Cabozantinib (Cometriq®)

Workshop dose escalation
EMA
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Phase 3 Study XL184-301 (EXAM): Design

Cabozantinib (XL184) is a multi-targeted TKI against VEGFR, RET, MET

- Design: multicenter, randomized, double blind, parallel arm
- Population: patients with progressive, unresectable locally advanced or metastatic MTC
- Arms: cabozantinib 175 mg QD (capsule formulation) vs placebo
  - 175 mg QD was the MTD established in Phase 1
  - Up to two dose reductions allowed (to 125 mg QD and 75 mg QD)
- Primary endpoint: PFS per blinded independent review
- Key secondary endpoints: OS, ORR

A total of 330 pts randomized (2:1 cabozantinib:placebo)

Note: all doses expressed herein as salt weights; doses in Cometriq package insert expressed as freebase equivalent weights (eg, 175 mg salt weight = 140 mg freebase weight)

Phase 3 Study XL184-301 (EXAM): Results

Efficacy

PFS:	11.2 months (cabozantinib) vs 4.0 months (placebo): HR 0.28, p<0.001
ORR:	28% (cabozantinib) vs 0% (placebo), p<0.001
Interim OS:	Non-significant trend toward improvement; final analysis pending Large improvement observed in subjects with RET M918T mutation

Study treatment - **cabozantinib arm**

- Median exposure: 204 days (vs 105 days placebo) at time of CSR cutoff
  - Had increased to 315 days for the cabozantinib arm with further follow-up
- 79% had one dose reduction, 41% two dose reductions
- Median time to dose reduction: 43 days
- Dose intensity: 63%
- Dose temporarily withheld in 65% of subjects due to AEs
- Treatment discontinued due to AE: 16% (vs. 8% in placebo arm)
- The most frequent AEs leading to a modification were PPE, diarrhea, fatigue, weight decreased, decreased appetite, and nausea.
  - These were also the most frequent AEs observed in the cabozantinib arm

Based on these data in MTC, cabozantinib was approved in US in 2012 and EU in 2014

A post-marketing study is required to explore a lower starting dose.

Post Marketing Study XL184-401 (EXAMINER): Design

- Goal: Evalute non-inferiority of lower-dose regimen to approved regimen
  - Non-inferiority margin chosen to preserve 50% of the PFS benefit cabozantinib demonstrated vs placebo in the Phase 3 study
- Design: multicenter, randomized, double blind, parallel arm
- Population: same as the Phase 3 study (MTC)
- Arms: cabozantinib 175 mg QD vs 75 mg QD
- Primary endpoint: PFS per blinded independent review
- Safety endpoints: selected AEs, dose reduction rate
- Sample size: 188 patients randomized 1:1 to each dose level

Cabozantinib in MTC

Questions:

- Was the MTD identified correctly?
- Was the MTD the appropriate Phase 3 dose?

Phase 1 Study XL184-001: Design

- First study of cabozantinib in humans (patients with various advanced cancers)
- 3+3 design to establish MTD, evaluate PK, and explore preliminary anti-tumor activity
- 28 days treatment and observation period for DLT
- Dose escalation cohorts to determine MTD
  - Explored escalating doses and two different schedules (intermittent and daily)
  - Capsule formulation was in development so initially evaluated suspension
- MTD Expansion Cohort (n=29), motivated by responses observed in MTC patients in prior cohorts
  - Primarily patients with MTC (25 of 29)
  - Capsules given on continuous daily schedule
  - Fixed dose level: 175 mg QD
  - MTD was the dose, regimen, and dosage form used in Phase 3

Phase 1 Study XL184-001: DLTs

Cohort(s)	Dose regimen	# DLTs	DLTs	Status
Cohorts 1-8	≤7.68mg/kg, suspension intermittent	0 / 29		
Cohort 9	11.52 mg/kg, suspension Intermittent	2 / 3	PPE AST elevations lipase elevation	MAD for intermittent suspension
Cohort 10	175mg daily suspension	0 / 3		MTD for daily suspension
Cohort 11	265mg daily suspension	2 / 10	mucositis	MAD for daily suspension
Cohort 12	175mg daily capsules	0 / 6		MTD for daily capsules
Cohort 13	250mg daily capsules	2 / 5	PPE AST elevation	MAD for daily capsules

MAD, maximum administered dose; MTD, maximum tolerated dose

Cabozantinib Plasma PK Summary (daily dosing)

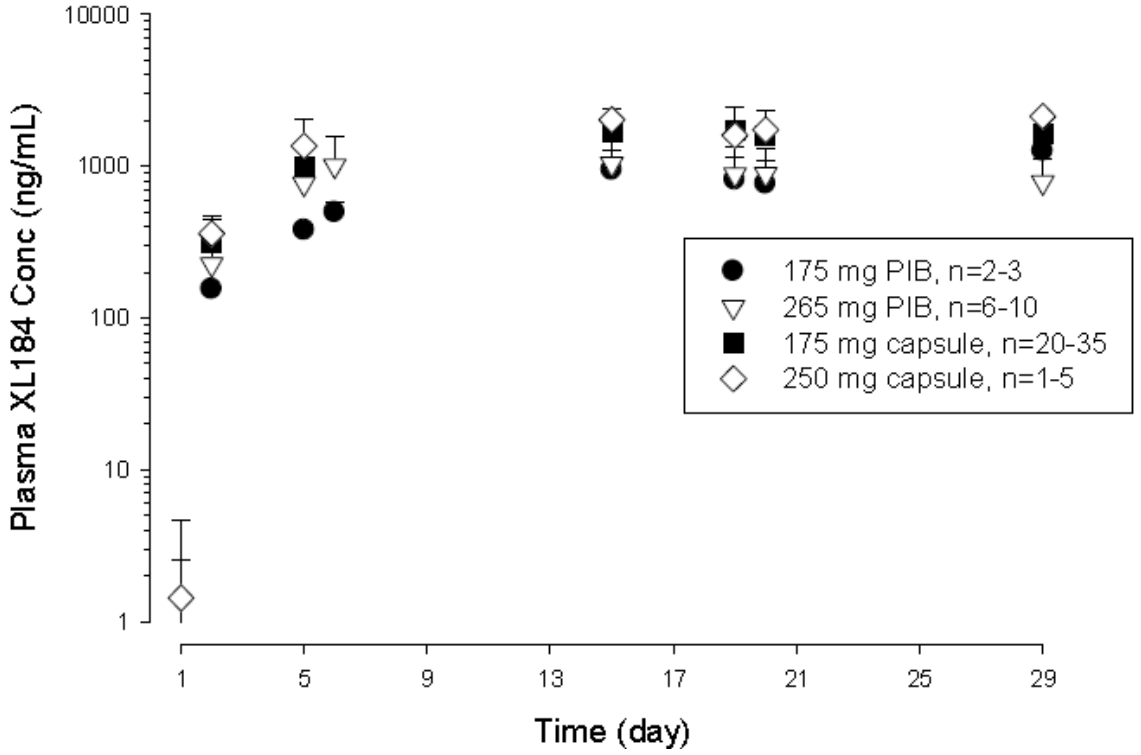
- Long half-life leads to accumulation with repeated dosing
- Steady state concentrations are variable between subjects

Parameter	Value
Effective half-life[a]	55 hours (predicts steady state)
Terminal half-life[b]	~120 hours (predicts washout)
Steady state[b]	by Day 15
Plasma accumulation[b]	4- to 5-fold
C_{min}/C_{max}[c]	0.64
Intersubject Variability (AUC_{0-24})[b]	38 - 43%

[a] Based on a population pharmacokinetic analysis of pooled qd data from XL184-001, XL184-201 and XL184-301 (1-compartment model).
[b] Based on a noncompartmental analysis of steady state data in multiple studies.
[c] Study XL184-301, uninterrupted 175 mg/day dosing.

Cabozantinib steady state achieved by Day 15, prior to the end of the DLT observation period (Day 28)

. Plasma cabozantinib trough concentrations (mean +SD) after daily dosing of 175 and 265 mg (powder-in-bottle [PIB] suspension) and 175 mg and 250 mg (capsule) for 29 days (Study XL184-001)



Phase 1 Study XL184-001: Results

- DLTs included elevated aminotransferases, elevated lipase, mucosal inflammation, and PPE
- Daily dosing schedule chosen to maintain minimum plasma concentrations above a target threshold level thought to be effective for target inhibition
- Capsule formulation was chosen for Phase 3 and eventual commercialization
- MTD for daily dosing of capsules established as 175mg based upon 28 day observation period
- At MTD (n=35)
  - median dose intensity was 69% and median duration of treatment was 197 days (429 days among tumor responders)
  - 69% treated at the MTD required a dose modification (at any time) due to an AE
  - 31% of subjects discontinued study treatment due to an AE
- Long median duration of treatment at MTD suggested that AEs could be adequately managed in most subjects by dose modifications and supportive care

Comparison of Phase 1 and Phase 3 Studies

Parameter	Phase 1 Study XL184-001 Treated at MTD 175mg caps daily N=35	Phase 3 Study XL184-301 175mg caps daily N=219
DLTs within first 28 days	0 of 6 in escalation cohort	NA
Median exposure	197 days	315 days
Median dose intensity	69%	63%
Required dose reduction	66%	79%
AEs leading to reduction	Diarrhea, fatigue, PPE, decreased appetite, rash, nausea, vomiting	Diarrhea, fatigue, PPE, decreased appetite, rash, nausea, weight decrease, stomatitis, asthenia
Discontinued due to AE	31%	16%
AEs leading to d/c	Sepsis/infection, nausea, fatigue, pneumonia, PPE, diarrhea, anorexia, renal failure, pulmonary embolism; increased transaminase	Lipase increase, hypocalcemia, PPE, diarrhea, nausea, vomiting, pancreatitis, fatigue, decreased appetite, tracheal fistula, hypertension
ORR	28%	28%
PFS	Not evaluated	HR=0.28, $p<0.001$

Closer look at Phase 3 Study XL184-301 (EXAM)

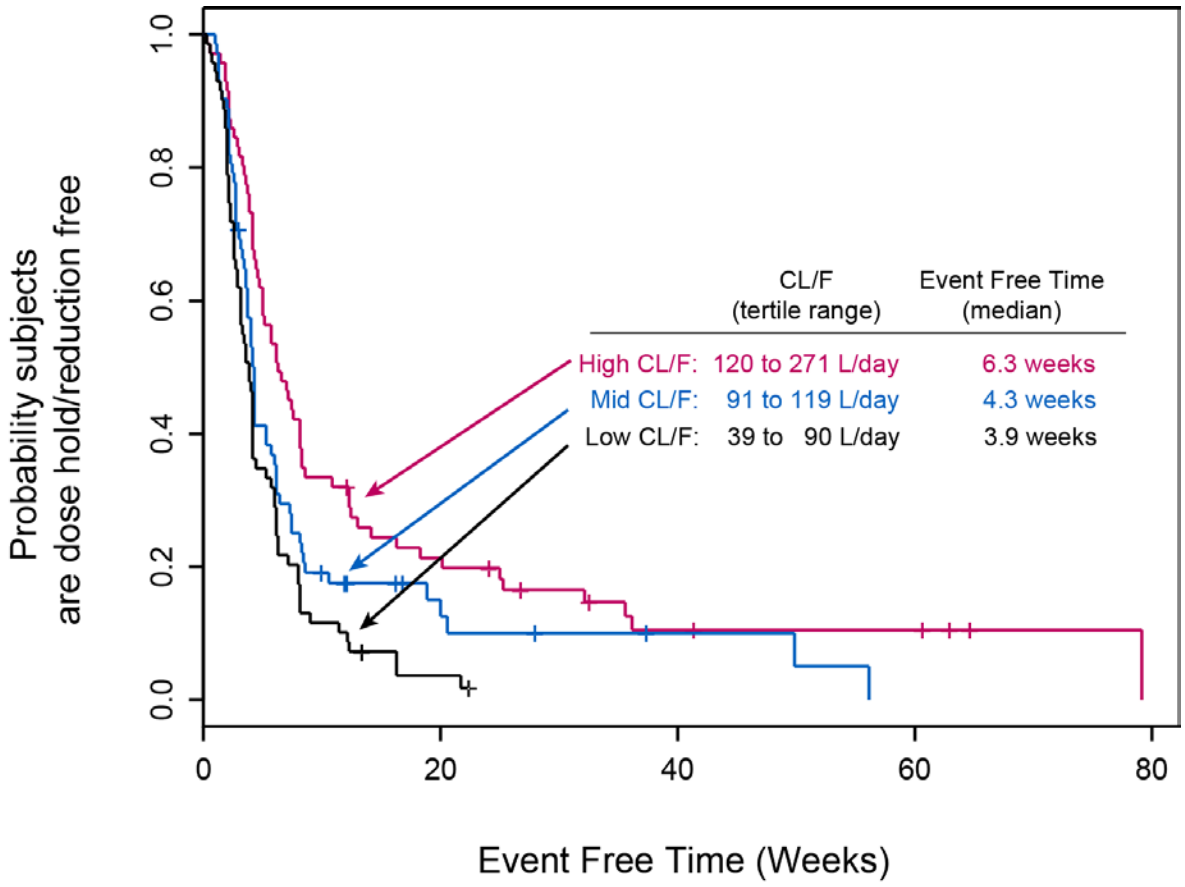
Despite the high frequency of dose reductions, a subset of subjects were able to tolerate the starting dose of 175mg QD:

Dose level	Proportion who received dose level as final dose level	Median duration of treatment
175mg QD (starting dose level)	25%	178 days
125mg QD (first reduced level)	33%	307 days
75mg QD (second reduced level)	42%	347 days

While duration of treatment was longer for subjects whose last dose was lower than the starting dose, the efficacy of lower starting doses is unknown.

Individual cabozantinib oral clearance (CL/F) values[1] vary over a large range (39 – 271 L/day)

- Low CL/F associated with earlier dose holds/reductions
- High CL/F associated with maintaining the initial 175 mg dose longer
- Patients with a low intrinsic CL/F will have higher exposure if the starting dose is maintained



[1] CL/F = Individual predicted oral clearance from PopPK model.

Summary

- Capsule MTD of 175 mg QD was technically well-determined per conventional methods in Phase 1
- 0 DLT among 6 patients in the Phase 1 175mg QD capsule dose escalation cohort during a 28 day observation period, however:
  - A high rate of dose reduction (66%) was observed among 35 patients treated at this dose in Phase 1
  - A high rate of reduction from this dose was also observed in Phase 3 (79%)
- Events that lead to dose reduction are generally tolerability issues rather than serious safety concerns
  - Cabozantinib is associated with other less-frequent serious safety risks typical of VEGFR agents that may be unrelated to dose level in the therapeutic range
- In Phase 3, long median duration of treatment (315d) and relatively low rate of discontinuation due to AE (16%) suggest that dose-related toxicities were well-managed with dose modifications and supportive care
- The regimen of a high starting dose with clear dose reduction guidance allows all patients to be exposed to highest dose level and to be titrated to their individual level of tolerance, and was associated with significantly prolonged PFS

General Discussion on Dose Finding in Oncology

- Instead of the traditional approach of establishing MTD on cohorts of 3-6 subject with short observation periods, should final MTD be based upon DLT and/or dose reduction rate observed in:
  - a Phase 1 expansion cohorts of 20-30 subjects?
  - a longer observation period based upon expected duration of treatment for planned indication(s)?

- Is it feasible to run Phase 3 studies with multiple arms for different dose levels of the experimental agent?

- Is the cabozantinib outcome necessarily a “problem”?
  - For fatal diseases, perhaps a high initial dose with dose reductions as needed, even if frequent, is an acceptable approach
  - Similar observations for other TKIs (e.g erlotinib, sunitinib, vandetanib)
  - Requiring post-marketing studies of different regimens of an approved agent is a reasonable option once efficacy has been definitively established

- Is the MTD the appropriate Phase 3 dose, or should a “minimum effective dose (MED)” be established?
  - Is it practical to identify a MED in Phase 1 or 2, which would require multiple arms of relatively large size to essentially explore non-inferiority among doses?
  - Are there strong enough surrogate endpoints suitable for finding an MED in Phase 1 or 2, in a reasonable timeline and with reasonable cost, that would predict treatment effect on the registration endpoint?