LUNG CANCER UPDATES
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Terapias dirigidas (I)

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Con el patrocinio de
Bristol-Myers Squibb

Iniciativa científica de:
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Efficacy of Lorlatinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer (NSCLC) and ALK Kinase Resistance Mutations

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Lorlatinib Covers the Broadest Range of ALK Resistance Mutations

- Secondary mutations in the ALK kinase domain can induce resistance to first- and second-generation ALK TKIs[1]
- Lorlatinib has broad-spectrum potency against most known ALK resistance mutations, including ALK G1202R[1,2]

IC_{50} ≤50 nM | IC_{50} >50–<200 nM | IC_{50} ≥200 nM

	Cellular ALK Phosphorylation Mean IC_{50} (nM)				
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
EML4-ALK	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0[a]	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

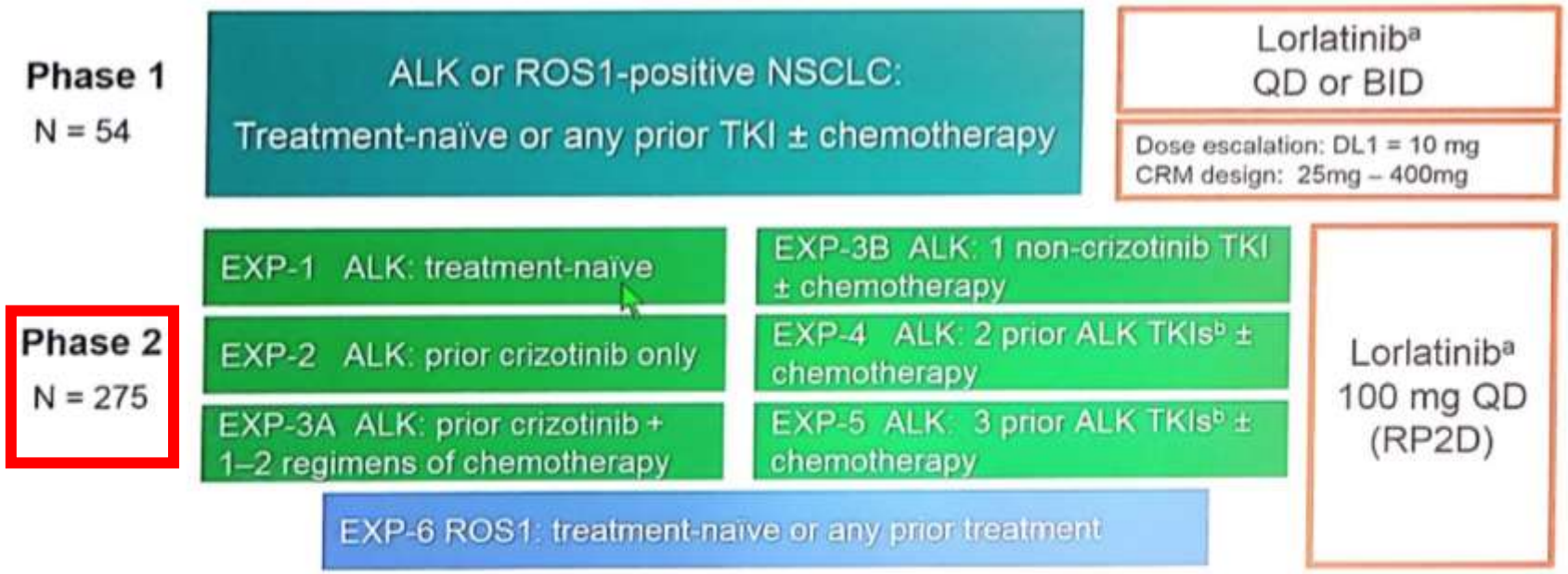
Adapted from Gainor JF, et al. *Cancer Discov.* 2016;6:1118–33.

IC_{50}, half-maximal inhibitory concentration; ND, not done

Presented by: Alice T Shaw

1. Gainor JF, et al. *Cancer Discov.* 2016;6:1118–1133.
2. Johnson TW, et al. *J Med Chem.* 2014;57:4720–4744.

Phase 1/2 Study of Lorlatinib: Design and Patient Populations



Asymptomatic brain mets were allowed in all cohorts. [a]Treatment until PD or unacceptable toxicity. [b]Lines of therapy (if the same TKI is given twice, this is counted as 2 prior lines of treatment).

twice daily; PD, progressive disease; QD, once daily.

Phase 2 Study Objectives

Primary Objective

- Overall and intracranial antitumor activity measured as confirmed overall and intracranial response by independent central review.

Secondary Objectives

- Secondary measures of clinical efficacy
- Safety and tolerability
- Patient-reported outcomes
- **Selected molecular profiling**

Biomarker Analyses

Tumor tissue analysis

- Mandatory de novo biopsy or archival tumor tissue
  - If de novo biopsy considered to pose a safety risk to the patient, only archival required
  - If no tumor tissue or if analysis failure for the de novo biopsy, reverted to archival tissue analysis
- Next Generation Sequencing assay (MolecularMD, Portland, OR, USA)
  - Validated in accordance with the Clinical Laboratory Improvement Amendments of 1988 regulations for the detection of ALK kinase domain mutations (exons 20–25)
  - Limit of detection: 2–5% allele frequency

Circulating-free DNA (cfDNA) analysis

- Peripheral blood samples were collected at screening, at the beginning of Cycle 3, and at the end of treatment visit for cfDNA analysis
- Next-Generation Sequencing 73-gene panel (Guardant360, Guardant Health, Inc., Redwood City, CA, USA)

Concordance Assessment of ALK Mutation Status by cfDNA and Tumor Tissue (Archival or De Novo)

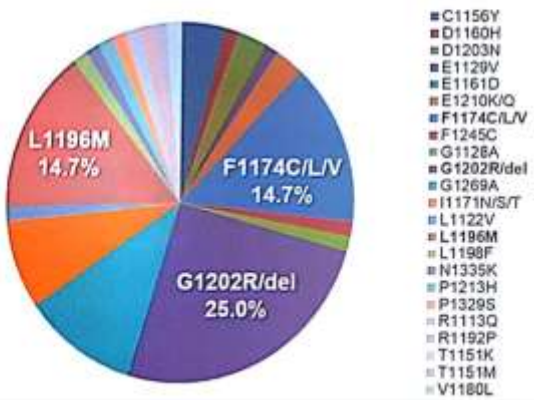
	≥1 prior ALK TKI EXP2–5
Patients with blood and tumor tissue data, N	**154**
Same mutations in blood and tumor, n (%)	112 (72.7)
Different mutations in blood and tumor, n (%)	42 (27.3)
Patients with blood and tumor tissue (de novo only) data, N	**69**
Same mutations in blood and tumor, n (%)	41 (59.4)
Different mutations in blood and tumor, n (%)	28 (40.6)

Patients who have blood CNA data only or tumor DNA data (archival or de novo) only are counted as not available (n=44).
Patients who have blood CNA data only or tumor DNA data (de novo) only are counted as not available (n=126).

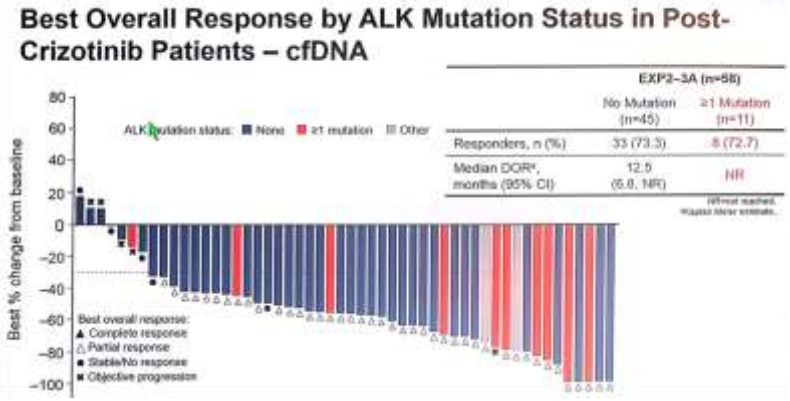
ALK Kinase Domain Mutations Detected in Previously Treated Patients

cfDNA analysis:

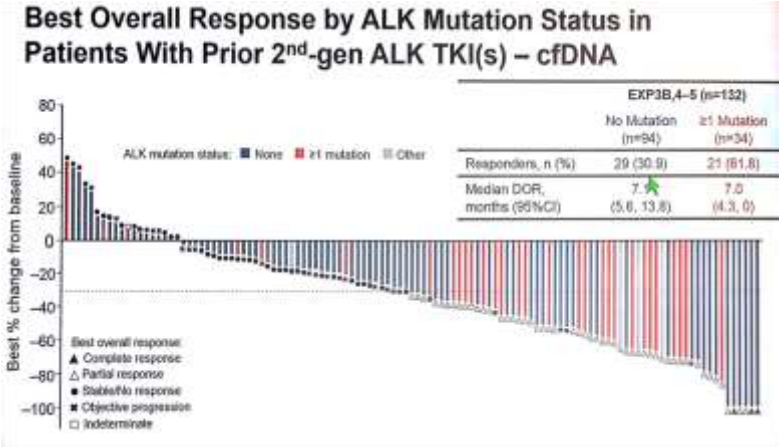
- 45/190 patients (24%) with 1 or more ALK kinase domain mutations
- 75 mutations detected (used for the frequency denominator)



Best Overall Response by ALK Mutation Status in Post-Crizotinib Patients – cfDNA



Best Overall Response by ALK Mutation Status in Patients With Prior 2nd-gen ALK TKI(s) – cfDNA



Best Overall Response by Presence/Absence of ALK Mutation – cfDNA or Tumor Tissue

	EXP2–3A: Post-Crizotinib (N=59)[a]	
	No Mutation[b] (n=43)	≥1 Mutation[b] (n=15)
BOR, n (%)		
CR	1 (2.3)	0
PR	30 (69.8)	11 (73.3)
SD	8 (18.6)	0
PD	4 (9.3)	2 (13.3)
IND	0	2 (13.3)
ORR, n (%)	**31 (72.1)**	**11 (73.3)**
95% CI	**56.3, 84.7**	**44.9, 92.2**

[a]1 patient sample was non-analyzable
[b]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

	EXP3B,4–5: Prior 2nd-gen TKI (N=139)[a]	
	No Mutation[b] (n=87)	≥1 Mutation[b] (n=49)
BOR, n (%)		
CR	2 (2.3)	1 (2.0)
PR	21 (24.1)	29 (59.2)
SD	36 (41.4)	10 (20.4)
PD	21 (24.1)	5 (10.2)
IND	7 (8.0)	4 (8.2)
ORR, n (%)	**23 (26.4)**	**30 (61.2)**
95% CI	**17.6, 37.0**	**46.2, 74.8**

[a]3 patients samples were non-analyzable
[b]Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

OR, best overall response; CR, complete response; IND, indeterminate, ORR, objective response rate, PD, progressive disease; PR, partial response, SD, stable disease.

Conclusions and Future Directions

- In patients relapsing on a second-generation ALK inhibitor, ALK mutations may serve as a biomarker to identity patients more likely to respond to lorlatinb
- Patients resistant to a second-generation ALK inhibitor are less likely to respond to lorlatinib in the absence of a detectable ALK mutation; however, some mutation-negative patientes do respond to lorlatinib (ORR:26%)
- Further investigations into tissue vs plasma genotyping of ALK mutations are ongoing
- Longitudinal profiling of cfDNA and/or tumor tissue Will help define the evolution and heterogenity of lung cancers treated with loratinib

Memorial Sloan Kettering Cancer Center

A phase I basket study of the PI3K inhibitor taselisib (GDC-0032) in *PIK3CA*-mutated locally advanced or metastatic solid tumors

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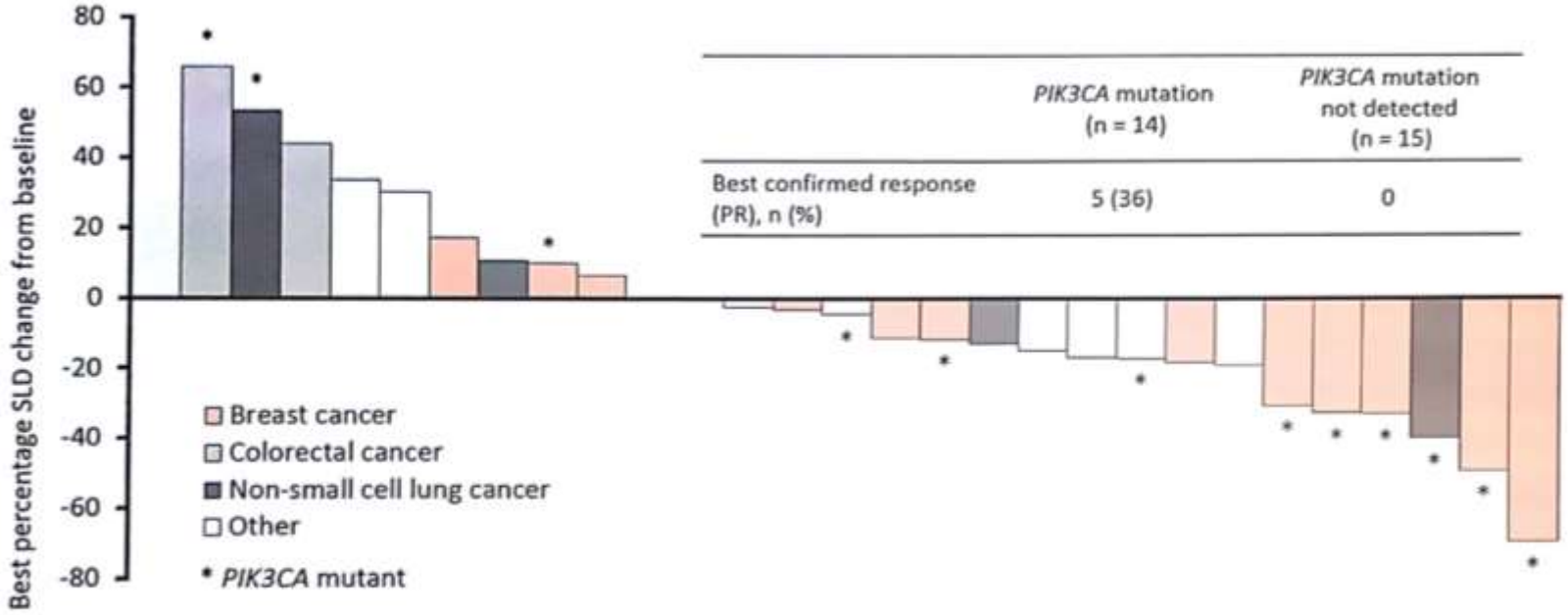
Taselisib: A mutant-selective PI3K inhibitor

Phase I dose-escalation data support* PIK3CA-*mutant selectivity



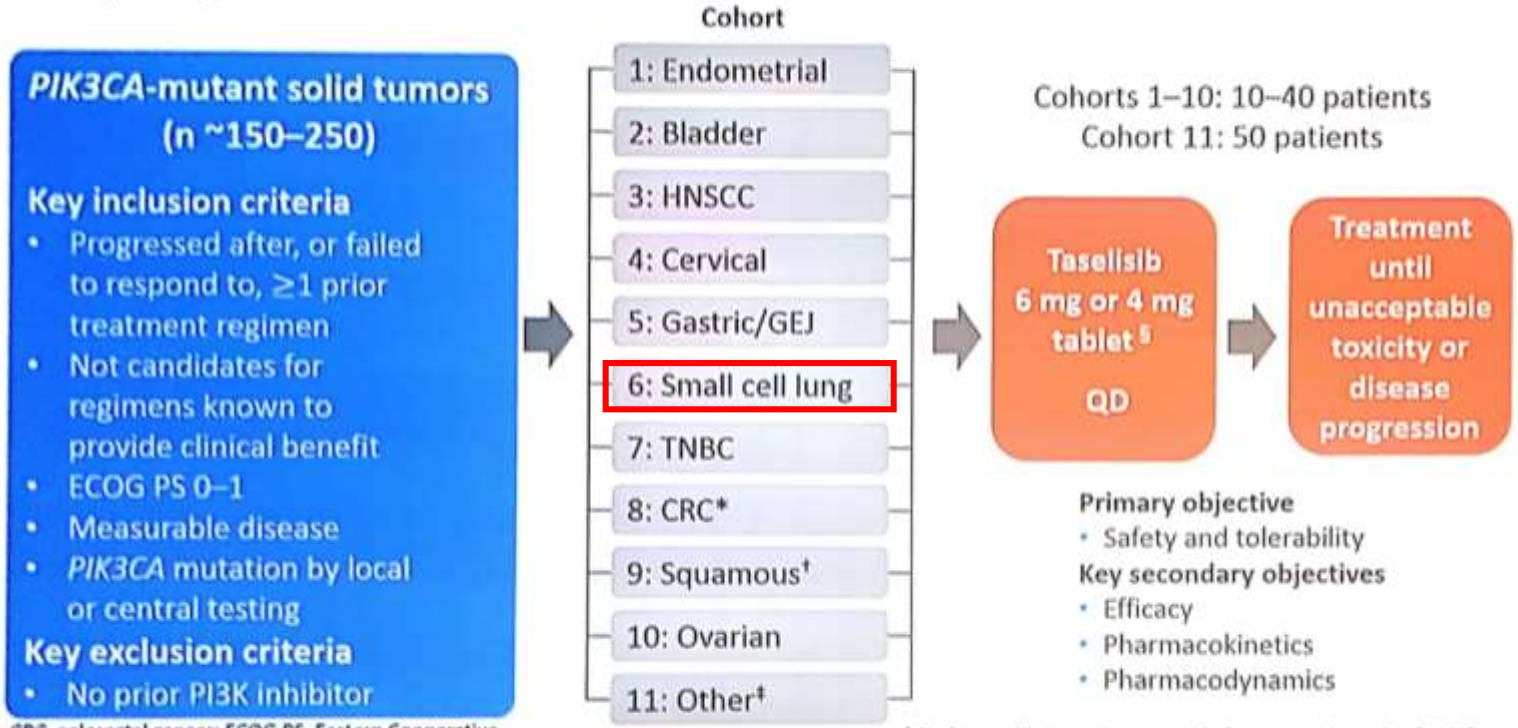
Single-agent taselisib showed responses in *PIK3CA*-mutant tumors[1]

PR, partial response; SLD, sum of longest diameter.

1. Juric D, *et al. Cancer Discov* 2017; 7:704–715.
Image reproduced with permission from Juric D, *et al.* 2017[1]

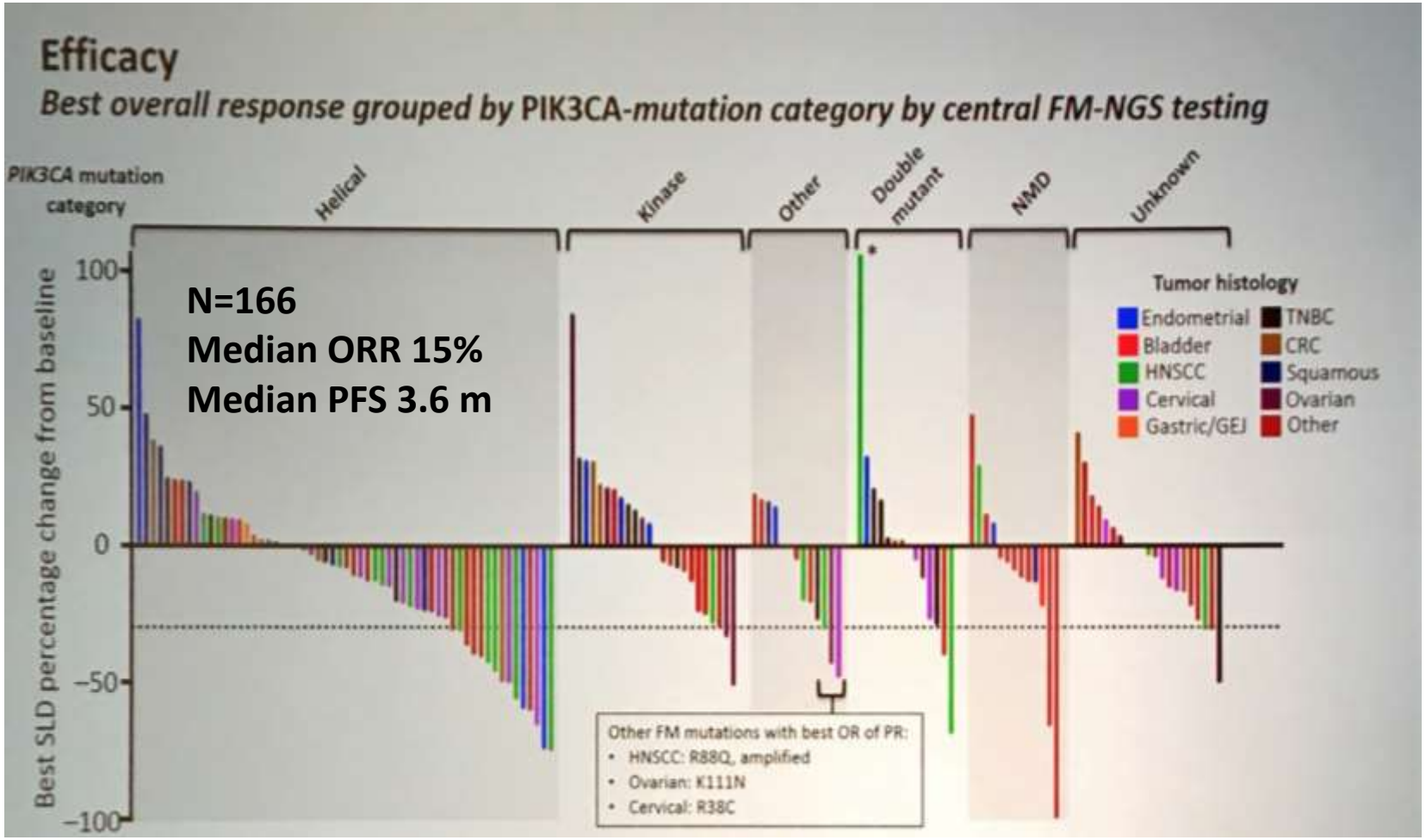
Taselisib *PIK3CA*-mutant basket study

Study design



CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HNSCC, head and neck squamous cell carcinoma; QD, daily; TNBC, triple-negative breast cancer.

* No known Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation. † Excluding histologies in Cohorts 1–8 and 10. ‡ Non-breast and non-lung. § May be given as an extemporaneous suspension (home administration) in Cohort 3 in patients with gastrostomy tubes (at sites where this is institutional review board-/ethics committee-approved).


Efficacy
Best overall response grouped by PIK3CA-mutation category by central FM-NGS testing
PIK3CA mutation category
Helical
Kinase
Other
Double mutant
NMD
Unknown
Best SLD percentage change from baseline
100
50
0
−50
−100
N=166
Median ORR 15%
Median PFS 3.6 m
Tumor histology
Endometrial
Bladder
HNSCC
Cervical
Gastric/GEJ
TNBC
CRC
Squamous
Ovarian
Other
Other FM mutations with best OR of PR:
• HNSCC: R88Q, amplified
• Ovarian: K111N
• Cervical: R38C