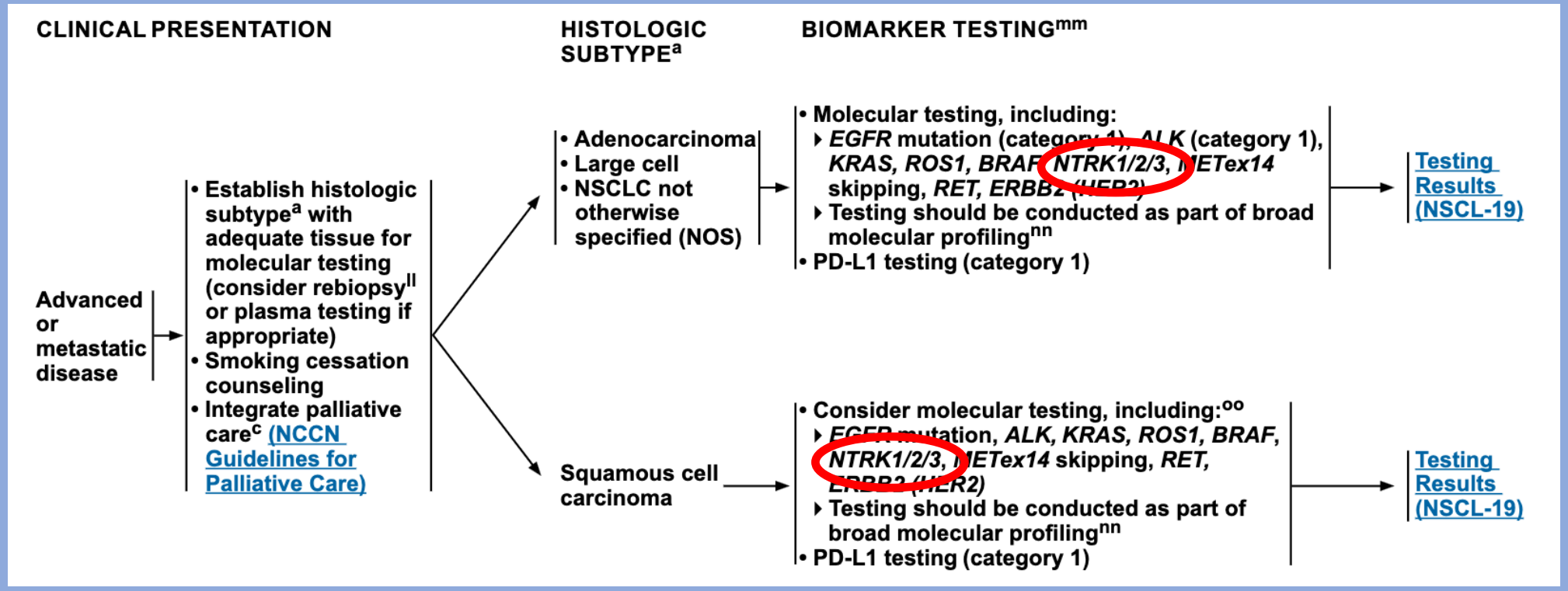
# NTRK
# and
# Antibody Drug Conjugates (ADCs)
# In
# Non-Small Cell Lung Cancer

Martin F. Dietrich, MD, PhD
Florida Cancer Specialists
Orlando, Florida

# Overview

1. NTRK targeting in NSCLC
2. Antibody-drug conjugates in NSCLC
   - Her2 mutations – Trastuzumab-Dxd
   - Trop2 – Datopotomab-Dxd and Sacituzumab-govintecan
   - CEACAM5 – Tusamitamab-ravtamsine
   - MET

# *Molecular Testing* is a mandatory part of guideline applicability in NSCLC

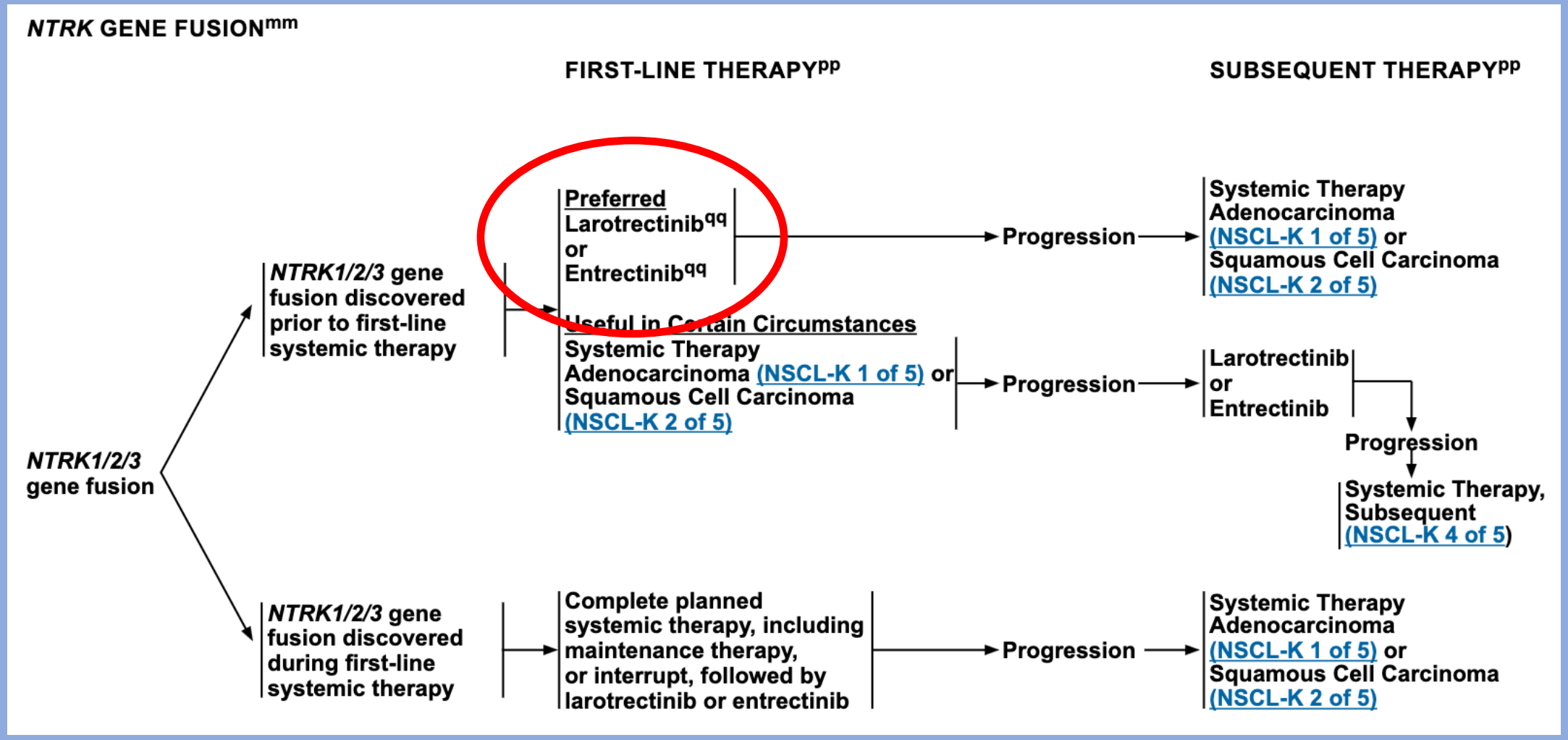


# NTRK1/2/3 follows independent treatment algorithm

**TESTING RESULTS**[ll,mm]

| | |
|---|---|
| ***EGFR*** **exon 19 deletion or exon 21 L858R mutation positive** | **NSCL-20** |
| ***EGFR*** **S768I, L861Q, and/or G719X mutation positive** | **NSCL-23** |
| ***EGFR*** **exon 20 insertion mutation positive** | **NSCL-24** |
| ***KRAS*** **G12C mutation positive** | **NSCL-25** |
| ***ALK*** **rearrangement positive** | **NSCL-26** |
| ***ROS1*** **rearrangement positive** | **NSCL-29** |
| ***BRAF*** **V600E mutation positive** | **NSCL-31** |
| ***NTRK1/2/3*** **gene fusion positive** | **NSCL-32** |
| ***MET*** **ex14 skipping mutation positive** | **NSCL-33** |
| ***RET*** **rearrangement positive** | **NSCL-34** |
| ***ERBB2 (HER2)*** **mutation positive** | **NSCL-35** |
| **PD-L1 ≥1% and negative for actionable molecular biomarkers above** | **NSCL-36** |
| **PD-L1 <1% and negative for actionable molecular biomarkers above** | **NSCL-37** |

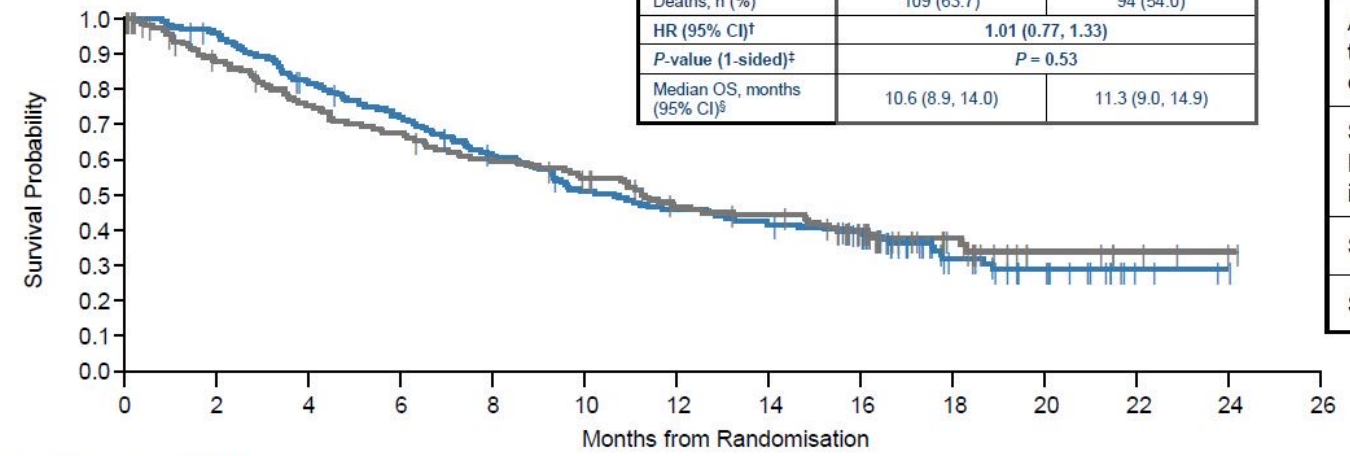
# Preferred Treatment is Targeted Therapy in 1st Line Treatment



# ADCs – Current 2nd line treatment and beyond

## OS: Sotorasib vs Docetaxel*

| | Sotorasib 960 mg oral daily (N = 171) | Docetaxel 75 mg/m² IV Q3W (N = 174) |
|---|---|---|
| Deaths, n (%) | 109 (63.7) | 94 (54.0) |
| HR (95% CI)† | 1.01 (0.77, 1.33) | |
| *P*-value (1-sided)‡ | *P* = 0.53 | |
| Median OS, months (95% CI)§ | 10.6 (8.9, 14.0) | 11.3 (9.0, 14.9) |



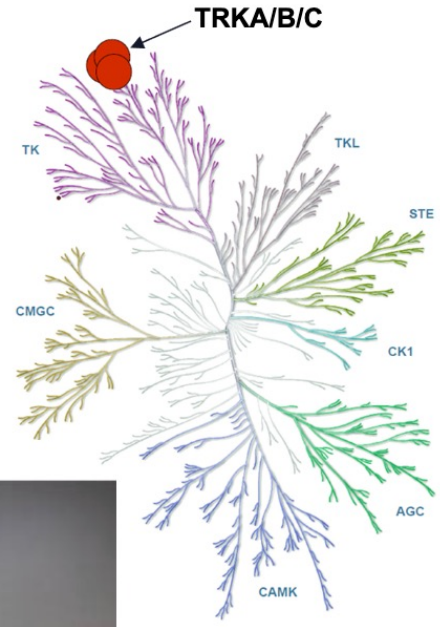

| | Sotorasib | Docetaxel |
|---|---|---|
| Any subsequent treatment, including crossover** | 36% | 42% |
| Subsequent $KRAS^{G12C}$ inhibitor, including crossover | 4% | 34% |
| Subsequent chemo | 21% | 12% |
| Subsequent IO | 9% | 6% |

*OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡ *P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

# Larotrectinib Is the First Selective Pan-TRK Inhibitor in Development[1]

- Larotrectinib is a highly potent and selective small-molecule inhibitor of TRKA, TRKB, and TRKC ($IC_{50}$ 5-11 nM in cellular assays)
- Prolonged responses in adult patients with TRK fusions (recommended phase 2 dose in adults is 100 mg BID)
- Promising tolerability profile
- Liquid formulation for pediatric patients

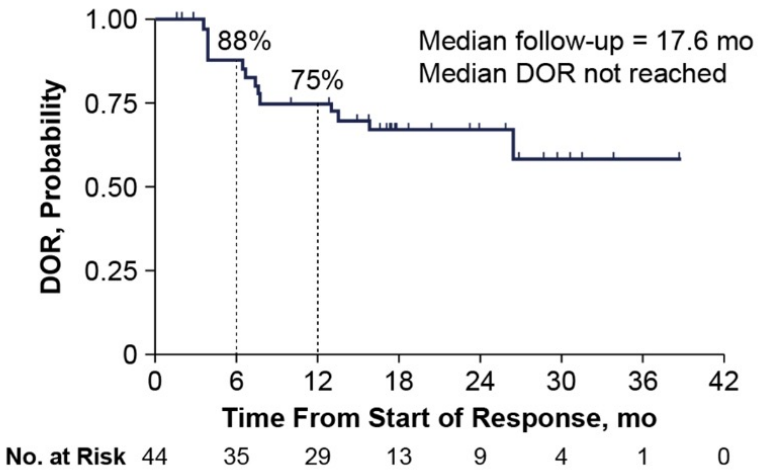



# Larotrectinib Has Tumor-Agnostic Activity in *NTRK* Gene Fusion-Positive Cancers (Cont'd)[1]

| Response | Investigator Assessment (N = 55) | Central Assessment (N = 55) |
|---|---|---|
| | Percent[a] | |
| ORR, % (95% CI)[b] | 80 (67-90) | 75 (61-85) |
| **Best response** | | |
| Partial response | 64[c] | 62 |
| Complete response | 16 | 13 |
| Stable disease | 9 | 13 |
| Progressive disease | 11 | 9 |
| Could not be evaluated | 0 | 4 |

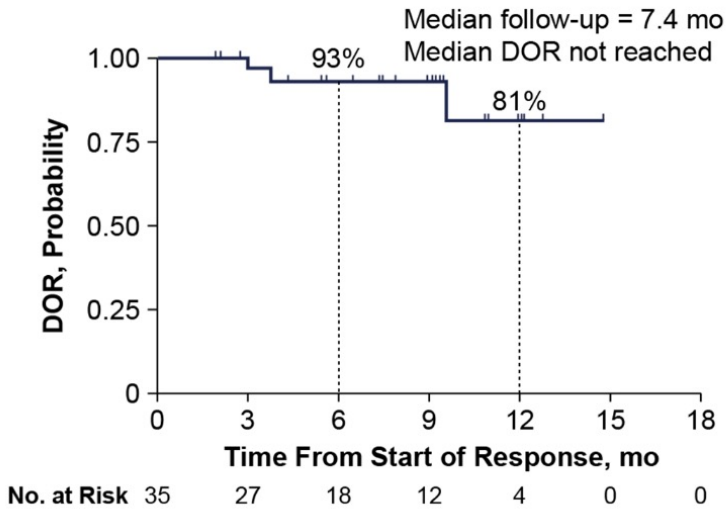
# Sustained Responses With Larotrectinib (DOR)[1]

**Primary Dataset**



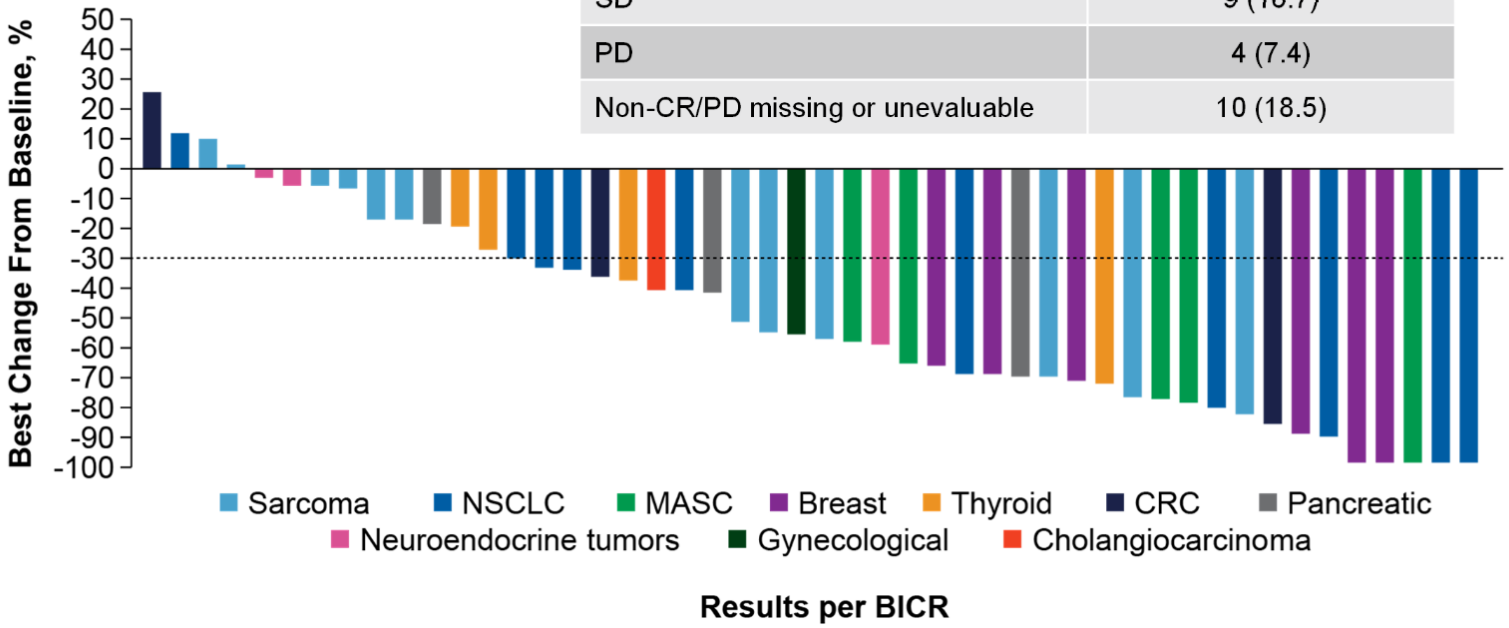

| | Kaplan–Meier Landmark Analysis | |
|---|---|---|
| | July 17, 2017 | July 30, 2017 |
| **6 mo, %** | 83 | 88 |
| **12 mo,%** | 71 | 75 |

**Supplementary Dataset**

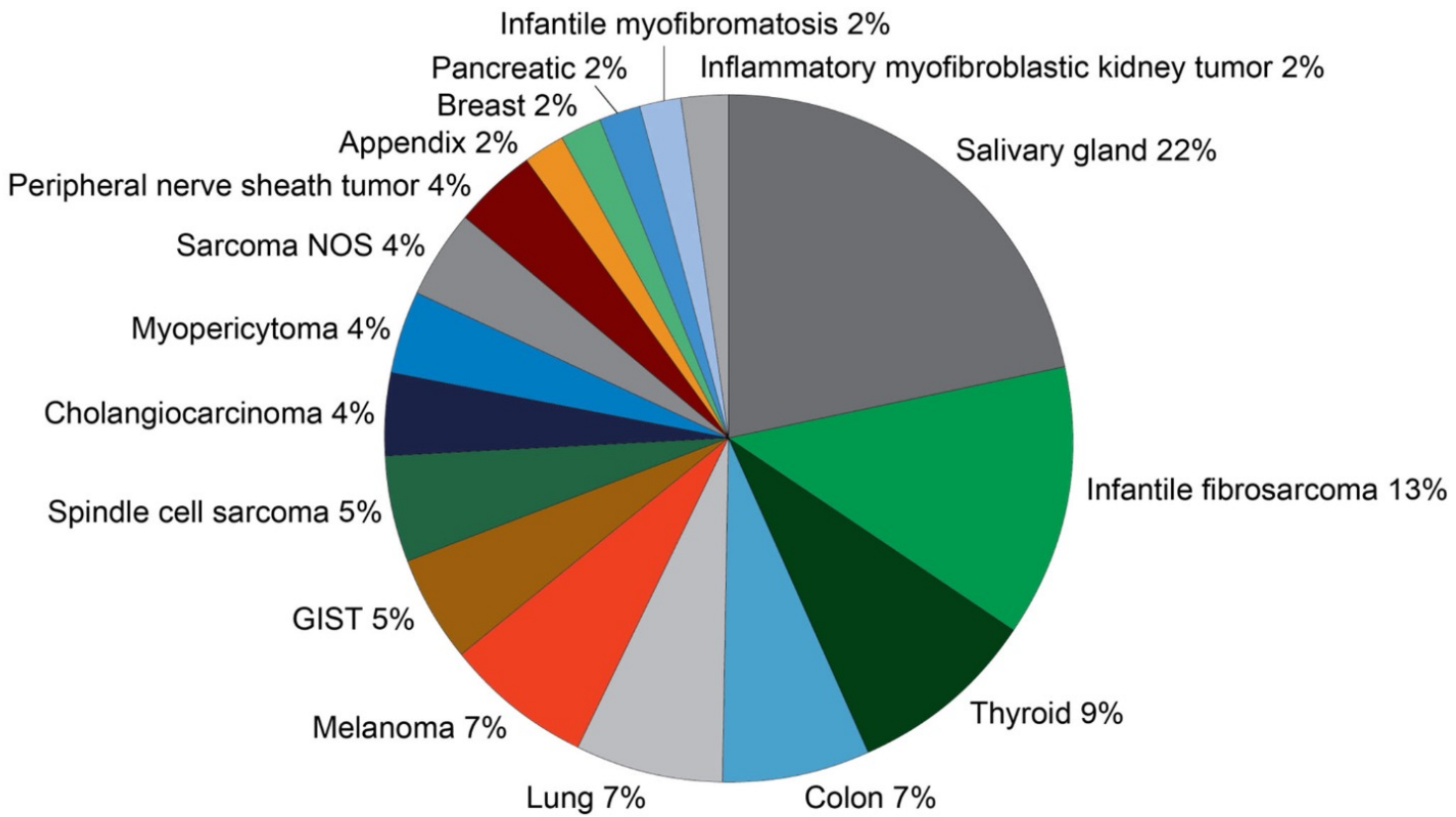


# Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Patient Responses by Tumor Type[1]

| | ***NTRK*+ Patients (n = 54)** |
|---|---|
| ORR (95% CI) | **57.4% (43.2-70.8)** |
| SD | 9 (16.7) |
| PD | 4 (7.4) |
| Non-CR/PD missing or unevaluable | 10 (18.5) |



# 17 Unique Cancer Types Were Treated With Larotrectinib[1,a]



# Conclusions

- NTRK1/2/3 fusions are highly actionable genomic alterations.
- Fusions can be found across the histological spectrum of all pediatric and adult solid tumors.
- Two agents are available for treatment : Larotrectinib and Entrectinib.
- Both agents produce high response rates and intracranial efficacy.
- RNA-based NGS testing provides highest sensitivity testing.

# Background : Her2 mutation targeting via ADC

- 2-3% of NSCLC carry activating Her2 mutations.
- Higher frequency in female patients, never smokers.
- Single agent immunotherapy responses have been suggested around 6%.
- PFS outcomes similar between chemotherapy and chemo-immunotherapy.
- Mutations occur typically in difficult-to-target exon 20.
  - Her2 TKI responses rate previously reported between 0-30%.
  - Small study suggested trastuzumab-DM1 with response rate of 44%.

# Destiny-Lung 02

- *Open label, single arm phase II trial for evaluation of T-Dxd in Her2mt NSCLC.*

# Demographic and Clinical Characteristics of the Patients at Baseline.*

1. 95% intracellular kinase domain, 7% extracellular kinase domains.
2. Pretreatment
   - 95% platinum-based chemotherapy.
   - 66% Anti-PD-1/PD-L1 Therapy.
   - 20% Docetaxel
   - 14% Her2 tyrosine kinase inhibitors
3. Smoking status
   - 57% never smokers, 41% former smokers.

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.***

| Characteristic | Patients (N=91) |
|---|---|
| Median age (range) — yr | 60 (29–88) |
| Female sex — no. (%) | 60 (66) |
| Race — no. (%)† | |
| Asian | 31 (34) |
| White | 40 (44) |
| Black | 1 (1) |
| Other | 19 (21) |
| Geographic region — no. (%) | |
| Asia | 23 (25) |
| North America | 35 (38) |
| Europe | 33 (36) |
| ECOG performance-status score — no. (%)‡ | |
| 0 | 23 (25) |
| 1 | 68 (75) |
| Location of *HER2* mutations — no. (%) | |
| Kinase domain | 85 (93) |
| Extracellular domain | 6 (7) |
| Previous cancer therapy — no. (%) | 90 (99)§ |
| No. of lines of previous cancer therapy — median (range) | 2 (0–7) |
| Previous cancer therapy — no. (%) | |
| Platinum-based therapy | 86 (95) |
| Docetaxel | 18 (20) |
| Anti–PD-1 or anti–PD-L1 treatment | 60 (66) |
| HER2 TKI | 13 (14) |
| Reason for discontinuation of previous cancer therapy — no./total no. (%) | |
| Disease progression | 63/90 (70) |
| Completed therapy | 6/90 (7) |
| Adverse event | 8/90 (9) |
| Investigator decision | 3/90 (3) |
| Patient choice | 1/90 (1) |
| Unknown | 5/90 (6) |
| Other | 4/90 (4) |
| CNS metastases at baseline — no. (%) | 33 (36) |
| Smoking history — no. (%) | |
| Current | 2 (2) |
| Former | 37 (41) |
| Never | 52 (57) |
| Previous lung resection — no. (%) | 20 (22) |

* Percentages may not total 100 because of rounding. CNS denotes central nervous system, HER2 human epidermal growth factor receptor 2, PD-1 programmed cell death 1, PD-L1 programmed death ligand 1, and TKI tyrosine kinase inhibitor.
† Race was reported by the patients.
‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores reflecting greater disability.
§ One patient was enrolled without having received previous cancer therapy.

BT Li et al. N Engl J Med 2022;386:241-251.

The NEW ENGLAND JOURNAL of MEDICINE

# Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

**Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.**

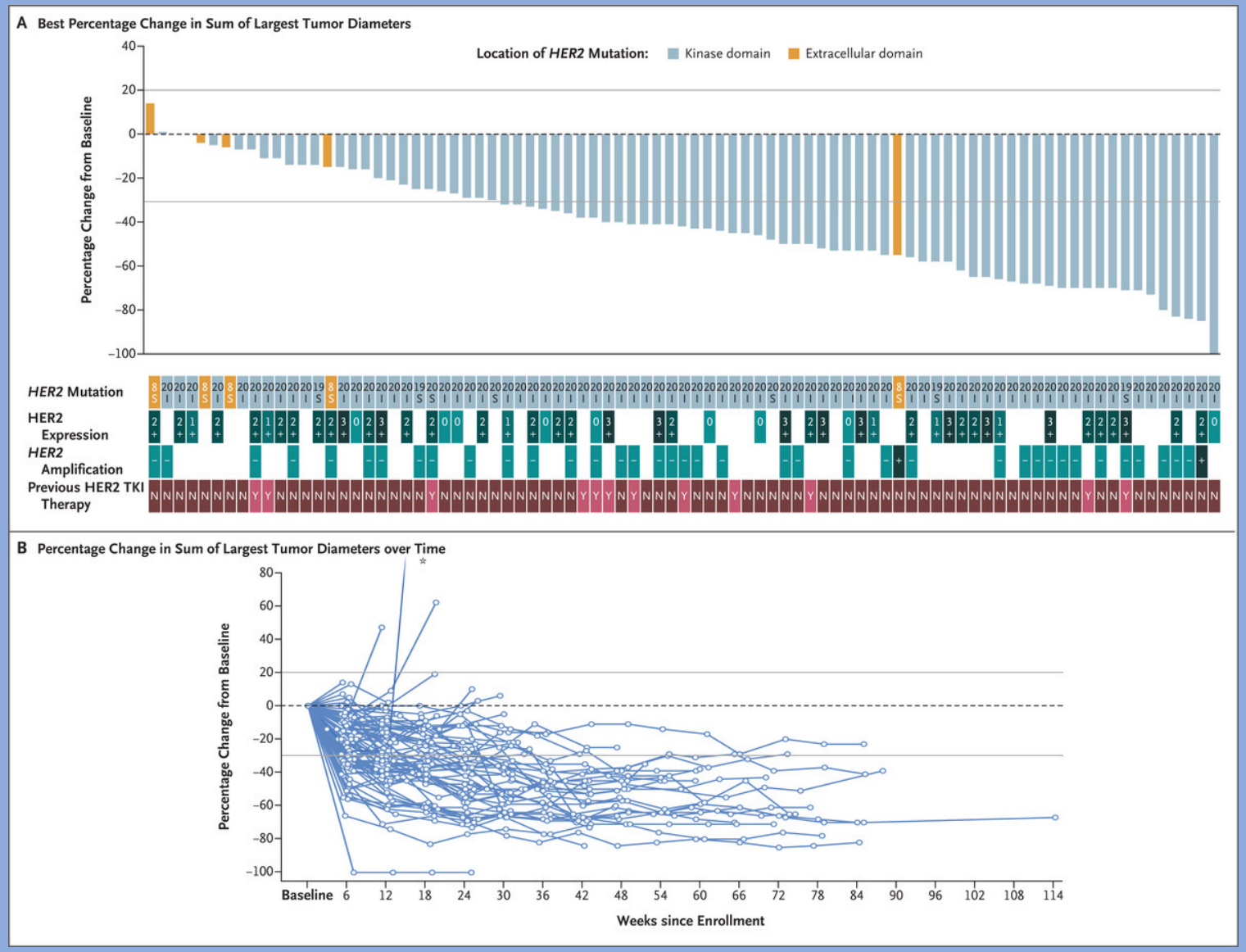
| Response Assessment | Patients (N=91) |
|---|---|
| Confirmed objective response* | |
| No. of patients | 50 |
| Percentage of patients (95% CI) | 55 (44–65) |
| Best response — no. (%) | |
| Complete response | 1 (1) |
| Partial response | 49 (54) |
| Stable disease | 34 (37) |
| Progressive disease | 3 (3) |
| Response could not be evaluated | 4 (4) |
| Disease control† | |
| No. of patients | 84 |
| Percentage of patients (95% CI) | 92 (85–97) |
| Median time to response (range) — mo‡ | 1.5 (1.2–9.3) |
| Median duration of response (95% CI) — mo‡ | 9.3 (5.7–14.7) |

* Confirmed objective response was assessed by independent central review on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Disease control was defined as complete response, partial response, or stable disease at 6 weeks with no progression.
‡ Analyses of time to response and duration of response included only the patients with a confirmed objective response.

BT Li et al. N Engl J Med 2022;386:241-251.

The NEW ENGLAND JOURNAL of MEDICINE

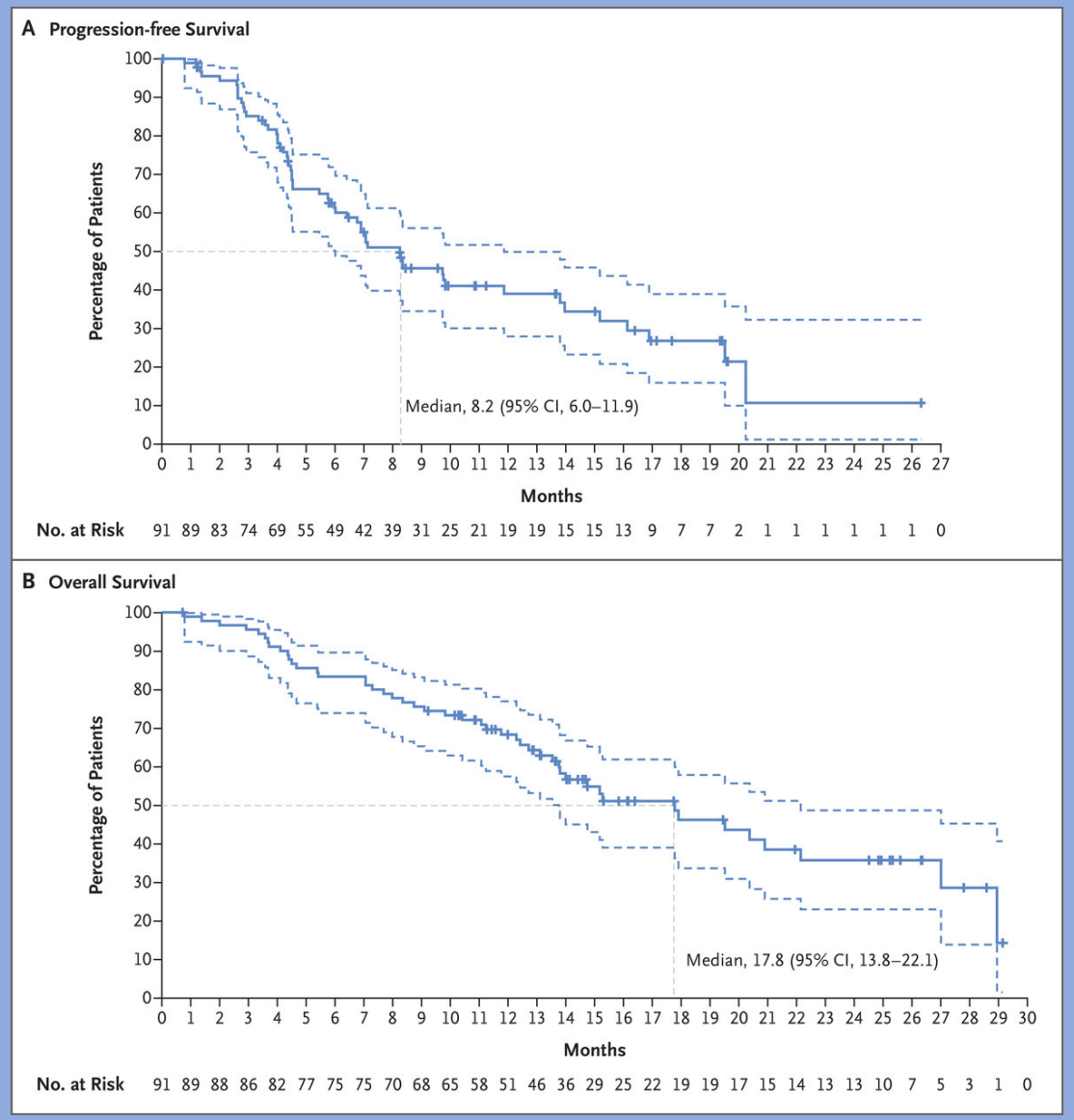
# Antitumor Activity.




BT Li et al. N Engl J Med 2022;386:241-251.

The NEW ENGLAND JOURNAL of MEDICINE

# Kaplan–Meier Analysis PFS and OS




Est. PFS 8.2 months

Est. OS 17.8 months

BT Li et al. N Engl J Med 2022;386:241-251.

The NEW ENGLAND JOURNAL of MEDICINE

# Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

**Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).**

| Event | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Overall |
|---|---|---|---|---|---|
| | *number of patients (percent)* | | | | |
| Drug-related adverse event | 46 (51) | 37 (41) | 4 (4) | 1 (1)* | 88 (97) |
| Drug-related adverse events with ≥20% incidence | | | | | |
| Nausea | 58 (64) | 8 (9) | 0 | 0 | 66 (73) |
| Fatigue† | 42 (46) | 6 (7) | 0 | 0 | 48 (53) |
| Alopecia | 42 (46) | 0 | 0 | 0 | 42 (46) |
| Vomiting | 33 (36) | 3 (3) | 0 | 0 | 36 (40) |
| Neutropenia‡ | 15 (16) | 14 (15) | 3 (3) | 0 | 32 (35) |
| Anemia§ | 21 (23) | 9 (10) | 0 | 0 | 30 (33) |
| Diarrhea | 26 (29) | 2 (2) | 1 (1) | 0 | 29 (32) |
| Decreased appetite | 27 (30) | 0 | 0 | 0 | 27 (30) |
| Leukopenia¶ | 17 (19) | 4 (4) | 0 | 0 | 21 (23) |
| Constipation | 20 (22) | 0 | 0 | 0 | 20 (22) |

* One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee. All adjudicated events of drug-related interstitial lung disease are reported in Table S5.

† This category includes the preferred terms fatigue, asthenia, and malaise.

‡ This category includes the preferred terms neutrophil count decreased and neutropenia.

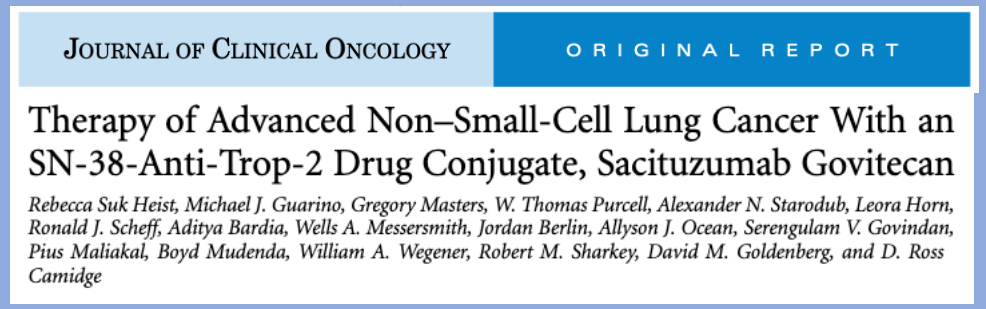
§ This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased.

¶ This category includes the preferred terms white-cell count decreased and leukopenia.

BT Li et al. N Engl J Med 2022;386:241-251.

The NEW ENGLAND JOURNAL of MEDICINE

# Single arm study of Sacituzumab-Govintecan (SG) in NSCLC

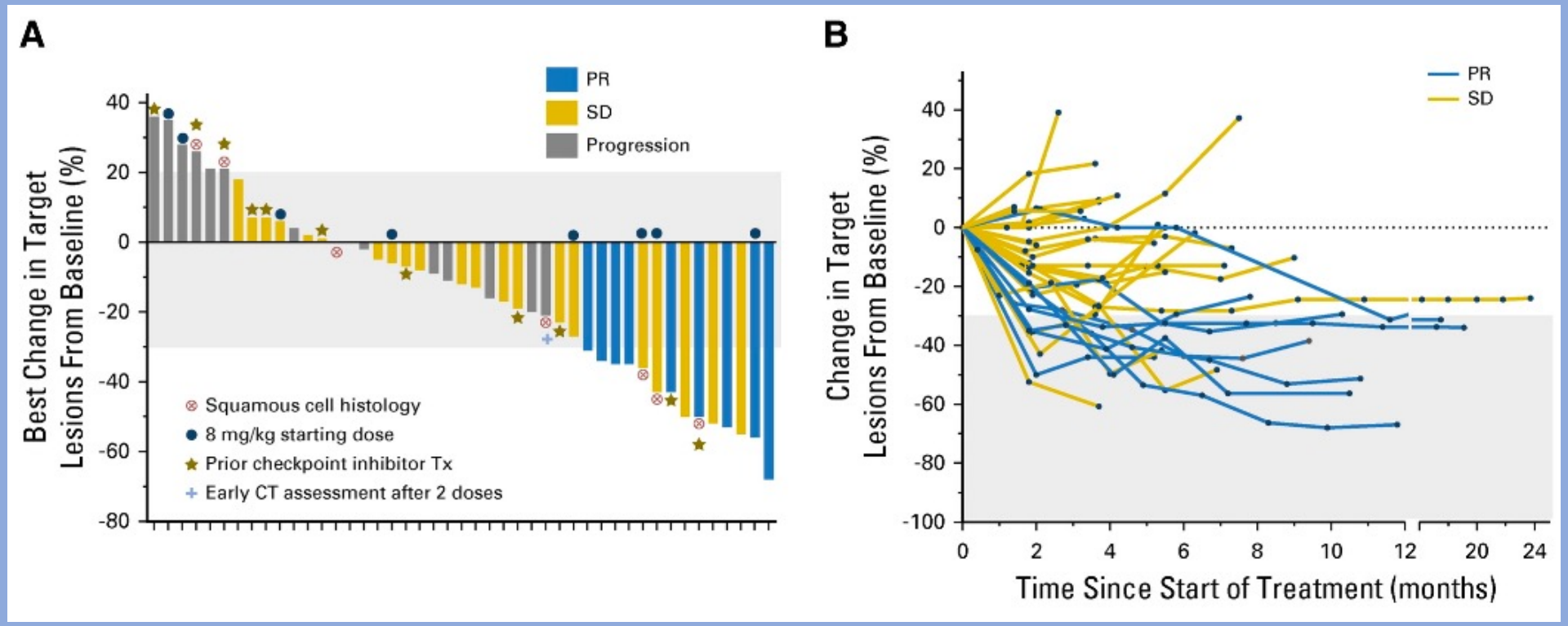


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

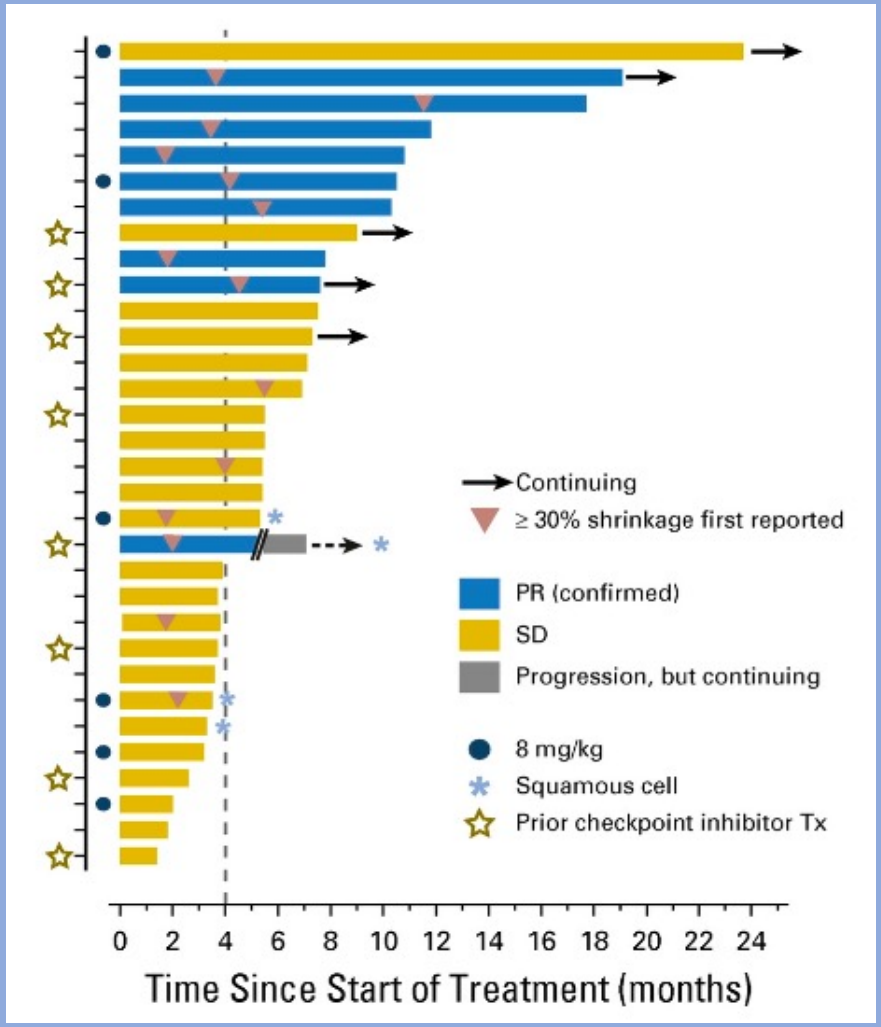
Therapy of Advanced Non–Small-Cell Lung Cancer With an SN-38-Anti-Trop-2 Drug Conjugate, Sacituzumab Govitecan

*Rebecca Suk Heist, Michael J. Guarino, Gregory Masters, W. Thomas Purcell, Alexander N. Starodub, Leora Horn, Ronald J. Scheff, Aditya Bardia, Wells A. Messersmith, Jordan Berlin, Allyson J. Ocean, Serengulam V. Govindan, Pius Maliakal, Boyd Mudenda, William A. Wegener, Robert M. Sharkey, David M. Goldenberg, and D. Ross Camidge*

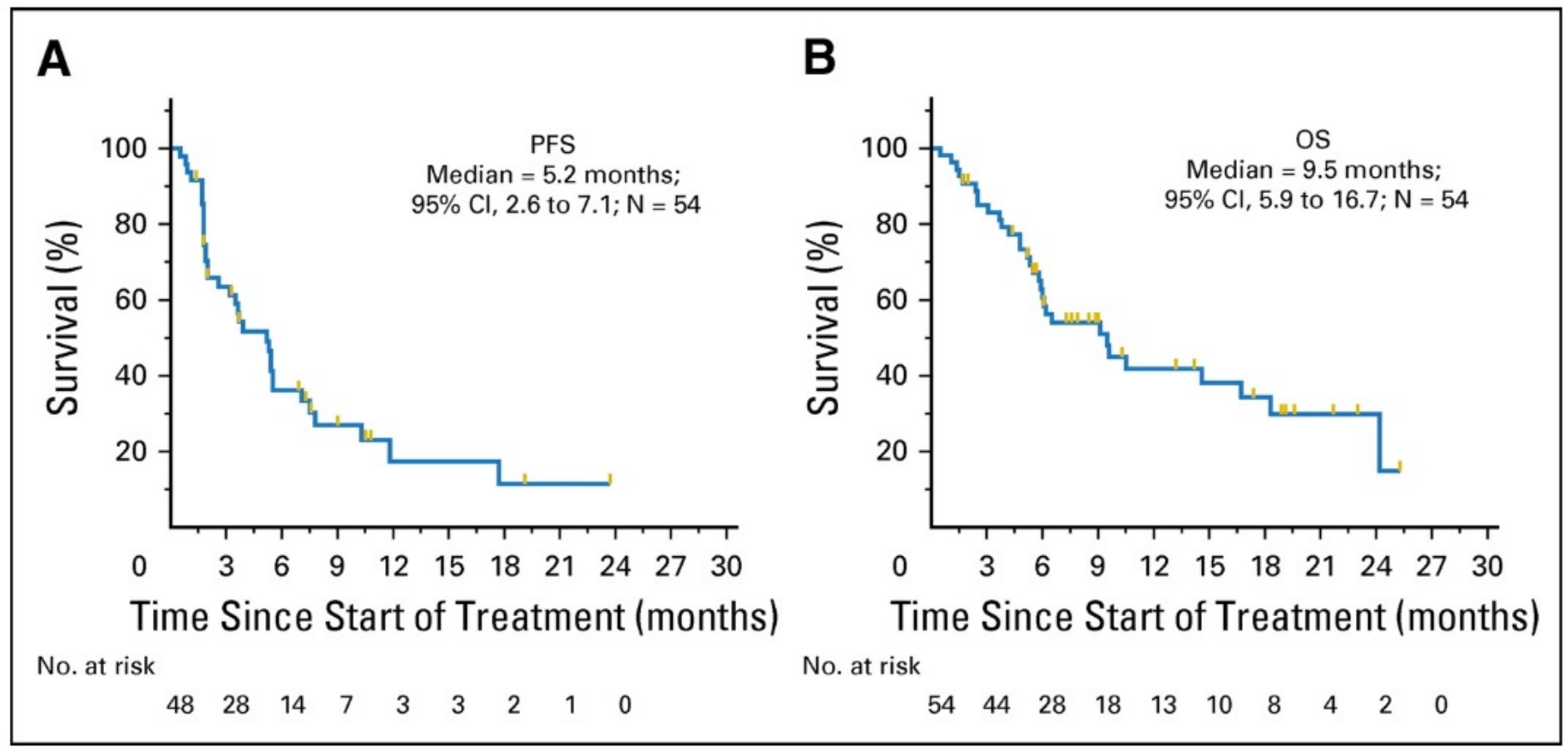
# ORR 19%; 67% with tumor reduction



# Durable Responses were observed with SG



# PFS 5.2 months (95%, CI 3.2-7.1) and OS 9.5 months



# Diarrhea and Neutropenia were most significant AE

**Table 2.** Frequency of Adverse Events Regardless of Causality

| Adverse Event | All Grades, No. (%) | | | Grade ≥ 3, No. (%) | | |
|---|---|---|---|---|---|---|
| | All Patients | 8 mg/kg Dose | 10 mg/kg Dose | All Patients | 8 mg/kg Dose | 10 mg/kg Dose |
| No. of patients | 54 | 8 | 46 | 54 | 8 | 46 |
| Nausea | 43 (80) | 7 (88) | 36 (78) | 4 (7) | 0 (0) | 4 (9) |
| Diarrhea | 33 (61) | 5 (63) | 28 (61) | 4 (7) | 1 (13) | 3 (7) |
| Fatigue | 25 (46) | 3 (38) | 22 (48) | 3 (6) | 0 (0) | 3 (7) |
| Alopecia | 21 (39) | 2 (25) | 19 (41) | NA | NA | NA |
| Neutropenia | 20 (37) | 2 (25) | 18 (39) | 15 (28) | 1 (13) | 14 (30) |
| Vomiting | 19 (35) | 4 (50) | 15 (33) | 2 (4) | 1 (13) | 1 (2) |
| Anemia | 17 (31) | 1 (13) | 16 (35) | 2 (4) | 0 (0) | 2 (4) |
| Constipation | 17 (31) | 3 (38) | 14 (30) | 0 (0) | 0 (0) | 0 (0) |
| Anorexia | 13 (28) | 0 (0) | 13 (28) | 1 (2) | 0 (0) | 1 (2) |
| Hypophosphatemia | 12 (22) | 1 (13) | 11 (24) | 1 (2) | 0 (0) | 1 (2) |
| Dehydration | 10 (19) | 0 (0) | 10 (22) | 2 (4) | 0 (0) | 2 (4) |
| Weight decrease | 10 (19) | 0 (0) | 10 (22) | 0 (0) | 0 (0) | 0 (0) |
| Leukopenia | 10 (19) | 2 (25) | 8 (17) | 5 (9) | 1 (13) | 4 (9) |
| Hypomagnesemia | 9 (17) | 0 (0) | 9 (20) | 0 (0) | 0 (0) | 0 (0) |
| Dyspnea | 8 (15) | 2 (25) | 6 (13) | 2 (4) | 1 (13) | 1 (2) |
| Pneumonia | 7 (13) | 1 (12) | 6 (13) | 5 (9) | 0 (0) | 5 (11) |

Abbreviation: NA, not applicable.

# Responses were seen independent of prior ICI exposure

**Table A1.** Sacituzumab Govitecan (IMMU-132) Therapy in Patients With Non–Small-Cell Lung Cancer With Prior Immune CPI Therapy

| Pt. | Age | Sex | Histology | No. of Prior Tx | CPI Tx | Lines of CPI | CPI Duration, months | IMMU-132 Doses | IMMU-132 Best Response | Change in Target Lesion, % | IMMU-132 PFS, months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 78 | M | S | 2 | Nivolumab | 2 | 8 | 9 | SD | 0 | 3.3 |
| 2 | 63 | F | NS | 6 | Nivolumab | 2 | 1 | 15 | SD | 7 | 3.7 |
| 3 | 57 | M | S | 4 | Nivolumab | 4 | 8 | 6 | PD | 26 | 2.0 |
| 4 | 62 | M | NS | 4 | Avelumab | 2 | 4 | 4 | PD | IER* | 1.1 |
| 5 | 53 | M | NS | 3 | Atezolizumab + chemotherapy | 1 | 10 | 4 | PD | IER* | 1.8 |
| 6 | 77 | F | NS | 1 | Atezolizumab | 1 | 23 | 14 | SD | −19 | 5.5 |
| 7 | 76 | M | S | 4 | Atezolizumab | 3 | 2 | 5 | PD | 21 | 2.0 |
| 8 | 61 | F | NS | 5 | Nivolumab | 5 | 2 | 6 | PD | 36 | 1.8 |
| 9 | 61 | M | NS | 6 | Atezolizumab | 4 | 3 | 20 | SD | −23 | 9.0+ |
| 10 | 66 | F | NS | 2 | Nivolumab | 2 | 9 | 18 | PR | −43 | 7.6+ |
| 11 | 69 | M | NS | 3 | Atezolizumab | 3 | 2 | 7 | SD | 1 | 2.9 |
| 12 | 74 | M | S | 3 | Pembrolizumab+ ipilimumab | 2 | 1 | | | | |
| | | | | | Nivolumab | 3 | 6 | 10 | PR | −50 | 5.2+ |
| 13 | 67 | F | NS | 3 | Nivolumab | 3 | 5 | 15 | SD | −7 | 7.3+ |
| 14 | 50 | F | NS | 3 | Nivolumab | 3 | 9 | 5 | SD | 7 | 1.4 |

NOTE. Patients with a + for IMMU-132 values were continuing sacituzumab govitecan treatment at the time of this report.
Abbreviations: CPI, checkpoint inhibitor; IER, inevaluable for response; NS, nonsquamous; PD, progressive disease; PFS, progression-free survival; PR, partial response; Pt., patient; S, squamous; SD, stable disease; Tx, therapy.
*Patients died as a result of disease progression before their first computed tomography assessment.

# Correlation of Trop2 Expression and Responses suggest Efficacy across All IHC Subtypes

**Table A2.** Evaluation of Immunohistochemical Staining Versus Best Overall Response in Patients With Metastatic Non–Small-Cell Lung Cancer Treated With an 8 or a 10 mg/kg Starting Dose of IMMU-132

| | Staining Score | | | | |
|---|---|---|---|---|---|
| Overall Best Response | 3+ | 2+ | 1+ | 0 | Not Assessable* |
| Partial response | 2 | 2 | 0 | 0 | 0 |
| Stable disease | 10 | 2 | 0 | 1 | 2 |
| Progressive disease | 5 | 0 | 1 | 0 | 0 |
| Inevaluable for response† | 2 | 1 | 0 | 0 | 0 |
| Total | 19 | 5 | 1 | 1 | 2 |

*Specimen was inadequate for evaluation.
†Patients did not have a response assessment.

# Conclusions

- Second line treatment for NSCLC is high area of unmet need.
- Taxotere +/- Ramucirumab (or other single agent chemotherapy) is current standard of care with PFS ~5 months.
- (Targeted) therapy options have supplemented the 2nd line setting : KRAS (adagrasib/sotorasib), EGFR exon 20 (amivantimab, mobocertinib), Her2 mutations (T-Dxd) etc.
- Antibody-drug conjugates are expected to expand the armamentarium in 2nd+ line NSCLC (Trop2, CEACAM5, Her2 IHC, Her3, Met)
- Molecular characterization remains critical for selection of 2nd line tx.

Thank you!