Phase 2 study of second-line dovitinib (TKI258) in patients with fibroblast growth factor receptor 2 (*FGFR2*)-mutated or -nonmutated advanced and/or metastatic endometrial cancer

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Abstract LBA27

Disclosure Information

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I have no relevant financial relationships to disclose

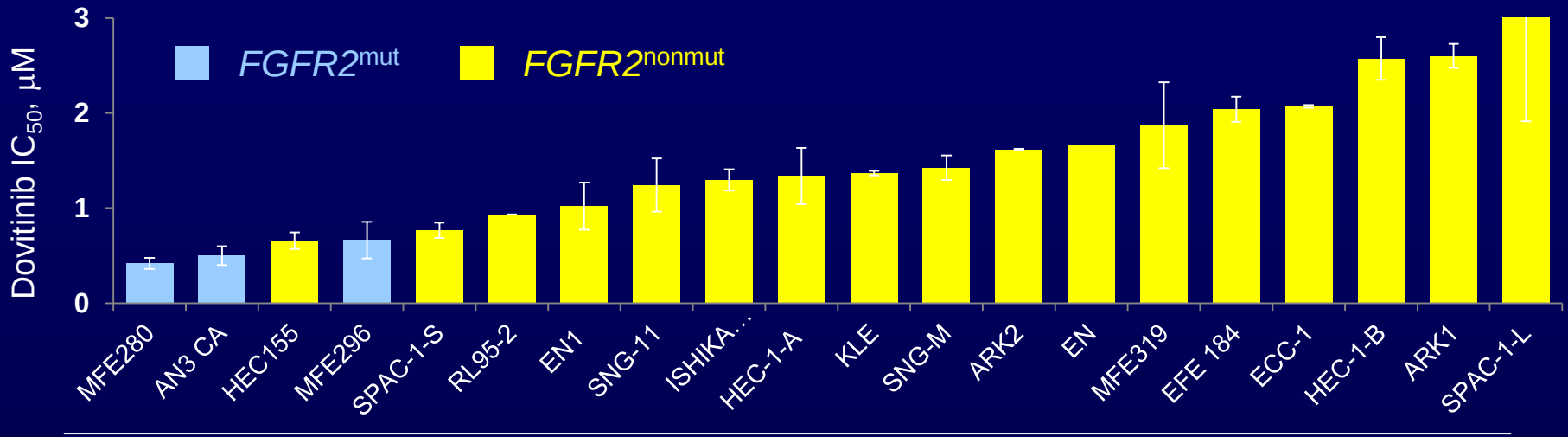
I will discuss the following investigational use in my presentation: clinical investigation of dovitinib (TKI258)

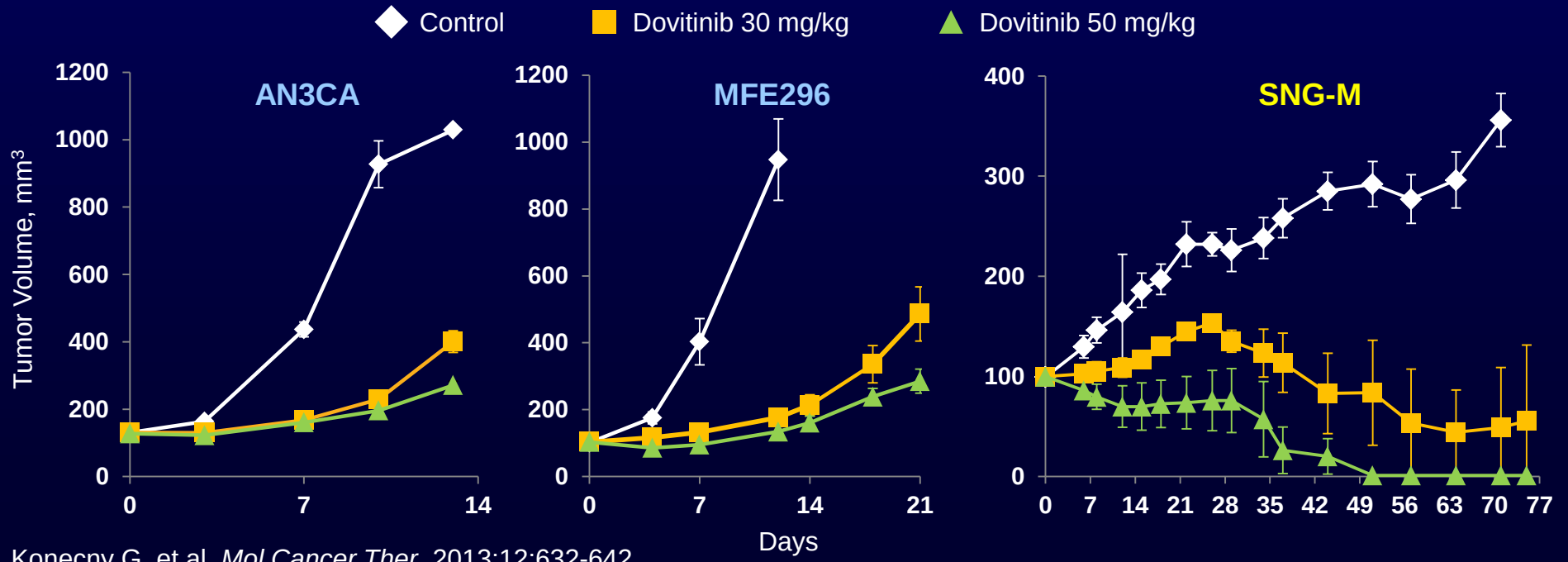
Background

- **Activating mutations in *FGFR2*, identified in 10%-15% of primary endometrial cancers, are associated with disease progression and poor outcome[1-4]**
- **Dovitinib (TKI258) is an oral tyrosine kinase inhibitor that targets FGFR, VEGFR, PDGFR, and other kinases[5]**
- **Dovitinib demonstrated dose-dependent growth inhibition of *FGFR2*-mutated and *FGFR2*-nonmutated endometrial xenografts[6]**

1. Pollock PM, et al. *Oncogene*. 2007;26:7158-7162. 2. Dutt A, et al. *Proc Natl Acad Sci U S A*. 2008;105-8713-8717.
3. Cheung LW, et al. *Cancer Discov*. 2011;1:170-185. 4. Byron SA, et al. *PLoS ONE*. 2012;7:e30801.
5. Lee SH, et al. *Clin Cancer Res*. 2005;11:3633-3641. 6. Konecny G, et al. *Mol Cancer Ther*. 2013;12:632-642.

Dovitinib Preclinical Activity in Endometrial Cell Lines/Xenografts





Konecny G, et al. *Mol Cancer Ther*. 2013;12:632-642.

Objective

- **Assess the efficacy and safety of dovitinib in *FGFR2*-mutated and *FGFR2*-nonmutated recurrent endometrial cancer**

Key Eligibility Criteria

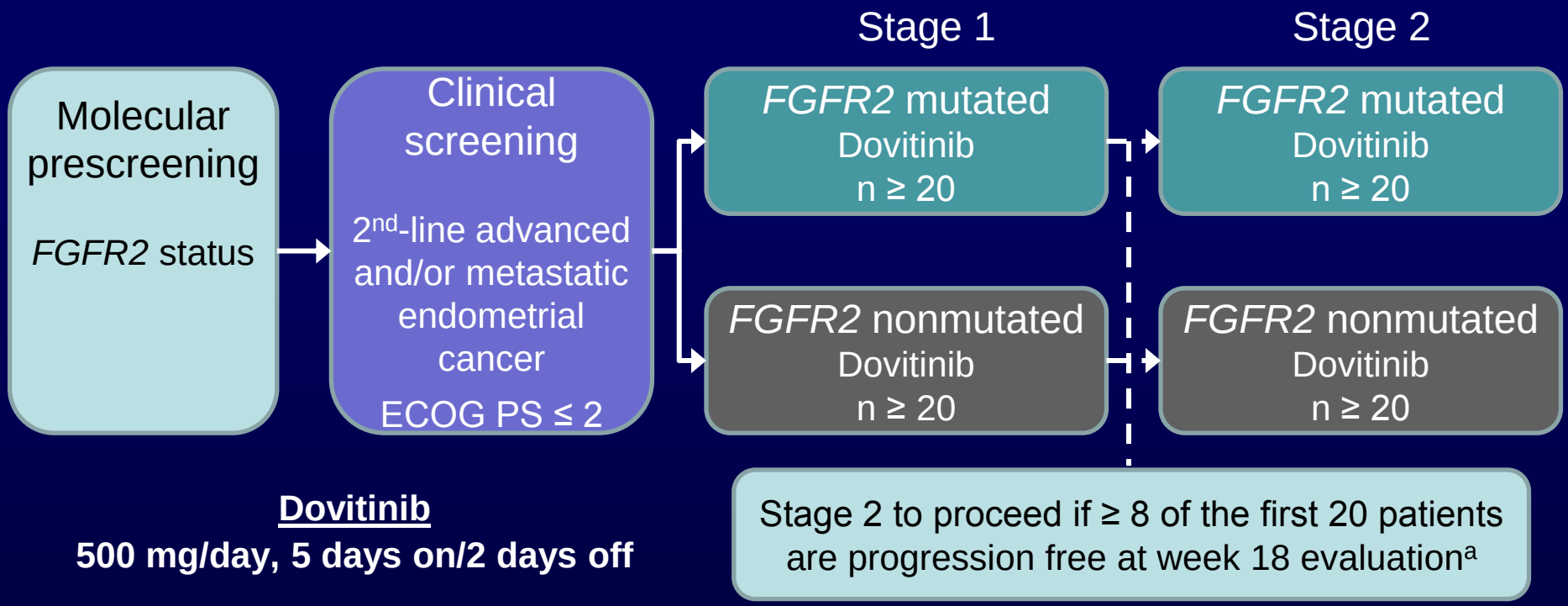
Inclusion

- **Progressive disease after first-line chemotherapy for advanced and/or metastatic endometrial cancer**
  - **Eligible histologies: endometrioid, serous, clear cell,**
  - **Prior treatment should include at least 1 cytotoxic agent**
  - **Prior hormonal therapy was not considered a line of treatment**

Exclusion

- **> 1 prior line of cytotoxic chemotherapy for advanced or metastatic disease**

Phase 2 Study Design



Dovitinib
500 mg/day, 5 days on/2 days off

Primary endpoint
Percentage of patients progression free after 18 weeks

Assessments

Efficacy

- Response assessed by local investigator every 6 ± 1 weeks according to RECIST v1.1[1]

Safety

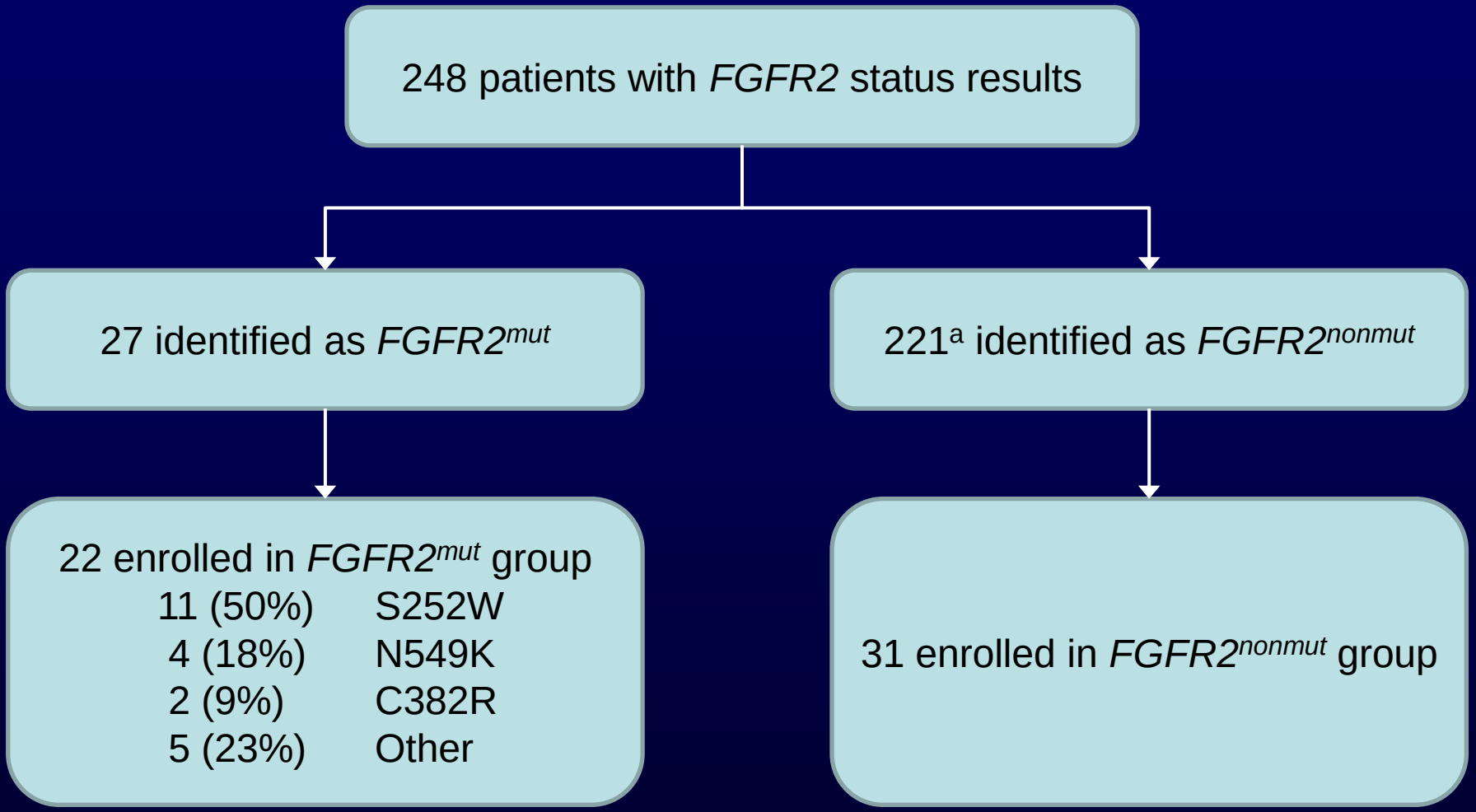
- Adverse events assessed according to CTCAE v4.03

Biomarkers

- *FGFR2* analysis performed on archival tumor blocks or fresh fixed tumor biopsies
  - *FGFR2*^{mut} identified by Sanger sequencing of the 5 main hotspot mutation sites reported for endometrial cancer

1. Eisenhauer EA, et al. *Eur J Cancer*. 2009;45:228-247.

FGFR2 Molecular Prescreening



FGFR2 mutation rate ≈ 11%

[a] 166 patients identified after enrollment to FGFR2^{nonmut} group complete.

Baseline Patient Characteristics

	FGFR2^{mut} n = 22	*FGFR2*^{nonmut} n = 31
Median age (range), years	64.5 (40-78)	65.0 (36-80)
Age ≥ 65 years, n (%)	11 (50)	18 (58)
ECOG performance status, n (%)		
0	15 (68)	14 (45)
1	7 (32)	17 (55)
Predominant histology, n (%)		
Endometrioid	19 (86)	19 (61)
Serous	1 (5)	6 (19)
Clear cell adenocarcinoma	1 (5)	6 (19)
Mucinous adenocarcinoma	1 (5)	0
Histologic grade, n (%)		
Well differentiated	3 (14)	3 (10)
Moderately differentiated	11 (50)	7 (23)
Poorly differentiated	7 (32)	18 (58)
Unknown	1 (5)	3 (10)

Patient Disposition

	FGFR2^{mut} n = 22	*FGFR2*^{nonmut} n = 31
Discontinued, n (%)	22 (100)	31 (100)
Primary reason for discontinuation, n (%)		
Progressive disease	13 (59)	22 (71)
Adverse event	7 (32)	7 (23)
Patient/guardian decision	2 (9)	2 (6)

Exposure to Study Drug

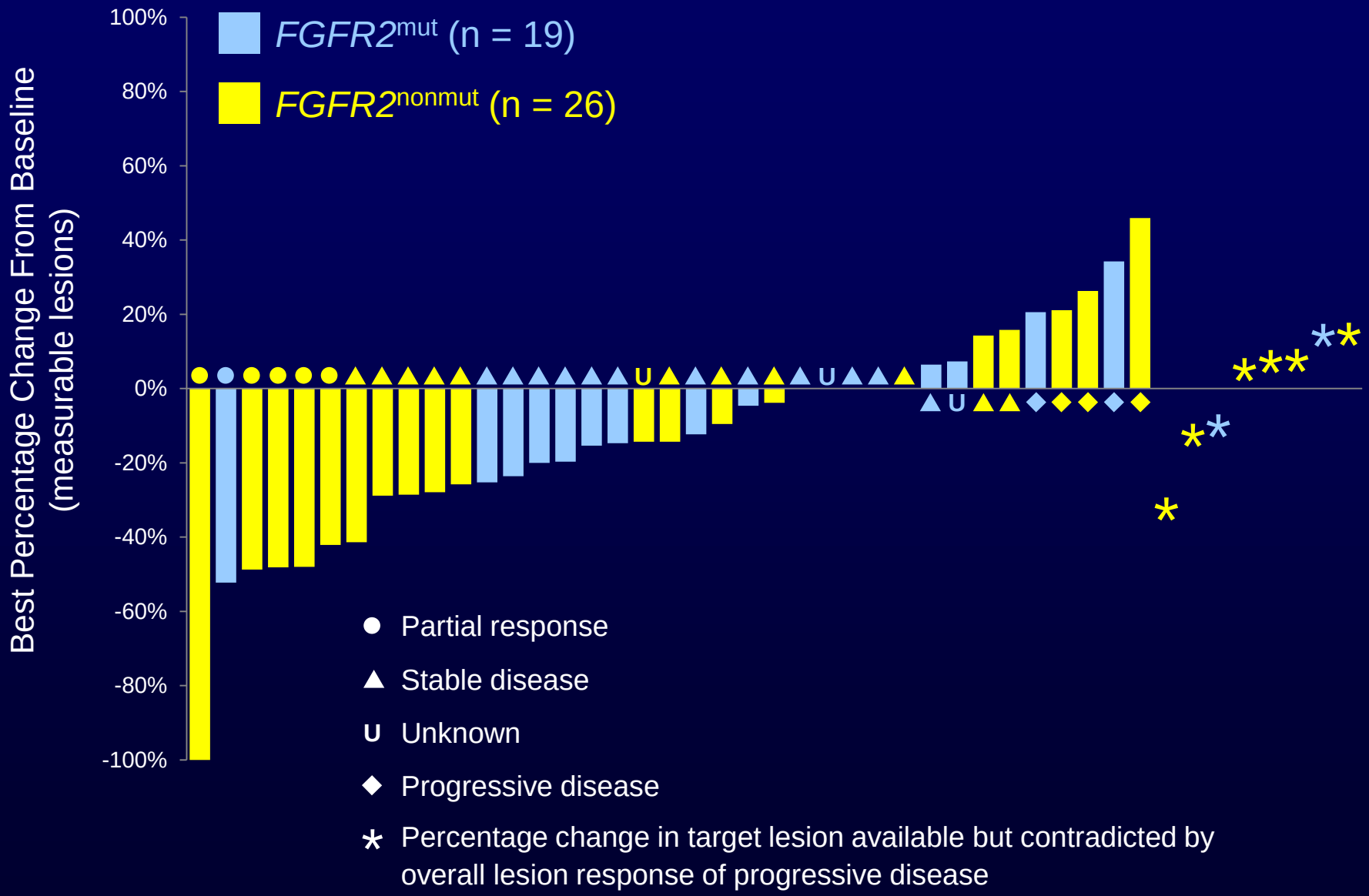
	FGFR2^{mut} n = 22	*FGFR2*^{nonmut} n = 31
Median exposure, weeks	15.9	11.1
Duration of exposure, n (%)		
< 6 weeks	8 (36)	11 (35)
6 to < 12 weeks	2 (9)	7 (23)
12 to < 18 weeks	3 (14)	4 (13)
≥ 18 weeks	9 (41)	9 (29)
Median relative dose intensity, %	96.8	94.8

Response Rate

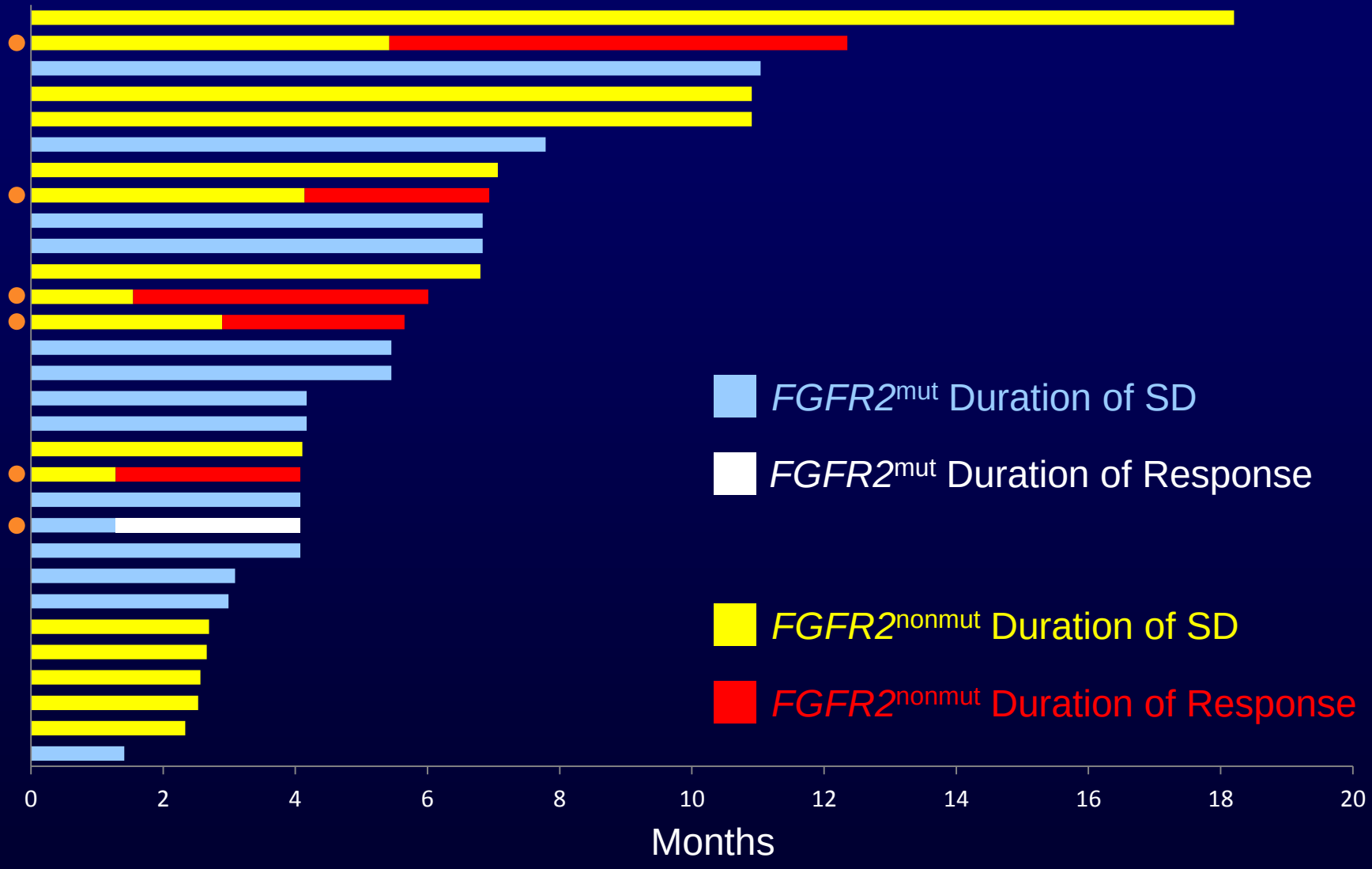
	FGFR2^{mut} n = 22	*FGFR2*^{nonmut} n = 31
18-week PFS rate, n (%)	7 (32)	9 (29)
Best overall response, n (%)		
Partial response	1 (5)	5 (16)
Stable disease	13 (59)	11 (35)
Progressive disease	4 (18)	9 (29)
Unknown	4 (18)	6 (19)

- 18-week PFS rate in first 20 patients was 7 (35%) and 5 (25%) in the *FGFR2*^{mut} and *FGFR2*^{nonmut} groups, respectively
  - The study did not proceed to stage 2 based on the predefined criteria

Best Change From Baseline

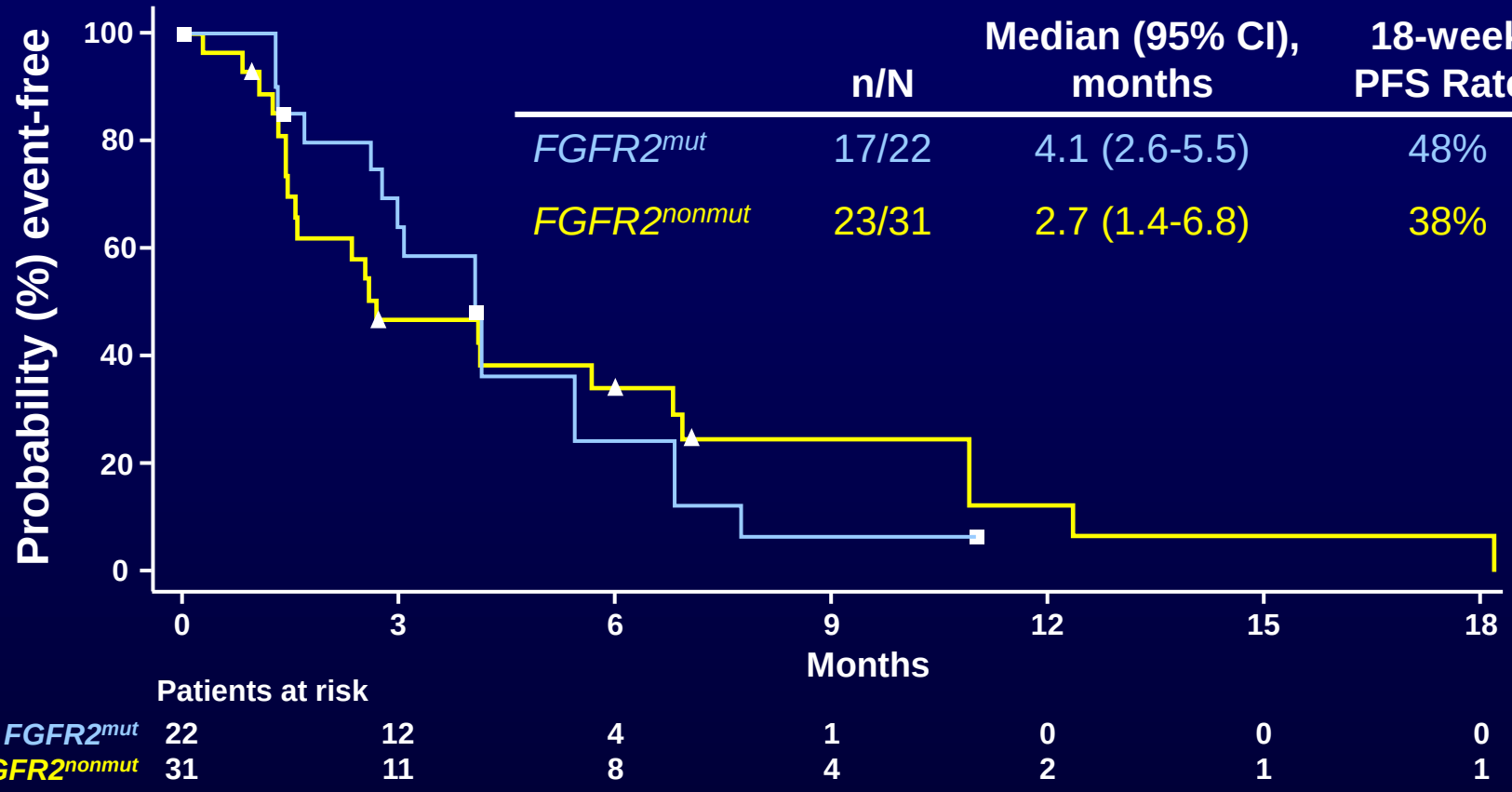


Duration of Stable Disease and Response



● Duration of response shown for patients with confirmed PR. Duration of SD includes duration of response.

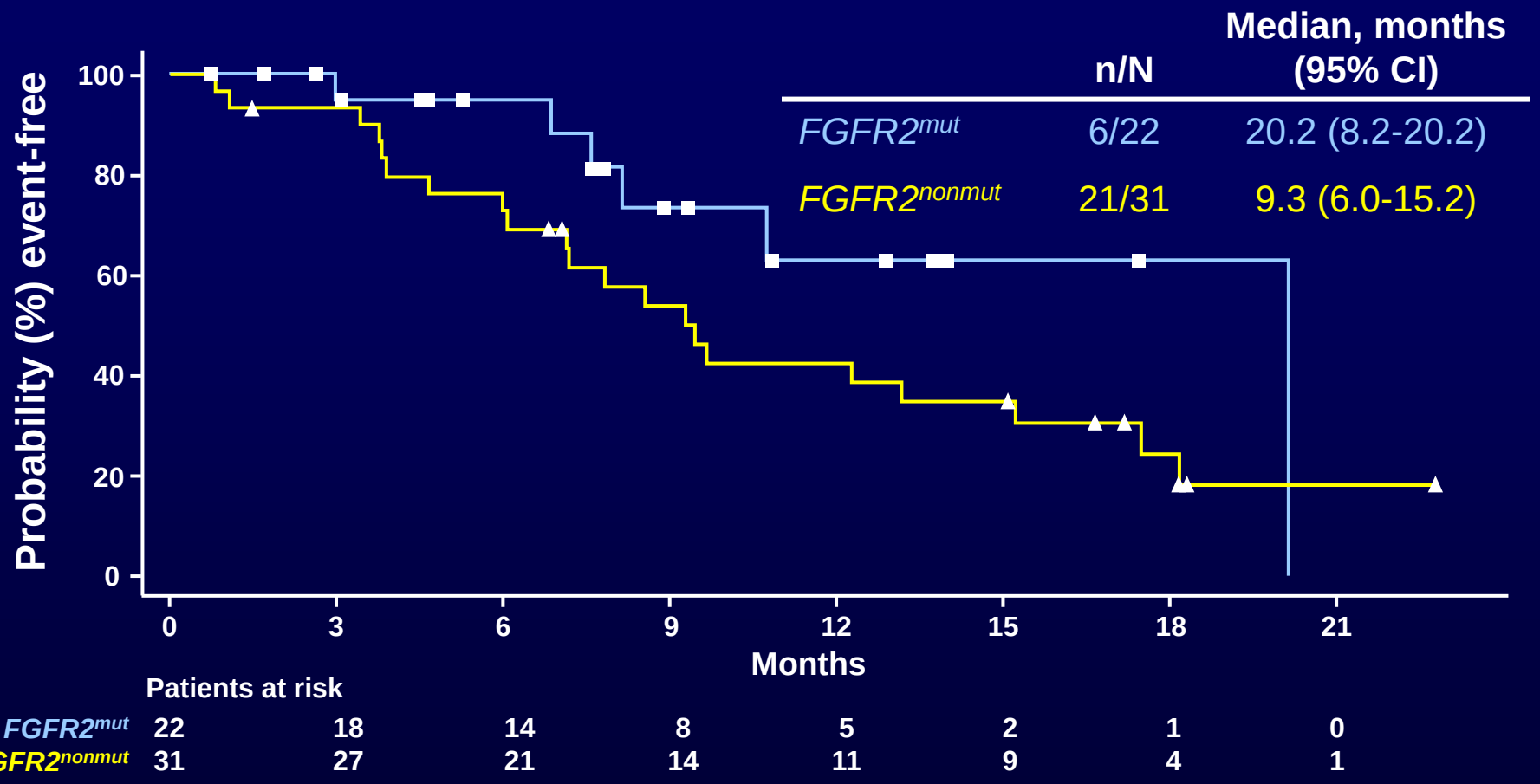
Progression-Free Survival



	n/N	Median (95% CI), months	18-week PFS Rate[a]
FGFR2^{mut}	17/22	4.1 (2.6-5.5)	48%
FGFR2^{nonmut}	23/31	2.7 (1.4-6.8)	38%

[a] 18-week PFS rate from Kaplan-Meier analysis.

Overall Survival



AEs Suspected Related to Study Drug
≥ 20% Any Grade or ≥ 5% Grade 3/4

	All Patients, N = 53		
	Any Grade	Grade 3	Grade 4
Total, n (%)	51 (96)	31 (58)	7 (13)
Diarrhea	36 (68)	5 (9)	0
Vomiting	34 (64)	2 (4)	0
Nausea	33 (62)	2 (4)	0
Fatigue	23 (43)	4 (8)	0
Rash	18 (34)	4 (8)	0
Decreased appetite	15 (28)	0	0
Blood alkaline phosphatase increased	11 (21)	2 (4)	0
Hypertension	10 (19)	9 (17)	0
Hypertriglyceridemia	9 (17)	3 (6)	1 (2)
Dehydration	4 (8)	3 (6)	0
Lipase increased	4 (8)	2 (4)	2 (4)
Pulmonary embolism	4 (8)	2 (4)	2 (4)
Thrombocytopenia	4 (8)	3 (6)	0

- Adverse events were similar between the 2 groups

Safety

- **The most common AEs leading to discontinuation were deep vein thrombosis, pulmonary embolism, and small intestinal obstruction (n = 2 each)**
- **36 patients (68%) had AEs that required dose interruption and/or reduction**
- **Of the 5 on-study deaths, 4 were due to endometrial cancer and 1 was due AE (cardiac arrest,[a] suspected to be study drug related)**

[a] Primary reason for death was cardiac arrest with contributing reason of pulmonary embolism (grade 4, suspected to be study drug related, occurring 4 days prior).

Conclusions

- **The overall safety profile was similar to that observed in other dovitinib trials**
  - **However, the incidence of thrombosis appeared more common in this patient population**
- **Single-agent dovitinib demonstrated clinically activity in both groups**
  - **The clinical benefit rate (PR + SD) was 64% and 51% in the *FGFR2*^{mut} and *FGFR2*^{nonmut} group, respectively**
  - **There was a trend toward greater median PFS and survival in the *FGFR2*^{mut} group**
  - **The PR rate was 5% and 16% in the *FGFR2*^{mut} and *FGFR2*^{nonmut} group, respectively**