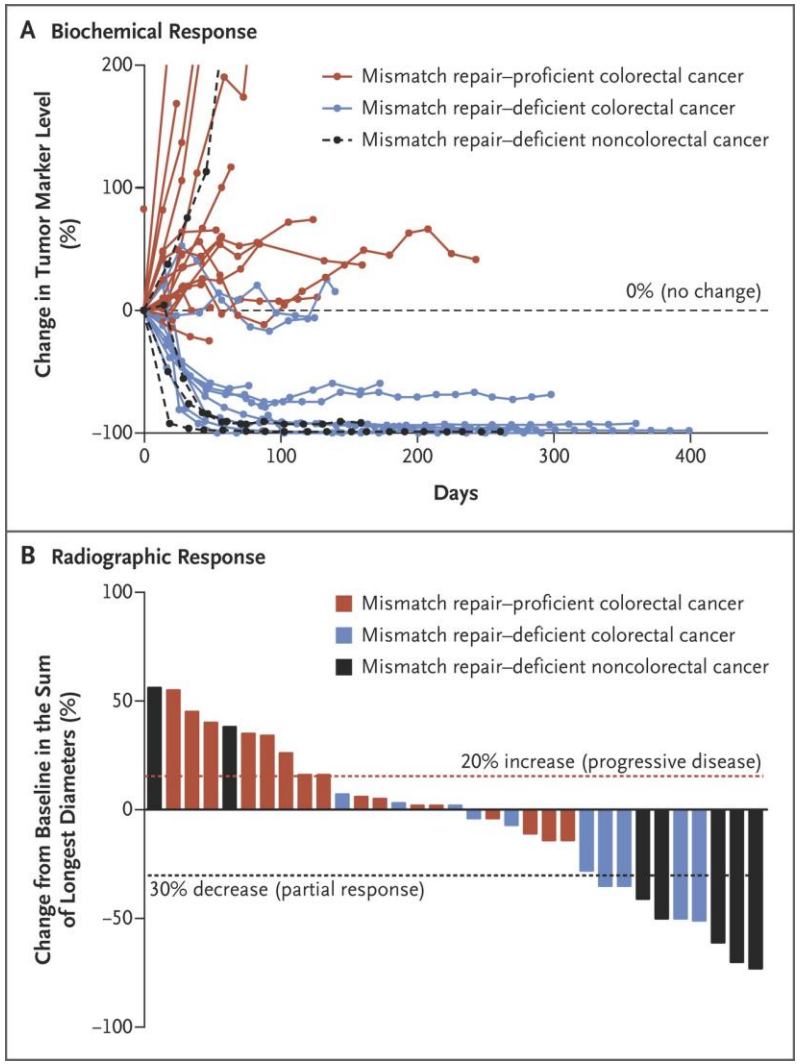
The Unique Challenges in Developing Biomarker-Driven Site-Agnostic Therapies

Richard L. Schilsky, MD, FACP, FSCT, FASCO

Senior Vice President and Chief Medical Officer

American Society of Clinical Oncology

Pembrolizumab in MSI-High Tumors



Le DT et al. N Engl J Med 2015;372:2509-2520

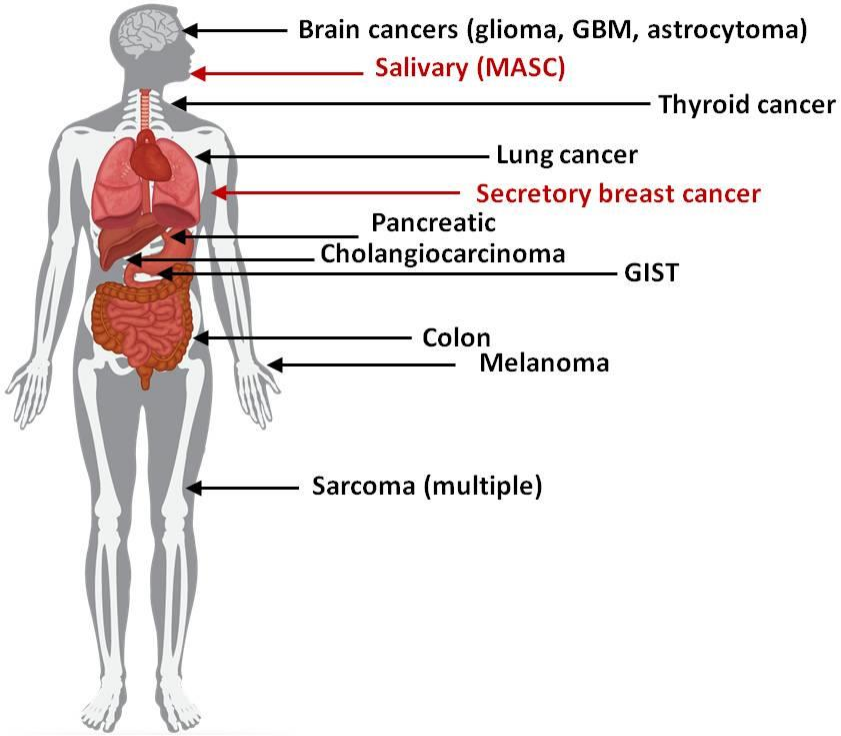
Pembrolizumab Response Rate by Tumor Type

Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

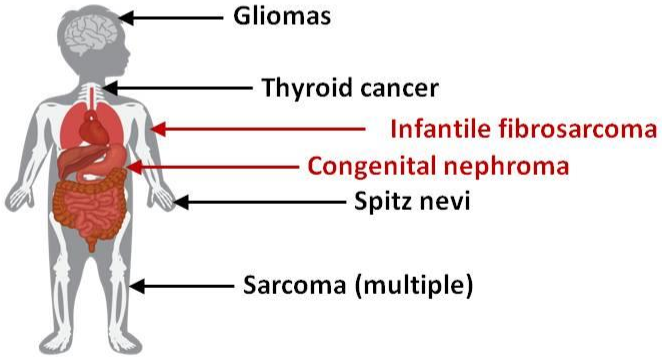
* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

TRK fusions found in diverse cancer histologies



■ Common cancer with low TRK fusion frequency

■ Rare cancer with high TRK fusion frequency



Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

Presented By David Hyman at 2017 ASCO Annual Meeting

Demographic and Clinical Characteristics of 55 Patients Treated with Larotrectinib

Tumor type — no. (%)	
Salivary-gland tumor	12 (22)
Other soft-tissue sarcoma‡	11 (20)
Infantile fibrosarcoma	7 (13)
Thyroid tumor	5 (9)
Colon tumor	4 (7)
Lung tumor	4 (7)
Melanoma	4 (7)
GIST	3 (5)
Cholangiocarcinoma	2 (4)
Appendix tumor	1 (2)
Breast tumor	1 (2)
Pancreatic tumor	1 (2)
CNS metastases — no. (%)	
No	54 (98)
Yes	1 (2)
TRK gene — no. (%)	
NTRK1	25 (45)
NTRK2	1 (2)
NTRK3	29 (53)

Drilon A et al. N Engl J Med 2018;378:731-739

Overall Response Rate to Larotrectinib

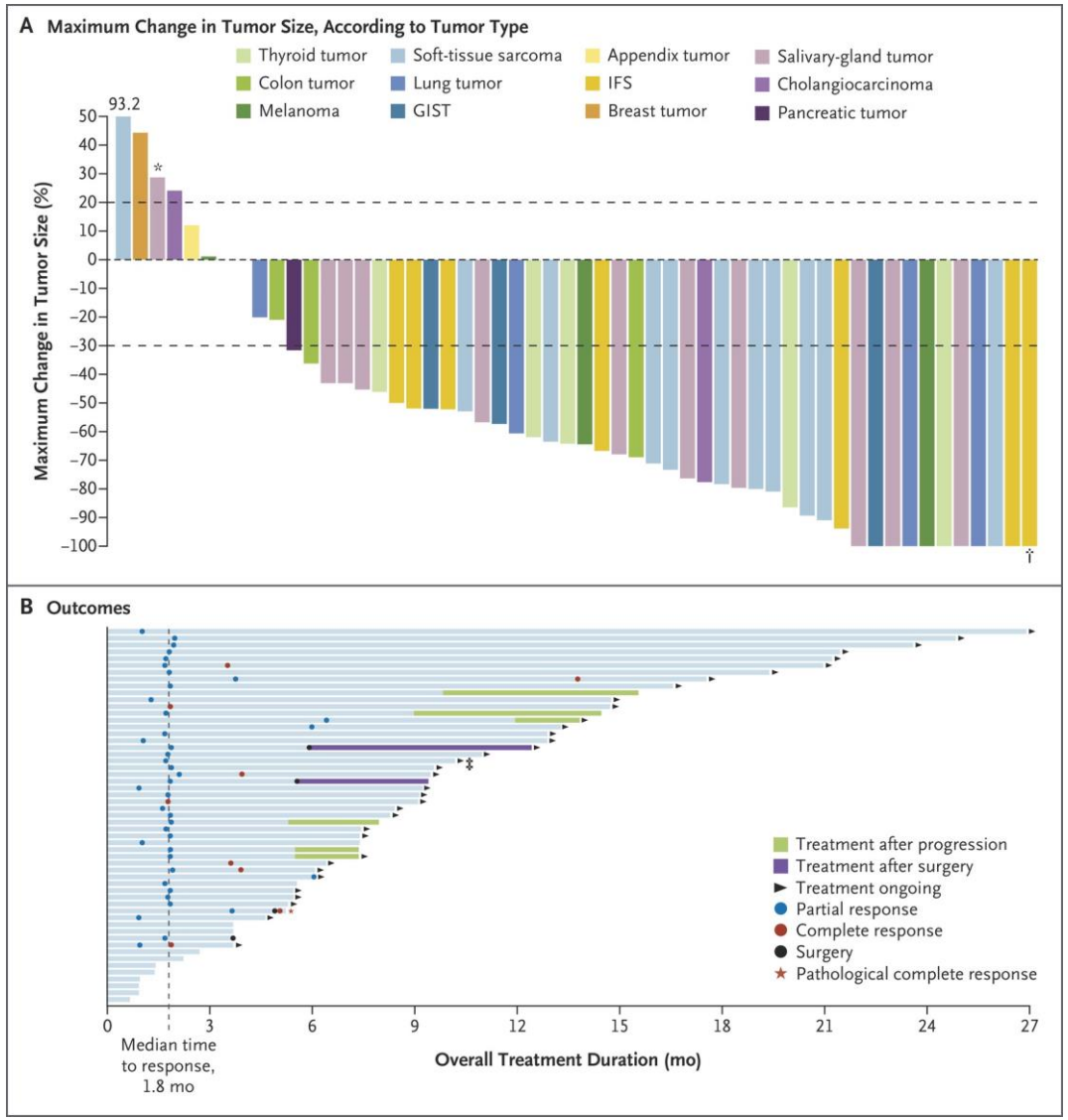
Table 2. Overall Response Rate, According to Investigator and Central Assessment.*

Response	Investigator Assessment (N=55)	Central Assessment (N=55)
	percent	
Overall response rate (95% CI)†	80 (67–90)	75 (61–85)
Best response		
Partial response	64‡	62
Complete response	16	13
Stable disease	9	13
Progressive disease	11	9
Could not be evaluated	0	4

* Percentages may not total 100 because of rounding.
† The best overall response was derived from the responses as assessed at specified time points according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
‡ Data include one patient who had a partial response that was pending confirmation at the time of the database lock. The response was subsequently confirmed, and the patient's treatment and response are ongoing.

Drilon A et al. N Engl J Med 2018;378:731-739

Efficacy of Larotrectinib



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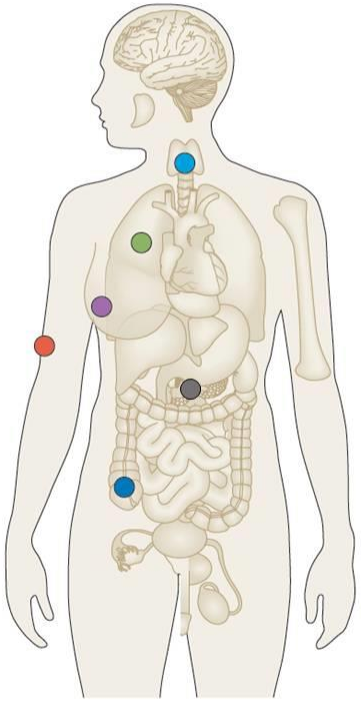
RET is activated by two major mechanisms in cancer

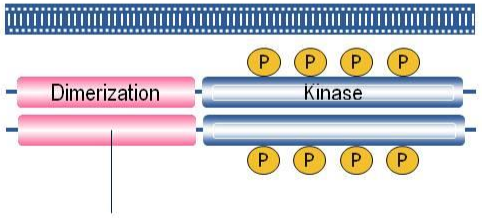
RET fusions



Non-small cell lung cancer (2%)

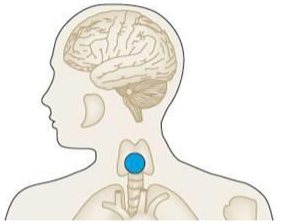
Papillary and other thyroid cancers (10–20%)

Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)



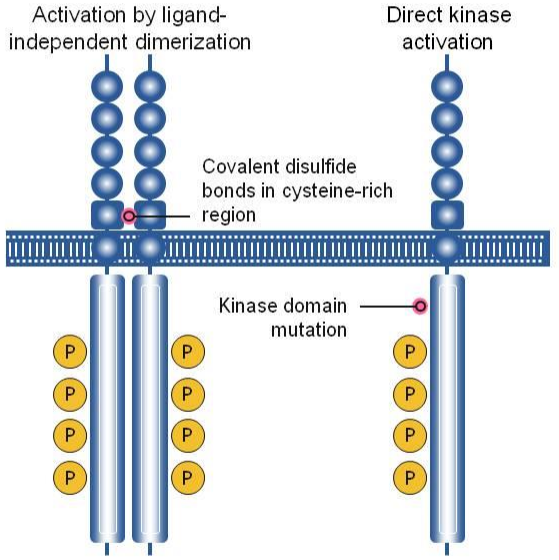
KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

RET mutations



Medullary thyroid cancer

sporadic (>60%)
hereditary (>90%)

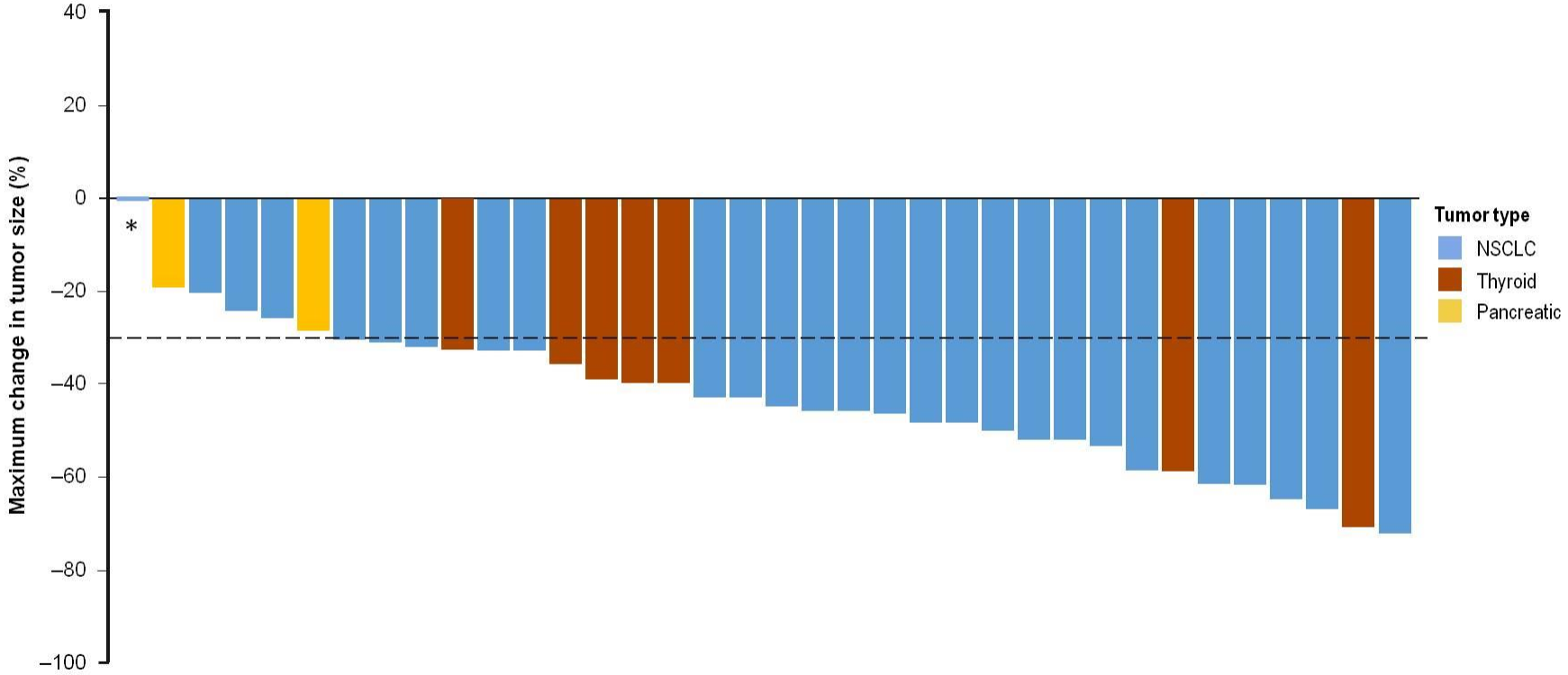


Common mutation: ***RET* M918T**

Drilon et al. Nat Rev Clin Oncol 2018;15:151–67; Kato et al. Clin Cancer Res 2017; 23:1988–97; Pietrantonio et al. Ann Oncol 2018;Mar 10; Su et al. PLoS One 2016;11(11)

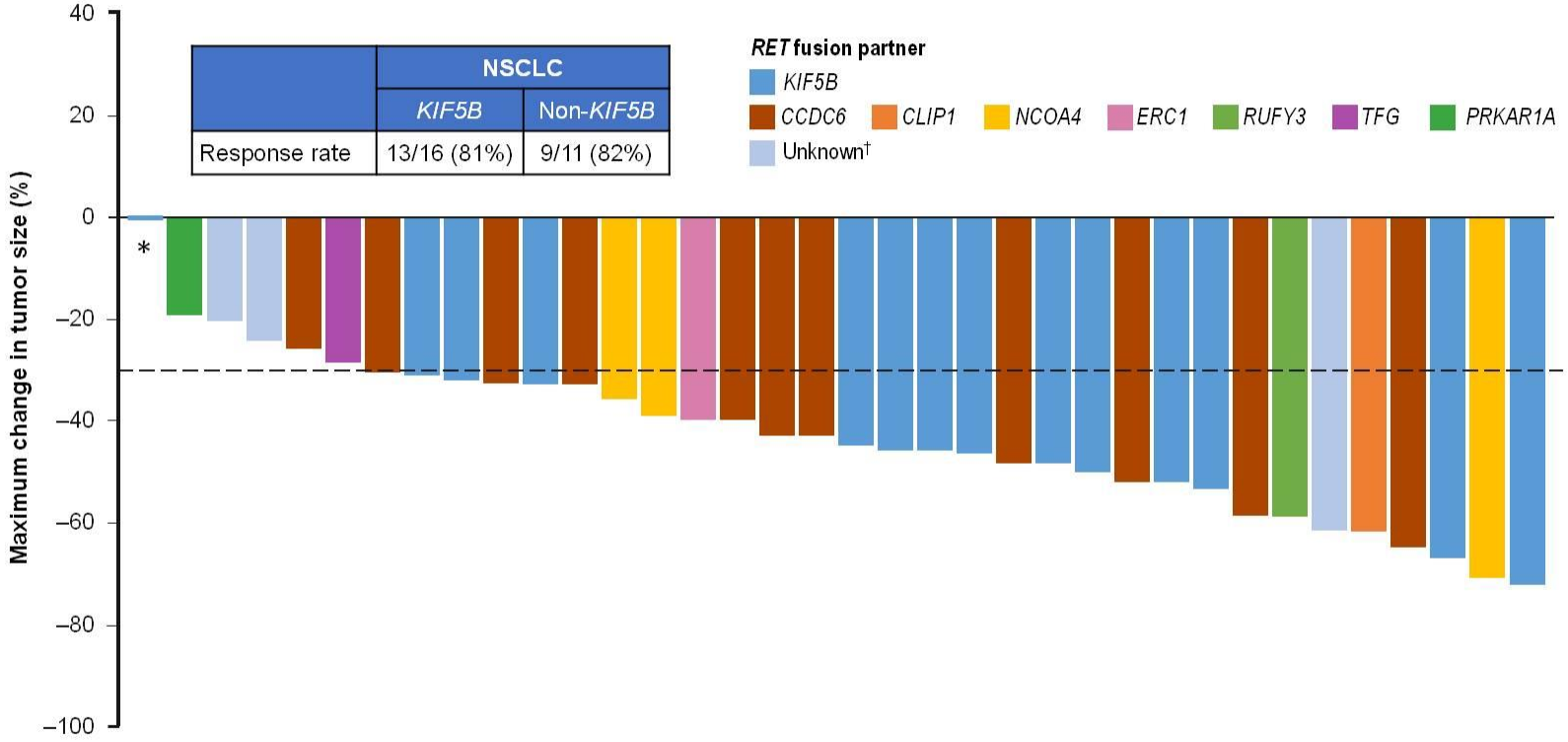
Presented By Alexander Drilon at 2018 ASCO Annual Meeting

Efficacy of LOXO-292 in *RET* fusion-positive cancers



NSCLC = non-small cell lung cancer
Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
April 2, 2018 data cut-off date

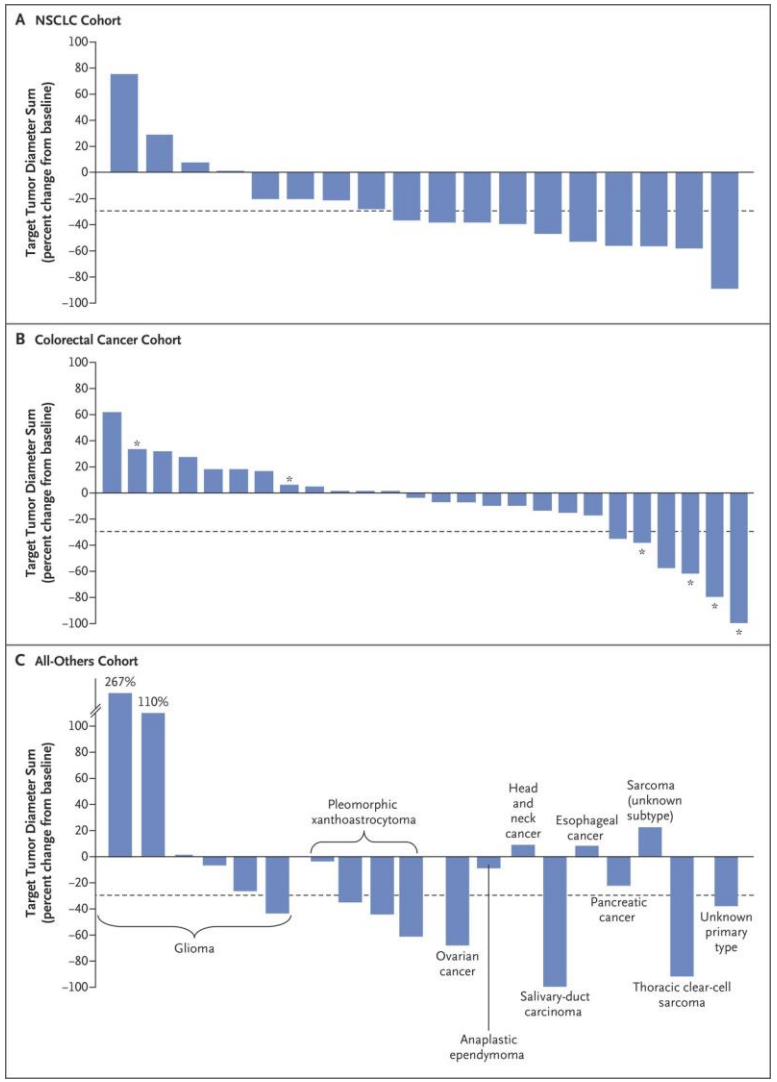
Efficacy of LOXO-292 regardless of *RET* fusion partner



Note: Three patients not displayed due to treatment discontinuation prior to first post-baseline response assessment; *Denotes patient with 0% maximum change in tumor size
†Fusion partner unknown due to FISH+ detection; April 2, 2018 data cut-off date

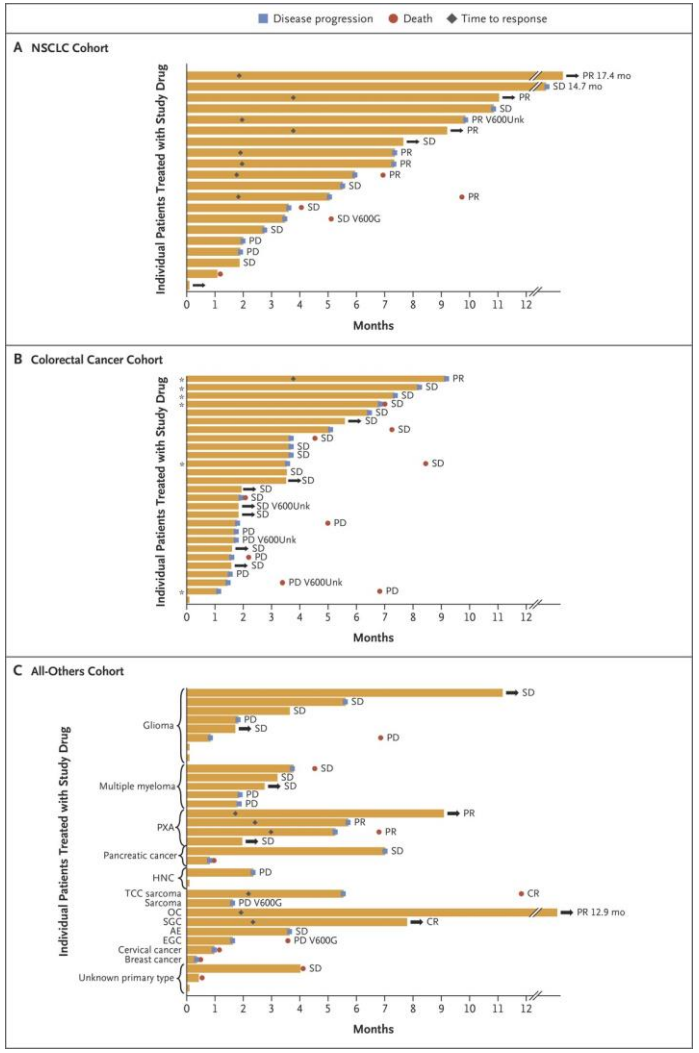
Presented By Alexander Drilon at 2018 ASCO Annual Meeting

Response in a BRAF Basket Trial



Hyman DM et al. N Engl J Med 2015;373:726-736

Time to Events in Individual Patients and According to the Best Overall Response



Hyman DM et al. N Engl J Med 2015;373:726-736

Efficacy of HER2-Directed Therapy in HER2-Amplified Tumors

Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

Primary Site	No. of Patients	Response, No. (%)			ORR, % (95% CI)
		CR	PR	SD > 120 Days	
Colorectal	37	0	14 (38)	4 (11)	38 (23 to 55)
Lung, non–small-cell	16	0	2 (13)	2 (13)	13 (2 to 38)
Bladder	9	1 (11)	2 (22)	2 (22)	33 (8 to 70)
Pancreas	9	0	2 (22)	1 (11)	22 (3 to 60)
Biliary	7	0	2 (29)	3 (38)	29 (4 to 71)
Ovary	8	0	1 (13)	0	13 (0 to 53)
Uterus	7	0	0	0	0
Salivary gland	5	0	4 (80)	0	80 (28 to > 99)
Other (11 sites)*	16	1 (6)	1 (6)	3 (19)	13 (2 to 38)
Total	114	2 (2)	28 (25)	16 (14)	26 (19 to 35)

NOTE. N = 114. Includes 12 patients with amplification/overexpression plus mutation.

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

*Responses occurred in patients with adenocarcinomas of the prostate (one) and skin (apocrine; one).

Published in: John D. Hainsworth; Funda Meric-Bernstam; Charles Swanton; Herbert Hurwitz; David R. Spigel; Christopher Sweeney; Howard Burris; Ron Bose; Bongin Yoo; Alisha Stein; Mary Beattie; Razelle Kurzrock; *JCO* **2018,** 36, 536-542.
DOI: 10.1200/JCO.2017.75.3780

Variable Efficacy of HER2-directed Therapy Across HER2-amplified Tumors

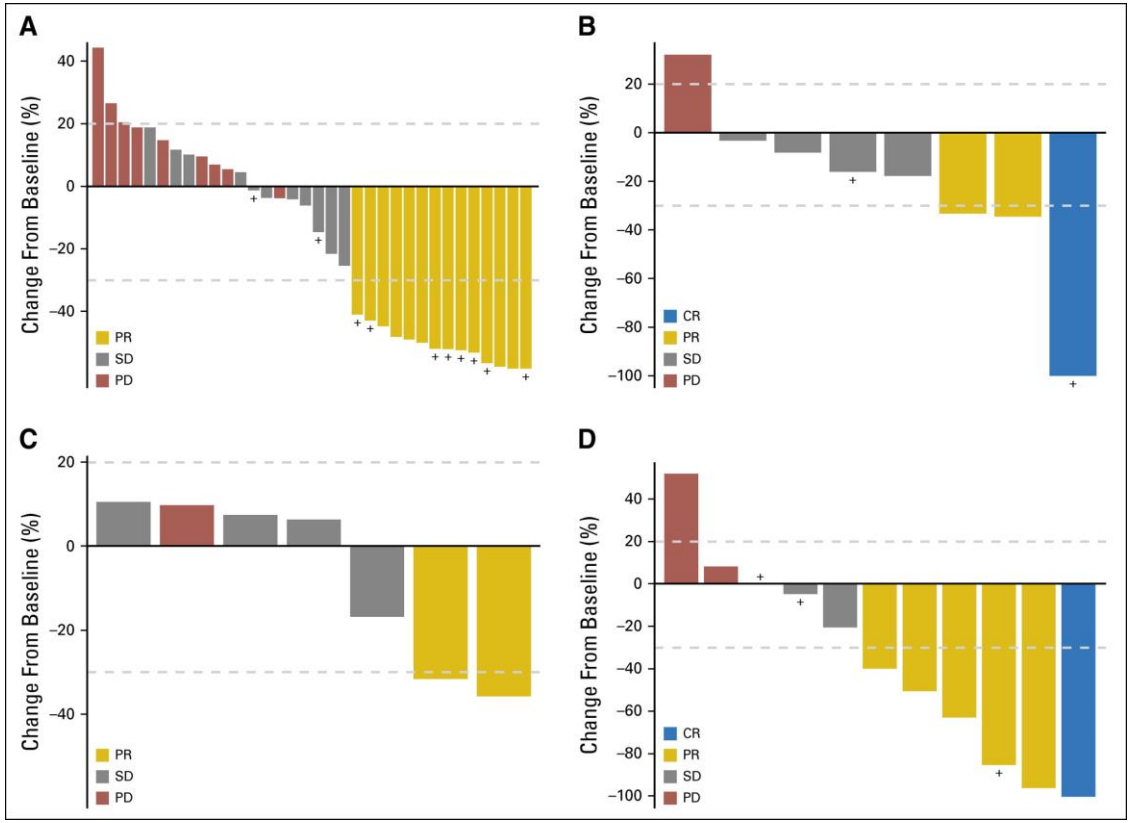


Fig 2. Waterfall plots of treatment response in patients with human epidermal growth factor receptor-2 (HER2)-amplified/overexpressing (A) colorectal, (B) bladder, and (C) biliary cancers, and (D) patients with murine sarcoma viral (v-raf) oncogene homolog B1 (BRAF) V600E-mutated non–small-cell lung cancer. Three patients with HER2-amplified/overexpressing colorectal cancer, one with HER2-amplified/overexpressing bladder cancer, and three with BRAF V600E-mutated non–small-cell lung cancer were not evaluated for response and are not included. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. + indicates treatment is ongoing.

Published in: John D. Hainsworth; Funda Meric-Bernstam; Charles Swanton; Herbert Hurwitz; David R. Spigel; Christopher Sweeney; Howard Burris; Ron Bose; Bongin Yoo; Alisha Stein; Mary Beattie; Razelle Kurzrock; *JCO* **2018,** 36, 536-542.
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Challenges

- Patient identification
- Small sample size for many tumor types
- Not all tumor types respond or respond equally well; wide CI around response rates
- Duration of response variable across tumor types
- Not all tumor types represented in any data set yet approval requested for all
- Are RCTs possible? What is appropriate control group?
- Biomarker prevalence/predictive value may vary across tumor types
- Molecular diagnostic tests not uniform, e.g., multiple platforms to assess MSI status (PCR, IHC, NGS, etc.)
- How much evidence is sufficient for a histology-agnostic approval?