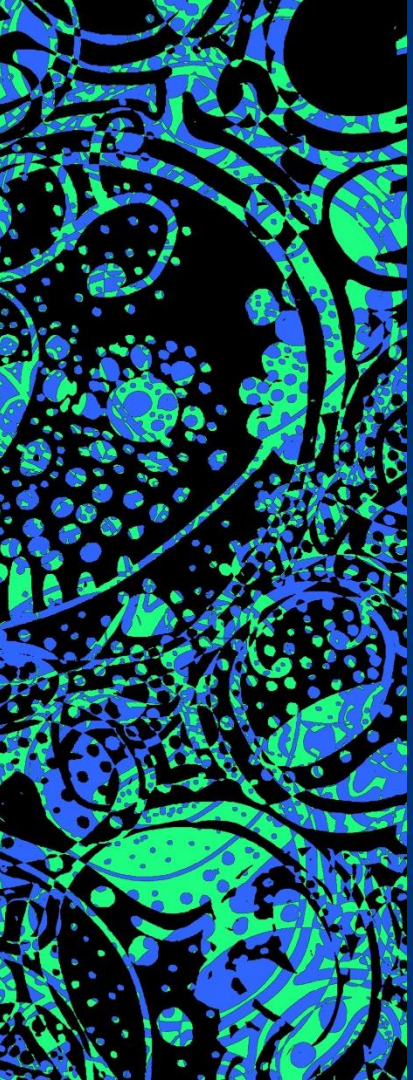


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Integrating Clinical & Genomics Real World Data to Support New Drug Application

A Case Study on Erdafitinib – First FGFRi approved in Patients with 2L Advanced/Metastatic Urothelial Cancer

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Michelle Hammer, *Silence*
Michelle Hammer is a NYC
native with Schizophrenia.



PHARMACEUTICAL COMPANIES OF
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Disclosures

- I am a full time Janssen employee
- I own stock and/or options in Janssen

Patients With Advanced UC Have Poor Outcomes

- Historically, second-line single-agent chemotherapy with taxanes or vinflunine yielded an ORR of ~10% and OS of ~7-9 months^{1,2}
- IO with PD-(L)1 inhibitors has improved outcomes, with an ORR of ~20% and OS of ~10 months, but not all patients benefit^{3,4}
- Responses to IO vary by TCGA subtype⁵⁻⁷; in particular, patients with the luminal I subtype UC may be immunologically “cold” and respond less to PD-(L)1 inhibition⁸
- Additional treatment options are needed

Abbreviations: IO, immunotherapy; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand 1; TCGA, The Cancer Genome Atlas; UC, urothelial carcinoma.

1. McCaffrey JA, et al. *J Clin Oncol*. 1997;15:1853-1857.

2. Bellmunt J, et al. *J Clin Oncol*. 2009;27:4454-4461.

3. Bellmunt J, et al. *N Engl J Med*. 2017;376:1015-1026.

4. Powles T, et al. *Lancet*. 2018;391:748-757.

5. Sharma P, et al. *Lancet Oncol*. 2017;18:312-322.

6. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920.

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8. McConkey DJ, et al. *Hematol Oncol Clin N Am*. 2015;29:377-394, x-xi.

Background: FGFR Status and Response to Immunotherapy

- FGFR alterations are associated with 'non-T-cell-inflamed' bladder tumors¹
- FGFR3 mutations found largely in the luminal 1 bladder cancer subtype which:
 - Exhibit low immune marker expression²
 - Show lower response rates to anti-PD-(L)1 therapy compared with other bladder cancer subtypes^{3,4}

Subtype (TCGA)	Response Rate	
	Atezolizumab Ph 2 ³	Nivolumab Ph 2 ⁴
Luminal 1	10%	18%
Luminal 2	34%	27%
Basal 1	16%	30%
Basal 2	20%	15%

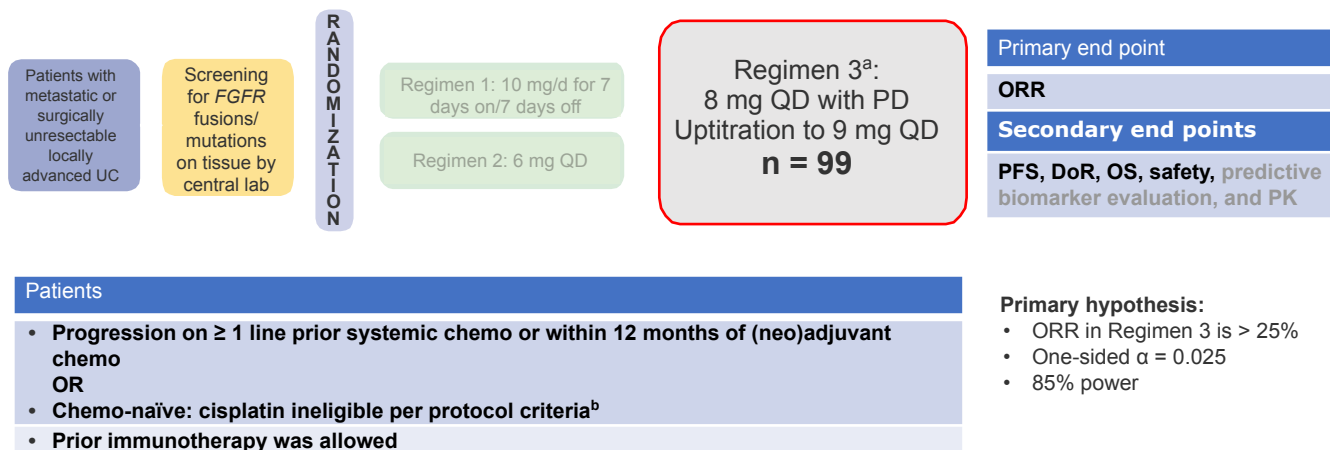
1. Sweis RF, Spranger S, Bao R, et al. Cancer Immunol Res. 2016 Jul;4(7):563-8.

2. Choi W, Ochoa A, McConkey DJ, et al. Eur Urol. 2017 Sep;72(3):354-365.

3. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Lancet. 2016 May 7;387(10031):1909-20.

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Phase 2 Study of Erdafitinib in FGFR+ Advanced UC (BLC2001)



^aDose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.

^bIneligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

Poor Response to Prior Anti-PD-(L)1 Treatment in FGFR + Patients

BLC2001	Pts with FGFR mutations or fusions	
	N=210 ^a	N=99
Prior treatment with anti-PD-(L)1	33 pts	22 pts
Responses on prior anti-PD-(L)1	2	1
ORR	6.1%	4.5%

^a includes all pts of Regimens 1-2-3

Rogaratinib Ph1¹:

10 subjects with FGFR3 mRNA overexpression received prior IO [6 anti-PD-(L)1]: No CR/PR, 1 SD

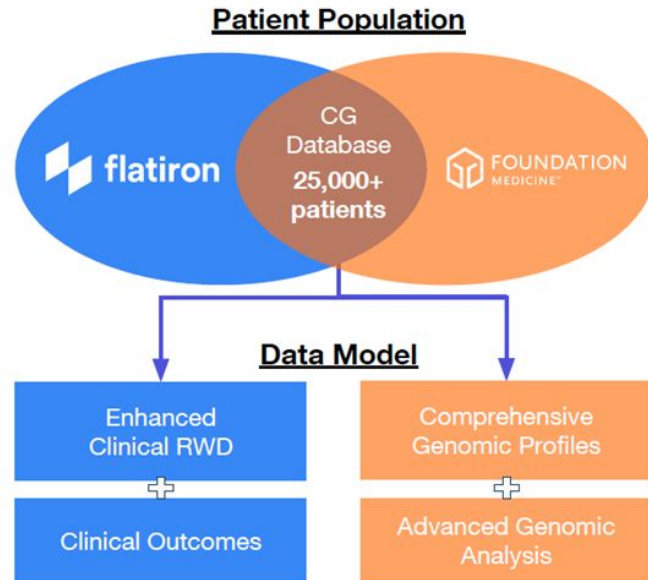
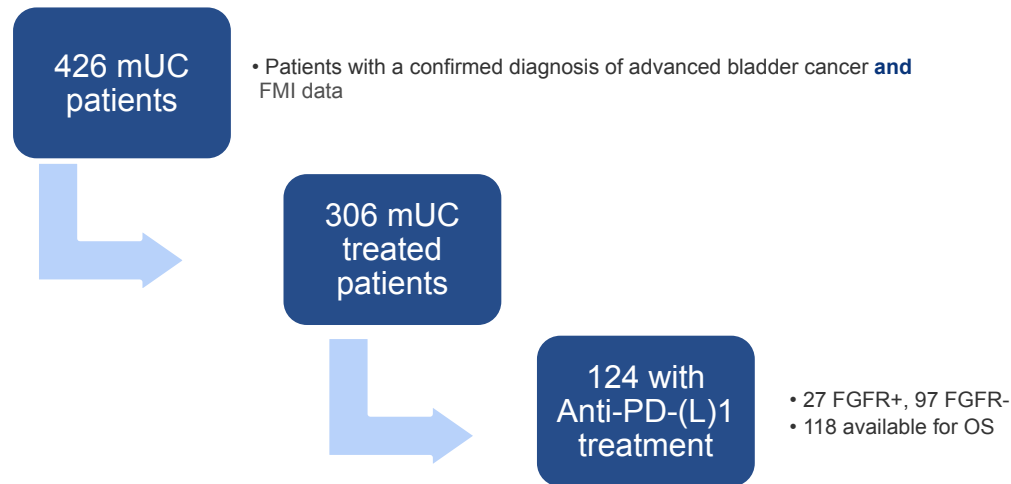
1. Joerger, M., et al., J Clin Oncol. 2018, suppl6S, Abstract 494.

Establishing Unmet Medical Need in the FGFR+ mUC Population

- What is the prognostic value of FGFR alterations in the advanced disease setting?
 - Comparison of OS in FGFR-altered vs non-altered urothelial tumors (Irrespective of type or line of therapy)
- What is the predictive value of FGFR alterations on outcomes with anti-PD-(L)1 treatment?
 - Comparison between FGFR-altered vs non-altered urothelial tumors treated with anti-PD-(L)1 treatment
 - Indirect matched comparison of FGFR-altered mUC Pts treated with Erdafitinib (BLC2001) vs anti-PD-(L)1 Therapy (FMI External Control Group)

Flatiron-FMI Real-World Data

- Clinico-Genomic Database linking Flatiron Health EHRs with genomic data from Foundation Medicine (FMI)
 - Full treatment histories and survival data
 - FGFR alteration assessment via FoundationOne NGS
- Patient Population (of 5,618 advanced UC in database)



Flatiron-FMI Data: Demographics & Baseline Characteristics

Patients, n (%)		FGFR+ (n=79)	FGFR- (n=347)
Age, median years (range)		68 (45-82)	66 (25-84)
Male		68%	69%
Smoking history	Yes	73%	66%
ECOG performance status	0	6%	6%
	1	11%	6%
	2	0	0.6%
	3	0	0.3%
	unknown	82%	87%
Tumour Mutation Burden (TMB)	Low	49%	34%
	Median	38%	53%
	High	13%	13%
Tumor Stage	Stage 0-III	15%	10%
	Stage IV	29%	41%
	Unknown	56%	49%
Hemoglobin Level	≥10 g/dL	89%	85%
	<10 g/dL	11%	15%
Tumor location	Bladder	67%	74%
	Urethra	1%	3%
	Ureter/renal pelvis	32%	23%

Prognostic Value of FGFR

Trend in Shorter Median OS in FGFR+ Patients *(Irrespective of type or line of therapy)*

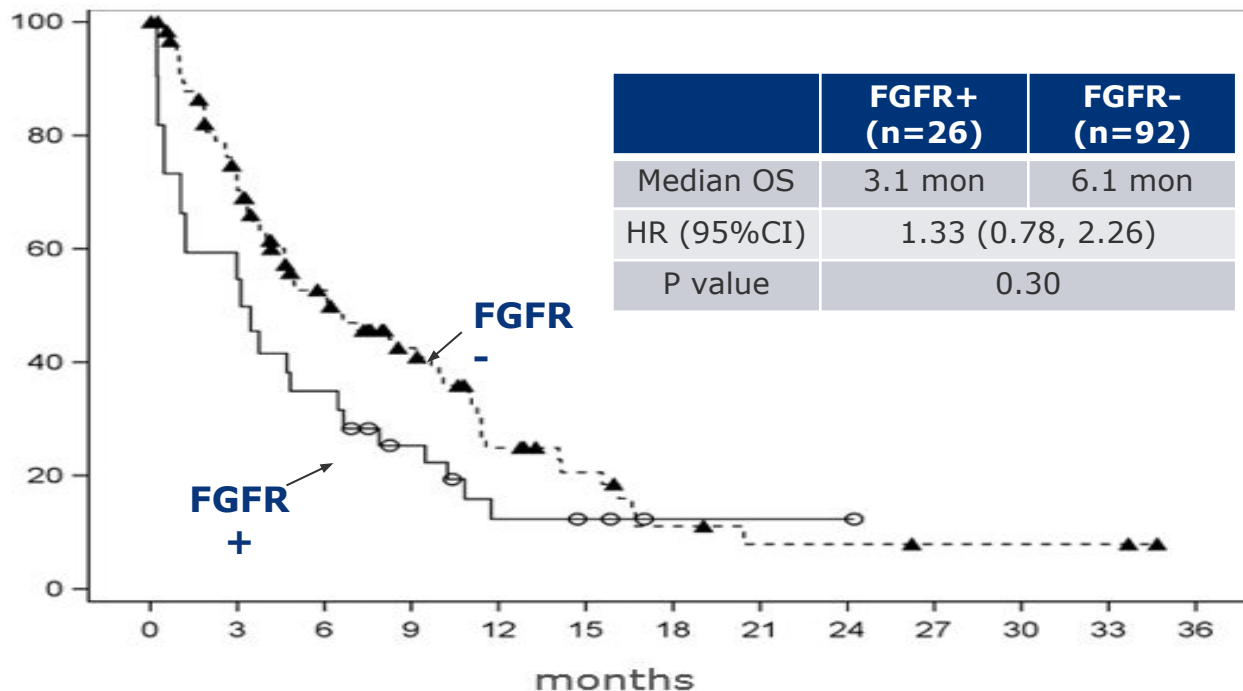
- Overall survival from 1st line of any therapy (e.g. chemotherapy or immunotherapy)

	FGFR+ (N=59)	FGFR- (N=247)
Median OS	7.2 mon	9.0 mon
HR (95% CI)	1.18 (0.84, 1.66)	
P value	0.35	

- Trend of shorter median OS in FGFR+ population irrespective of type or line of therapy was maintained in bivariate and multivariate Cox regression models adjusting for baseline covariates

Predictive Value of FGFR with Anti-PD-(L)1 Therapy

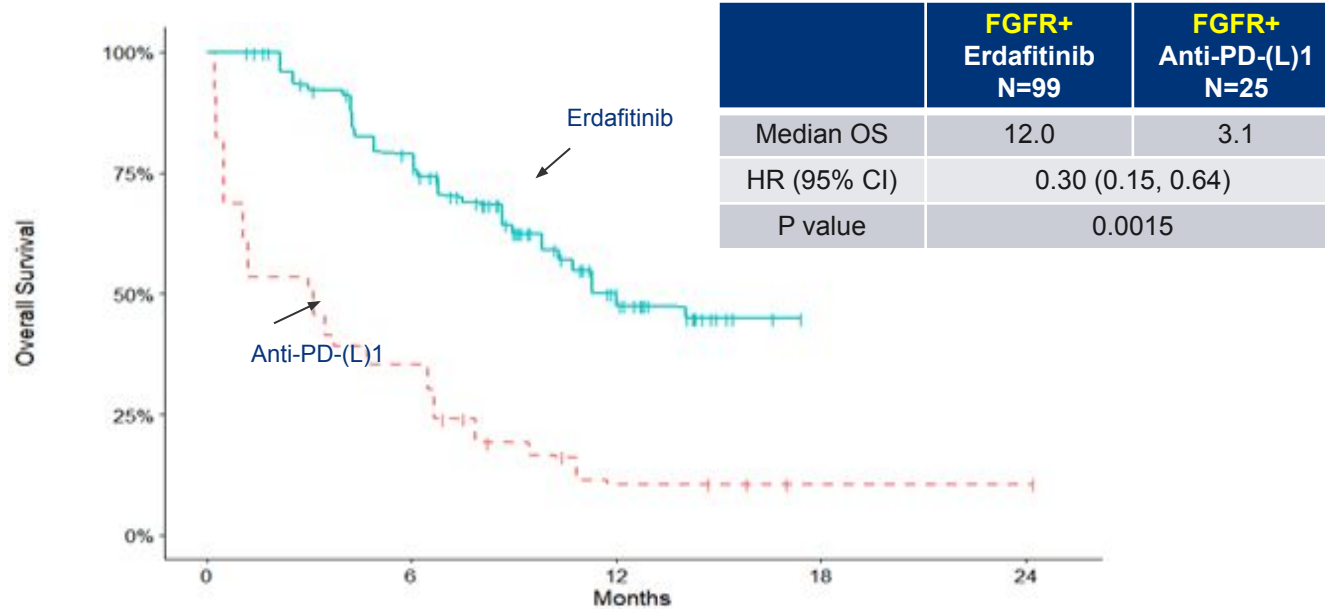
Shorter Median OS in FGFR+ve



FGFR alteration associated with shorter Median Overall Survival was maintained in bivariate and multivariate Cox regression models adjusting for baseline covariates

Indirect Comparison

Propensity Score Analysis of Overall Survival:

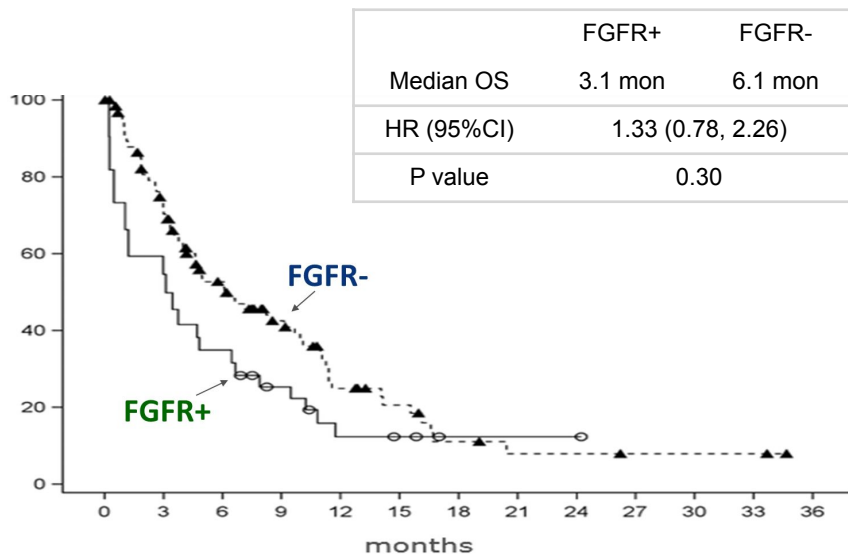


- Average treatment effect for overlap population (ATO) weighting adjusting for: line of therapy, age, sex, hemoglobin, smoking history, primary tumor location, and time since most recent therapy.
- Anti-PD-(L)1: Pembrolizumab, Nivolumab, Durvalumab, Atezolizumab, and Avelumab.

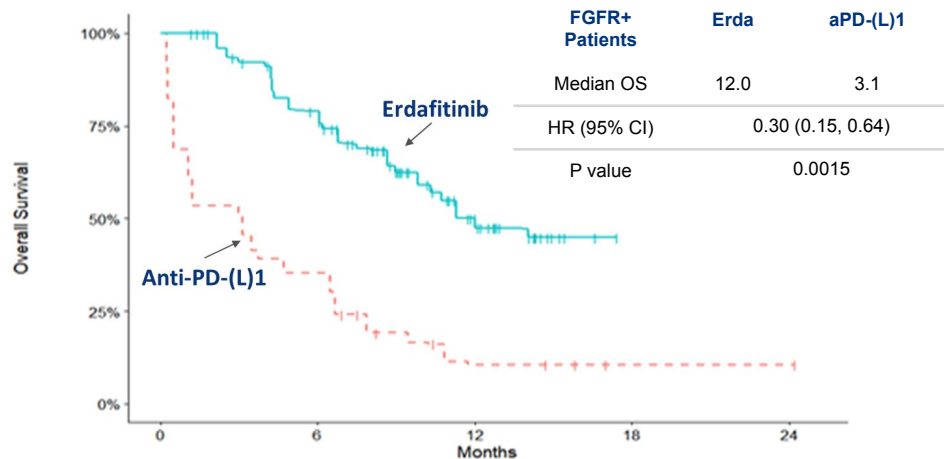
Summary

RWE Analyses Support Unmet Medical Need in FGFR+ mUC

Shorter Overall Survival Post Anti-PD-(L)1 Therapy in FGFR+ mUC Patients



Propensity Score Analysis of Overall Survival: FGFR+ Patients Treated with Erdafitinib Have Better OS than Anti-PD-(L)1



Average treatment effect for overlap population (ATO) weighting adjusting for: line of therapy, age, sex, hemoglobin, smoking history, primary tumor location, and time since most recent therapy.

Comparison of External Control Groups: RWE vs Clinical Trials/Literature

Flatiron-FMI RWE

- Contemporaneous
- Broad access to available therapies in US centers
- Comprehensive genomic profiles
- Rigorous and validated data extraction process to ensure high quality
- Tumor response as described in clinical visit notes, radiology reports

Clinical Trials/Literature

- Historical controls
- May not reflect all available therapies
- Genomic profiling may not be complete
- Variable quality depending on source
- Tumor response more rigorously assessed via quantitative RECIST criteria

Limitations with RWE

Clinical

- Selection bias (community clinics)
- Unmeasured and missingness of key confounders (i.e ECOG, baseline comorbidity, smoking, HgB)
- Less stringent criteria
- Differential selection of comparison group
- Differential treatment misclassification

Statistical

- Small sample size
- Potential misclassification on exposure
- Missed information on outcome ascertainment and follow-up time
- Incomplete capture of death information
- Survivorship bias by excluding subjects who did not undergo molecular testing
- Application of delayed entry model using left truncation method for statistical analyses to avoid survivorship bias

Considerations for RWE Studies

- Adequate sample size vital, additional data sources may be necessary
- Linkage to other data sources such as claims data to capture more complete information and minimize missing data
 - Increase the accuracy and improve ascertainment
- Apply same inclusion/exclusion criteria (and endpoint criteria) to the control cohort
- Minimize ascertainment of exposure by providing complete information on treatment regimen, duration, interruption and discontinuation of treatment
- Minimize ascertainment of outcome by providing complete and accurate information on deaths and other outcome measures (response rate, progression, censoring)
- All efforts should be made to retrieve as much as possible information on important confounding factors

Other Considerations

- Allow sufficient time for data privacy review and contracting
 - Involve privacy group and other stakeholders early, while still in planning stages
- Consider regulatory filings in contracting language
 - Ability to share data with health authorities and full filing support from data vendor
- Protocol and statistical plan must be in place prior to analyses
 - Data fields should be pre-specified, data cleaning plan should be in place and output should be assessed for completeness prior to any analyses
- Rigor of data preparation for RWE is equal to that for submission of trial data
 - Be submission-ready!

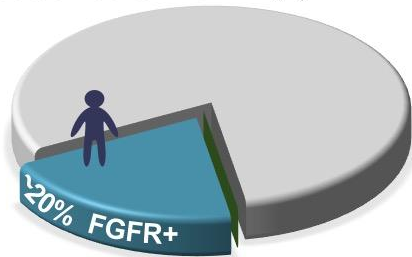
Conclusions

Leveraging Real World Evidence Data to Support Erdafitinib NDA

Anti-PD-(L)1 treatment
is SOC in 2L UC

Hypothesis:

FGFR+ Pts have Poorer
Outcomes to Anti-PD-(L)1



Predictive value of FGFR alterations to
anti-PD-(L)1 treatment outcomes

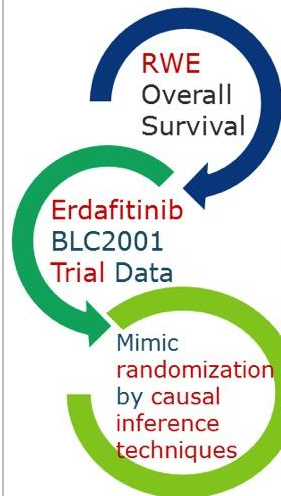
Prognostic value of FGFR alterations
in advanced UC

Real World
Data Sources



eHealth Records
+ Genomic Data

Support Erdafitinib NDA



FGFR+ pts are a **unique**
UC population **underserved**
by anti-PD-(L)1 therapy

Shorter Overall Survival
Post Anti-PD-(L)1
Therapy in FGFR+ mUC
Patients



NEVER SETTLE

**CONQUER
CANCER**