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KEY TAKEAWAY

- Presence of *FGFRalt* highly enriches for mUC tumors exhibiting a LumP subtype
- Treatment with erdafitinib trended towards improved clinical outcomes in a biomarker-defined LumP patient population compared with overall cohort

FGFRalt, fibroblast growth factor receptor alteration; LumP, luminal papillary; mUC, metastatic urothelial cancer.

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CONCLUSIONS

- Molecular subtypes were evenly distributed in *FGFR WT* tumors with a large proportion constituting the LumP subtype
- LumP subtype was enriched in *FGFR*-altered tumors
- Both *FGFR* mutations and fusions enrich for LumP tumor subtype

FGFRalt, fibroblast growth factor receptor alteration; LumP, luminal papillary; WT, wild type.

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INTRODUCTION

- Erdafitinib is an oral pan-FGFR TKI approved to treat adult patients with locally advanced or mUC with susceptible *FGFR*alt, and whose disease progressed on ≥1 line of prior systemic therapy
- In non-muscle invasive and resectable muscle-invasive UC, *FGFR*alt is highly associated with luminal subtype characterized by expression of luminal markers, low expression of basal markers, and with immune cold/poor immune infiltration
- In a randomized open-label phase 3 THOR study (Cohort 2), erdafitinib showed improvement in objective response and PFS compared with pembrolizumab, with no significant improvement in OS in patients with mUC and selected *FGFR* gene aberrations[1]
- In this study, a molecular analysis was performed exploring subtypes of tumor samples submitted for the THOR study (cohort 2) to further understand clinical findings

erda, erdafitinib; FGFR, fibroblast growth factor receptor; FGFRalt, fibroblast growth factor receptor alteration; mUC, metastatic urothelial cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; UC, urothelial cancer.

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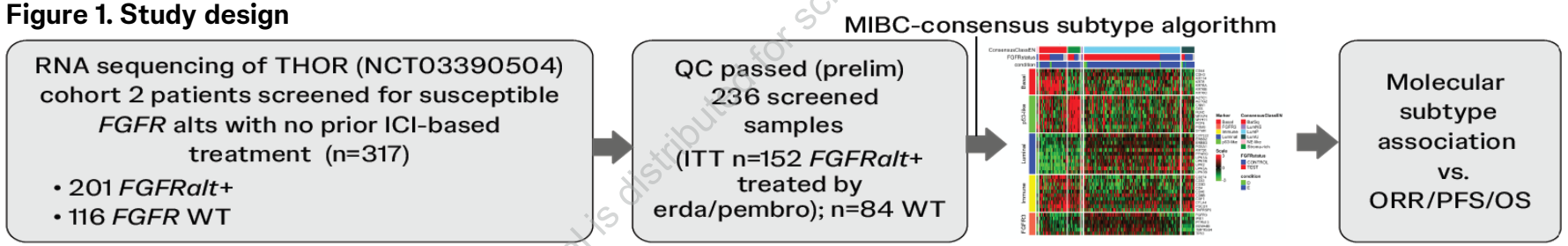
METHODS

- All available tumors from patients enrolled in THOR Cohort 2 (NCT03390504; *FGFR*alt positive, N=201) and a subset of *FGFR* WT (N=116), who were anti-PDL1/PD1 naïve, were used to perform whole transcriptome RNA sequencing, of which 152 and 84, respectively, passed quality control (**Figure 1**)
- *FGFR* status was determined using Qiagen therascreen *FGFR* RT-PCR test
- Consensus single-sample classifier was applied to the RNAseq data to determine molecular subtypes
- Tumor subtypes were correlated with treatment response to erdafitinib or pembrolizumab, ORR, PFS, and OS

Figure 1. Study design



erda, erdafitinib; FGFRalt, fibroblast growth factor receptor alteration; ICI, immune checkpoint inhibitor; ITT, intent-to-treat; MIBC, muscle invasive bladder cancer; ORR, overall response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; QC, quality control; WT, wildtype.

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RESULTS

- In erdafitinib- and pembrolizumab-treated groups, majority of patients harbored a *FGFR* mutation (76.9% and 80.5%) vs. translocation (23.1% and 17.2%), respectively (**Table 1**)

Table 1. Baseline characteristics

	Erdafitinib (N=65)	Pembrolizumab (N=87)
Age, years		
< 65	26 (40.0)	29 (33.3)
≥ 65	39 (60.0)	58 (66.7)
Sex		
Female	15 (23.1)	26 (29.9)
Male	50 (76.9)	61 (70.1)
Race		
Not reported	23 (35.4)	16 (18.4)
Asian	11 (16.9)	8 (9.2)
White	31 (47.7)	63 (72.4)
Geographic regions		
Europe	48 (73.8)	67 (77.0)
North America	1 (1.5)	3 (3.4)
Rest of the World	16 (24.6)	17 (19.5)
Visceral metastasis[a]		
Absent	20 (30.8)	19 (21.8)
Present	45 (69.2)	68 (78.2)
ECOG PS		
0	34 (52.3)	39 (44.8)
1	25 (38.5)	41 (47.1)
2	6 (9.2)	7 (8.0)
***FGFR* alterations**		
Multiple	0	2 (2.3)
Mutation	50 (76.9)	70 (80.5)
Translocation	15 (23.1)	15 (17.2)
Number of prior lines of systemic therapy		
1	62 (95.4)	87 (100)
2	2 (3.1)	0
Missing	1 (1.5)	0

Data are n (%). [a]In bone, lung, or liver.

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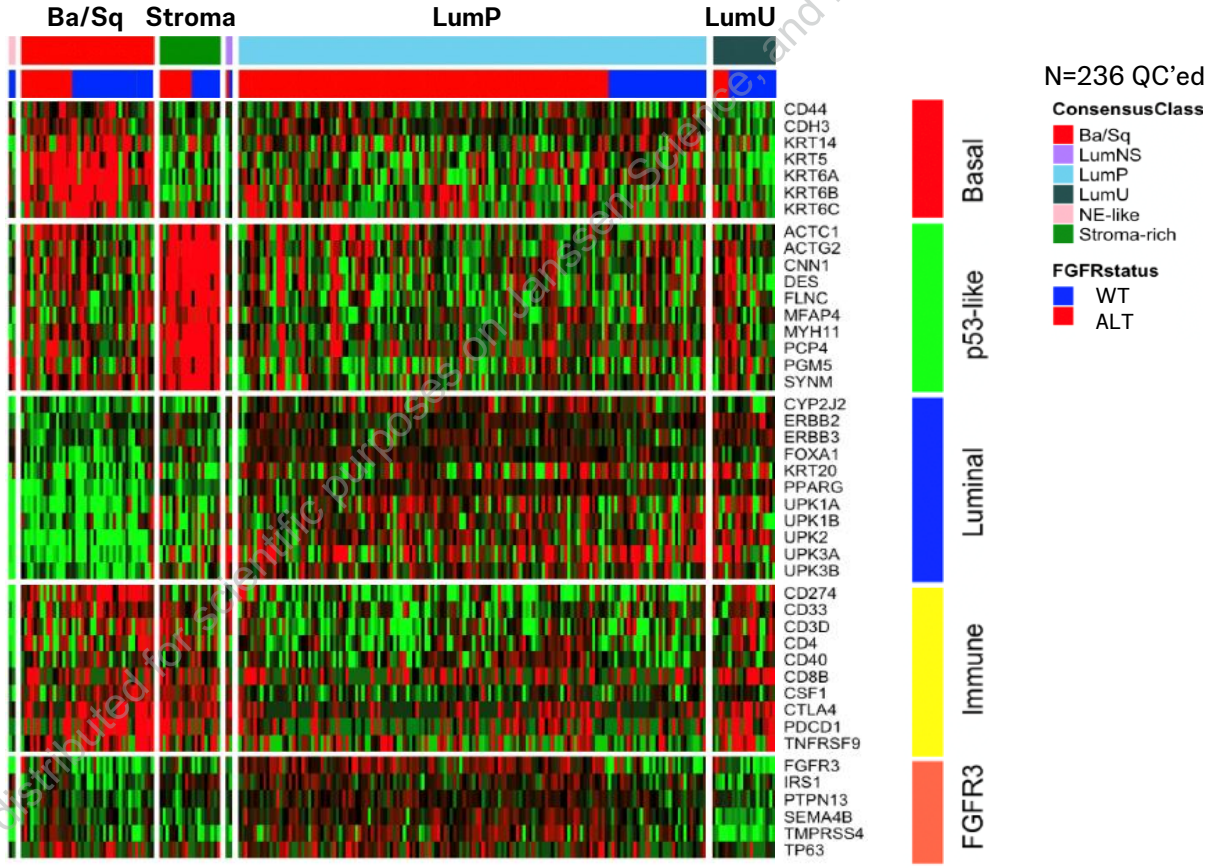
RESULTS

- Molecular classification of tumors (**Figure 2**) identified a significant proportion of LumP subtype in tumors harboring *FGFR*alt compared with *FGFR* WT (78.3% vs. 36.9%, $p<0.001$) and versus other subtypes: basal/squamous (Ba/Sq; 11.2% vs. 31.0%), stroma-rich (6.6% vs. 10.7%), NE-like (0% vs. 2.4%), LumU (3.3% vs. 17.9%), and LumNS (0.7% vs. 1.2%), respectively (**Figure 3**)

Figure 2. Molecular subtype classification of tumor samples



ALT, alteration; Ba/Sq, basal/squamous; FGFR, fibroblast growth factor receptor; LumNS, luminal non-specified; LumP, luminal papillary; LumU, luminal unstable; NE-like, neuroendocrine-like; QC, quality control; WT, wildtype.

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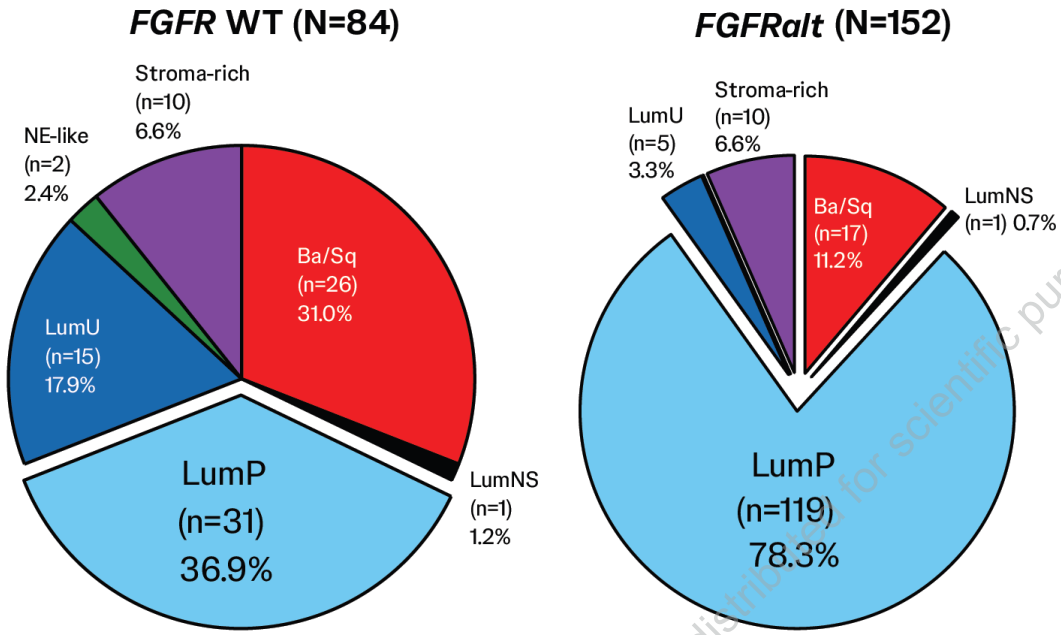
RESULTS

Figure 3. *FGFR*-altered tumors enrich for luminal-P



	FGFR WT	*FGFR Alt*[a]
LumP, %	36.9	78.3
Non-LumP, %	63.1	21.7

[a]*p*<<4.991e-10 (LumP vs. Non-LumP).

Ba/Sq, basal/squamous; FGFR, fibroblast growth factor receptor; FGFRalt, fibroblast growth factor receptor alteration; lumNS, luminal non-specified; lumP, luminal papillary; lumU, luminal unstable; NE, neuroendocrine; non-LumP, all other subtypes excluding LumP; QC, quality control; WT, wildtype.

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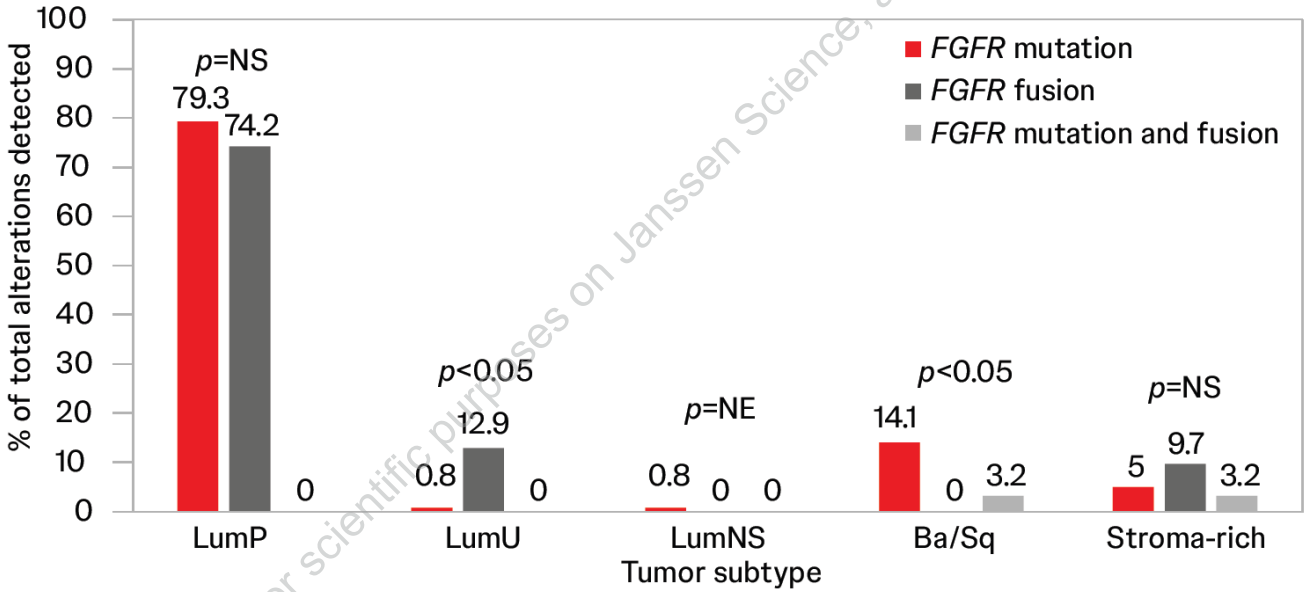
RESULTS

- *FGFR*alt type showed differential association with subtypes; 3.2% of fusions and 14.1% of mutations were detected in Ba/Sq subtype while 74.2% and 79.3%, respectively, were detected in LumP (**Figure 4**)

Figure 4. *FGFR* alterations and subtypes



p values indicate comparisons within each tumor subtype.

Ba/Sq, basal/squamous; FGFR, fibroblast growth factor receptor; lumNS, luminal non-specified; lumP, luminal papillary; lumU, luminal unstable; NE, non-existent; NS, not significant.

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RESULTS

- Clinical outcomes evaluated within LumP subset showed a significant improvement in ORR of erdafitinib-treated versus pembrolizumab-treated patients (41.7 vs. 19.7%; *p*=0.01), which was consistent with ITT population (40.0% vs. 21.6%) (**Table 2**)

Table 2. ORR by tumor subtype

Subtype	Erdafitinib		Pembrolizumab		*P* value
	N	ORR (95% CI)	N	ORR (95% CI)	
Non-LumP	17	**41.2%** [18.4%, 67.1%]	16	**25.0%** [10.3%, 56.0%]	
LumP	48	**41.7%** [27.6%, 56.8%]	71	**19.7%** [11.2%, 30.9%]	0.0129
ITT[1]	175	40.0%	176	21.6%	

ITT, intent-to-treat; lumP, luminal papillary; non-LumP, all other subtypes excluding LumP; ORR, overall response rate.

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RESULTS

- Numerical improvement were observed in PFS in LumP subtype between erdafitinib vs. pembrolizumab (5.5 vs 2.7 months) compared with the ITT population (4.4 vs 2.7) (**Table 3**)

Table 3. PFS by tumor subtype

Subtype	Erdafitinib		Pembrolizumab		*P* value
	Events/N	mPFS (95% CI), mo	Events/N	mPFS (95% CI), mo	
Non-LumP	17/17	**4.83** [1.97, 8.25]	16/16	**2.74** [1.28, 9.23]	NS
LumP	41/48	**5.52** [4.40, 6.34]	62/71	**2.73** [1.68, 4.17]	NS
ITT[1]	175	4.4 [4.1, 5.5]	176	2.7 [1.6, 3.0]	NS

erda, erdafitinib; ITT, intent-to-treat; lumP, luminal papillary; mPFS, median progression-free survival; non-LumP, all other subtypes excluding LumP; NS, not significant; pembro, pembrolizumab; PFS, progression-free survival.

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RESULTS

- Improvement in ORR and PFS of erdafitinib over pembrolizumab in LumP subtype did not translate to OS (10.9 vs. 12.9 months), which was similar to ITT population (10.9 vs. 11.1 months) (**Table 4**)

Table 4. OS by tumor subtype

Subtype	Erdafitinib		Pembrolizumab		*P* value
	Events/N	mOS (95% CI), mo	Events/N	mOS (95% CI), mo	
Non-LumP	16/17	**12.35** [7.92, 23.3]	12/16	**8.08** [3.78, NA]	NS
LumP	37/48	**10.94** [8.31, 18.8]	51/71	**12.94** [9.95, 20.9]	NS
ITT[1]	175	10.9 [9.2, 12.6]	176	11.1 [9.7, 13.6]	NS

erda, erdafitinib; ITT, intent-to-treat; lumP, luminal papillary; mOS, median overall survival; non-LumP, all other subtypes excluding LumP; NS, not significant; pembro, pembrolizumab.

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1. Siefker-Radtke AO, et al. Ann Oncol. 2024;35:107-117.

DISCLOSURES:

ASR served on scientific advisory boards for Astellas Pharma, AstraZeneca, Basilea, Bavarian Nordic, G1 Therapeutics, Genentech, Gilead Sciences, Immunomedics, Janssen, Loxo, Merck, Mirati, Nektar Therapeutics, Seattle Genetics, and Taiho Oncology. A complete list of author disclosures are available on the ASCO website.

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