LUNG CANCER UPDATES
ASCO HIGHLIGHTS
1-5 JUNIO 2018, CHICAGO

New options for old and new targets in NSCLC

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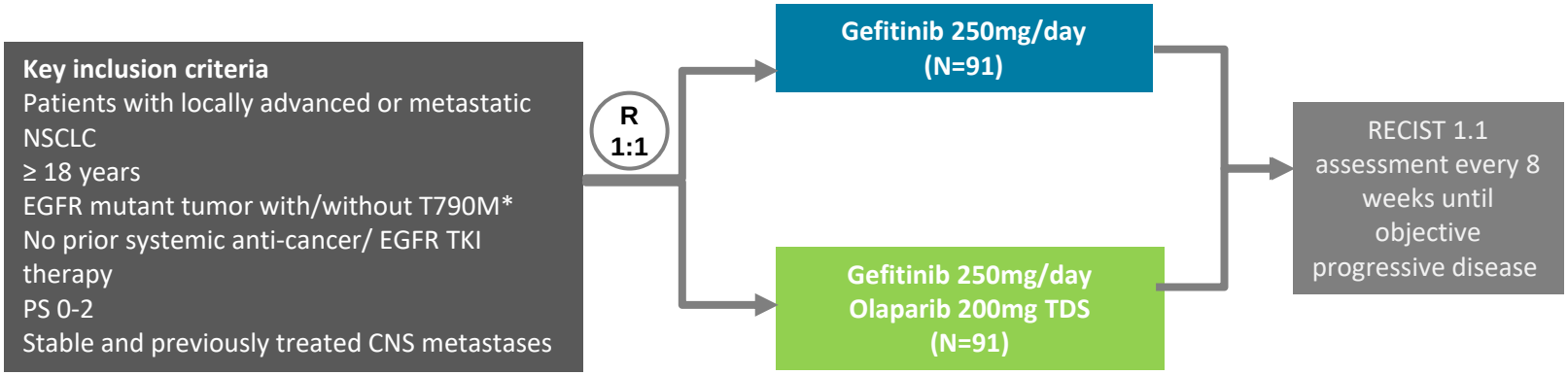
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Phase II GOAL TRIAL DESIGN



- ENDPOINTS
- Primary endpoint:
  - To assess the efficacy in terms of progression-free survival (PFS) of gefitinib in combination with olaparib, compared with gefitinib alone, in 1st line advanced NSCLC patients with EGFR mutations according to RECIST v1.1.
    - With alpha error = 0.05 and potency of 80% number of events 116 needed to test the superiority hypothesis (HR 0.63). Total planned number of inclusions: 186 P

- Secondary endpoints:
  - Overall survival (OS)
  - Tumor response rate (ORR) per RECIST v1.1 criteria
  - Toxicity profile of the drug combination (CTCAE v4.0)
  - To identify the influence of BRCA1 mRNA expression, EGFR mutations and T790M on PFS
  - To monitor EGFR mutations (including T790M) in serum
  - Ancillary molecular analysis

**Mutations could be first assessed locally by a local or national certified laboratory; for all patients tumor material had to be submitted to the reference laboratory for central EGFR confirmatory testing. EGFR mutations were centrally confirmed based on laser microdissection and TaqMan assay in the presence of a PNA designed to inhibit the amplification of the wild-type allele*

GOAL: Phase Ii Trial Results

Figure 2. Progression-free Survival (mITT)

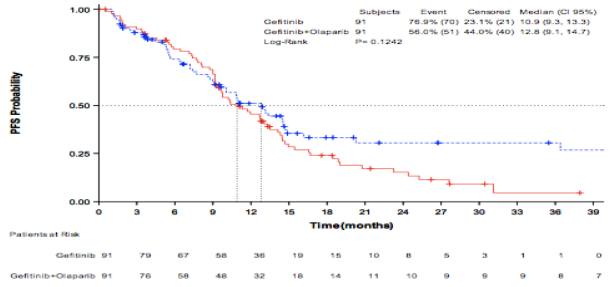


Figure 5. Overall Survival (mITT)

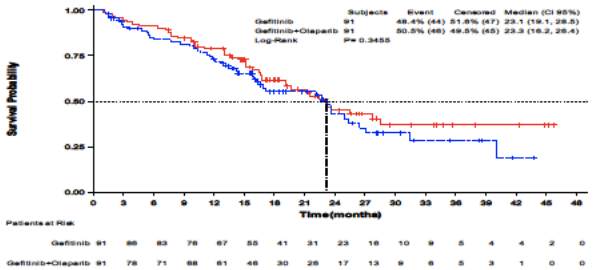
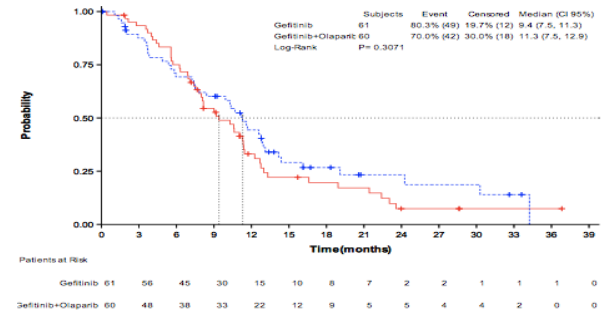


Table 2. Response Rate (PP)

Best Response n (%)	Gefitinib (N=90)	Gefitinib+Olaparib (N=84)
CR	2 (2.22)	1 (1.19)
PR	59 (65.56)	59 (70.24)
SD	21 (23.33)	12 (14.29)
PD	6 (6.67)	8 (9.52)
NE	2 (2.22)	4 (4.76)

Figure 3. Median duration of response



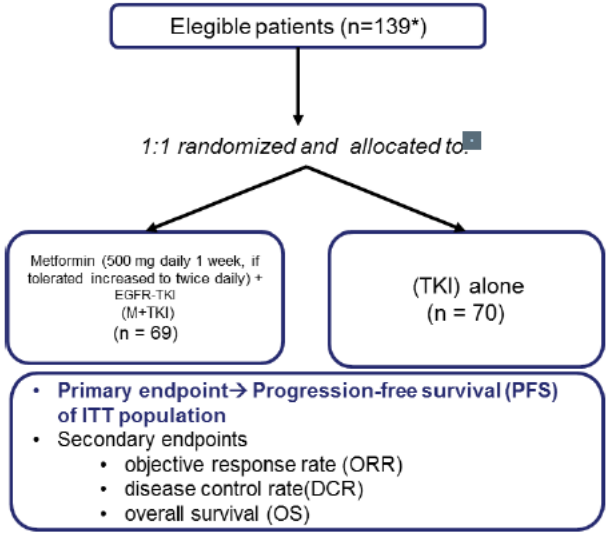
SAFETY

Table 3. Treatment related Adverse Events in ≥15% of Patients

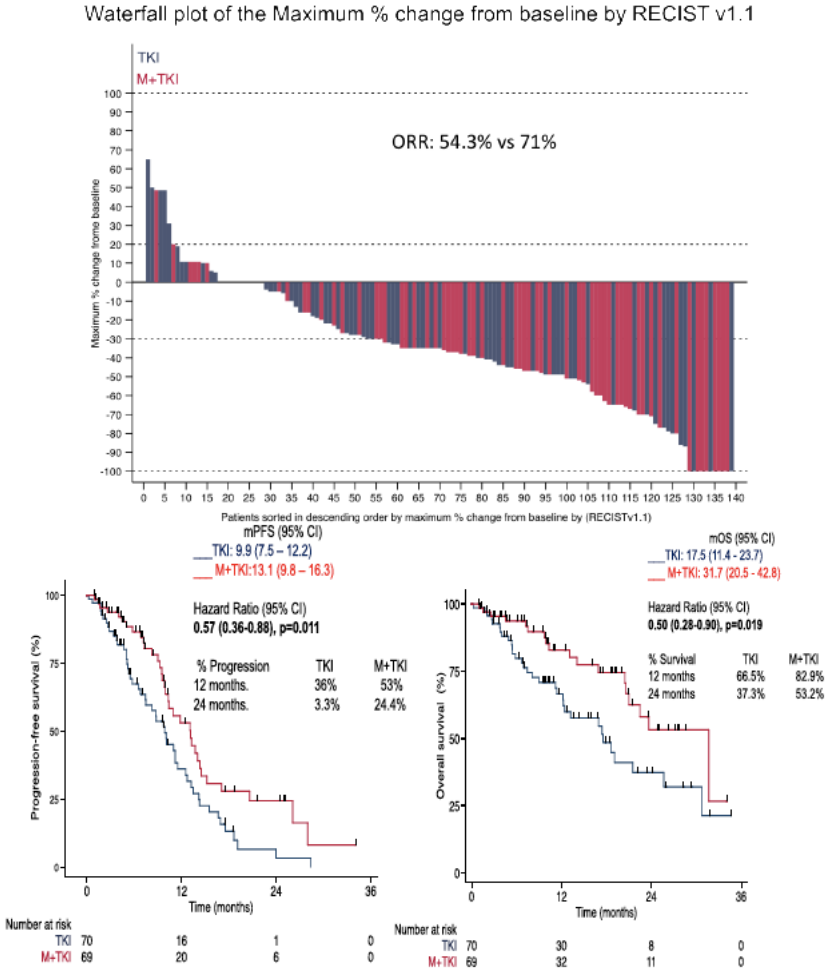
AE Term (CTC V4.0), N (%)	Gefitinib (N=91)			Gefitinib+Olaparib (N=91)		
	G1-G2	G3-G4	Total	G1-G2	G3-G4	Total
DIARRHEA	53 (58)	2 (2.20)	55 (60.44)	55 (60.44)	4 (4.40)	59 (64.84)
ANEMIA	33 (36)	2 (2.20)	35 (38.46)	56 (61.54)	15 (16.48)	71 (78.02)
RASH ACNEIFORM	42 (46.15)	-	42 (46.15)	42 (46.15)	2 (2.20)	44 (48.35)
FATIGUE	27 (29.67)	2 (2.20)	29 (31.87)	28 (30.77)	8 (8.79)	36 (39.56)
NAUSEA	15 (16.48)	-	15 (16.48)	42 (46.15)	3 (3.30)	45 (49.45)
ANOREXIA	15 (16.48)	-	15 (16.48)	27 (29.67)	6 (6.59)	33 (36.26)
DRY SKIN	21 (23.08)	-	21 (23.08)	18 (19.78)	-	18 (19.78)
MUCOSITIS ORAL	20 (21.98)	1 (1.10)	21 (23.08)	17 (18.68)	-	17 (18.68)
VOMITTING	8 (8.79)	-	8 (8.79)	29 (31.87)	1 (1.10)	30 (32.97)
AST INCREASED	20 (21.98)	3(3.30)	23 (25.27)	8 (8.79)	1 (1.10)	9 (9.89)
ALT INCREASED	17 (18.68)	1 (1.10)	18 (19.78)	8 (8.79)	-	8 (8.79)
PRURITUS	10 (10.99)	-	10 (10.99)	12 (13.19)	1 (1.10)	13 (14.29)
PARONYCHIA	13 (14.29)	2 (2.20)	15 (16.48)	7 (7.69)	-	7 (7.69)
DYSGEUSIA	6 (6.59)	-	6 (6.59)	13 (14.29)	1 (1.10)	14 (15.38)

Garcia Campelo et al. Abstr 9012

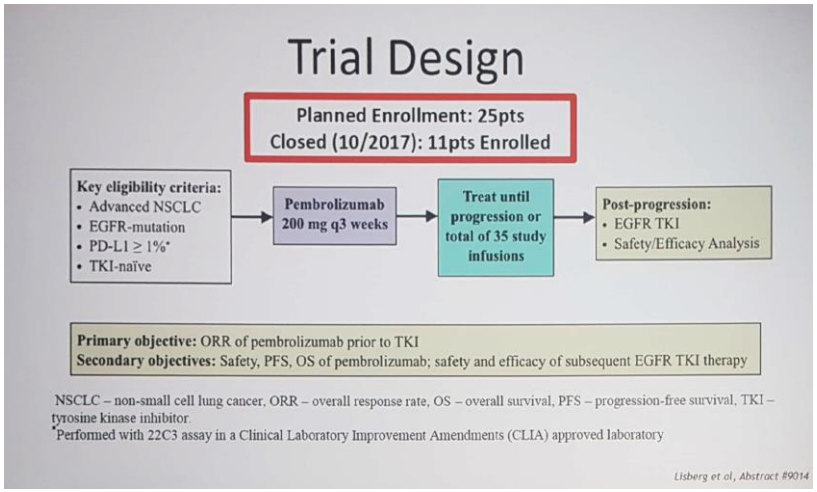
Combination of metformin plus TKI vs. TKI alone in EGFR(+) LUNG adenocarcinoma: A randomized phase II study Clinicaltrial (NCT03071705)



ORR 71% vs 54%
PFS 13.1 vs 9.9
OS 31.7m vs 17.5m



Pembrolizumab in EGFR mutant NSCLC



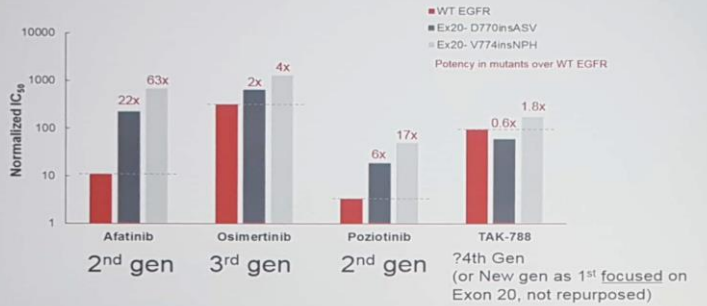
- In EGFR+ NSCLC with PDL1 expression, is first line pembrolizumab an appropriate option?
  - No
  - Lack of responses (0/10) though most had PD-L1 TPS ≥ 50%
  - Potential impact on safety of subsequent TKI
- For patients with a sensitizing EGFR mutation, first line TKI therapy remains the standard of care, independent of PD-L1

Targeting EGFR exon 20 mutations

Doebele et al, Abstract 9015 ASCO 2018

Preclinical Inhibitory Profile of TAK-788 Against EGFR Exon 20 Insertions

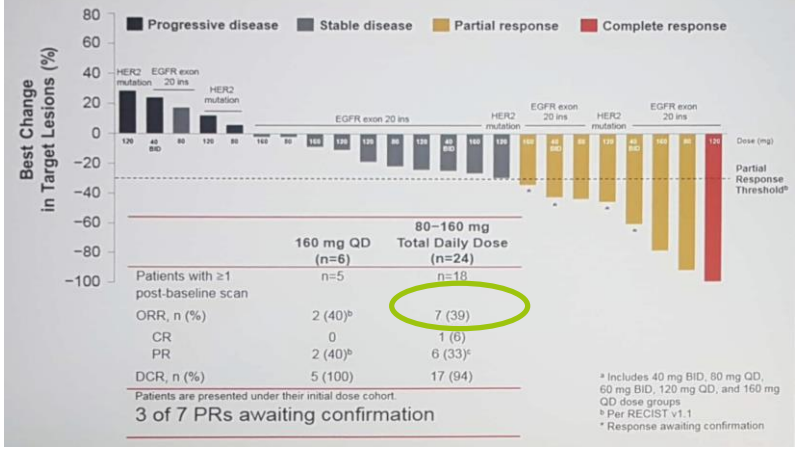
- Compared Ba/F3 IC_{50} for 2 EGFR exon 20 insertions with WT EGFR IC_{50} (P-EGFR: A431, H2073)



1. What exposure is needed?
2. What exposure is achievable? – pharmacokinetics and tolerability!
3. NOT all insertions are equally drug sensitive (important when looking at ORR in small N series)

TAK32788

Antitumor Activity in All Patients Treated with TAK-788 at a Total Daily Dose ≥80–160 mg[a]



	160 mg QD (n=6)	80–160 mg Total Daily Dose (n=24)
Patients with ≥1 post-baseline scan	n=5	n=18
ORR, n (%)	2 (40)[b]	7 (39)
CR	0	1 (6)
PR	2 (40)[b]	6 (33)[c]
DCR, n (%)	5 (100)	17 (94)

Patients are presented under their initial dose cohort.

3 of 7 PRs awaiting confirmation

[a] Includes 40 mg BID, 80 mg QD, 60 mg BID, 120 mg QD, and 160 mg QD dose groups
[b] Per RECIST v1.1
[c] Response awaiting confirmation

TAK32788 comments

- As with poziotinib – proof of principle that EGFR (and HER2) exon 20 mutations can be actionable
- N too small and too many 'awaiting confirmation' datapoints to compare ORR vs poziotinib – and ?all exon 20s same sensitivity?
- Data too immature to compare DoR, PFS vs poziotinib
- Preclinical data suggest greater potential for efficacy:toxicity ratio with TAK32788 and therefore potential to sustain exposure at efficacious levels longer - but clinical data not currently confirming this (based on 6 patient dose reduction rate)

Trastuzumab deruxtecan

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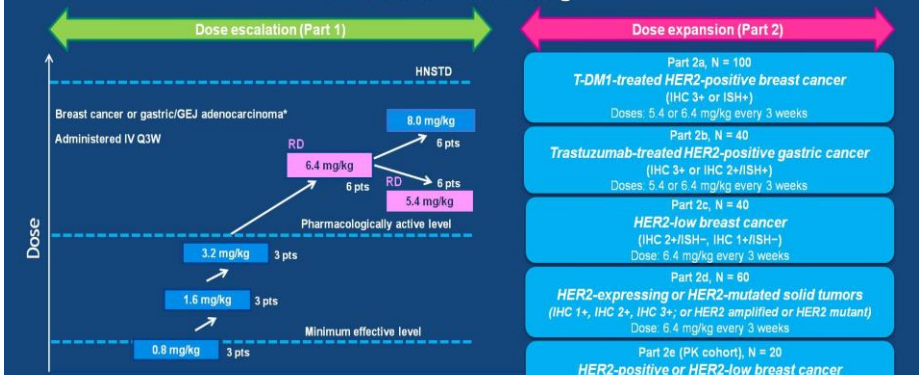
Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing advanced solid tumors: Long-term efficacy and safety from a first-in-human phase 1 study with multiple expansion cohorts

Hiroji Iwata,[1] Kenji Tamura,[2] Toshihiko Doi,[3] Junji Tsurutani,[4] Shanu Modi,[5] Haeseong Park,[6] Ian Krop,[7] Yasuaki Sagara,[8] Charles Redfern,[9] Rashmi Murthy,[10] Rebecca Redman,[11] Kohei Shitara,[3] Yoshihiko Fujisaki,[12] Masahiro Sugihara,[12] Lin Zhang,[13] Javad Shahidi,[13] Antoine Yver,[13] Shunji Takahashi[14]

[1]Aichi Cancer Center Hospital, Nagoya, Japan; [2]National Cancer Center Hospital, Tokyo, Japan; [3]National Cancer Center Hospital East, Chiba, Japan; [4]Kindai University Faculty of Medicine, Osaka, Japan; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [6]Washington University School of Medicine, St Louis, MO, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]Social medical corporation Hakuaikai Sagara Hospital, Kagoshima City, Japan; [9]Sharp HealthCare, San Diego, CA, USA; [10]University of Texas M. D. Anderson Cancer Center, Houston, TX, USA; [11]The University of Louisville, Louisville, KY, USA; [12]Daiichi Sankyo Co., LTD, Tokyo, Japan; [13]Daiichi Sankyo Pharma Development, Basking Ridge, NJ, USA; [14]The Cancer Institute Hospital of Japanese Foundation For Cancer Research, Tokyo, Japan

Phase 1 Trial Design



- HER2 status was assessed on archival tissue in both parts 1 and 2

*Subjects in part 1 were not required to have HER2-positive (IHC 3+ or IHC2+/ISH+) tumors.
HER2, human epidermal growth factor receptor 2; HNSTD, highest non-severely toxic dose; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; PK, pharmacokinetic; Q3W, once every 3 weeks; RD, recommended dose for dose expansion; T-DM1, trastuzumab emtansine.

Presented By Hiroji Iwata at 2018 ASCO Annual Meeting

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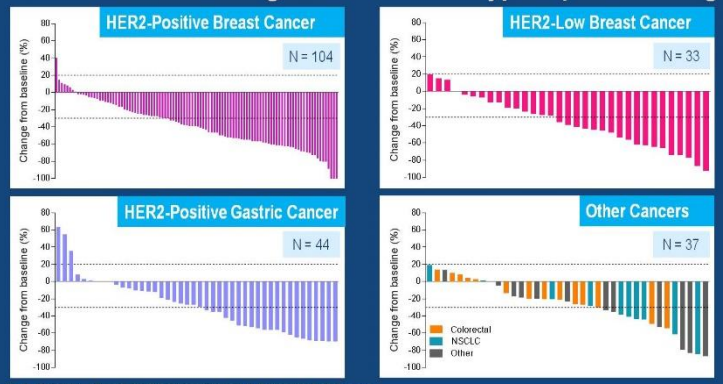
Consistent Tumor Shrinkage Across Tumor Types: (5.4 or 6.4 mg/kg)



- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR* in the overall population is 49.3%

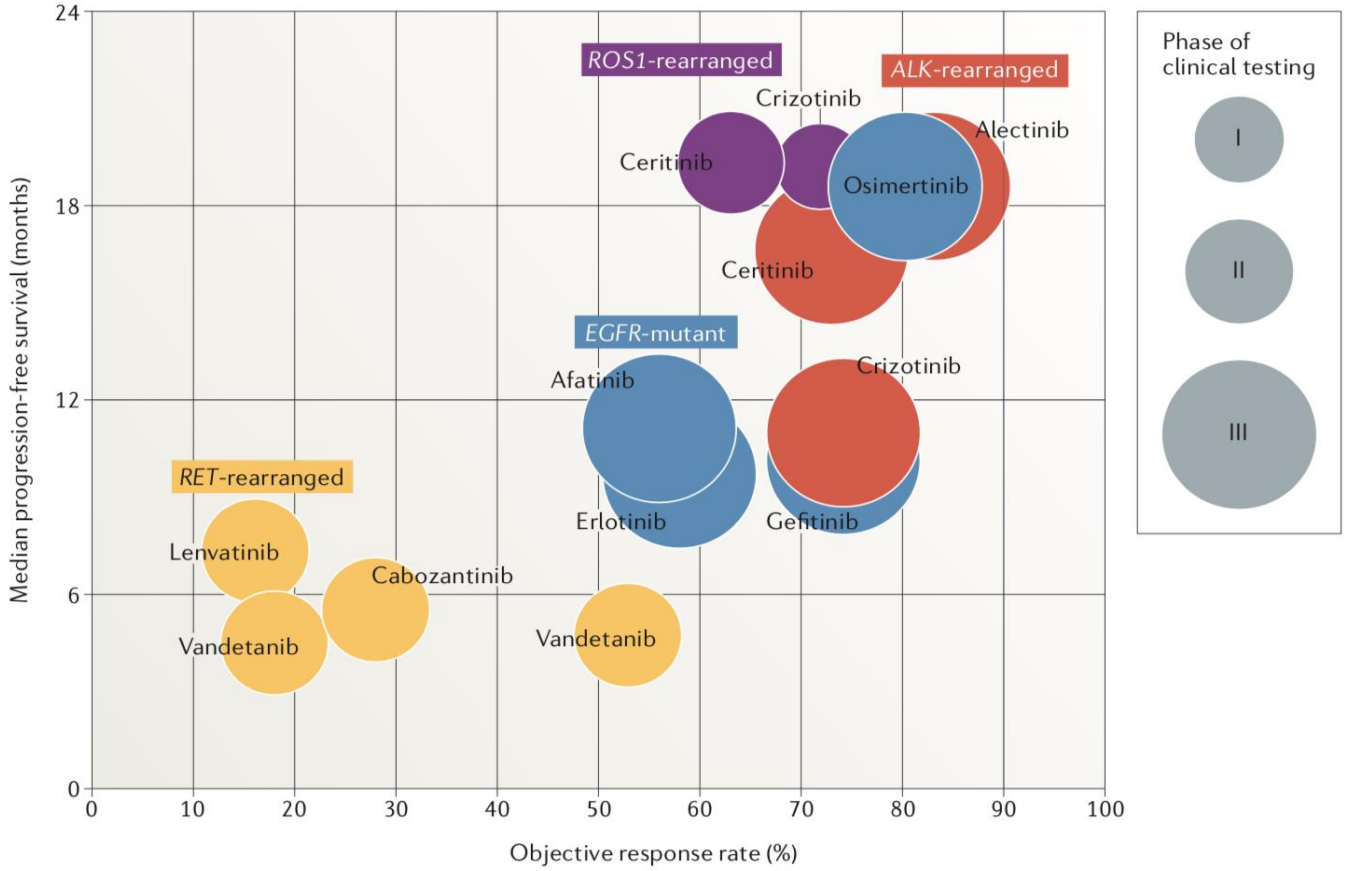
Includes subjects who had ≥1 postbaseline scan. Dotted lines denote 20% increase and 30% reduction in tumor size, respectively.
*Confirmed response includes subjects who had ≥2 postbaseline scans, progressive disease, or discontinued treatment for any reason prior to second postbaseline scan. Data cutoff is April 18, 2018.

Efficacy Outcomes by Cancer Type (5.4 or 6.4 mg/kg)

	HER2-Positive BC N = 111	HER2-Low BC N = 34	HER2-Positive GC N = 44	Other Cancers N = 51
Confirmed ORR*, % (n/N)	54.5% (54/99)	50.0% (17/34)	43.2% (19/44)	38.7% (12/31)
DCR, % (n/N)	93.9% (93/99)	85.3% (29/34)	79.5% (35/44)	83.9% (26/31)
ORR in modified ITT**, % (n/N)	48.6% (54/111)	50.0% (17/34)	43.2% (19/44)	23.5% (12/51)
DOR				
Median, (95% CI), months	NR	11.0 (NA)	7.0 (NA)	12.9 (2.8, 12.9)
PFS				
Median, (95% CI), months	NR	12.9 (NA)	5.6 (3.0, 8.3)	12.1 (2.7, 14.1)
Min, max	1.0, 22.2+	0.5, 19.6+	1.2, 19.6+	0.7, 14.1+

*Confirmed response includes subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.
**Modified ITT population included all subjects who received ≥1 dose of DS-8201a at either 5.4 or 6.4 mg/kg, including those subjects who were too early to assess, but are ongoing on study.
+after value indicates censoring
BC, breast cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; GC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; NA, not available; NR, not reached; ORR, overall response rate; PFS, progression-free survival.
Data cutoff for this analysis is April 18, 2018.

RET-directed targeted therapy is lagged behind other oncogenes



Alexander Drilon, Nature reviews 2018

Clinical activity of LOXO-292 in *RET*-altered cancers

	RET fusion-positive cancers			*RET*-mutant MTC	No known activating *RET* alteration
	All	NSCLC	Other[1]		
Enrolled	49	38	11	29	4
Eligible for response evaluation[2]	39	30	9	22	3
Overall Response Rate (95% CI)[3]	**77% (61% – 89%)**	**77% (58% – 90%)**	**78% (40% – 97%)**	**45% (24% – 68%)**	**0% (0% – 71%)**
Confirmed Overall Response Rate[3,4]	74%	74%	71%	33%	0%
CR	–	–	–	1	–
uCR[5]	–	–	–	1	–
PR	25	20	5	5	–
uPR[5]	5	3	2	3	–
SD	6	4	2	9	2
PD	–	–	–	2	1
Not evaluable[6]	3	3	–	1	–

1. Patients eligible for response evaluation include thyroid cancer (n=7), pancreatic cancer (n=2). 2. Excludes patients recently enrolled that remain on treatment, but have not had a first post-baseline response assessment. 3. Response status per RECIST 1.1. Overall response rate = CR+uCR+PR+uPR. Overall response rate, Confirmed overall response rate: all *RET* fusion-positive (30/39, 25/34), *RET* fusion-positive NSCLC (23/30, 20/27), *RET* fusion-positive other (7/9, 5/7), *RET*-mutant MTC (10/22, 6/18). 4. Excludes patients with unconfirmed CR/PR pending confirmation at time of data cut-off. 5. Unconfirmed responses in patients that remain on treatment awaiting a confirmatory response assessment. 6. Patients that discontinued treatment prior to a first post-baseline response assessment.

NSCLC = non-small-cell lung cancer; MTC = medullary thyroid cancer; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
April 2, 2018 data cut-off date

New options for RET

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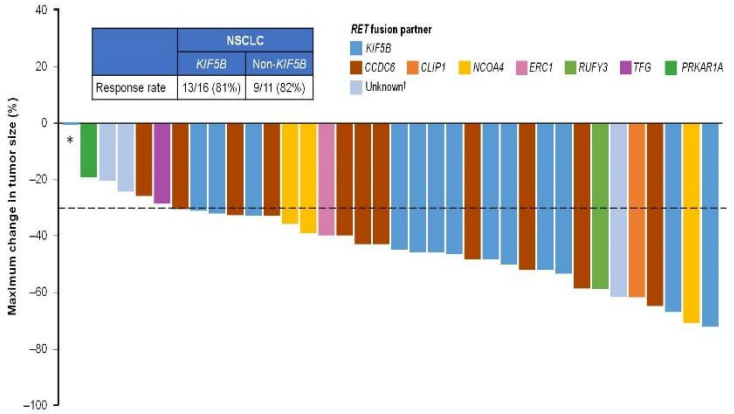
Efficacy of LOXO-292 regardless of *RET* fusion partner



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PRESENTED BY: Dr. Alexander Drilon
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–deletion; April 2, 2018 data cut-off date
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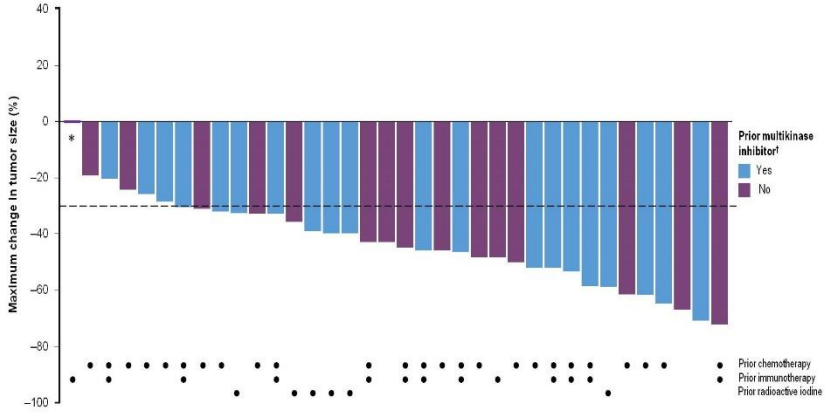
Efficacy of LOXO-292 regardless of prior therapy



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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; †Includes alectinib, cabozantinib, lenvatinib, pazopanib, ponatinib, ROCK-105, sitravatinib, sorafenib, and vandetanib; April 2, 2018 cut-off date
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Presented By Alexander Drilon at 2018 ASCO Annual Meeting

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VISION: A Phase II, Single-arm Trial to Investigate Tepotinib in Advanced NSCLC With METexon14-Skipping Alterations

- Advanced/metastatic NSCLC
  - all histologies
- *MET*exon14-skipping mutation-positive by NGS
  - tissue and blood based
- 1st, 2nd, 3rd line of therapy
- N = up to 120
- Regions: EU, US, Japan

Tepotinib
500 mg QD

Primary endpoint

- Objective response rate by independent review

Secondary endpoints

- Objective response rate by investigator assessment
- Safety
- Duration of response
- Progression free survival
- Overall survival

Efficacy: Best Overall Response Independent Review

- Efficacy analysis includes only patients having at least 2 post-baseline assessments or who discontinued treatment for any reason (n=28)

Tepotinib 500 mg	L+ (n=16)	T+ (n=26)	Combined analysis set (n=28)
Complete response	0 (0)	0 (0)	0 (0)
Partial response	9 (56.3)	11 (42.3)	12 (42.9)
Stable disease	2 (12.5)	6 (23.1)	6 (21.4)
Progressive disease	3 (18.8)	5 (19.2)	5 (17.9)
Non-evaluable	2 (12.5)	4 (15.4)	5 (17.9)
Objective response rate,* n (%) [95% CI]	9 (56.3) [29.9, 80.2]	11 (42.3) [23.4, 63.1]	12 (42.9) [24.5, 62.8]
Disease control rate,† n (%) [95% CI]	11 (68.8) [41.3, 89.0]	17 (65.4) [44.3, 82.8]	18 (64.3) [44.1, 81.4]

*Confirmed complete response/partial response; †Confirmed complete response/partial response or stable disease.
CI, confidence interval; L+, *MET*exon14-skipping mutation-positive in ctDNA; T+, *MET*exon14-skipping mutation-positive in tumor

Safety Results

All TEAEs*	Tepotinib 500 mg (N=38)	
	Any grade	Grade ≥3
≥1 TEAE	**34 (89.5)**	**18 (47.4)**
≥1 drug-related TEAE, n (%)	**26 (68.4)**	**7 (18.4)**
Drug-related TEAEs reported in ≥3 patients at any grade, or ≥1 patient at grade ≥3, n (%)		
Peripheral edema	13 (34.2)	0 (0.0)
Diarrhea	10 (26.3)	0 (0.0)
Amylase increased	4 (10.5)	2 (5.3)
Asthenia	4 (10.5)	1 (2.6)
Blood creatinine increased	4 (10.5)	0 (0.0)
Decreased appetite	4 (10.5)	0 (0.0)
Alanine aminotransferase increased	3 (7.9)	1 (2.6)
Aspartate aminotransferase increased	3 (7.9)	1 (2.6)
Nausea	3 (7.9)	0 (0.0)
Gamma glutamyl transferase increased	2 (5.3)	1 (2.6)
Lipase increased	2 (5.3)	1 (2.6)
Dizziness	2 (5.3)	1 (2.6)
Generalized edema	1 (2.6)	1 (2.6)
Pneumonia	1 (2.6)	1 (2.6)
Hyperkalemia	1 (2.6)	1 (2.6)

Serious TEAEs	Tepotinib 500 mg (N=38)	
	Any grade	Grade ≥3
Serious TEAEs, n (%)	**15 (39.5)**	**13 (34.2)**
≥1 serious drug-related TREAE, n (%)	**4 (10.5)**	**3 (7.9)**
Serious drug-related TEAEs, n (%)		
Pneumonia	1 (2.6)	1 (2.6)
Generalized edema	1 (2.6)	1 (2.6)
Asthenia	1 (2.6)	1 (2.6)
Dizziness	1 (2.6)	1 (2.6)
Interstitial lung disease	1 (2.6)	0 (0.0)

- Median number of 21-day cycles = 4.1
- Grade ≥4 TEAEs were reported in 4 (10.5%) patients; all were serious TEAEs. None were considered drug-related
- TEAEs led to treatment discontinuation in 5 (13.2%) patients
- 8 (21.1%) patients had ≥1 dose reduction
- Seven patients have died:
  - 4 non-treatment related AEs
  - 1 progressive disease/disease-related condition
  - 2 primary cause unknown

Updated efficacy and safety data from the global phase III ALEX study of alectinib(AL) versus crizotinib(CZ) in untreated advanced ALK+ NSCLC

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Figure 1. Investigator-assessed PFS.

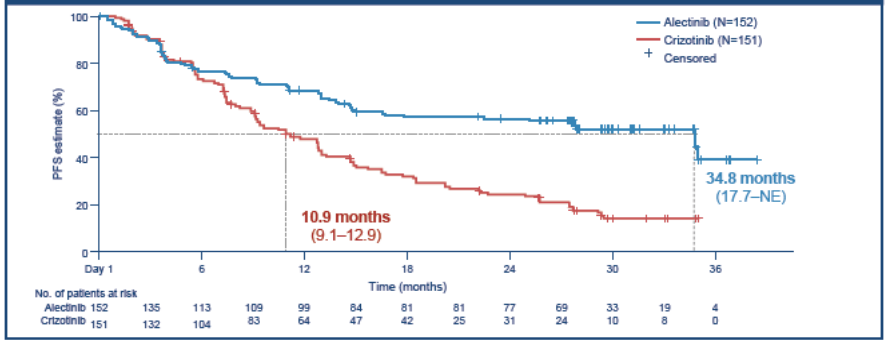


Figure 3. Duration of response in responders.

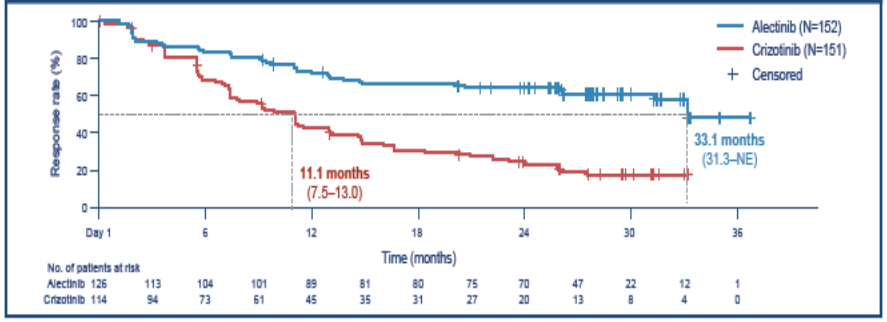
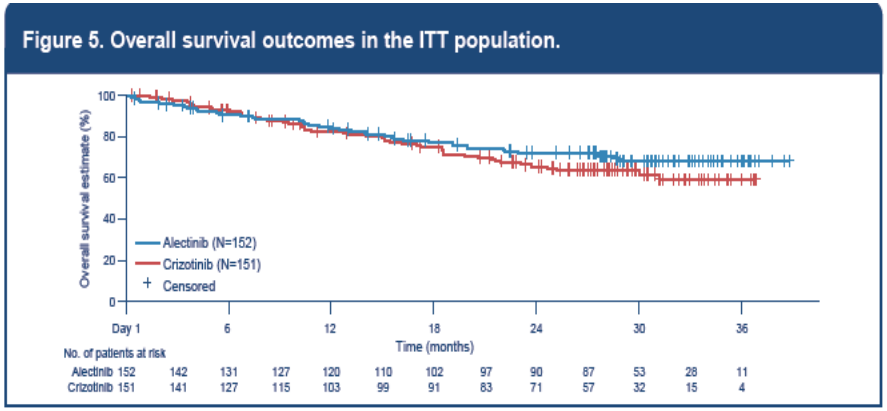


Figure 5. Overall survival outcomes in the ITT population.



Camidge R, Abstr 9043

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