA in blood collected prior to treatment with U3-1402 using GuardantOMNI assay are included. For cfDNA analysis, a minor allelic frequency of 1% was used as a threshold for detection of mutations. The copy number data from cfDNA are not shown.
cfDNA, cell-free DNA; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; PR, partial response; SoD, sum of diameters; TKI, tyrosine kinase receptor.

Source: Yu-H *et al.*, Abstract #MA21.06, WCLC 2019

U3-1402: Antitumor Activity in Patients With or Without a History of CNS Metastases



A phase 1 study of U3-1402 in NSCLC (NCT03260491). CNS, central nervous system; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.

Source: Yu-H *et al.*, Abstract #MA21.06, WCLC 2019

U3-1402: Dose Escalation Summary

- U3-1402 demonstrated a manageable safety profile
- HER3 expression was observed in all evaluable patients
- Antitumor activity with U3-1402 was observed in patients with *EGFR*-mutant TKI-resistant NSCLC and across multiple resistance mechanisms
- Durable systemic disease control observed in patients with and without a history of CNS metastases
- The RDE of U3-1402 was determined to be 5.6 mg/kg IV Q3W

Dose Expansion

1
- Adenocarcinoma *EGFR*-mutant NSCLC
- ≥1 prior EGFR TKI and ≥ 1 prior platinum-based chemotherapy regimen

Enroll 45 patients

2
- Squamous and nonsquamous NSCLC
- ≥ 1 prior platinum-based chemotherapy regimen and a prior anti-PD(L)-1 antibody-based regimen

Stage 1: Evaluate ORR and HER3 correlation	Stage 2: Enrollment based on Stage 1 analysis
Enroll 30 patients	Enroll up to an additional 30 patients

Targeting HER3 with U3-1402 may provide clinical benefit to patients with *EGFR*-mutant NSCLC with diverse mechanisms of TKI resistance

A phase 1 study of U3-1402 in NSCLC (NCT03260491).
CNS, central nervous system; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IV, intravenously; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD(L)-1, programmed death 1/ligand 1; Q3W, every 3 weeks; RDE, recommended dose for expansion; TKI, tyrosine kinase receptor; WT, wild-type.

Source: Yu-H *et al.*, Abstract #MA21.06, WCLC 2019

U3-1402: What It Means for Daiichi Sankyo?

U3-1402 appears active in NSCLC, adding to breast cancer activity previously reported

Appears to offer **option in EGFRm TKI failing patients**, without the need to select for activated pathway that putatively drives the resistance to pEGFR suppression by TKI

Fast-to-market US path emerging in NSCLC

Today's Agenda

DS-1062: data update / what it means for Daiichi Sankyo

U3-1402: data update / what it means for Daiichi Sankyo

Recent Milestones

Upcoming Events

Recent Milestones

DS-8201

HER2 positive mBC pivotal phase 2 study

- JP: **NDA submitted and accepted on September 9, 2019**
- US: **BLA completing rolling submission within 1HFY2019 on track**
- Data planned to be presented at SABCS

Pexidartinib

Tenosynovial giant cell tumor

- US: **approved on August 2, 2019 and launched**

Underlined in red: new or update from FY2019 Q1 Earnings Call

Today's Agenda

DS-1062: data update / what it means for Daiichi Sankyo

U3-1402: data update / what it means for Daiichi Sankyo

Recent Milestones

Upcoming Events

Upcoming Events

FY2019 Second Quarter Results Briefing

Date	• October 31st (Thursday) 4:00-5:30pm (JST) @ HQ
Speaker	• Sunao Manabe, CEO • Junich Koga, Global Head of R&D

FY2019 R&D Day

Date	• December 17th (Tuesday) afternoon @ Tokyo • December 19th (Thursday) TBD @ NY
Speakers	• Sunao Manabe, CEO • Antoine Yver, Global Head of Oncology R&D
What to Expect	• R&D new research and development strategy • Data update (DS-8201 SABCS 2019) • Updated development plan (DS-8201, DS-1062, U3-1402)

Inquiries about this document

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