Quantitative Translational Approaches In Oncology
ASCPT Pre-Conference, March 8, 2016

Dose Optimization by Safety Guided Titration Approaches: Axitinib as a Case Example

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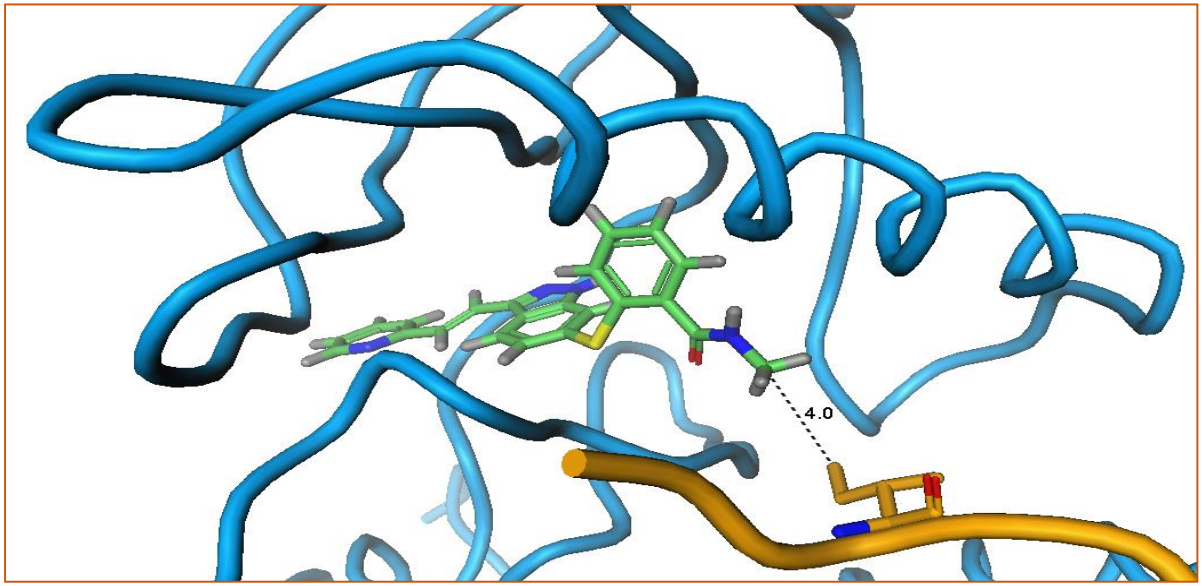
Axitinib

- Axitinib, a potent, selective, second-generation vascular endothelial growth factor (VEGF) receptor inhibitor
- Approved for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy, based on randomized Phase 3 head-to-head AXIS trial comparing it with sorafenib



Co-crystal Structure Modeling for Axitinib Binding to JM Domain-containing VEGFR-2 Kinase

Solowiej J. et al, Biochemistry 2009;48:7019

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OUTLINE

I. INLYTA DOSE TITRATION: **WHY?**

1. Justification for axitinib 5mg BID **starting dose**
2. Axitinib dose titration rationale: retrospective analysis of phase II mRCC data

II. INLYTA DOSE TITRATION: **HOW?**

1. Dose titration algorithm, timing, metrics
2. Design of prospective study to evaluate benefit of dose titration
3. Results from prospective study

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Justification for axitinib 5 mg BID starting dose

- **Phase I study in 36 patients receiving axitinib at doses ranging from 5 to 30 mg by mouth twice daily[1]:**
  - Maximum-tolerated dose of axitinib was 5 mg, twice daily
- **Axitinib dosing needs to be twice a day based on the plasma half-life range of 2.5–6.1 hours[1]**
  - 5 mg BID resulted in approximately 1.4-fold accumulation compared with administering a single dose
- **Therefore, the recommended starting dose of INLYTA® is 5 mg BID, with titration as required[2]**

1. Rugo HS, et al. J Clin Oncol 2005;23(24):5474
2. INLYTA® USPI 2012

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Justification for axitinib 5 mg BID starting dose

- **Pharmacodynamics**
  - AUC at 5 mg BID resulted in near maximal decrease in blood flow/permeability and soluble VEGFR-2 in plasma
- **Efficacy**
  - 5 mg BID associated with robust clinical response (44% ORR) in Phase 2 RCC study A4061012

Setting	ORR	PFS
Cytokine-refractory[1,2]	44%	13.7 months

1. Rixe O, et al. Lancet Oncol 2007;8:975-84 3. Motzer RJ, et al. J Clin 2. Oncol 29: 2011 (suppl; abstr 4547)

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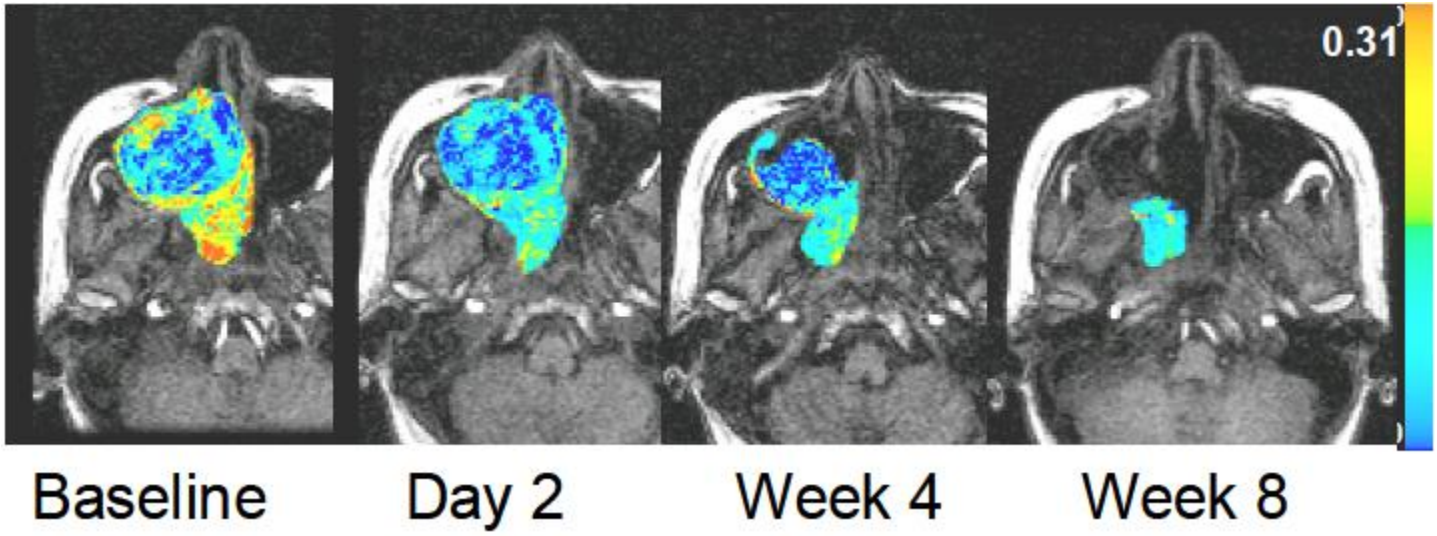
Axitinib-Related Changes in Blood Flow/Permeability: Phase 1 (FIH) Study



Representative DCE-MRI images from a patient with adenoid cystic carcinoma showing a decline in tumor perfusion after exposure to axitinib

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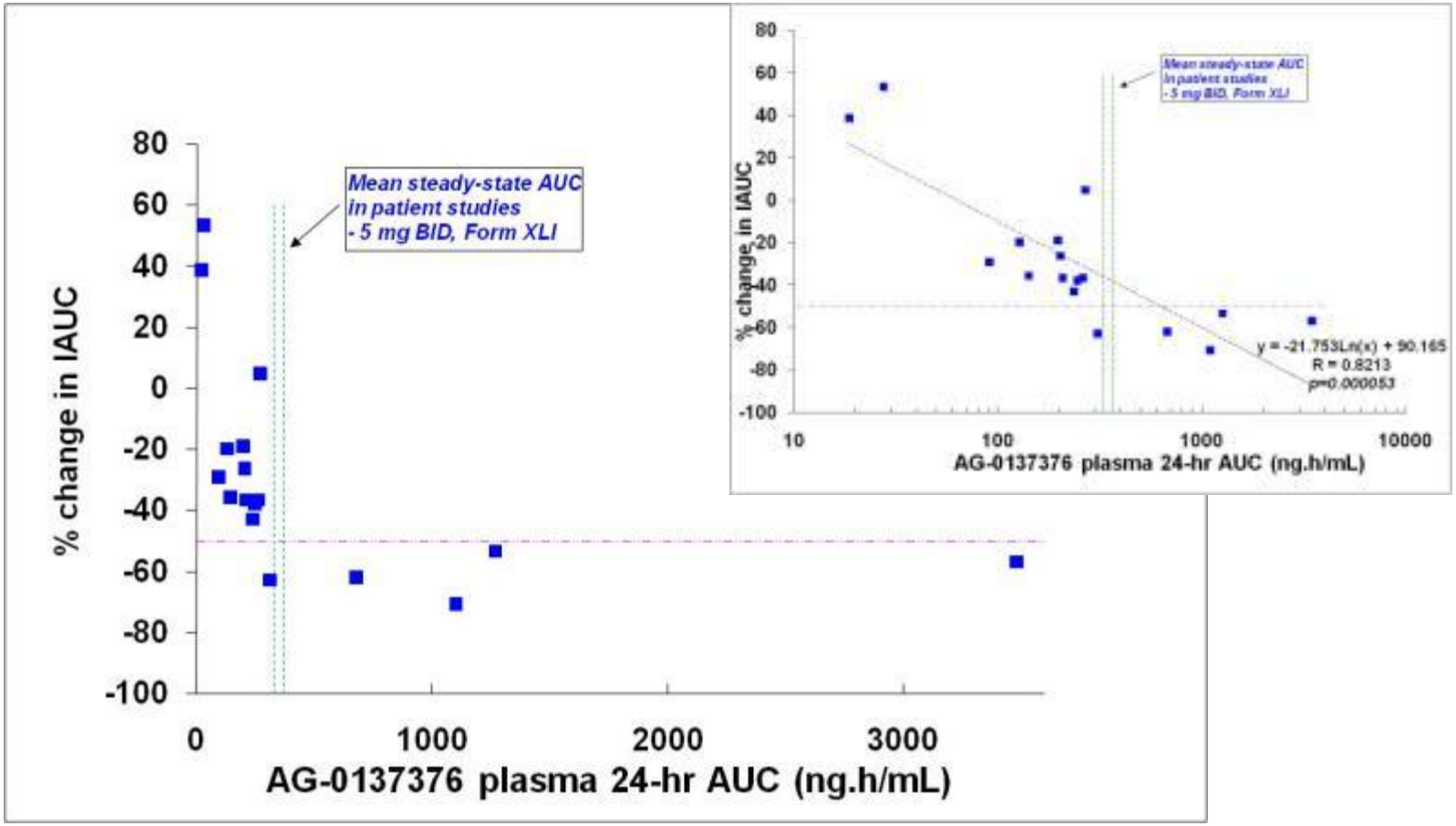
Liu G, 2005, JCO 23(24), 2005.

Axitinib-Related Changes in Blood Flow/Permeability: Phase 1 (FIH) Study



Near-maximal reduction in blood flow/permeability at 5 mg BID dose

Liu G, 2005, JCO 23(24), 2005.

Mean steady state plasma exposures obtained in patients at 5 mg BID with Form XLI are overlaid with vertical lines.

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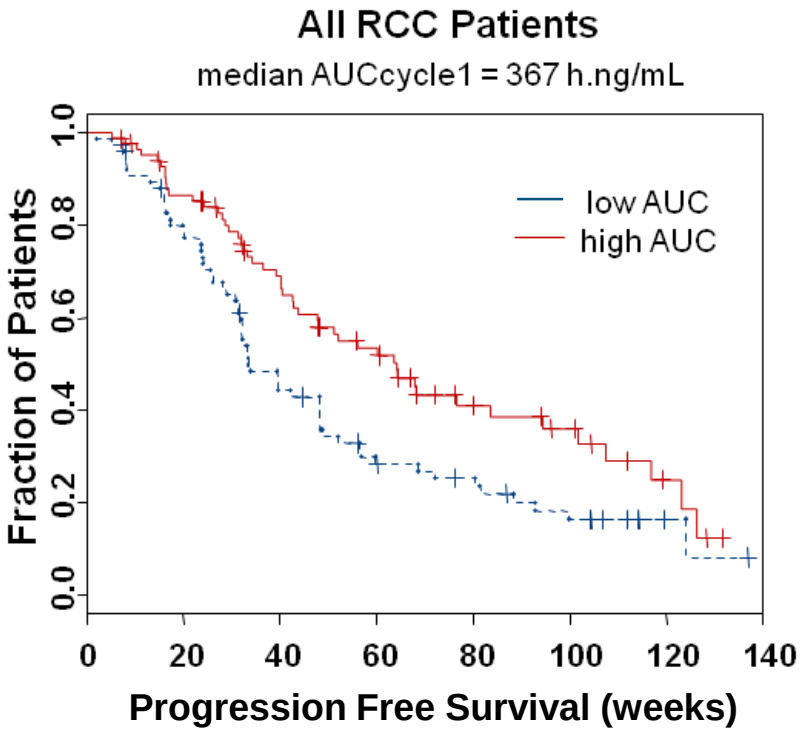
Higher AUC Associated with Longer PFS using pooled data from Ph 2 mRCC Studies



Studies	Median PFS, weeks (95% CI)		Hazard Ratio (95% CI)	P- value
	low AUC (< median)	high AUC (≥ median)		
A4061012 A4061023 A4061035	**33 (32, 48)** n=86, 60	**64 (48, 102)** n=87, 49	**0.608** (0.416, 0.888)	**0.00926**

n=number of patients meeting AUC criterion, number of PFS events assessed by investigator

AUC cycle1 refers to average AUC across first cycle of treatment

Based on analysis reported by Rini et al, Journal of Clinical Pharmacology, 53(5), 2005.

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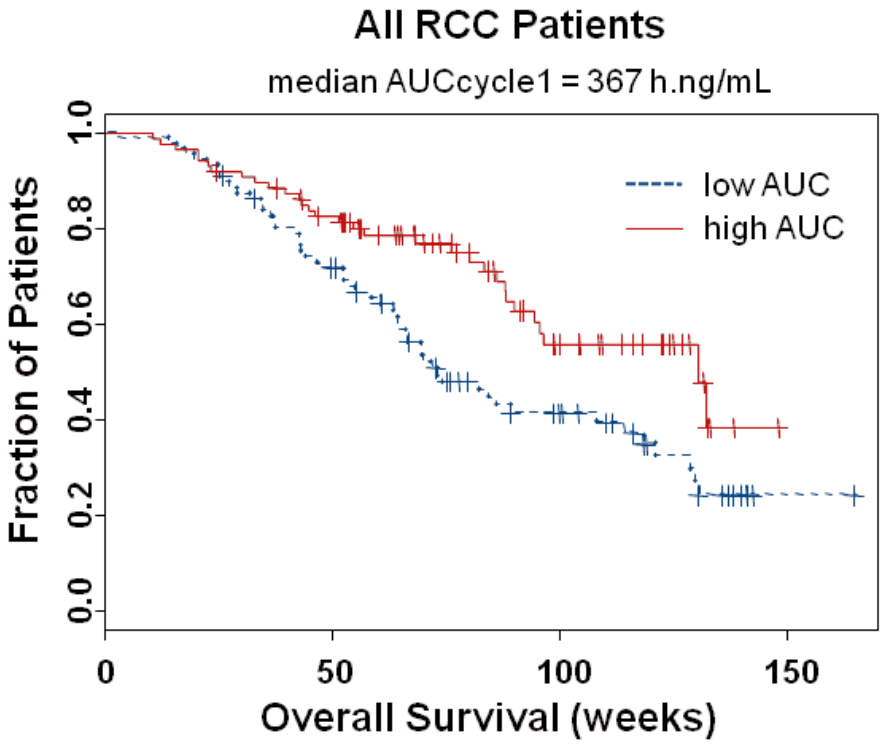
Higher AUC Associated with Longer OS in Ph 2 mRCC Patients



Studies	Median OS, weeks (95% CI)		Hazard Ratio (95% CI)	*P*-value
	low AUC (< median)	high AUC (≥ median)		
A4061012 A4061023 A4061035	**72 (64, 118)** n=86, 53	**131 (95, NA)** n=87, 31	**0.54** (0.347, 0.842)	**0.00579**

n=number of patients meeting AUC criterion, number of OS events

AUC cycle1 refers to average AUC across first cycle of treatment

Based on analysis reported by Rini et al, Journal of Clinical Pharmacology, 53(5), 2005.

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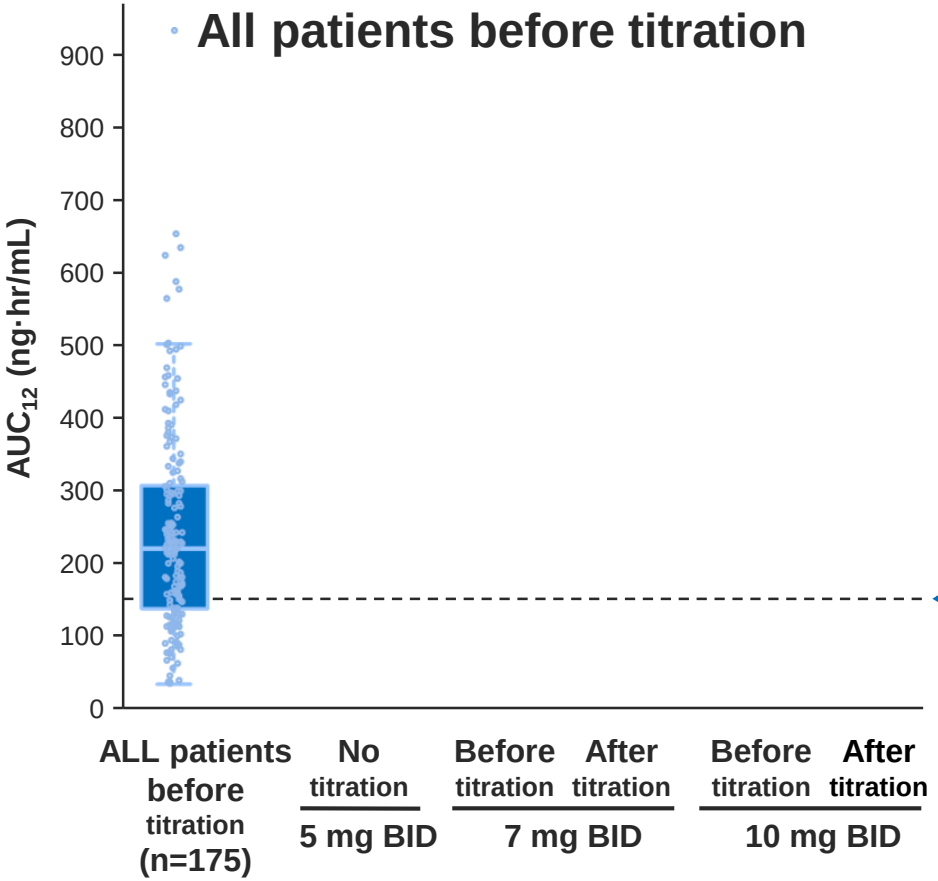
Axitinib dose titration rationale : Retrospective analysis of phase II mRCC data



Median AUC_{12} ng·hr/mL (range)	5 mg BID n=129	7 mg BID n=30	10 mg BID n=16
BEFORE titration			
AFTER titration			

← Sub-therapeutic exposure defined as AUC_{12} <150 ng·h/mL

- **Before titration: variable level of drug exposure and significant percentage of patients below the therapeutic threshold (AUC_{12} <150 ng·h/mL)**

AUC_{12} = area under the plasma concentration-time curve from 0 to 12 hr

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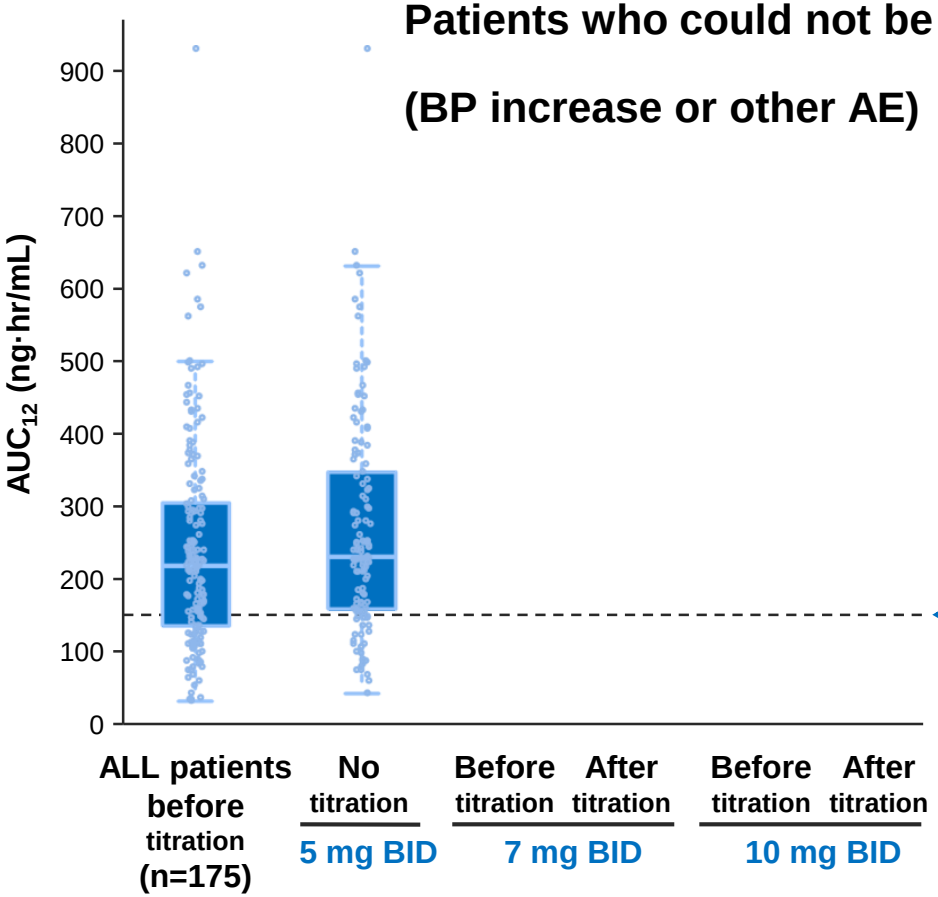
Rini et al. ASCO 2012 Abstract 4503

Axitinib dose titration rationale : Retrospective analysis of phase II mRCC data

Patients who could not be titrated based on clinical criteria

(BP increase or other AE)



Median AUC_{12} ng·hr/mL (range)	5 mg BID n=129	7 mg BID n=30	10 mg BID n=16
BEFORE titration	231 (42–931)		
AFTER titration			

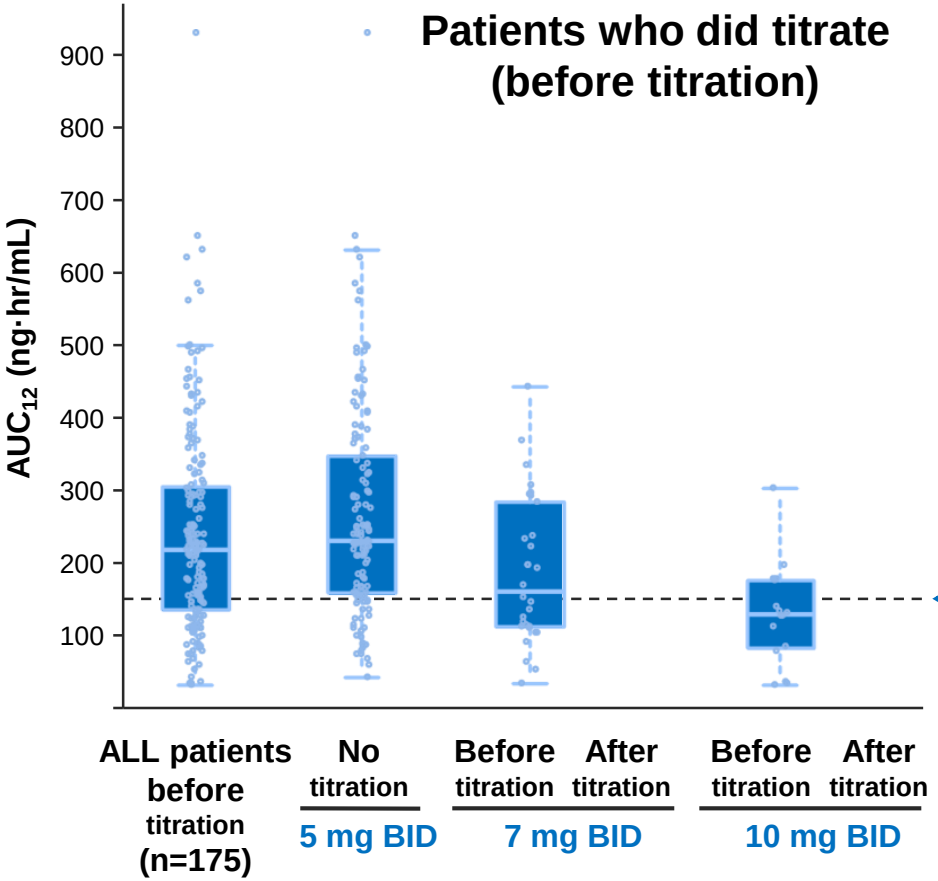
← Sub-therapeutic exposure defined as AUC_{12} <150 ng·h/mL

- **These patients were largely although not entirely above the therapeutic threshold (AUC_{12} 150 ng·h/mL) with an average value of 231**

BP = blood pressure; AE = adverse event

Rini et al. ASCO 2012 Abstract 4503

Axitinib dose titration rationale : Retrospective analysis of phase II mRCC data



Median AUC_{12} ng·hr/mL (range)	5 mg BID n=129	7 mg BID n=30	10 mg BID n=16
BEFORE titration	**231** (42–931)	**160** (32.8–443)	**129** (31.9–304)
AFTER titration			

← Sub-therapeutic exposure defined as AUC_{12} <150 ng·h/mL

- **Before titration, many if not most patients were below what is considered to be therapeutic exposure**

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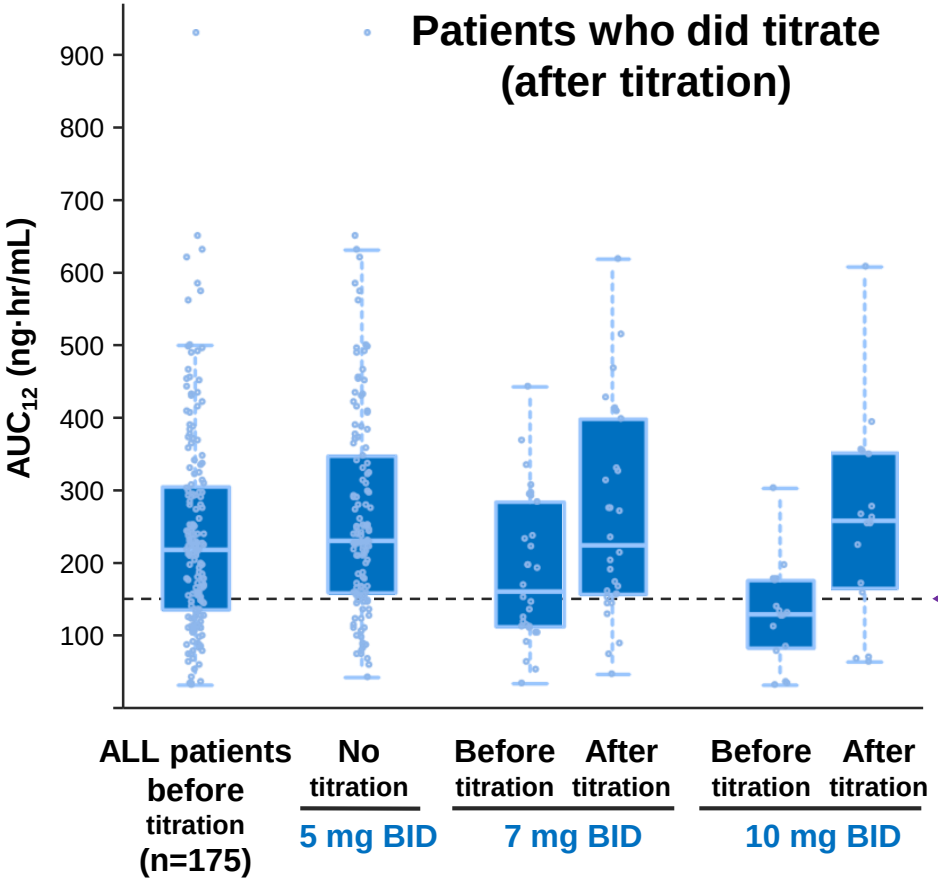
Rini et al. ASCO 2012 Abstract 4503

Axitinib dose titration rationale : Retrospective analysis of phase II mRCC data



Median AUC_{12} ng·hr/mL (range)	5 mg BID n=129	7 mg BID n=30	10 mg BID n=16
BEFORE titration	**231** (42–931)	**160** (32.8–443)	**129** (31.9–304)
AFTER titration		**225** (45.9–620)	**258** (63.9–608)

Sub-therapeutic exposure defined as AUC_{12} <150 ng·h/mL

- **After axitinib dose titration (7 or 10mg BID), most patients achieved therapeutic drug levels**

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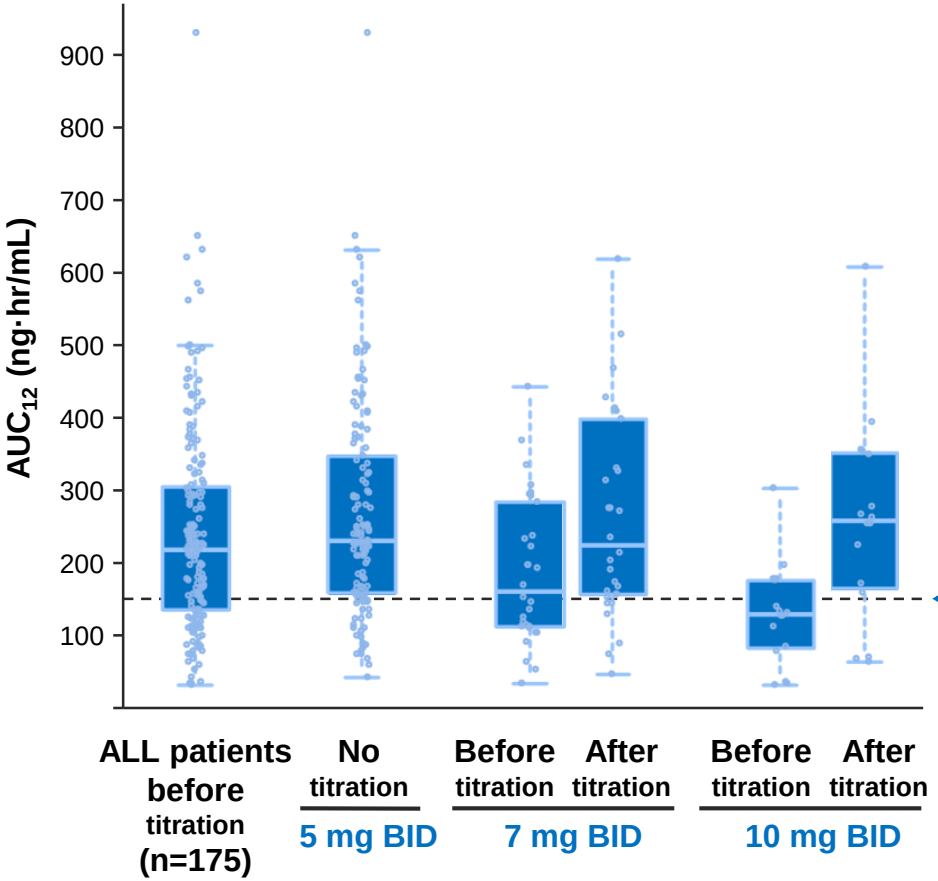
Axitinib dose titration rationale : Retrospective analysis of phase II mRCC data



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← Sub-therapeutic exposure defined as AUC_{12} <150 ng·h/mL

- **Pharmacokinetic data confirm normalization of plasma exposures with dose titration in patients who tolerate 5 mg BID**

Rini et al. ASCO 2012 Abstract 4503

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Dose-titration Scheme implemented in clinical program

Dose Escalation Algorithm in Ph 3

- Patients may have their dose increased by one dose level to maximum of 10 mg BID if they meet the following criteria within a consecutive 2-week period:
  i. patient has no adverse events > CTCAE Grade 2 related to study drug, and
  ii. patient is normotensive (BP < 150/90 mm Hg), and
  iii. Patient is not taking any anti-hypertensive medication
- Clinical judgment of the treating physician should be exercised in titrating axitinib dose.

Axitinib Dose Level	Dose
+2	10 mg BID
+1	7 mg BID
0 (Starting Dose)	5 mg BID
-1	3 mg BID
-2	2 mg BID

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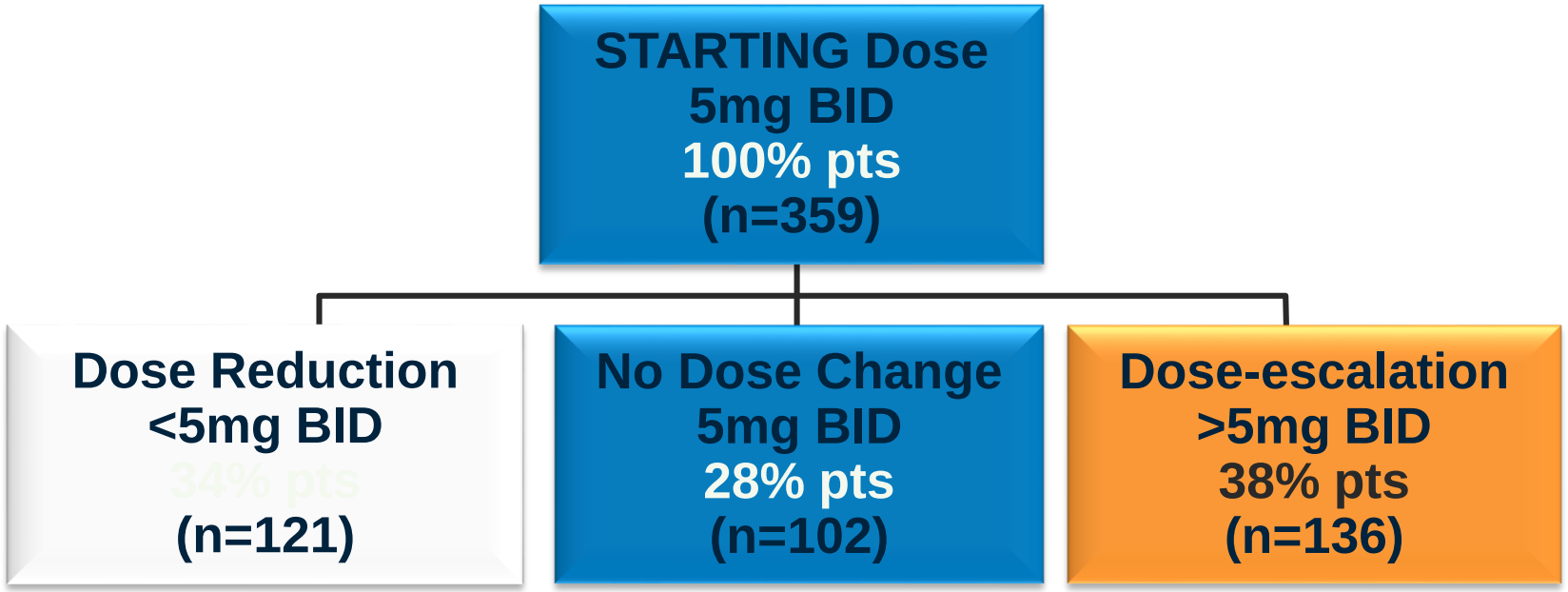
Dose titration in the axitinib Phase 3 study

Percentage of patients with dose modifications



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Motzer et al. Lancet Oncol 2013; 14:352-62

Titration based on tolerability vs. therapeutic drug monitoring (TDM)

- Phase 3 study implemented dose titration based on individual patient tolerability
- Titration based on TDM not been prospectively studied for axitinib
- No data to indicate whether concentration-driven dose-escalationwould be better than current schema based on tolerability
- Due to short plasma half-life, axitinib concentrations rise and fall significantly during a dosing interval. Also, there is minimal accumulation at steady-state. Hence unlikely that a PK sample collected at a single time will be adequate to make dosing decisions.
- Specific plasma concentration to be targeted for TDM need to be validated

Time to Initiation of Dose-Titration

Dose titration allowed after *at least* **2 consecutive weeks** of dosing at the 5 mg BID starting dose

- With 2.5-6.1 hour plasma half-life, steady state expected in 2-3 days of dosing
- Intent is to optimize drug exposure prior to first on-treatment study scan, usually ~ 6-8 weeks after study start
- Pts could come off study (due to disease progression) by week 6, and in an attempt to facilitate adequate drug exposure prior to this, dose-titration permitted as early as 2 weeks after initiation of treatment.
- Many AEs emerge within first cycle of treatment, and dose-reduction permitted **at any time** in response to drug-related AEs

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Prospective study

- A prospective, **randomized, double-blind,** study (N=200) in 1st line RCC patients was initiated to evaluate the benefit of dose-titration

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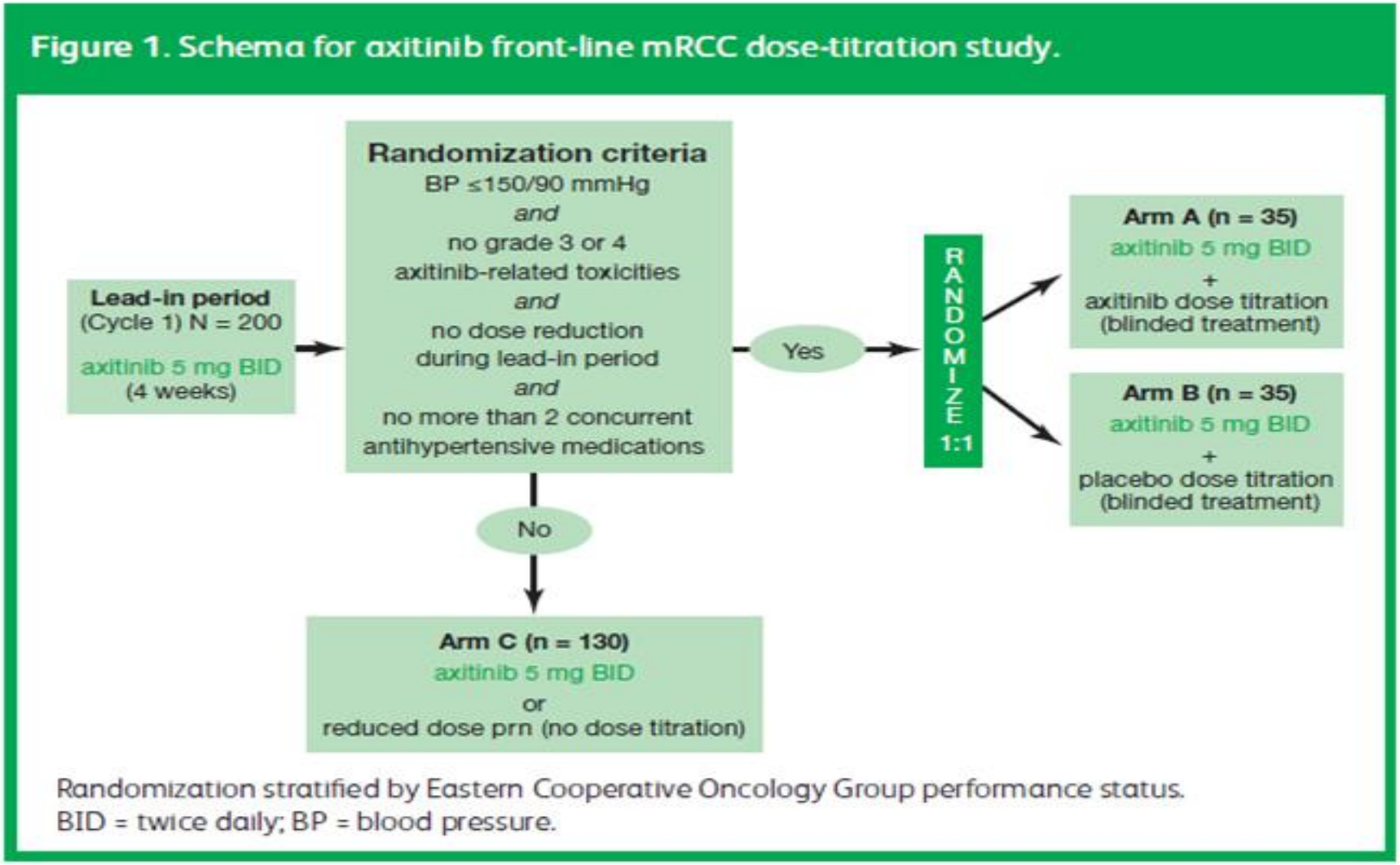
Study Design



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Rini et al, ASCO 2012, abstract 4503

Prospective Phase II study on axitinib dose titration, blood pressure and exposure in mRCC

- Primary objective
  - To compare the ORR in patients receiving axitinib plus dose titration (Arm A) vs. axitinib plus placebo (Arm B)
    - 80% power to detect ≥ 25% improvement in ORR

- Secondary objectives
  - PFS, OS, safety, duration of response, axitinib plasma pharmacokinetics, BP measurements, biomarker and pharmacogenetic analyses

Rini et al. ASCO 2012 Abstract 4503;
Rini et al. ASCO GU 2013 Abstract LBA349

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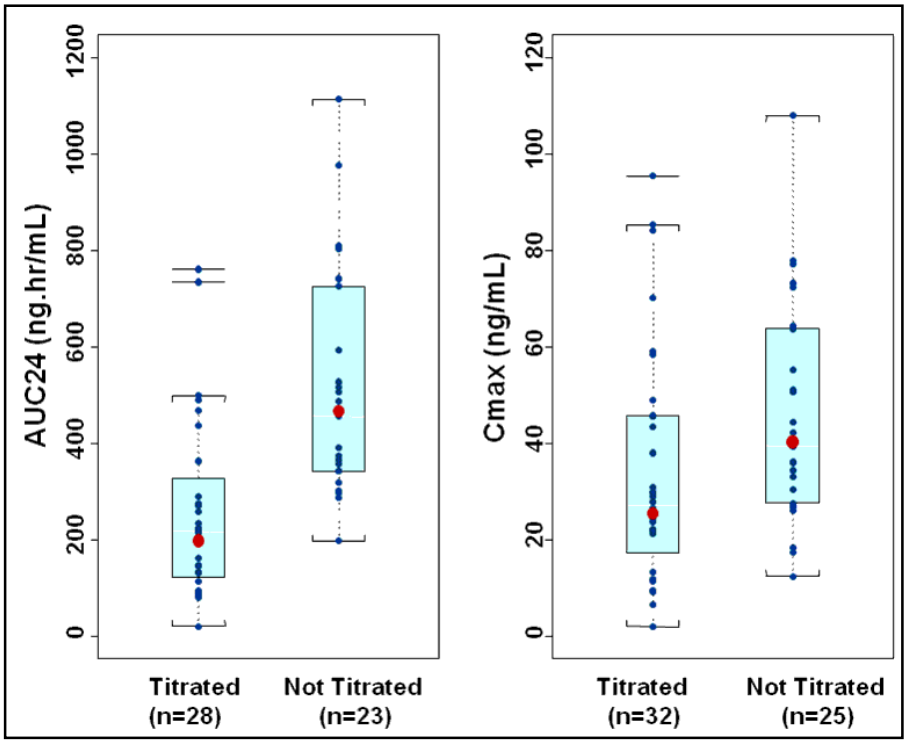
Results: Pharmacokinetics

Patients who get dose-escalated have lower exposures initially at the starting dose

	Arms A + B Eligible for dose titration	Arm C Not eligible for dose titration	*P* value
AUC_{24} ng•h/mL (n)	198 (n=28)	467 (n=23)	<0.0001
C_{max} ng/mL (n)	25.5 (n=32)	40.3 (n=25)	0.065



Axitinib pharmacokinetic parameters on Cycle 1 Day 15

AUC_{24} = area under the plasma concentration-time curve from 0 to 24 hr; C_{max} = maximum observed plasma concentration

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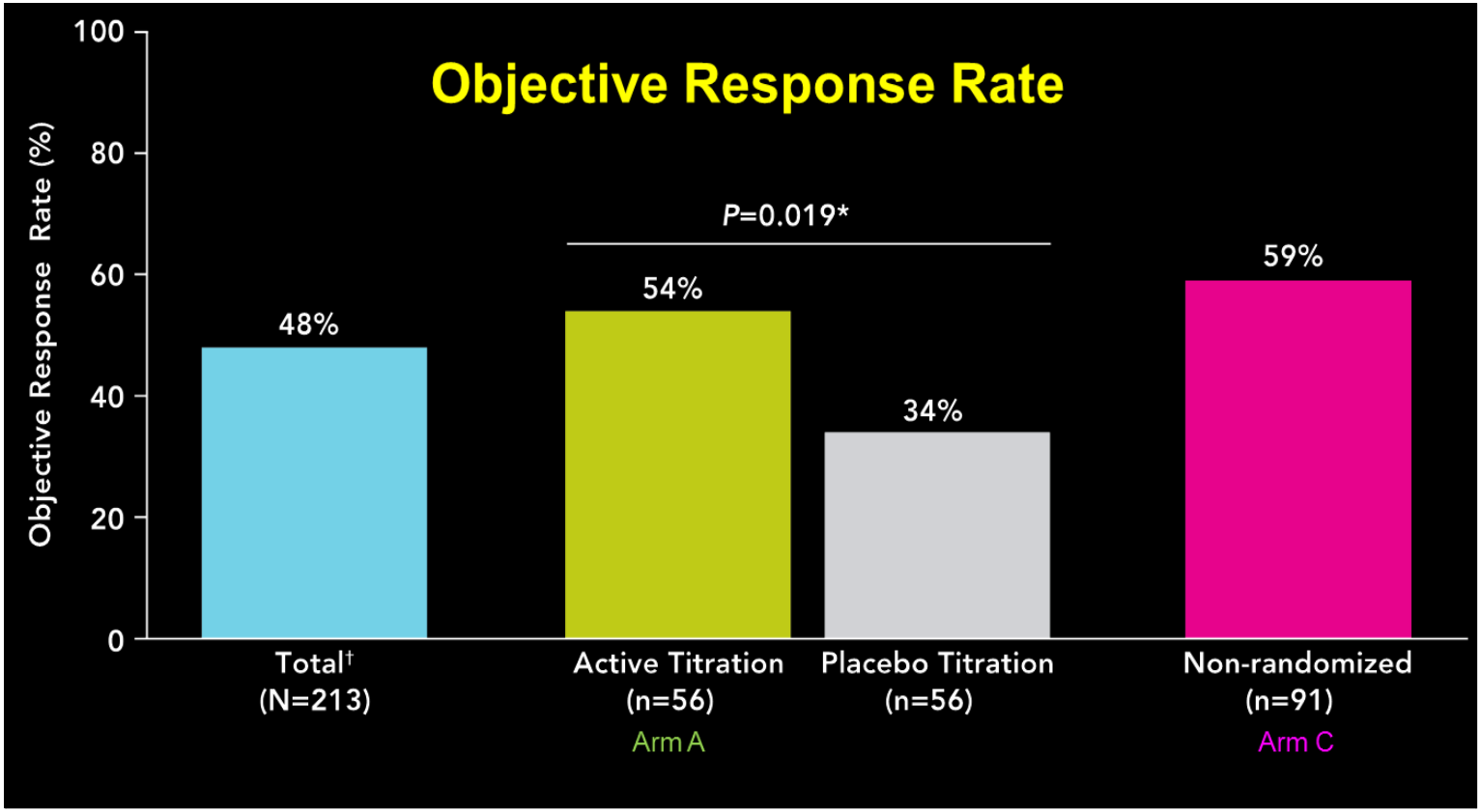
Grünwald et al. ECCO ESMO 2011 Abstract 7140

Results: Primary Endpoint (ORR)



- **Patients with axitinib dose titration had a significant increase in ORR vs.patients with placebo dose titration**
- **Patients not eligible for dose titration (Arm C) based on randomisation criteria had similar ORR than patients with dose axitinib titration (Arm A)**

* *P* value is from a 1-sided Cochran-Mantel-Haenszel test stratified by ECOG PS from randomization system.
† Includes 10 patients who withdrew during lead-in period.

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Rini et al. ASCO GU 2013 Abstract LBA349

Results: PFS and OS (secondary endpoints)

	Active Titration (Arm A) (n=56)	Placebo Titration (Arm B) (n=56)	Non-randomized (Arm C) (n=91)
PFS			
Median, mo	14.5	15.7	16.6
(95% CI)	(9.2, 24.5)	(8.3, 19.4)	(11.2, 22.5)
HR (95% CI)†; *P* §	0.85 (0.54, 1.35); *P*=0.244		
OS			
Median, mo	42.7	30.4	41.6
(95% CI)	(24.7, NE)	(23.7,45.0)	(33.0, NE)
HR (95% CI)†; †; *P* §	0.785 (0.485-1.272); *P*=0.1616		

- Although study wasn't powered to show statistical differences in PFS or OS for dose titration, there was a trend in favor of dose titration for both.

•Includes 10 patients who withdrew during lead-in period; NE = nto estimable
•† Assuming proportional hazards, HR <1 indicates a reduction in favor of active titration; HR >1 indicates a reduction in favor of placebo titration.

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival

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Rini et al. ASCO GU 2013 Abstract LBA349
Rini et al. J Clin Oncol. 2015;33 (suppl; abstr 4545).

Results: Safety

	Total* (N=213)		Active Titration (n=56)		Placebo Titration (n=56)		Non-randomized (n=91)	
Adverse Events, (%)†	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension	65	30	61	18	43	9	82	50
Diarrhea	60	8	61	13	63	4	63	9
Fatigue	49	7	45	5	46	4	54	8
Dysphonia	40	1	32	2	36	0	48	0
Decreased appetite	36	3	38	5	30	0	39	4
Hypothyroidism	35	0	32	0	23	0	45	0
Nausea	34	2	38	5	34	0	34	1
Hand–foot syndrome	32	4	32	4	18	2	44	6
Proteinuria	30	1	20	4	20	0	43	0

* Includes 10 patients who withdrew during lead-in period.
† Treatment-emergent, all-causality adverse events reported in >30% of treated patients.

Rini et al. ASCO GU 2013 Abstract LBA349

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Prospective Study: Conclusions

- Patients titrated with active axitinib
  - Experienced a significant improvement in ORR (54% vs. 34%; *P*=0.019)
  - Experienced a 15% reduction in the risk of disease progression/death and 21% reduction in risk of death
    - This study was not powered to compare PFS or OS between treatment arms
- Patients with presumed optimal drug dose (Arm C):
    - Demonstrated 59% ORR
- Increases in the dose of INLYTA in patients in Arm A were not correlated with any new or unexpected adverse events
- Clinical parameters for dose titration based on individual tolerability are useful for identifying pts with sub-therapeutic axitinib exposure at 5-mg BID starting dose

Acknowledgments

- Patients and families for their participation in clinical trials
- Study personnel at participating clinical sites
- All investigators who participated in axitinib trials, and in particular, Dr Brian Rini
- Axitinib Clinical Development team
  - In particular, Glen Andrews, Angel Bair, Ying Chen, May Garrett, Sinil Kim, Kourosh Parivar, Alison Russell, Jamal Tarazi, Michael Tortorici

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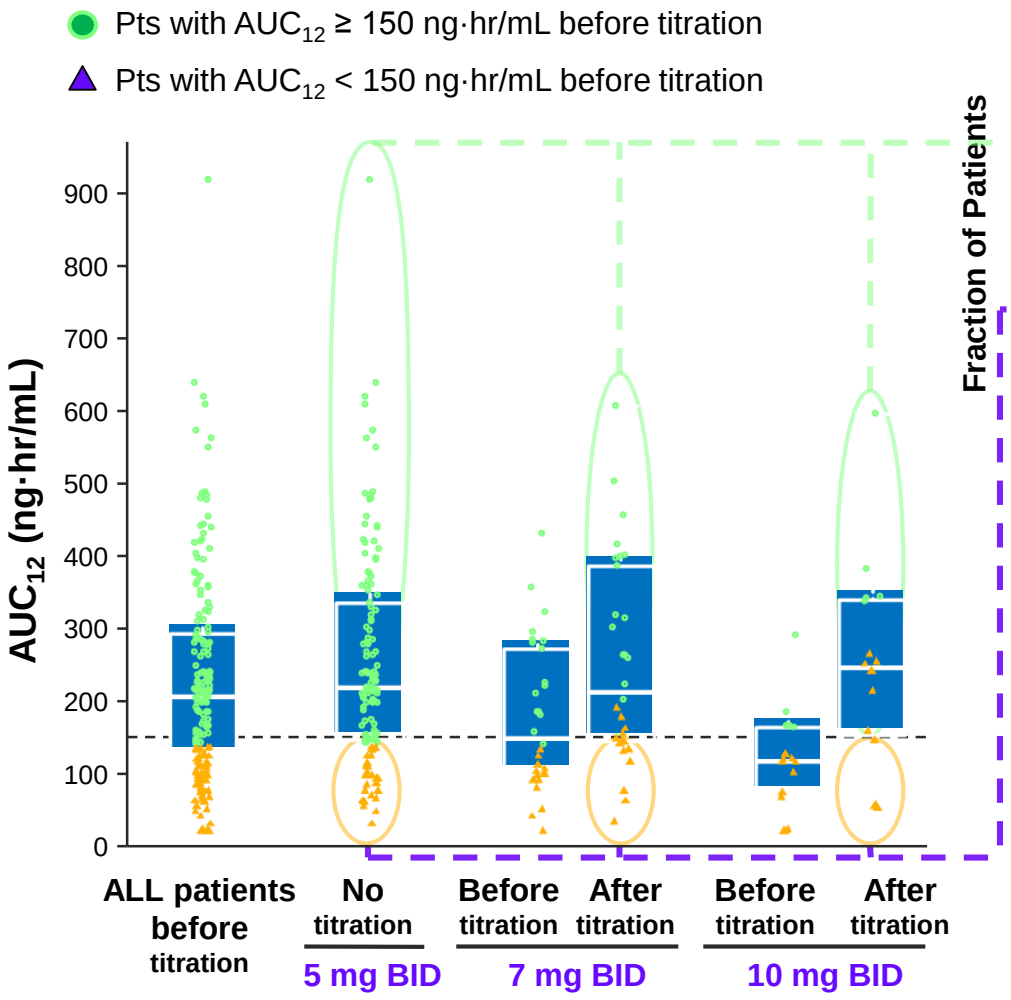
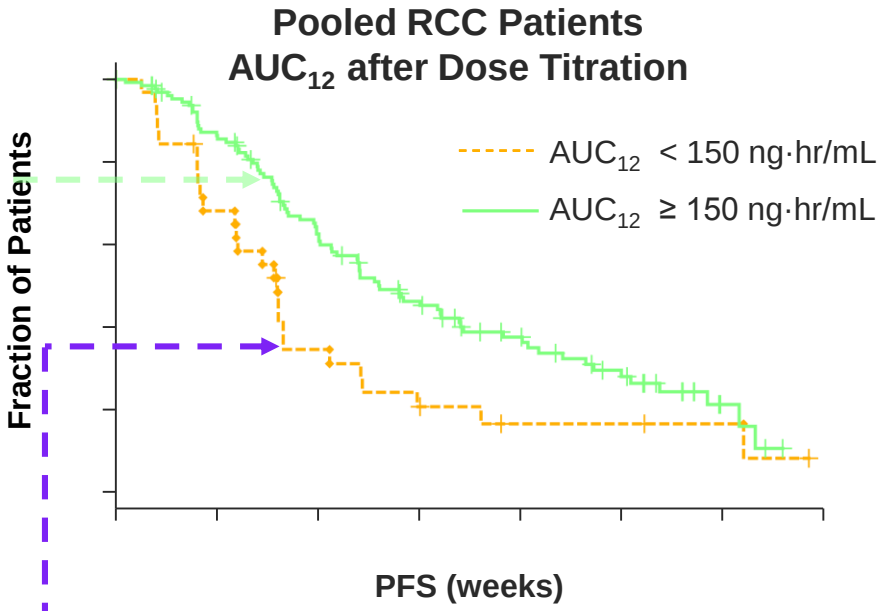
BACKUP slides

Axitinib dose titration rationale : Retrospective analysis of phase II mRCC data





mPFS, wks (95% CI)		HR (95% CI)
AUC_{12} < 150 ng·hr/mL	AUC_{12} ≥ 150 ng·hr/mL	
32 (24, 48) n=36, 26	52 (43, 69) n=139, 83	0.56 (0.359, 0.874)

n=number of patients meeting AUC criterion, number of PFS events assessed by investigator

AUC_{12} = area under the plasma concentration-time curve from 0 to 12 hr

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Rini et al. ASCO 2012 Abstract 4503

Prospective Dose Titration Study
Baseline Patient Characteristics

Characteristic	Axitinib (N=213)
Mean age, yr (range)	61 (28-87)
Gender, n (%)	
Male / Female	143 (67) / 70 (33)
Race, n (%)	
White	162 (76)
Black	2 (1)
Asian	46 (22)
Other	3 (1)

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Rini et al, ASCO 2012, abstract 4503

Clinical Outcome According to Diastolic Blood Pressure on Cycle 1 Day 15

Blood pressure parameter		mPFS, mo	ORR	AUC_{12}, ng·h/mL[a]
ΔdBP	≥10 mmHg, n=39	16.7	59%	176
	<10 mmHg, n=22	8.3	45%	63
ΔdBP	≥15 mmHg, n=20	19.3	60%	235
	<15 mmHg, n=41	11.1	51%	93
dBP	≥90 mmHg, n=17	22.5	65%	195
	<90 mmHg, n=46	13.7	50%	110

[a] Geometric mean

dBP = diastolic blood pressure (per ambulatory blood pressure monitoring); ΔdBP = change in dBP from baseline; mPFS = median progression-free survival; ORR = objective response rate

Rini et al, ASCO 2012, abstract 4503

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