Agnostic Tumor Drug Development

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MIAMI CANCER MEETING

Disclosures

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EDITORIAL

Tumor Type-Agnostic Treatment and the Future of Cancer Therapy

Luis E. Raez[1] · Edgardo S. Santos[2]

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It is fascinating to see how the science of cancer therapy has evolved. We first classified tumors as "solid" or "liquid" and created the specialties of oncology and hematology to later discover that the shape of the tumors has nothing to do with their etiology, so we ended up combining both specialties. Next, we proceeded to classify cancers according to the organ they grow in, thinking that the origin of the tumors is what causes their biological behaviors, and could guide us in understanding and fighting them properly. After so many years taking this approach, with both tremendous successes and deep disappointments, we are now beginning to appreciate that there is much more complexity to cancer biology than simply the tissue that tumors arise from.

Molecular mechanisms (DNA mutations, translocations

In the current issue, Kummar and Lassen [2] present a very comprehensive review of NTRK gene aberrations as one example of success in using this tumor site-agnostic approach. The authors review the diagnostic and treatment strategies that are being implemented to deal with NTRK-fusion genes and the diseases that they cause.

NTRK genes encode for the Trk-family of tyrosine kinases: TrkA, TrkB, and TrkC (encoded by NTRK1, NTRK2, and NTRK3). Normally, these proteins are involved in the development of the nervous system [3]. However, Trks are also present in solid tumors as fusion proteins responsible for the growth of cancer cells, and these oncogenic fusions are associated with poor survival in lung cancers and other tumor

types [4]. As seen with several other oncogenes (e.g., ALK

- NTRK Inhibitors
- BRAF (v600) inhibitors
- MMR and MSI guided Immunotherapy

NTRK inhibitors

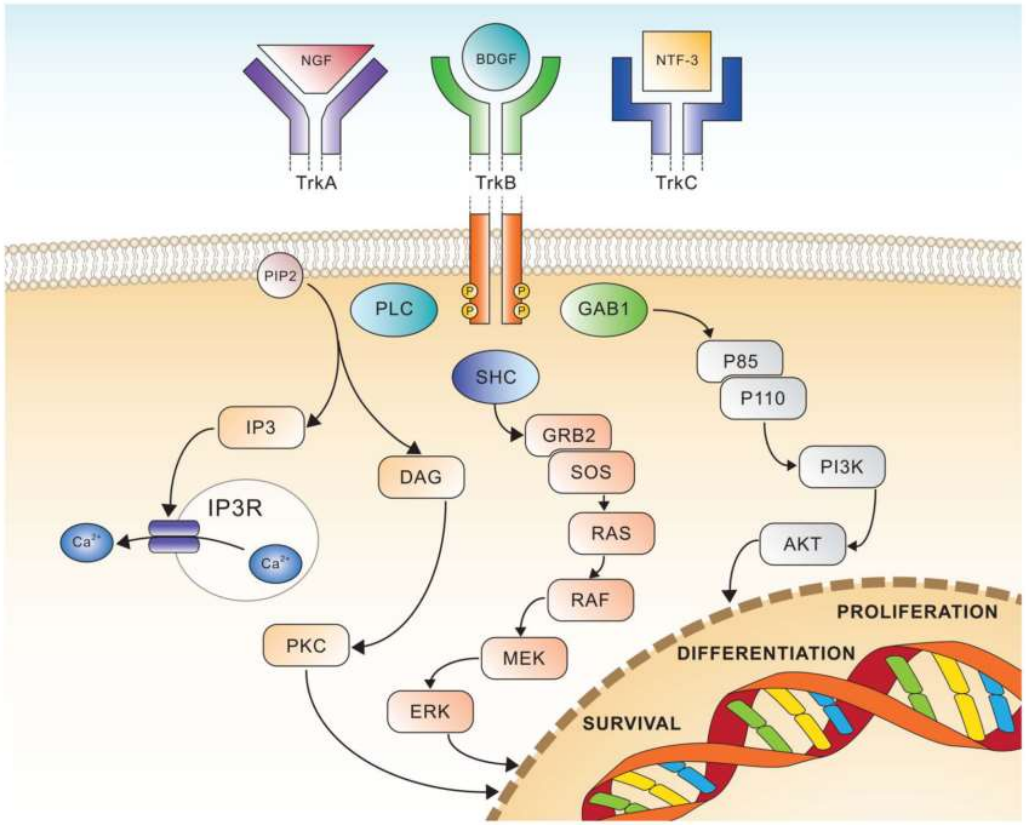
Larotrectenib

Entrectinib

LOXO 195

An Introduction to *NTRK*

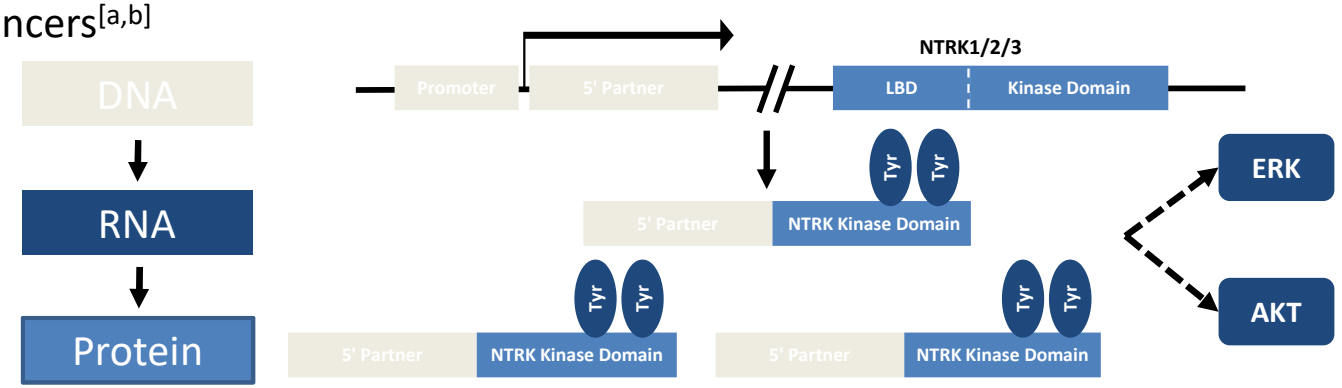
- *NTRK* genes: 1, 2, and 3 encode TRK proteins: A, B, and C
- Normally regulate neuronal development in utero and sensation of pain, proprioception, and appetite postnatally
- *NTRK* gene fusions found in large number of solid tumors and leukemias
  - Common in rare cancers:
    - Infantile fibrosarcoma/cellular CMN
  - Rare in more common cancers
    - NRSTS, gliomas, melanomas, thyroid cancer, breast cancer, other adult epithelial cancers



- Amatu A, et al. *ESMO Open.* 2016;1:e000023.

NTRK Fusions

- Beyond the embryo, TRK proteins are primarily limited to the nervous system[a]
- 3 neurotrophin receptors encoded by 3 distinct genes that regulate specific normal functions[a,b]
  - NTRK1 → TRKA → Pain, thermoregulation
  - NTRK2 → TRKB → Movement, memory, mood, appetite, body weight
  - NTRK3 → TRKC → Proprioception
- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers[a,b]



- a. Drilon A, et al. *N Engl J Med.* 2018;378:731-739; b. Vaishnavi A, et al. *Cancer Discov.* 2015;5:25-34.

Larotrectinib in *TRK*-fusion cancers

Diseases

Tumor type	#/ percentage
Salivary gland tumor	12 (22%)
Soft tissue sarcoma	11 (20%)
Infantile fibrosarcoma	7 (13%)
Thyroid cancer	5 (9%)
Colon cancer	4 (7%)
Lung cancer	4 (7%)
Melanoma	4 (7%)
GIST	3 (5%)
Cholangiocarcinoma	2 (4%)
Appendix	1 (2%)
Breast	1 (2%)
Pancreas	1 (2%)

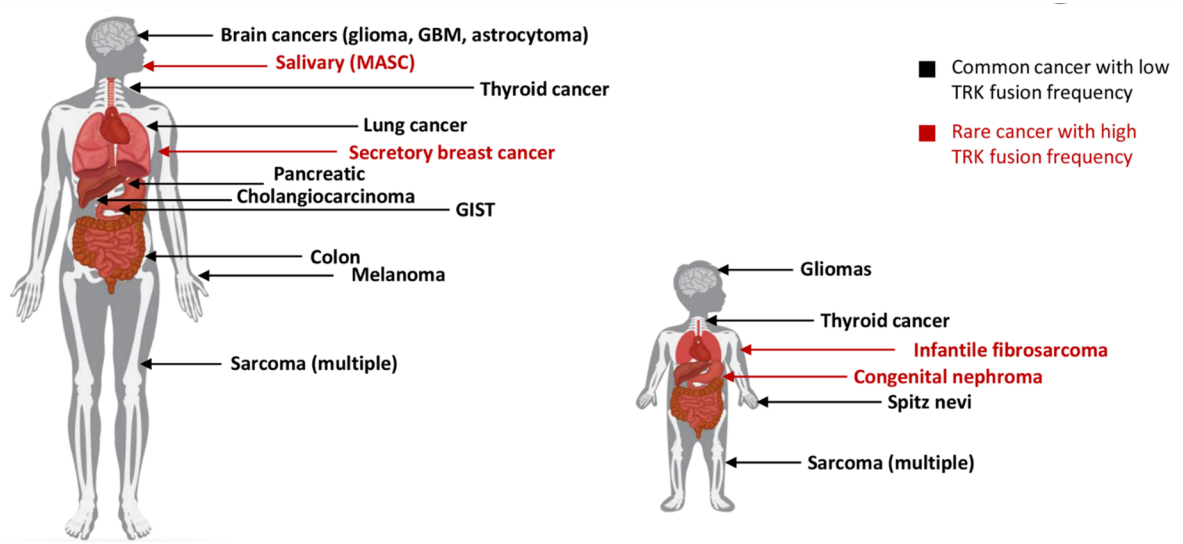
Efficacy

Parameter	Result
ORR	75% (41/55)
Median time to response	1.8 months
Median duration of response	NR
Median PFS	NR
1-year PFS	55%

Drilon et al NEJM 2018

Prevalence

- Estimated 1500 to 5000 US patients with *NTRK* fusion-positive cancers[a]



- *NTRK1* fusions are found in approximately 1% of adenocarcinomas of the lung[b]

- a. Hyman DM, et al. ASCO® 2017. Abstract LBA2501; b. Tsao AS, et al. *J Thorac Oncol.* 2016;11:613-638.

The NEW ENGLAND JOURNAL of MEDICINE

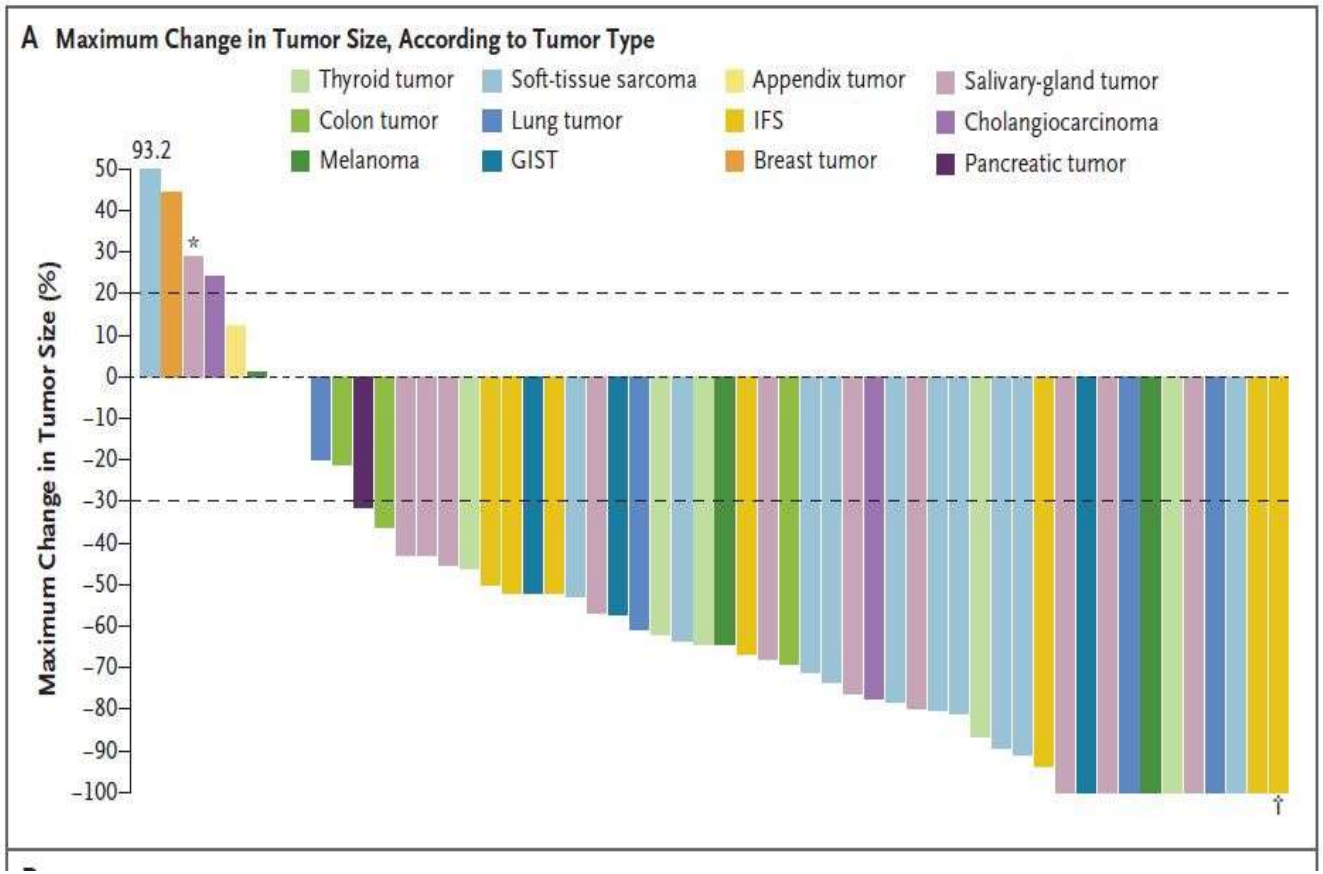
ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

ABSTRACT

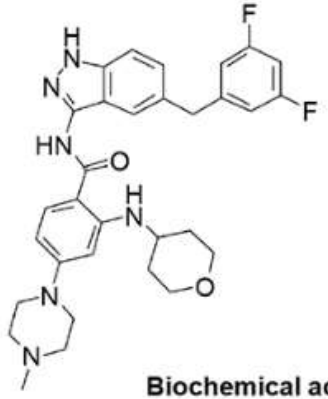
BACKGROUND


A Maximum Change in Tumor Size, According to Tumor Type
Thyroid tumor
Soft-tissue sarcoma
Appendix tumor
Salivary-gland tumor
Colon tumor
Lung tumor
IFS
Cholangiocarcinoma
Melanoma
GIST
Breast tumor
Pancreatic tumor
93.2
*
†
Maximum Change in Tumor Size (%)
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100

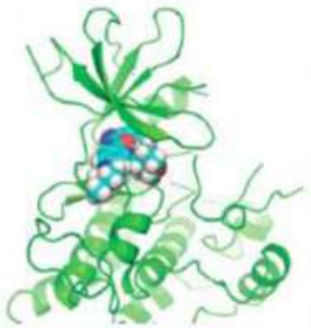
Entrectinib: Pan-TRK/ROS1/ALK Inhibitor[1]

- Orally administered inhibitor of TRKA/B/C, ROS1, and ALK

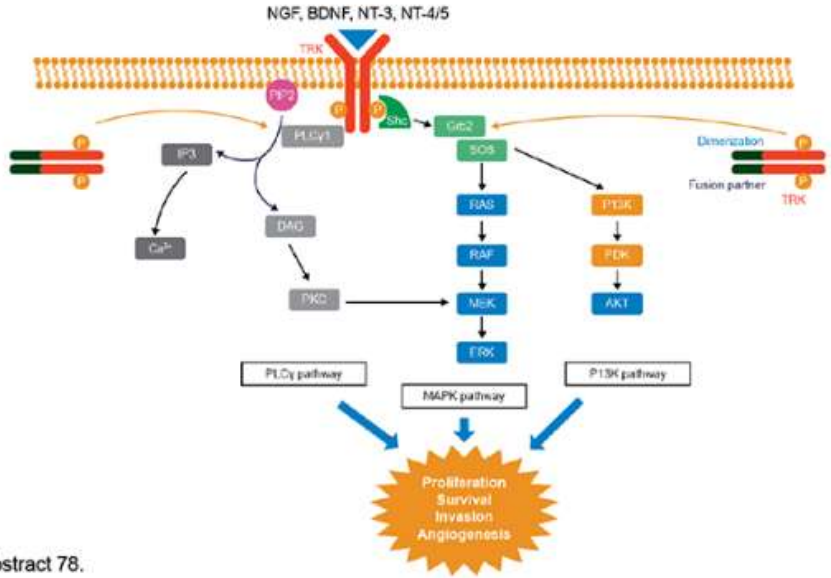
Chemical structure of entrectinib



X-ray crystallography model of entrectinib binding in the kinase pocket of TRKA



Signaling pathways of TRK and TRK fusions



Biochemical activity of entrectinib

Target	TRKA	TRKB	TRKC	ROS1	ALK
IC_{50} (nM)	1.7	0.1	0.1	0.2	1.6

1. Wei G et al. 2016 EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium. Abstract 78.

Entrectinib Development Program: Combined Phase 1 Studies[1]

ALKA-372-001 (N = 54)

- Dosing: Intermittent and continuous
- *NTRK/ROS1/ALK* alterations
- Italy
  - FIH study: Nerviano Medical Sciences in October 2012 → Ignyta assumed responsibility in November 2013

STARTRK-1 (N = 65)

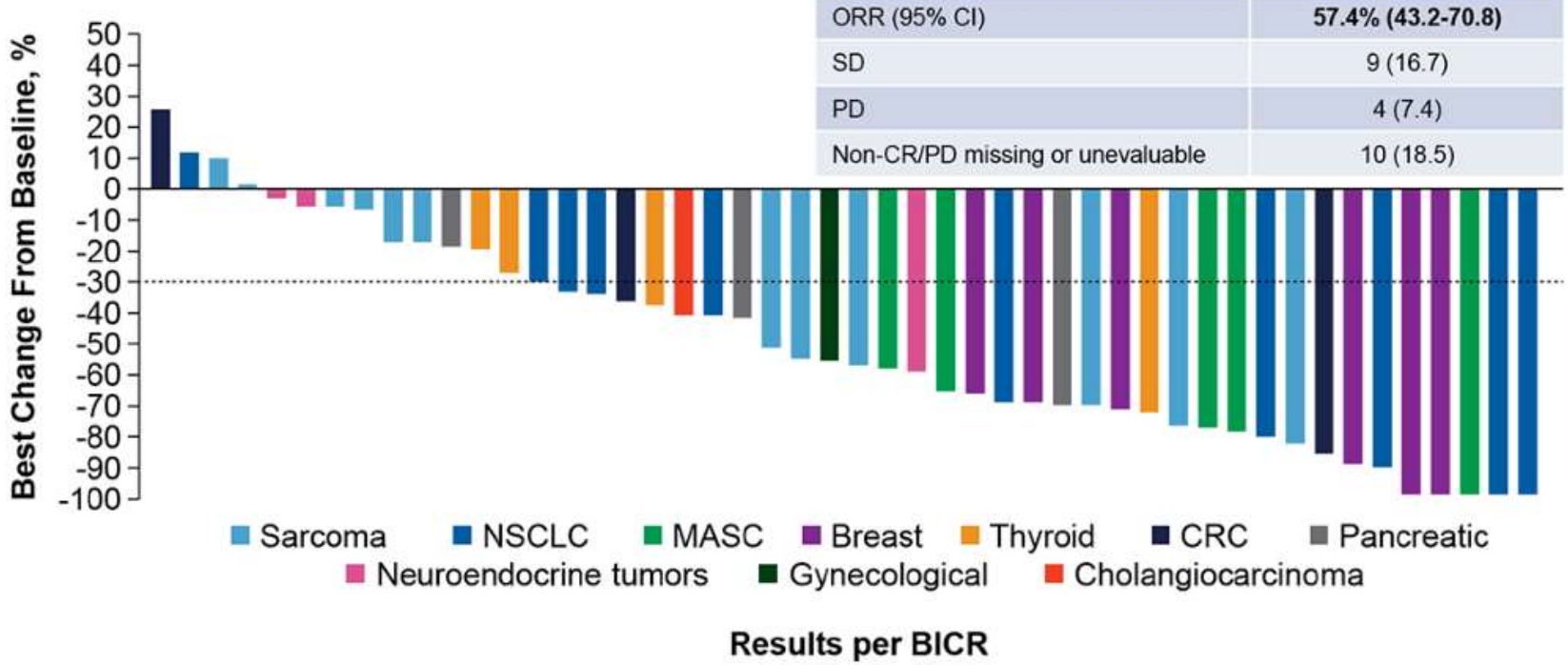
- Dosing: Continuous
- *NTRK/ROS1/ALK* alterations
- US, EU, and Asia
  - Ignyta initiated in July 2014

- RP2D: 600 mg PO once daily, continuous
- Total clinical experience (n = 119 patients)
  - Updated safety and efficacy data
  - Data cut-off: March 7, 2016

1. Drilon A et al. *Cancer Discov*. 2017;7:400-409.

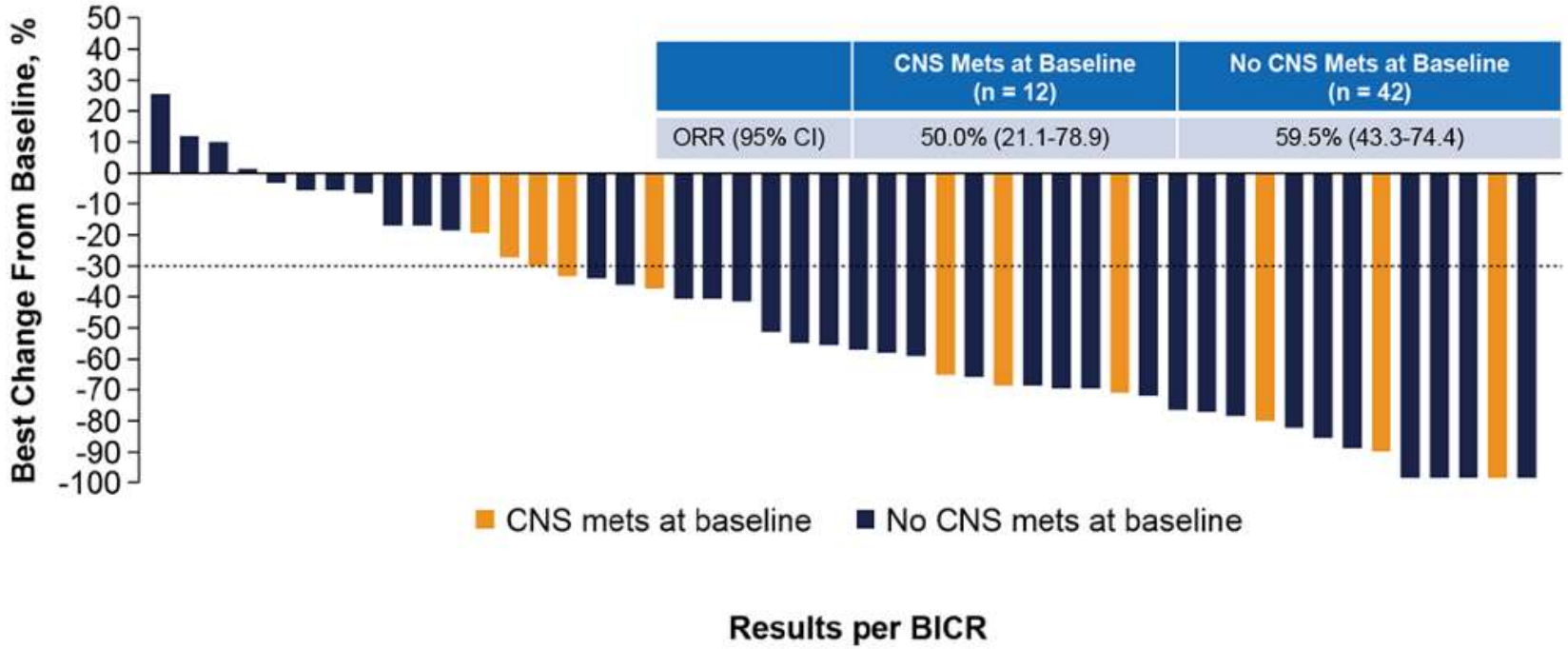
Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Patient Responses by Tumor Type[1]

	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)



1. Demetri GD et al. ESMO 2018. Abstract LBA17.

Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Responses by CNS Mets Status[1]



1. Demetri GD et al. ESMO 2018. Abstract LBA17.

Entrectinib: Safety Overview[1]

Treatment-Related AEs Reported in ≥10% of Patients	*NTRK* Fusion-Positive Safety Population (n = 68)		Overall safety population (N = 355)	
Patients, n (%)	Grades 1/2	Grade 3	Grades 1/2	Grade 3
Dysgeusia	32 (47.1)	0	146 (41.1)	1 (0.3)
Constipation	19 (27.9)	0	83 (23.4)	1 (0.3)
Fatigue	19 (27.9)	5 (7.4)	89 (25.1)	10 (2.8)
Diarrhoea	18 (26.5)	1 (1.5)	76 (21.4)	5 (1.4)
Oedema peripheral	16 (23.5)	1 (1.5)	49 (13.8)	1 (0.3)
Dizziness	16 (23.5)	1 (1.5)	88 (24.8)	2 (0.6)
Blood creatinine increase	12 (17.6)	1 (1.5)	52 (14.6)	2 (0.6)
Paraesthesia	11 (16.2)	0	67 (18.9)	0
Nausea	10 (14.7)	0	74 (20.8)	0
Vomiting	9 (13.2)	0	48 (13.5)	0
Arthralgia	8 (11.8)	0	42 (11.8)	2 (0.6)
Myalgia	8 (11.8)	0	52 (14.6)	2 (0.6)
Weight increased	8 (11.8)	7 (10.3)	51 (14.4)	18 (5.1)
AST increase	7 (10.3)	0	35 (9.9)	3 (0.8)
Muscular Weakness	6 (8.8)	1 (1.5)	22 (6.2)	3 (0.8)
Anaemia	5 (7.4)	8 (11.8)	27 (7.6)	16 (4.5)

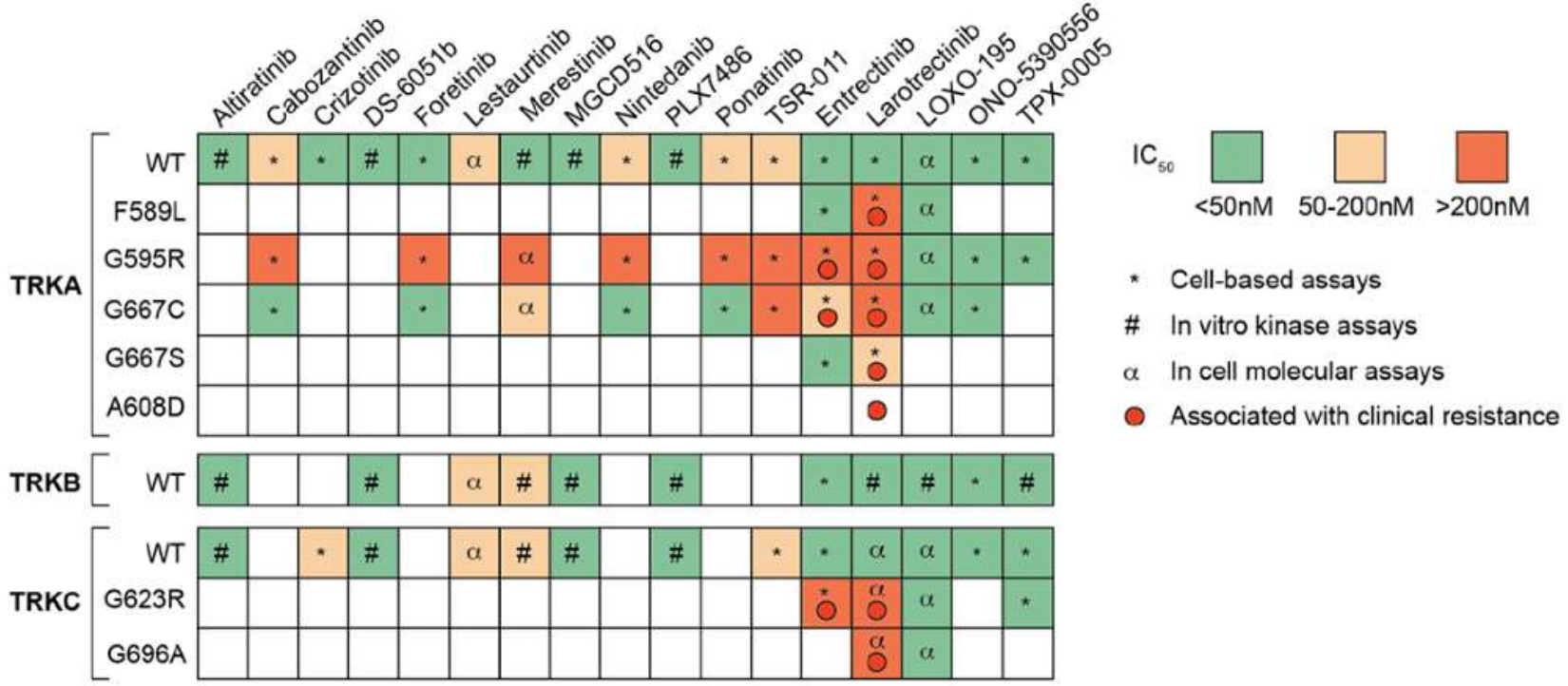
Overall safety population (N = 355)

- Most adverse events were grades 1/2 and reversible
- Treatment-related AEs leading to
  - **Dose reduction: 27.3%**
  - **Dose interruption: 25.4%**
  - **Discontinuation** from treatment: **3.9%**
- No grade 5 treatment-related events

Treatment-related AEs in the *NTRK* fusion–positive safety population are consistent with the overall safety population

1. Demetri GD et al. ESMO 2018. Abstract LBA17.

TRK Inhibitors Have Different Levels of Activity Against Emergent Mutations[1]



1. Cocco E et al. *Nat Rev Clin Oncol.* 2018;15:731-747.

TRK inhibition

Table 1. Active clinical trials of TRK inhibitors in patients with *NTRK* fusion tumors[a]

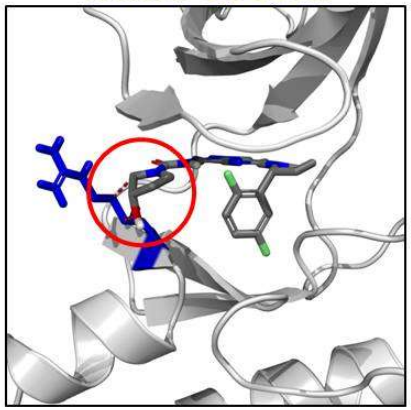
Agent	Kinase targets	Phase	*NTRK* fusion tumor type	Start date	Status	Estimated participants
Larotrectinib	TRKA, TRKB, TRKC	I	Advanced solid tumors	May 2014	Recruiting	90
		II	Advanced solid tumors	October 2015	Recruiting	151
		I/II	Advanced solid or primary CNS tumors (pediatric)	December 2015	Recruiting	92
Entrectinib	TRKA, TRKB, TRKC, ALK, ROS1	I	Locally advanced or metastatic solid tumors[b]	June 2014	Recruiting	125
		II	Locally advanced or metastatic solid tumors[b]	October 2015	Recruiting	300
		I/Ib	Recurrent or refractory solid tumors and primary CNS tumors (pediatric)	December 2015	Recruiting	190
DS-6051b	TRKA, TRKB, TRKC, ROS1	I	Advanced solid tumors[c]	September 2014	Not recruiting	70
		I	Advanced solid tumors (Japanese patients)	February 2016	Not recruiting	15
TSR-011	TRKA, TRKB, TRKC, ALK	I/IIa	Advanced solid tumors and lymphomas[d]	October 2012	Unknown	72
TPX-0005[e]	TRKA, TRKB, TRKC, ALK, ROS1	I/II	Locally advanced or metastatic solid tumor (including non-Hodgkin lymphoma)[b]	February, 2017	Recruiting	450
LOXO-195[e]	TRKA, TRKB, TRKC	I/II	Advanced solid tumor progressing after prior TRK inhibitor treatment	July, 2017	Recruiting	93

CNS central nervous system
[a]As registered with ClinicalTrials.gov.
[b]Inclusion of patients with *ROS1*, or *ALK* gene rearrangements permitted.
[c]Inclusion of patients with *ROS1* gene rearrangements permitted.
[d]Inclusion of patients with *ALK* gene rearrangements permitted.
[e]Second generation TRK inhibitor with activity against TRK proteins with resistance mutations.

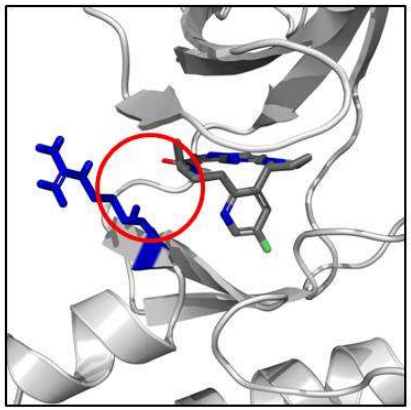
LOXO-195 to Address TRK Acquired Resistance

TRKA G595R

Larotrectinib



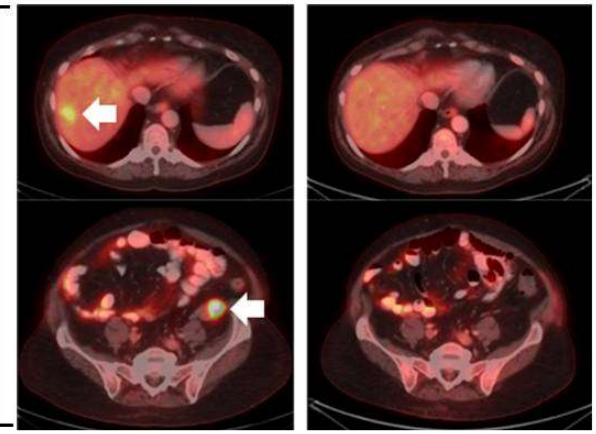
LOXO-195



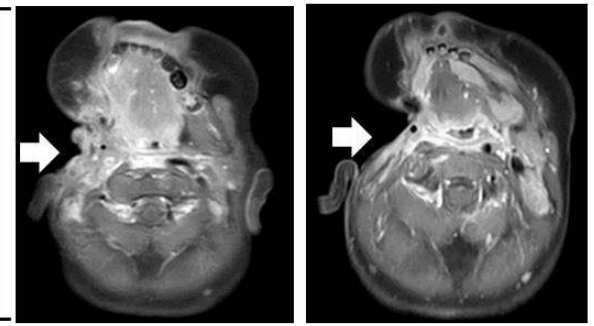
Tumor type	Fusion	Resistance mutation
Colorectal	TPM3-NTRK1	TRKA G595R
Colorectal	LMNA-NTRK1	TRKA G595R
NSCLC	TPR-NTRK1	TRKA G595R
Sarcoma[❖]	TPM3-NTRK1	TRKA G595R
IFS	ETV6-NTRK3	TRKC G623R
Cholangio[❖]	LMNA-NTRK1	TRKA F589L[*] + GNAS Q227H

TRK solvent front mutations detected in 5 of 6 patients with acquired resistance. First 2 patients successfully treated with LOXO-195.

LOXO-195 Treatment



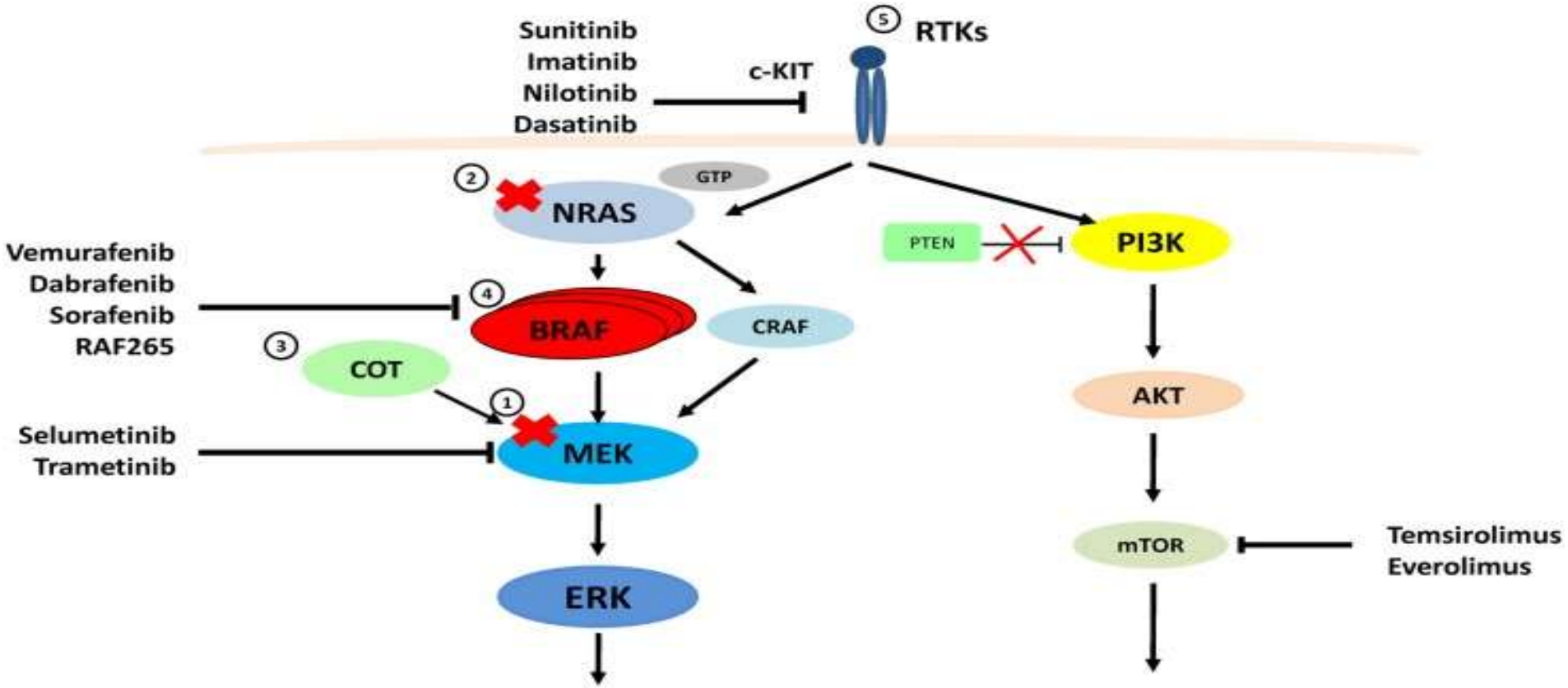
Baseline | On Treatment



❖ Oligometastatic progression, continue on larotrectinib * Gatekeeper mutation
Drilon A, *Cancer Discovery*, Online First (03-JUNE-2017)

BRAF/MEK Inhibitors

- Dabrafenib/Trametinib
  - Melanoma metastatic and adjuvant
  - Lung cancer metastatic
  - Anaplastic Thyroid cancer
- Cobimetinib/Vemurafenib*
  - Melanoma metastatic
  - Erdheim-Chester Disease*
- Binimetinib/Encorafenib
  - Melanoma metastatic
  - Colon Cancer metastatic** (with cetuximab)



1. MEK1 mutations
2. NRAS mutations
3. COT overexpression
4. BRAF amplification/ splicing
5. RTKs overexpression/activation (PDGFRβ, IGR1F)

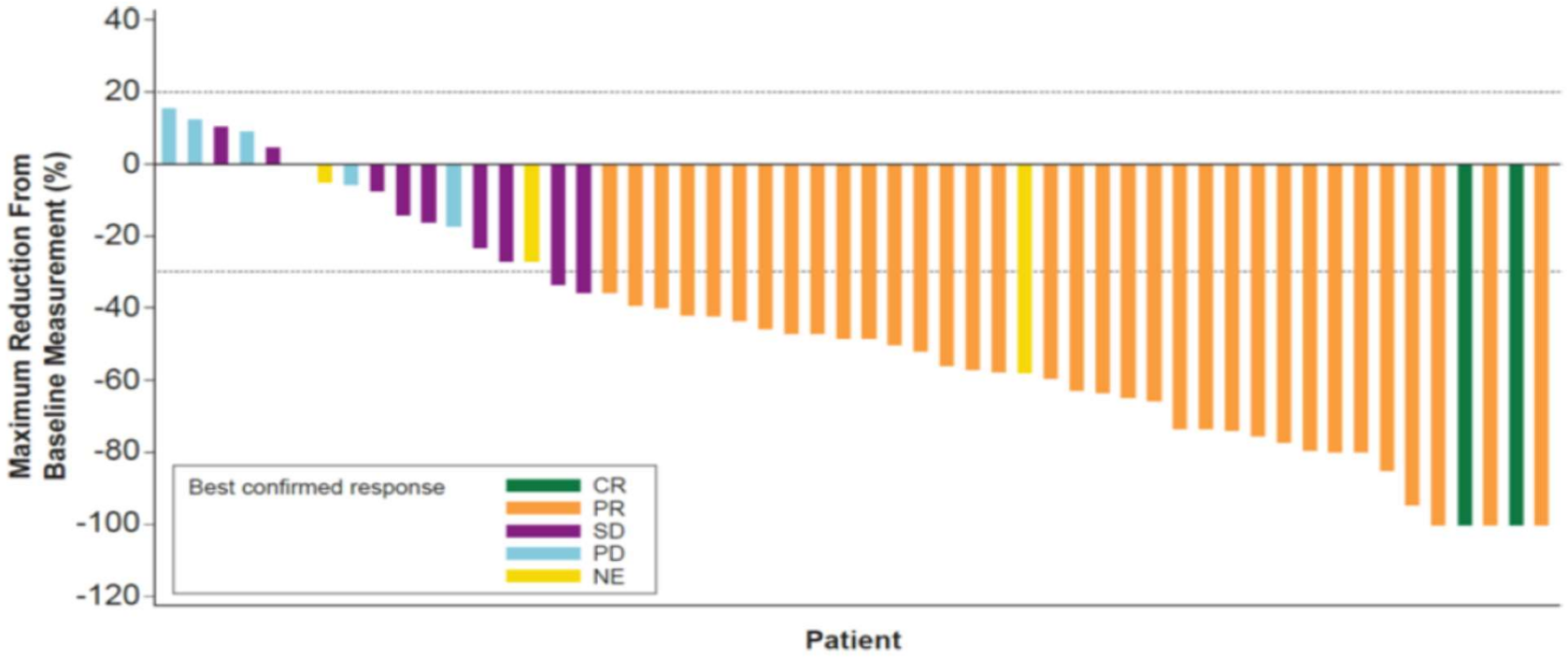


Figure 2. Tumor responses to dabrafenib + trametinib in *BRAF* V600E–mutant non-small cell lung cancer

Maximum reduction from baseline sum of lesion diameters by best investigator-assessed confirmed response in ≥ second-line patients (n=57). CR=complete response. NE=not evaluable. PD=progressive disease. SD=stable disease.

Antitumor activity in ≥ second-line patients

	Investigator Assessment (N=57)	Independent Assessment (N=57)
Best response, n (%)		
Complete response (CR)	2 (3·5)	0
Partial response (PR)	34 (59·6)	36 (63·2)
Stable disease (SD)	9 (15·8)	4 (7·0)
Progressive disease (PD)	7 (12·3)	8 (14·0)
Non-CR/non-PD	0	3 (5·3)
Not evaluable	5 (8·8)	6 (10·5)
Overall response (CR + PR), n (%) [95% CI]	36 (63·2) [49·3–75·6]	36 (63·2) [49·3–75·6]
Disease control rate (CR + PR + SD), n (%) [95% CI]	45 (78·9) [66·1–88·6]	43 (75·4) [62·2–85·9]
Progression-free survival, median (95% CI), months	9·7 (6·9–19·6)	8·6 (5·2–19·1)
Duration of response, median (95% CI), months	9·0 (6·9–18·3)	9·0 (5·8–17·6)

MMR and MSI guided Immunotherapy

- Pembrolizumab (All tumors)
- Nivolumab/Ipilimumab (colon cancer)

Mismatch repair (MMR) proteins are a group of nuclear enzymes, which participate in repair of base-base mismatch, that occur during DNA replication. The proteins form complexes (heterodimers) that bind to areas of abnormal DNA and initiates its removal.

Loss of MMR proteins leads to an accumulation of DNA replication errors particularly in areas of the genome with short repetitive nucleotide sequences, a phenomenon known as microsatellite instability (MSI).

MMR protein deficiency in cells is closely related to a high degree of MSI (MSI-H), in contrast to cells with a low degree of MSI (MSI-L) and cells that are MSI stable (MSS).

In November 2015, pembrolizumab was granted a breakthrough therapy designation by the FDA for patients with MSI-high metastatic CRC. The decision was based on results from an ongoing phase II study in which pembrolizumab demonstrated high response rates in heavily pretreated patients with CRC who had mismatch repair (MMR) deficiency, a condition that causes MSI.

Results showed that the objective response rate was 62% with pembrolizumab in MMR-deficient CRC tumors compared with 0% in MMR-proficient tumors.
Median progression-free survival and overall survival were not reached, with many patients responding to treatment for longer than 12 months in the MMR-deficient arm.

On May 23, 2017, the FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

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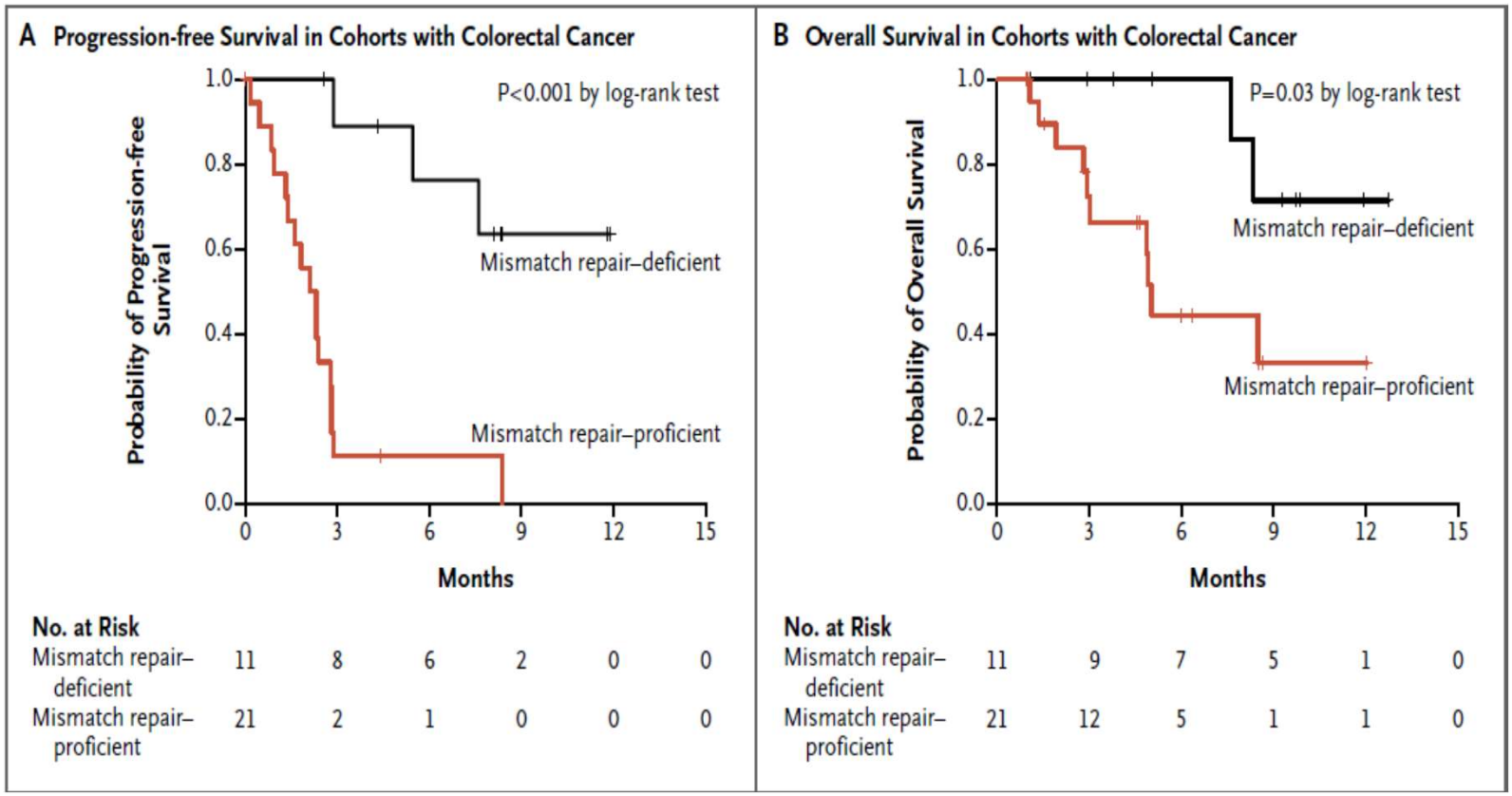
ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.


A Progression-free Survival in Cohorts with Colorectal Cancer
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
P<0.001 by log-rank test
Mismatch repair–deficient
Mismatch repair–proficient
0
3
6
9
12
15
Months
No. at Risk
Mismatch repair–deficient 11 8 6 2 0 0
Mismatch repair–proficient 21 2 1 0 0 0
B Overall Survival in Cohorts with Colorectal Cancer
Probability of Overall Survival
P=0.03 by log-rank test
Mismatch repair–deficient
Mismatch repair–proficient
Months
No. at Risk
Mismatch repair–deficient 11 9 7 5 1 0
Mismatch repair–proficient 21 12 5 1 1 0

Programmed death-1 blockade in mismatch repair deficient colorectal cancer

Dung T. Le, Jennifer N. Uram, Hao Wang, Bjarne Bartlett, Holly Kemberling, Aleksandra Eyring, Nilofer S. Azad, Daniel Laheru, Ross C. Donehower, Todd S. Crocenzi, Richard Goldberg, George Fisher, James Lee, Tim Greten, Minori Koshiji, Peter Kang, Bob Anders, James Eshleman, Bert Vogelstein and Luis A. Diaz, Jr.

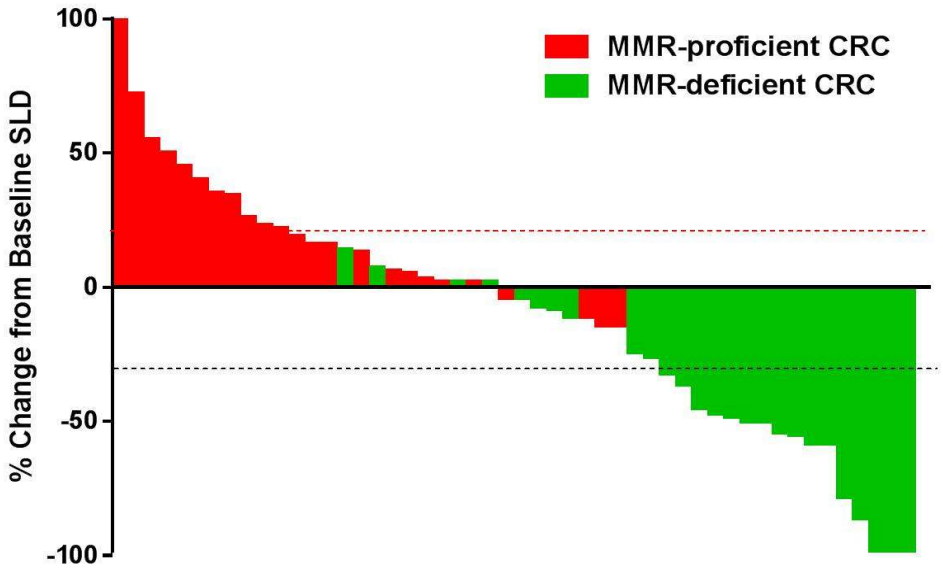
PRESENTED AT: ASCO ANNUAL MEETING '16

Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=28)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=30)**

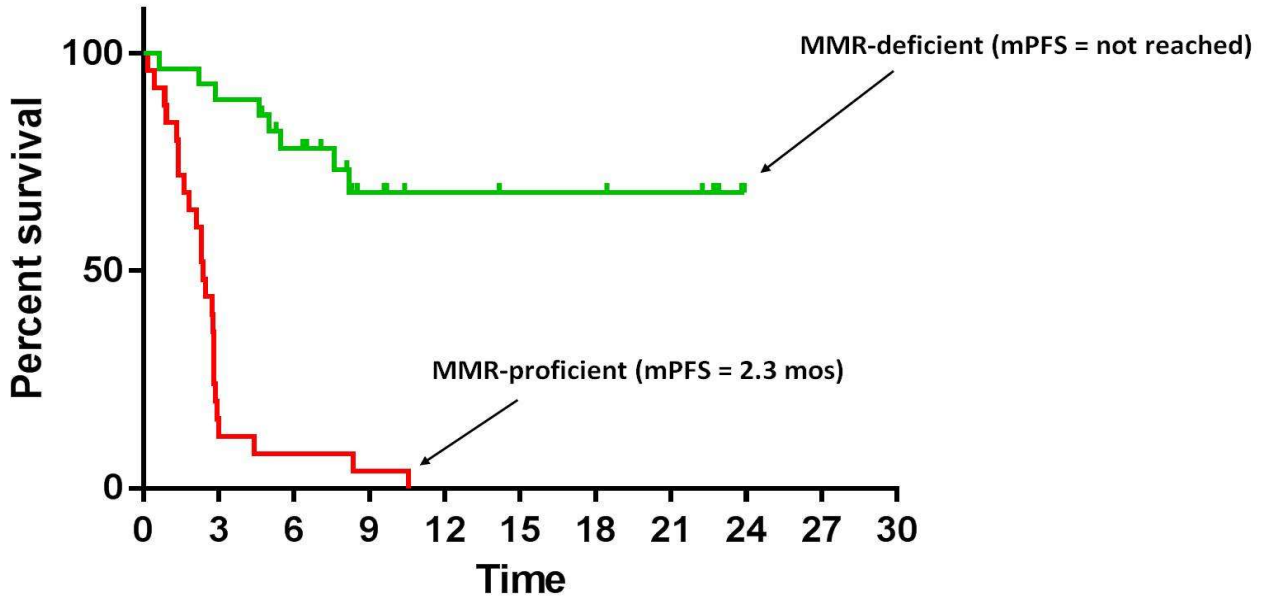
- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Here we report and update from the original 13 CRC Cohort A patients reported at ASCO 2015

Best Radiographic Response



Presented By Dung Le at 2016 ASCO Annual Meeting

Progression-free Survival



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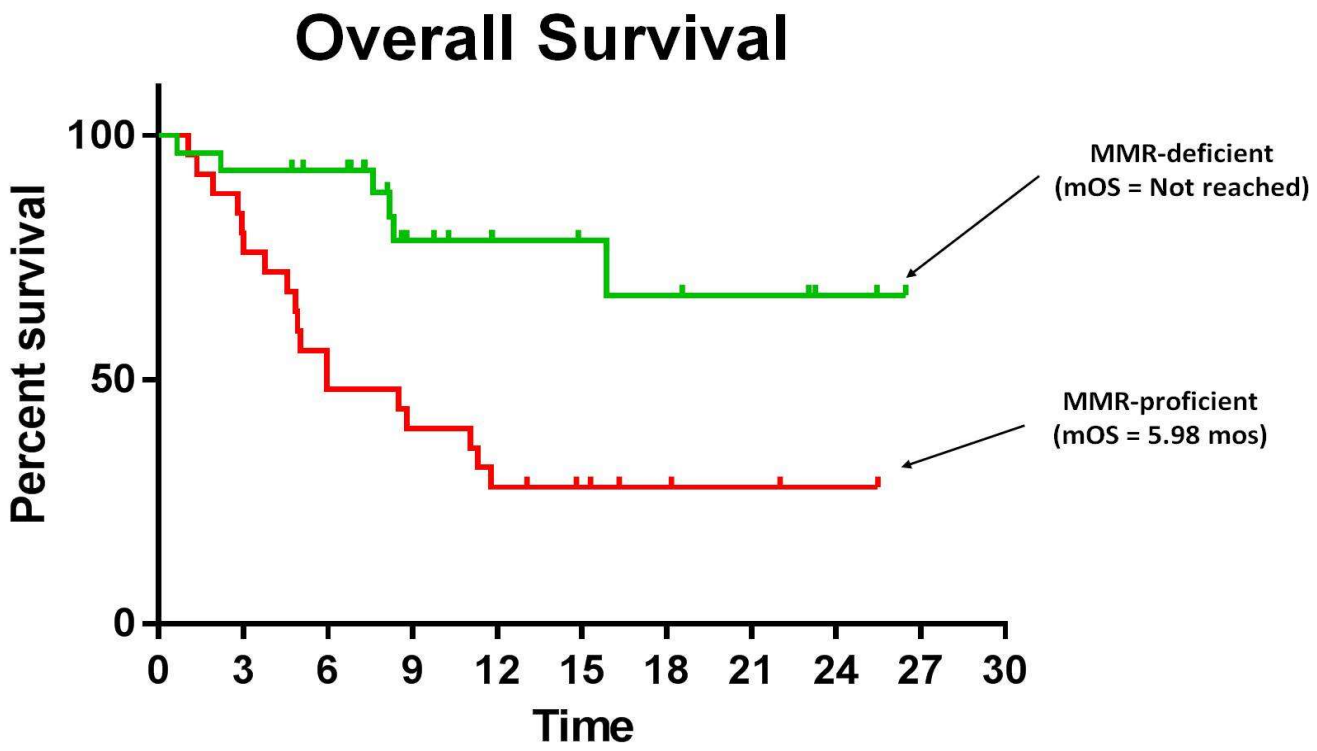

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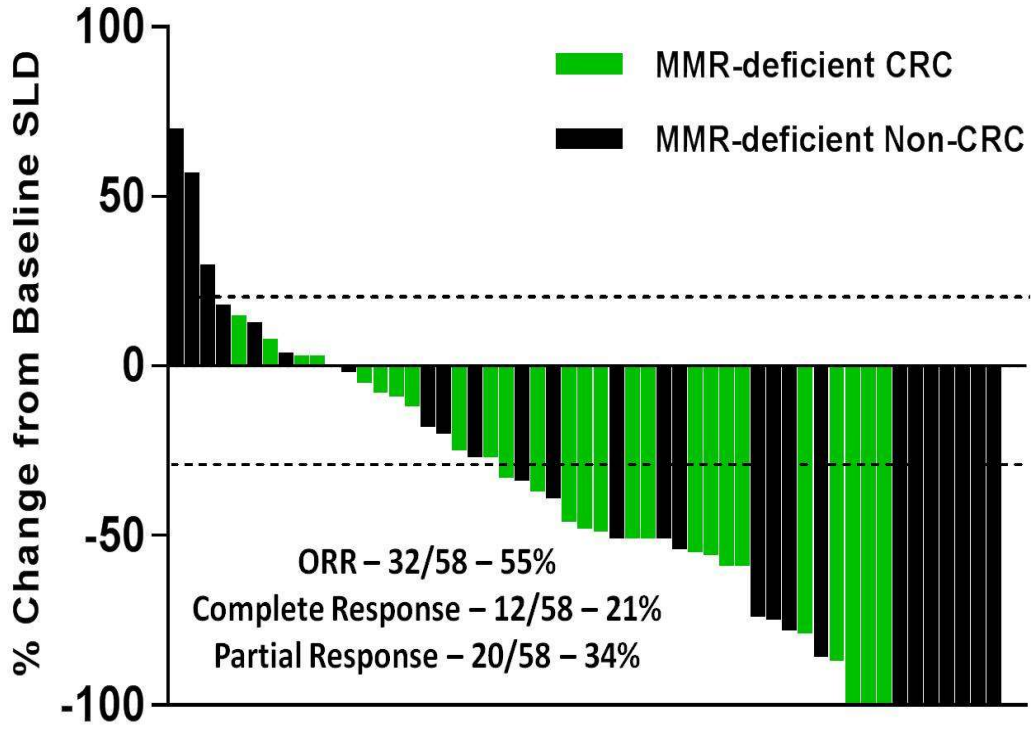
Histology-independent MRD Tumors

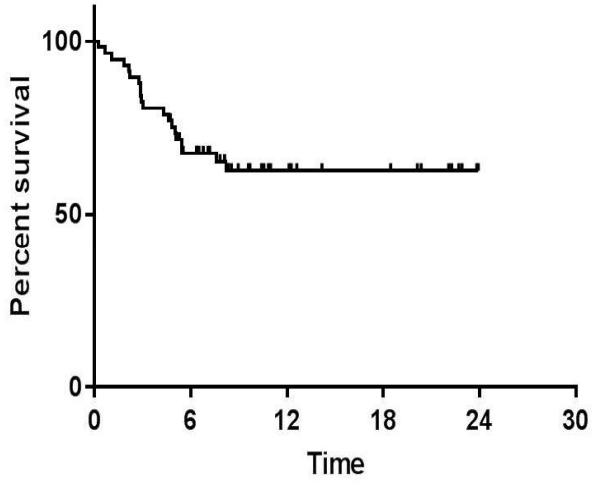


Primary Histologies

Colorectal Cancer
Endometrial Cancer
Ampullary/Bililary Cancer
Pancreatic Cancer
Small Bowel
Gastric Cancer
Prostate Cancer
Thyroid Cancer

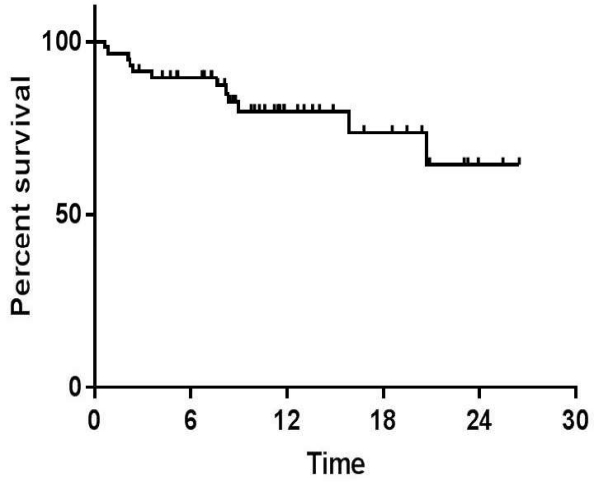
Histology-independent MRD Tumors

Progression-free Survival



Median Progression-free Survival (mos)	Not Reached
12-month PFS rate	63%
18-month PFS rate	63%

Overall Survival



Median Overall Survival (mos)	Not Reached
12-month OS rate	80%
18-month OS rate	74%

Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results

Michael Overman,[1] Scott Kopetz,[1] Ray McDermott,[2] Joseph Leach,[3] Sara Lonardi,[4] Heinz-Josef Lenz,[5] Michael Morse,[6] Jayesh Desai,[7] Andrew Hill,[8] Michael Axelson,[9] Rebecca A. Moss,[9] Chen-Sheng Lin,[9] Monica Goldberg,[9] Thierry Andre[10]

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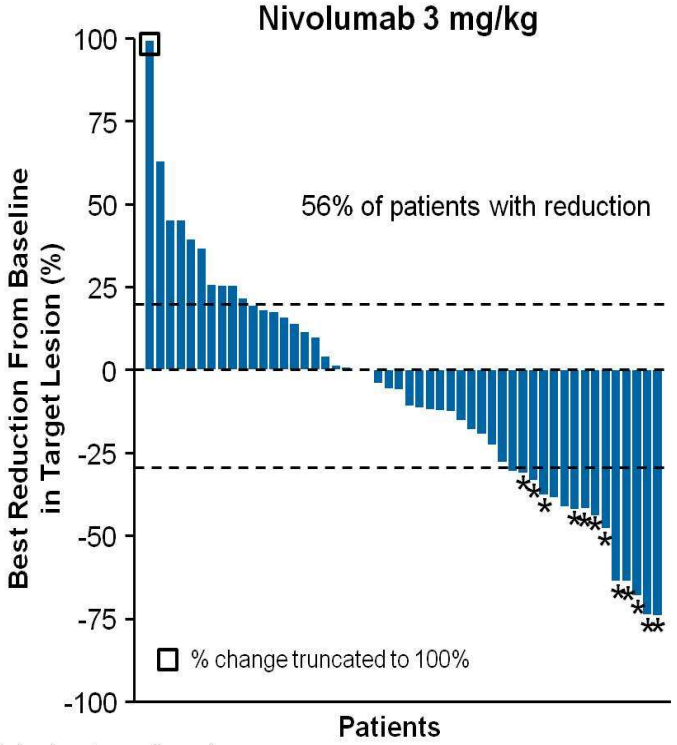
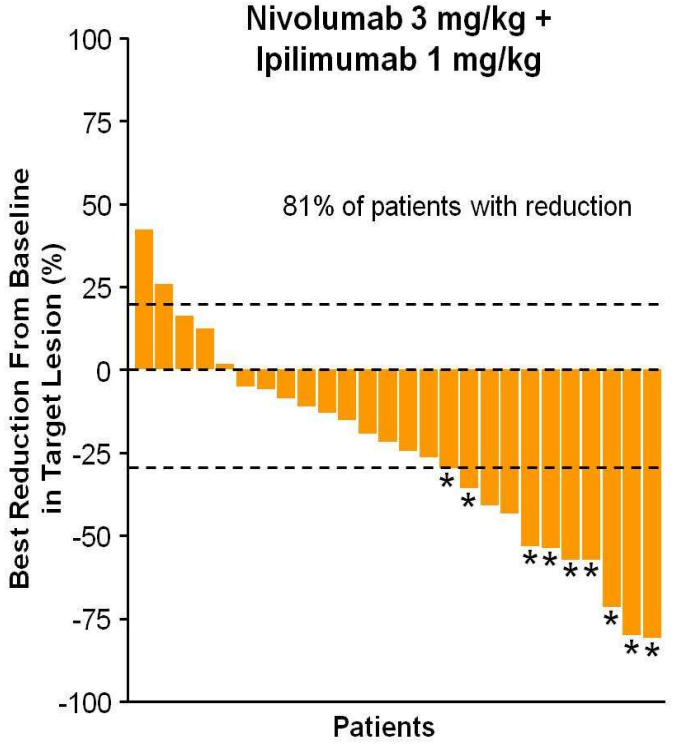
Best Reduction in Target Lesion Size in Patients With MSI-H





*Asterisks denote confirmed responses

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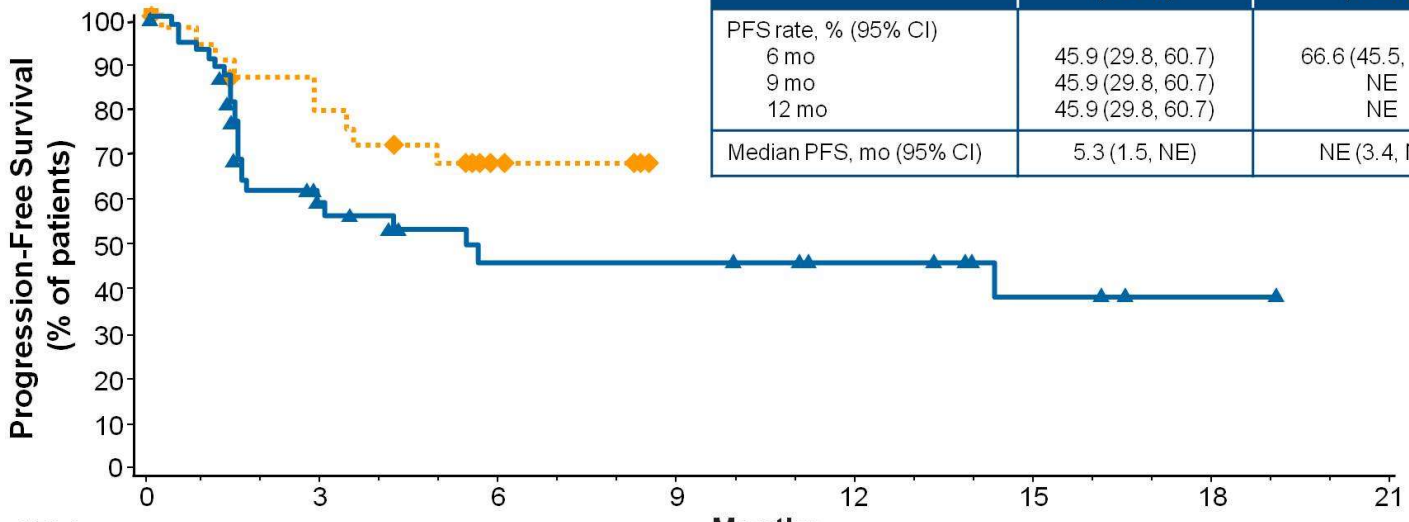
Investigator-Assessed PFS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
PFS rate, % (95% CI)		
6 mo	45.9 (29.8, 60.7)	66.6 (45.5, 81.1)
9 mo	45.9 (29.8, 60.7)	NE
12 mo	45.9 (29.8, 60.7)	NE
Median PFS, mo (95% CI)	5.3 (1.5, NE)	NE (3.4, NE)



No. at Risk								
Nivolumab	70	19	13	13	9	5	1	0
Nivolumab + Ipilimumab	30	21	7	0	0	0	0	0

NE = not estimable

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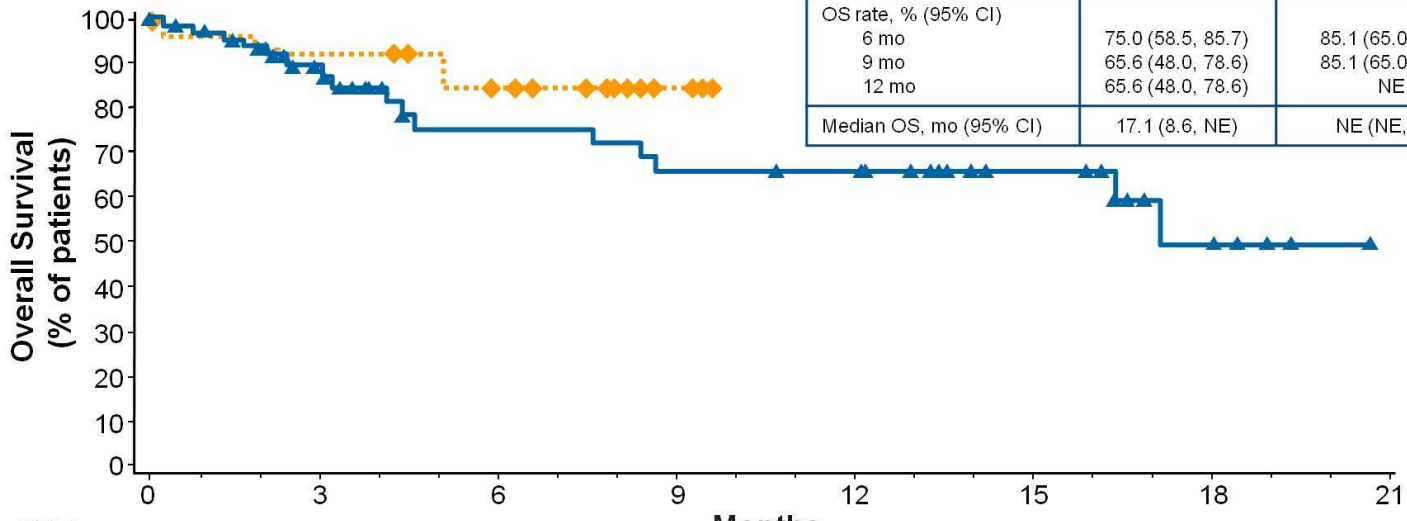
OS in Patients With MSI-H

Nivolumab ± Ipilimumab in Metastatic CRC

	Nivolumab 3 mg/kg (n = 70)	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)
OS rate, % (95% CI)		
6 mo	75.0 (58.5, 85.7)	85.1 (65.0, 94.2)
9 mo	65.6 (48.0, 78.6)	85.1 (65.0, 94.2)
12 mo	65.6 (48.0, 78.6)	NE
Median OS, mo (95% CI)	17.1 (8.6, NE)	NE (NE, NE)



No. at Risk								
Nivolumab	70	34	24	21	20	12	5	0
Nivolumab + Ipilimumab	30	26	21	4	0	0	0	0

NE = not estimable

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FDA grants accelerated approval to nivolumab/ipilimumab for MSI-H or dMMR metastatic colorectal cancer

- On July 10, 2018, the FDA granted accelerated approval to ipilimumab+nivolumab for patients MSI-H or dMMR metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- The data from Study CHECKMATE 142 that enrolled 82 patients with dMMR or MSI-H mCRC with PD after chemotherapy.
- Overall response rate (ORR) was 46% and 89% of responding patients had response durations of ≥ 6 months. The ORR was higher than that observed in a separate cohort of 58 patients with dMMR/MSI-H mCRC with PD that failed chemotherapy who received nivolumab alone, with an ORR of 28% with 67% having response durations of ≥ 6 months.

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