Head and Neck Cancer Post ASCO 2012: Three steps backward, one leap forward

EMORY
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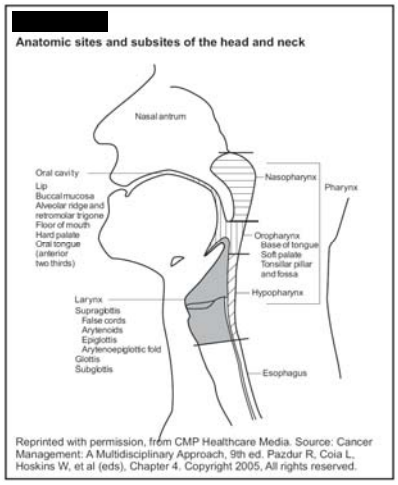
Disclosure and Conflict of Interest Management

- **I have no financial conflicts of interest.**
- **I have received research funding from Sanofi-Aventis, BMS, Onyx, Ligand , Oxigene, Pfizer, Genentech, and Novartis for investigator initiated research in drug development and head & neck, and lung cancers over the last 15 years.**
- **I have received more than ten-fold more peer reviewed government funding (NCI, DoD) than total pharmaceutical funding over the last 15 years.**
- **My opinions on approaches to the treatment of lung cancer are my own and, while evidence based, are potentially controversial.**

Head and Neck Cancer: Heterogeneity

- Heterogeneous group of cancers of varying primary sites—95% are SCC
  - Oral cavity
  - Oropharynx/hypopharynx
  - Larynx
  - Nasopharynx
  - Paranasal sinuses
  - Lip
  - Salivary glands

Anatomic Sites and Subsites of the Head and Neck

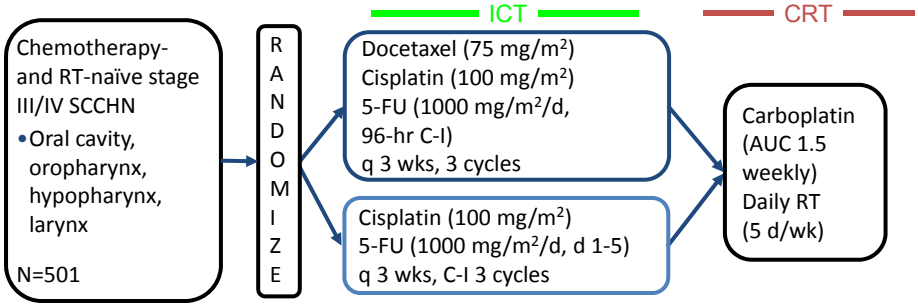


Devlin. *Expert Rev Anticancer Ther*. 2007;7:331; Patel. *CA Cancer J Clin*. 2005; 55:242.

Head and Neck Cancer: Current Standards of Care

- Limited- or early-stage disease (stage I and II): 40% of patients
  - Surgery or radiation alone
- Locally advanced disease (stage III and IV)
  - Newly diagnosed, and resectable or unresectable: platinum-based concomitant CRT and sequential therapy
  - Recurrent: surgery followed by radiation if resectable; concomitant CRT if unresectable
  - Metastatic: combination or single-agent chemotherapy for patients with good PS; best supportive care for patients with poor PS

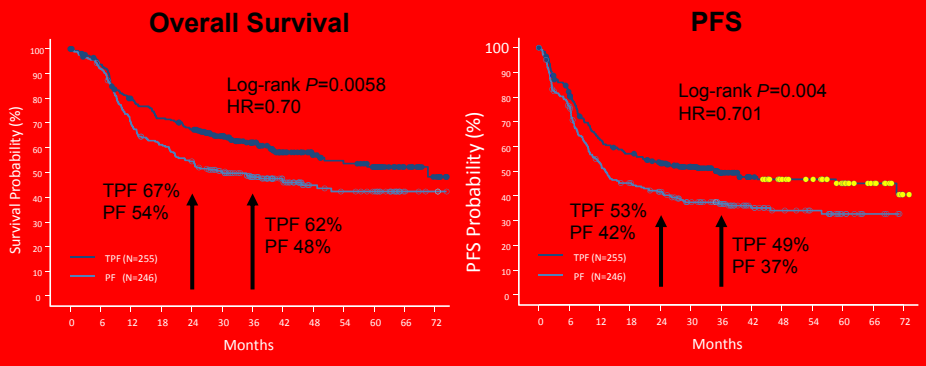
TAX 324 Phase III Trial of Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN



Response	TPF N=255 (95% CI)	PF N=246 (95% CI)	*P* Value
ORR (ICT)	72% (65.8-77.2)	64% (57.9-70.2)	0.07
CR (ICT)	17% (12.1-21.6)	15% (10.8-20.1)	0.66
ORR (ICT+CRT)	77% (70.8-81.5)	72% (65.5-77.1)	0.21
CR (ICT+CRT)	35% (29.4-41.5)	28% (22.5-34.1)	0.08

AUC=area under the curve.
Posner. *N Engl J Med.* 2007;357:1705.

TAX 324: Results



- TPF significantly improves survival and PFS compared with PF in an ICT regimen followed by CRT
- Survival advantage of TPF versus PF retained at 5 year follow-up
  - OS: 71 months versus 35 months (HR=0.74; *P*=0.013)
  - PFS: 38.1 months versus 13.2 months (HR=0.75; *P*=0.014)

Lorch. *ASCO.* 2010 (abstr 5512); Posner. *N Engl J Med.* 2007;357:1705.

TAX 324: Toxicity

	Grade 3/4 Toxicity	TPF	PF
During ICT N=251 TPF, 243 PF	Stomatitis	21%	27%
	Nausea	14%	14%
	Lethargy	5%	10%
	Vomiting	8%	10%
	Diarrhea	7%	3%
	Anorexia	12%	12%
	Neutropenia	84%	56%
	Febrile neutropenia	12%	7%
	Neutropenic infection	12%	9%
During CRT N=203 TPF, 184 PF	Stomatitis	37%	38%
	Dysphagia	23%	24%
	Mouth, nose dryness	5%	4%
	Nausea	6%	6%
	Rash/itch	5%	2%

Posner. *N Engl J Med.* 2007;357:1705.

Doc**e**taxel Based **C**hemoradiotherapy Plus or Minus **I**nduction Chemotherapy to **D**ecrease **E**vents in Head and Neck Cancer

(**DeCIDE**)

Results of a Phase III Multicenter, International Study

Ezra E. W. Cohen, Theodore Karrison, Masha Kocherginsky, Chao H. Huang, Mark Agulnik, Bharat B. Mittal, Furhan Yunus, Sandeep Samant, Bruce Brockstein, Luis E. Raez, Ranee Mehra, Priya Kumar, Frank Ondrey, Tanguy Y. Seiwert, Victoria M. Villaflor, Daniel J. Haraf, Everett E. Vokes

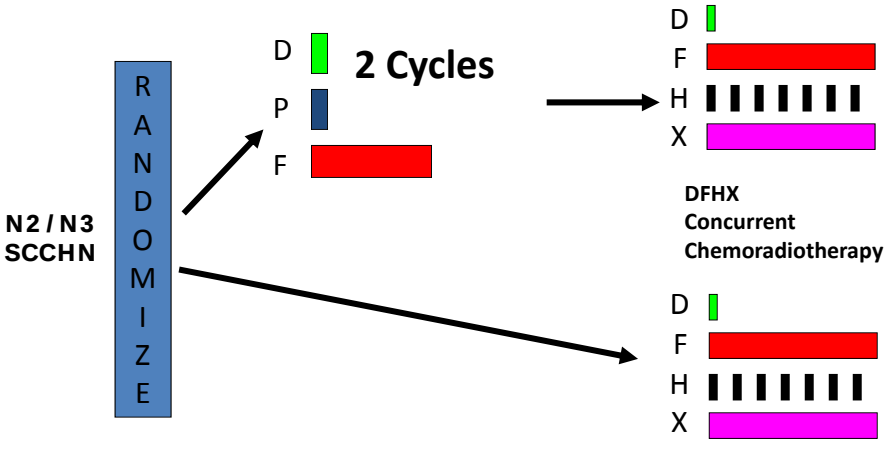
Sponsored by University of Chicago
Funded by a grant from Sanofi-Aventis

Background

- Subjects with N2C-N3 disease are at highest risk for distant failure[1]
- MACH-NC results[2]
  - IC improves OS by 2.4%, HR = 0.96 (0.9;1.02), p=0.18
    - CDDP/5FU studies demonstrate HR = 0.9 (0.82;0.99)
- TAX 323/324 demonstrate TPF superior to PF[3]
  - Both studies demonstrate improvement in overall survival
  - TPF established as a standard of care

[1]Ann Oncol 15:1179; [2]Radiother Oncol 92:4; [3]NEJM 357:1695; [3]NEJM 357:1705

DeCIDE Schema



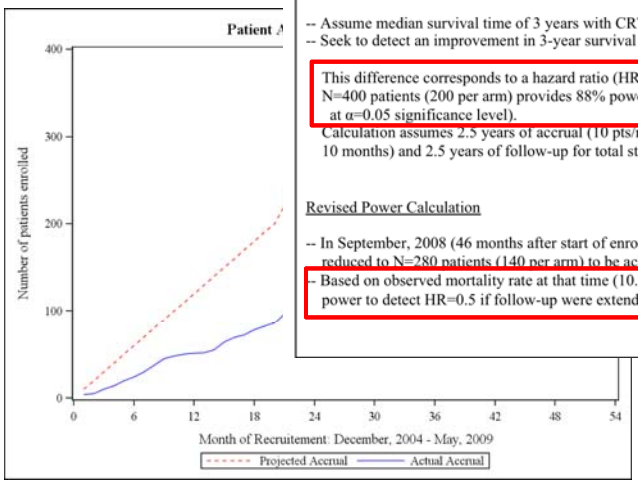
TPF: Docetaxel (75 mg/m²) + Cisplatin (75 mg/m²) + 5-FU (750 mg/m², 120 hours) Q3 weeks

DFHX: Docetaxel + Hydroxyurea + 5FU + Hyperfractionated RT

DFHX Schema

Docetaxel (25mg/m^2)	
5-Fluorouracil (600mg/m2/day)	
Hydroxyurea (500mg PO 12h)	
XRT (150 cGy bid)	XX XX XX XX XX
Day	1 2 3 4 5 6 7 8 9 10 11 12 13 14

Subject Accrual and Sample Size



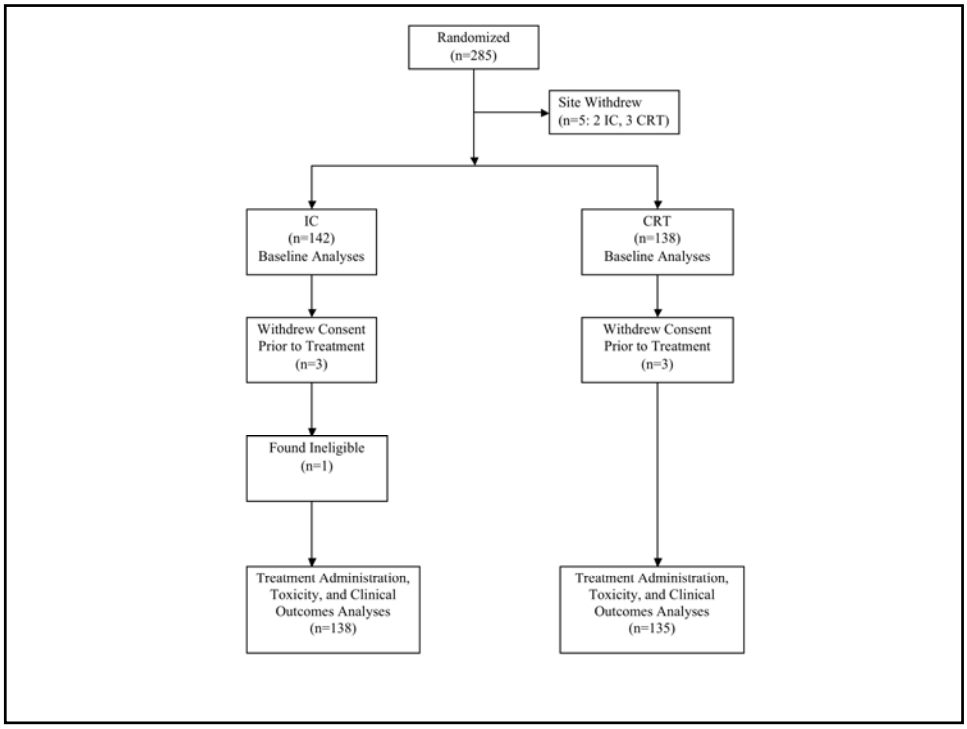
Initial Power Calculation

-- Assume median survival time of 3 years with CRT (3-year survival rate of 50%)
-- Seek to detect an improvement in 3-year survival rate to 65% with IC

This difference corresponds to a hazard ratio (HR) = 0.625.
N=400 patients (200 per arm) provides 88% power (two-sided logrank test at α=0.05 significance level).
Calculation assumes 2.5 years of accrual (10 pts/mo for 20 months; 20 pts/mo for 10 months) and 2.5 years of follow-up for total study duration of 5 years.

Revised Power Calculation

-- In September, 2008 (46 months after start of enrollment), target sample size was reduced to N=280 patients (140 per arm) to be achieved by May, 2009.
-- Based on observed mortality rate at that time (10.2%/year) this would provide 80% power to detect HR=0.5 if follow-up were extended to July, 2012.



Baseline Distributions by Treatment Arm

Variable	IC (n=142)	CRT (n=138)	p-value
Age (mean, range)	56.6 (31-74)	57.1 (38-82)	0.60
Gender			0.10
Male	114 (80.3%)	121 (87.7%)	
Female	28 (19.7%)	17 (12.3%)	
Karnofsky PS[b]			0.59
70-80	19 (13.7%)	22 (16.3%)	
90	53 (38.1%)	56 (41.5%)	
100	67 (48.2%)	57 (42.2%)	
Tumor Site[c]			0.55
Oropharynx	87 (61.7%)	76 (55.1%)	
Oral Cavity	21 (14.9%)	19 (13.8%)	
Hypopharynx	10 (7.1%)	9 (6.5%)	
Other	12 (8.5%)	19 (13.8%)	
Unknown	11 (7.8%)	15 (10.9%)	

No. missing: [a]n=2, [b]n=6, [c]n=1, [d]n=4, [e]n=5, [f]n=8

Toxicity

Most common grade 3/4 AEs occurring during Induction (N=136)

Toxicity	N	(%)
ANC	49	(36.0)
WBC	38	(27.9)
Neutropenia	13	(9.6)
Mucositis (Clinical)	12	(8.8)
Fatigue	10	(7.4)
Anorexia	10	(7.4)
GlucHyper	10	(7.4)
Mucositis (Functional)	9	(6.6)

Most common grade 3/4 AEs occurring during CRT (N=258)

	I+CRT (n=125)		CRT Only (N=133)		Total		
Toxicity	N	(%)	N	(%)	N	(%)	P-value
Mucositis (Clinical)	63	(50.4)	63	(47.4)	126	(48.8)	0.34
Mucositis (Functional)	58	(46.4)	56	(42.1)	114	(44.2)	0.78
Dermatitis	22	(17.6)	31	(23.3)	53	(20.5)	0.27
WBC	32	(25.6)	15	(11.3)	47	(18.2)	0.0041*
Dysphagia	15	(12.0)	20	(15.0)	35	(13.6)	0.55
Infection	14	(11.2)	19	(14.3)	33	(12.8)	0.33
Anorexia	14	(11.2)	18	(13.5)	32	(12.4)	0.64
ANC	17	(13.6)	5	(3.8)	22	(8.5)	0.025
Dehydration	12	(9.6)	9	(6.8)	21	(8.1)	0.80
NOSPain	13	(10.4)	8	(6.0)	21	(8.1)	0.15
GlucHyper	10	(8.0)	7	(5.3)	17	(6.6)	0.45
TumorPain	6	(4.8)	8	(6.0)	14	(5.4)	1.00
Nausea	7	(5.6)	6	(4.5)	13	(5.0)	0.56

Response Rate
Induction Chemotherapy

Response to Induction Chemotherapy	
CR	10 (8.8%)
PR	63 (55.3%)
SD	26 (22.8%)
PD	5 (4.4%)
Resected	6 (5.3%)
Died	4 (3.5%)

64%

No. patients randomized to induction therapy: 142
No. patients with non-measurable disease: -11
No. withdrawn before beginning therapy: -4
No. patients with missing or inconsistent lesion specification: -13
No. assessable: 114

Response Rate Chemoradiotherapy

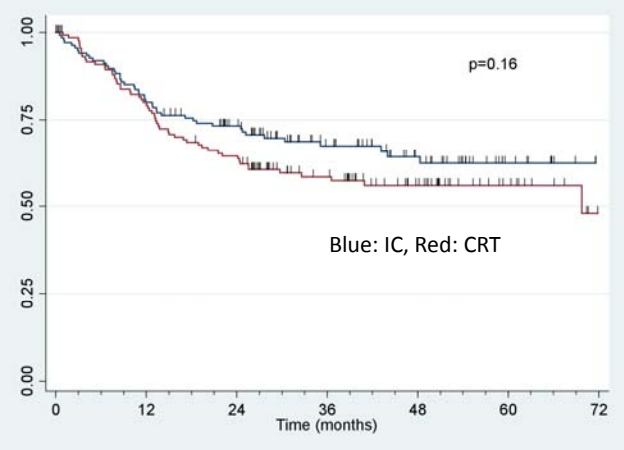
Best Response	I+CRT arm	CRT arm
CR	17 (18.9%)	16 (15.1%)
PR	50 (55.6%)	59 (55.7%)
SD	3 (3.3%)	11 (10.4%)
PD	7 (7.8%)	8 (7.6%)
Resected	4 (4.4%)	8 (7.6%)
Died	9 (10.0%)	4 (3.8%)

	Total	I+CRT	CRT
No. patients randomized:	280	142	138
No. patients with non-measurable disease:	-19	-11	- 8
No. withdrawn before beginning therapy	- 6*	-4	- 2*
No. patients with missing or inconsistent lesion specification:	- 59	-37	- 22
No. assessable:	196	90	106

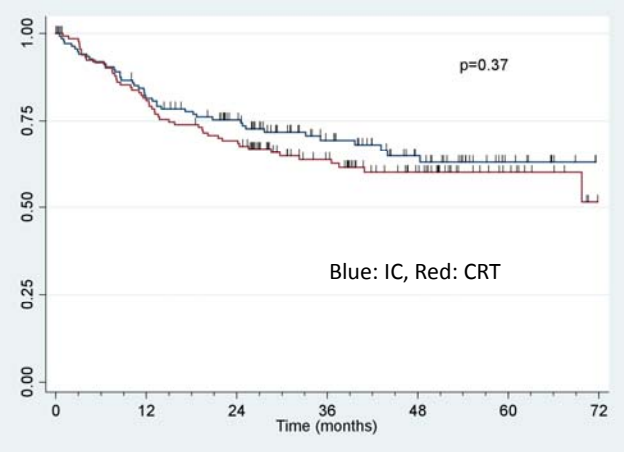
*One patient with non-measurable disease also withdrew

These summaries are preliminary. The inconsistent lesion specifications for these data have note yet been reviewed.

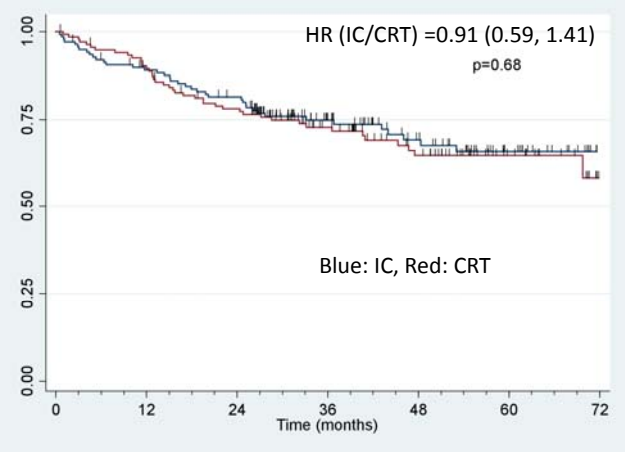
Recurrence-Free Survival by Treatment Arm



Distant Failure Free Survival by Treatment Arm

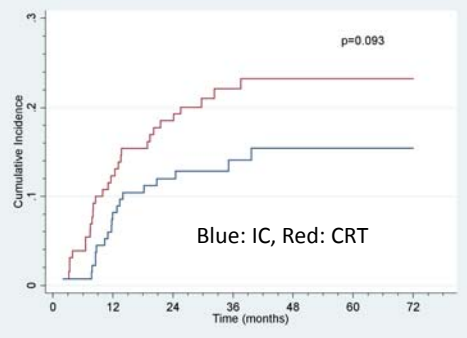


Overall Survival by Treatment Arm Primary Endpoint

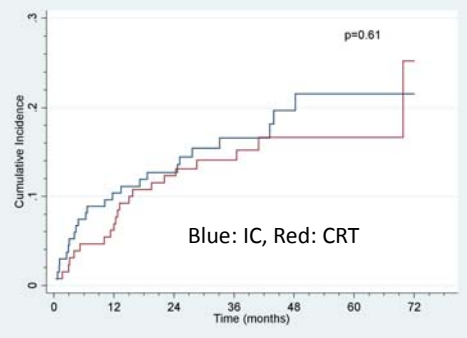


Cumulative Incidence of Distant Recurrence or Death

Distant Recurrence



Death without Distant Recurrence



Conclusion

- In this study (TPF X 2 → DFHX), IC did not improve survival
- IC improves cumulative incidence of distant failure
- DFHX results in excellent OS and disease control
  - Feasible in multi-institutional setting
  - Non-platin containing alternative to existing regimens

Why was DeCIDE negative?

- Statistical limitations
  - Originally powered (N=400) to demonstrate 15% difference in 3-year survival (HR=0.625)
  - Revised sample size (N=280) and follow-up powered to detect HR=0.5
  - In addition to 6 early withdrawals, 23 patients were lost to follow-up prior to 1/1/2011 (14 IC, 9 CRT)

Why was DeCIDE negative?

- 2 cycles of TPF was potentially not enough
  - AE data would suggest that 3rd cycle would be difficult to deliver without compromising subjects proceeding to CRT
  - Nonetheless, some groups may benefit from intensified induction chemotherapy
    - N2C/N3, HPV
- Control arm did much better than expected
  - Impact of HPV was not considered in the original assumptions
- Distant failure events are not frequent enough in this selected population (N2-N3)

The PARADIGM Study: A Phase III Study Comparing Sequential Therapy (ST) to Concurrent Chemoradiotherapy (CRT) in Locally Advanced Head and Neck Cancer

Robert I. Haddad, Guilherme Rabinowits, Roy B. Tishler, Douglas Adkins, Fadlo Raja Khuri, Joseph Clark, Jochen H. Lorch, Sewanti Atul Limaye, Lori J. Wirth, Anne O'Neill, Sarah Riley, Marshall R. Posner

Objectives

Primary

Compare The 3-year Survival Achieved By Docetaxel/ Cisplatin/ 5-fluorouracil *(TPF)* Based Sequential Therapy (ST) With Platinum Based Chemoradiotherapy (CRT) In Patients With Locally Advanced SCCHN

Hypothesis

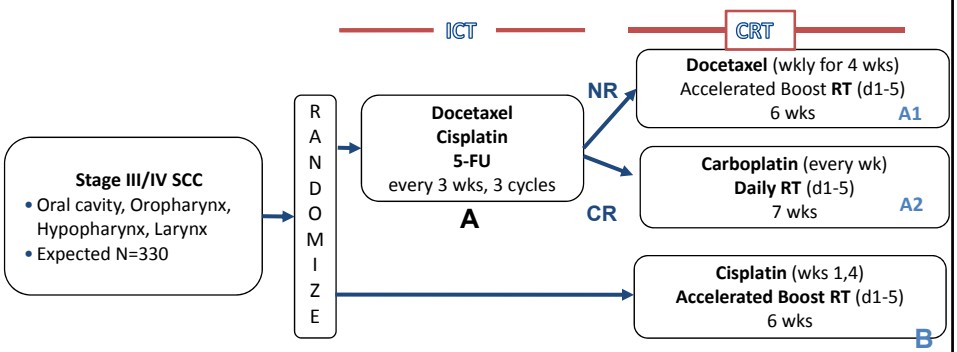
An Absolute Improvement In 3-year Survival of 15% From 55% for CRT To 70% for TPF

Objectives

Secondary

- 2-year progression free survival achieved by Docetaxel/ Cisplatin/ 5-fluorouracil *(TPF)* based sequential therapy with platinum based Chemoradiotherapy in patients with locally advanced SCCHN
- Overall Survival at 5 years
- Progression Free Survival at 3 and 5 years
- Site-specific survival within and between each arm.
- Toxicity of each treatment regimen

PARADIGM Study Design



US National Institutes of Health website. http://clinicaltrials.gov/ct/show/NCT00095875?order=1. Accessed 11/2/07.

PARADIGM: Study Population

Accrual: 145 patients
08/'04 - 12/'08
Halted 12/08 for Slow Accrual

Arm A :70 pts

Arm B: 75 pts

Median Follow up 49 Months
(01/2012)

PARADIGM: Patients Characteristics

	Arm A (70)	Arm B (75)
Age	55 (35-72)	54 (36-74)
Gender - M/F	91%/9%	84%/16%
PS: 0 - 1	67%/33%	67%/33%
Primary site		
✓ **Oropharynx**	**56%**	**55%**
✓ Larynx	14%	19%
✓ Hypopharynx	11%	9%
✓ Oral Cavity	19%	17%
Stage III/IV	14%/86%	15%/85%

PARADIGM: Pattern of Failure

Cancer Failures N=36	Arm A 17/70 (24%)	Arm B 19/75 (25%)
Local/Regional Only	9 (53%)	6 (32%)
Distant Only	3 (18%)	3 (16%)
Both	2 (12%)	5 (26%)
Total Local/Regional	11 (65%)	11 (58%)
Total Distant	5 (30%)	8 (42%)
Unknown	3 (17%)	5 (26%)

PARADIGM: Progression Free Survival

	Arm A (ST)	Arm B (CRT)
#PFS Events	23	22
3 Year PFS	67%	69%
HR(.95CI) p-value	1.07^ (0.59-1.92) 0.82	
3 Year PFS -Non Oropharynx	66%	55%
3 Year PFS-Oropharynx	67%	83%

^Sequential vs. Concurrent

PRESENTED BY:

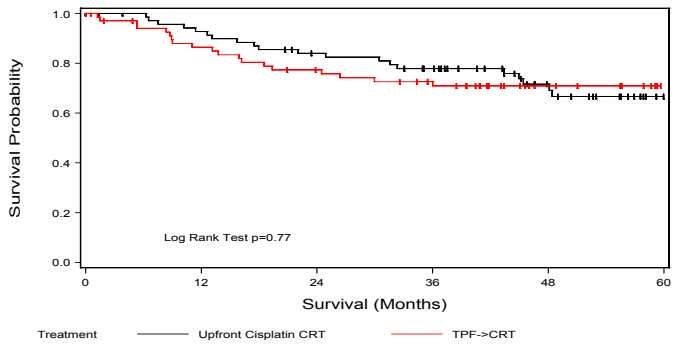
PARADIGM: Overall Survival

	Arm A (ST)	Arm B (CRT)
# Deaths	20	21
3 Year OS	73%	78%
HR(.95CI) p-val	1.09^(0.59 to 2.03) 0.77	
3 Year OS -Non Oropharynx	73%	72%
3 Year OS-Oropharynx	73%	83%

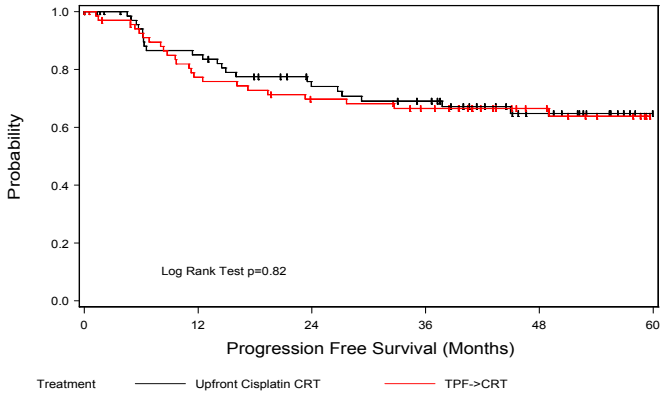
^Sequential vs. Concurrent

PRESENTED BY:

PARADIGM: Overall Survival



PARADIGM: Progression Free Survival



Arms A1 and A2

	3 Year PFS	3 Year OS
A1	44%	52%
A2	86%	92%

PRESENTED BY:

PARADIGM: Toxicities

- Acute Toxicities
  - Febrile Neutropenia
    - Arm A:10 Patients Grade 3 and 6 Patients Grade 4
    - Arm B: 1 Patient Grade 4
- No Difference In Mucositis, Pain Scores, Xerostomia, PEG
- Early Deaths:

Four patients in Arm A died within the first year
*Two died following CRT at 1 and 8 mo post-therapy
*Two died during induction
One Patient in Arm B died within the first year

PARADIGM: Conclusions

- Study terminated early limiting its Interpretation:
  - No difference in OS and PFS seen in this study
  - Survival in CRT arm was much better then anticipated in study planning
  - Excellent survival seen in both arms.
- No Stratification for HPV was performed.
- Some suggestion of more impact for TPF in Non-Oropharynx sites . Needs further study
- Sequential and Concurrent Chemoradiotherapy are appropriate and highly effective options for locally advanced Head and Neck Cancer

Phase III Trial of Radiotherapy Plus Cetuximab for Locoregionally Advanced SCCHN

Stage III/IV nonmetastatic SCCHN
- Oropharynx, hypopharynx, larynx
- No prior surgery/RT for SCCHN

N=424

RANDOMIZE

RT* + Cetuximab
(400 mg/m^2, then 250 mg/m^2/wk)
N=211

RT* alone
N=213

*Choice of:
- Once-daily RT: 70 Gy in 35 fractions
- Twice-daily RT: 72-76.8 Gy in 60-64 fractions
- Concomitant boost: 72 Gy in 42 fractions

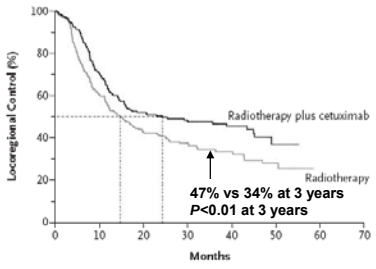
- Primary endpoint: locoregional control
- Secondary endpoints: PFS, OS, ORR, safety

Grades 3-5 Toxicity	RT Alone (N=212)	RT + Cetuximab (N=208)	*P* Value
Mucositis	**52%**	**56%**	**0.44**
Acneiform Rash	**1%**	**17%**	**<0.001**
Infusion Reaction	**0%**	**3%**	**0.01**
Anemia	**6%**	**1%**	**0.006**

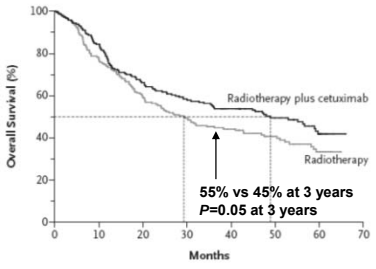
Bonner. *N Engl J Med.* 2006;354:567.

Radiotherapy Plus Cetuximab for Locoregionally Advanced SCCHN: Results

Locoregional Control



OS



Bonner. *N Engl J Med.* 2006;354:567.

A Phase 2, Randomized Trial (CONCERT-1) of Chemoradiotherapy (CRT) With or Without Panitumumab in Patients (pts) With Unresected, Locally Advanced Squamous Cell Carcinoma of the Head and Neck (LASCCHN)

J Giralt,[1] A Fortin,[2] R Mesía,[3] H Minn,[4] M Henke,[5] A Yunes Ancona,[6] A Cmelak,[7] A Markowitz,[8] S Hotte,[9] S Singh,[10] A Chan,[11] M Merlano,[12] A Zhang,[13] K Oliner,[13] A VanderWalde[13]

[1]Hospital Vall d'Hebron, Barcelona, Spain; [2]Centre Hospitalier Universitaire de Quebec-Hotel-Dieu de Quebec, Quebec, Canada; [3]Institut Catala d'Oncologia (ICO) - L'Hospitalet, Barcelona, Spain; [4]Turku University Hospital, Turku, Finland; [5]Albert-Ludwigs-Universität Freiburg, Freiburg, Germany; [6]Unidad de Oncología Servicios de Salud del Edo. de Puebla, Puebla, Mexico; [7] Vanderbilt-Ingram Cancer Center, Nashville, Tennessee; [8]University Of Texas, Medical Branch, Galveston, Texas; [9]Juravinski Cancer Centre, Hamilton, Ontario, Canada; [10]Sunnybrook Health Sciences Centre - Odette Cancer Centre, Toronto, Ontario, Canada;[11]Sir YK Pao Center for Cancer, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong; [12]Oncologia Medica A.S.O.S. Croce E Carle, Cuneo, Italy; [13]Amgen Inc., Thousand Oaks, California

Objectives

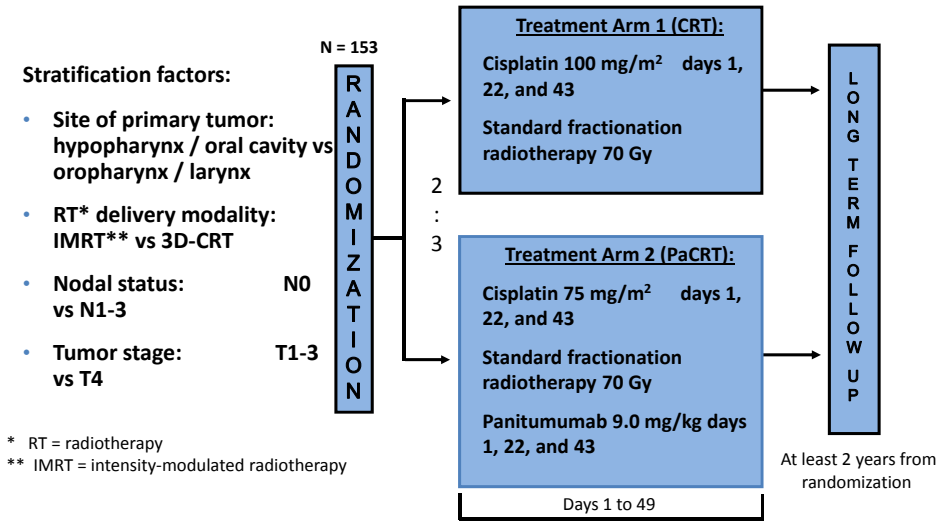
Primary Endpoint

- Local-regional control (LRC) rate at 2 years in patients receiving panitumumab plus CRT (PaCRT) vs CRT alone

Other Key Endpoints

- Duration of LRC
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety
- Exploratory biomarker endpoints

CONCERT-1 Study Schema



Amgen Trial 20062080; ClinicalTrials.gov identifier NCT00500760

Patient Demographics and Disease Characteristics at Baseline

		CRT (N = 63)	PaCRT (N = 87)
Sex	Male	90%	85%
	Female	10%	15%
Age	< 65 years	81%	78%
	≥ 65 years	19%	22%
Tobacco use	Never	16%	15%
	Current	35%	31%
	Former	49%	54%
ECOG PS	0	71%	66%
	1	29%	34%
Primary site	Oropharynx	52%	54%
	Oral cavity	11%	8%
	Hypopharynx	24%	16%
	Larynx	13%	22%

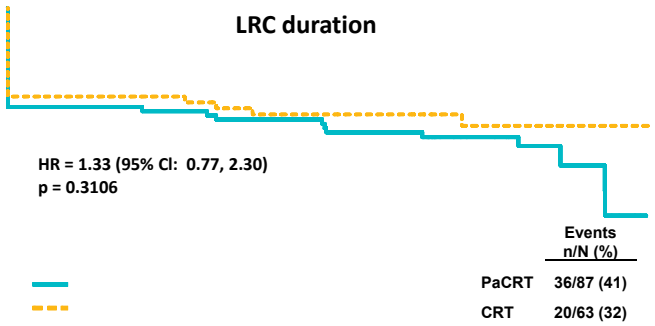
Treatment Received

Treatment parameter	CRT (N = 63)	PaCRT (N = 87)
Cisplatin		
Median cumulative dose*	297 mg/m^2	223 mg/m^2
Median relative dose intensity	97.0%	98.4%
Radiotherapy**		
Randomized to IMRT	67%	60%
Randomized to 3D-CRT	33%	40%
Total dose ≥ 66 Gy	94%	95%
RT major deviations	8%	14%
Treatment interruptions > 10 days	3%	16%
Panitumumab		
Median relative dose intensity	-	98.9%

*Planned per protocol: Cisplatin 75 mg/m2 for PaCRT and 100 mg/m2 for CRT for 3 cycles during standard RT
**Radiotherapy quality assurance was performed

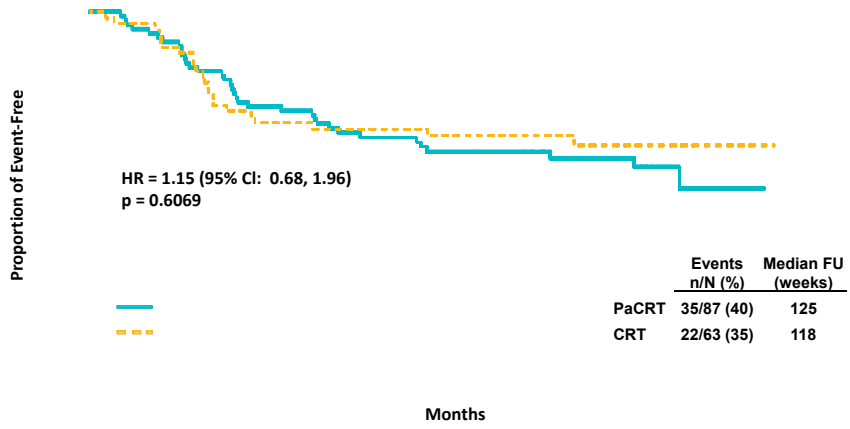
Local-Regional Control

KM estimate (95% CI)	CRT (N = 63)	PaCRT (N = 87)	Difference PaCRT vs CRT
LRC at 24 months (Primary Endpoint)	68% (54%, 78%)	61% (50%, 71%)	-7% (-23%, 9%)

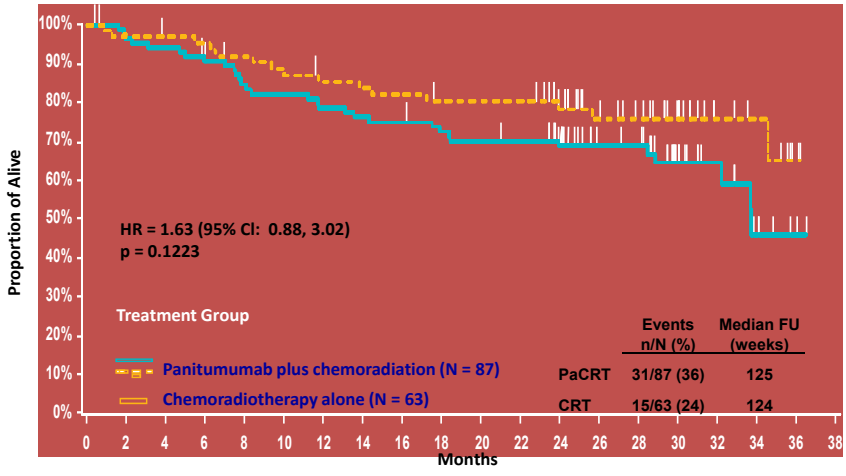


Patients at risk:

Progression-free Survival



Overall Survival



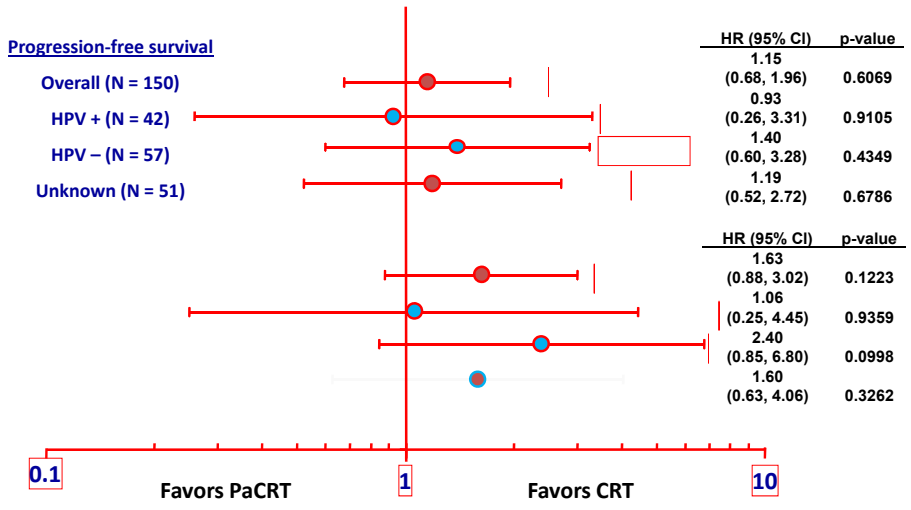
Selected Grade 3 or Higher Adverse Events

Any grade ≥ 3 adverse event	CRT (N = 63)	PaCRT (N = 87)
Mucosal toxicity		
Mucosal inflammation	24%	55%
Dysphagia	27%	40%
Stomatitis	5%	11%
Skin toxicity		
Radiation skin injury	13%	28%
Rash	0%	11%
Acne / Dermatitis	0%	14%
Other		
Infection	0%	8%
Weight decreased	0%	6%
Neutropenia	11%	2%

Patient Characteristics by HPV Status

		HPV+ (N = 42)	HPV- (N = 57)	All Subjects (N = 150)
Tobacco use	≤ 10 pack-years	40%	9%	22%
	> 10 pack-years	55%	88%	71%
Region	North America	55%	26%	36%
	Western Europe	38%	47%	45%
	Rest of World	7%	26%	19%
T stage	T1-2	55%	21%	32%
	T3-4	45%	79%	68%
Nodal stage	N0	10%	14%	14%
	N+	90%	86%	86%
Primary site	Oropharynx	81%	39%	53%
	Other	19%	61%	47%

Forest Plots for PFS and OS by HPV Status



Summary

- No differences in LRC, PFS, or OS with addition of panitumumab to chemoradiotherapy vs CRT alone
  - General trend toward worse outcome in OS with PaCRT
- Factors possibly contributing to poorer outcomes observed in the panitumumab arm include
  - Lower cisplatin dose
  - More radiotherapy interruptions
- Increased grade 3+ toxicity in PaCRT arm
  - Attributable to on-target effects of panitumumab
- No differences in efficacy by tumor HPV status
  - Trend favored CRT for OS in HPV negative group only, though wide confidence intervals limit interpretability

An international, double-blind, randomized, placebo-controlled Phase 3 trial (EXAM) of Cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline

P Schöffski,[1] R Elisei,[2] S Müller,[3] M Brose,[4] M Shah,[5] L Licitra,[6] B Jarzab,[7] V Medvedev,[8] MC Kreissl,[9] B Niederle,[10] EEW Cohen,[11] L Wirth,[12] H Ali,[13] C Hessel,[14] Y Yaron,[14] D Ball,[15] B Nelkin,[15] S Sherman[16] and M Schlumberger[17]

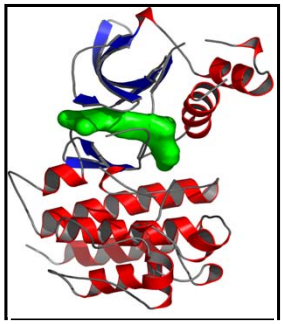
[1]University Hospitals Leuven, KU Leuven; [2]Universita di Pisa; [3]Universitätsklinikum Essen; [4]University of Pennsylvania Health System; [5]Ohio State University Medical Center; [6]Fond. IRCCS Instituto Nazionale Tumori; [7]Centrum Onkologii-Instytut im. Marii Sklodowskiej-Curie Oddzial w Gliwicach; [8]Medical Radiology Research Center of RAMS;[9]Universitätsklinikum Würzburg [10]Medizinische Universität Wien; [11]University of Chicago; [12]Massachusetts General Hospital; [13]Henry Ford Health System; [14]Exelixis Inc; [15]Johns Hopkins University School of Medicine; [16]University of Texas MD Anderson Cancer Center; [17]Institut Gustave Roussy, University Paris-Sud

MTC Disease Biology

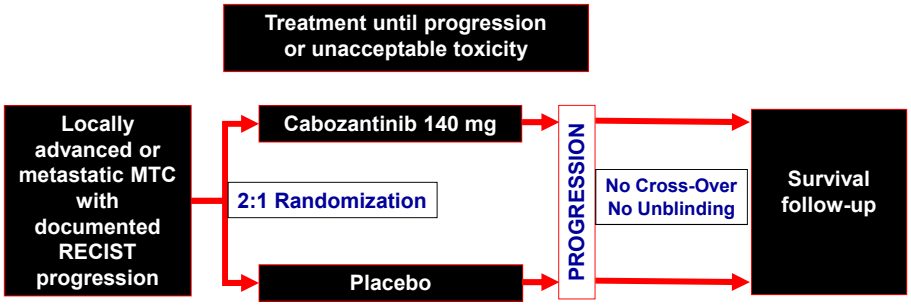
- MTC accounts for 5-8% of thyroid cancers[1]
  - Patients with distant metastases have a median survival of ~2 years[2]
  - Radiographically progressive MTC is an unmet medical need not previously studied in a phase 3 trial
- 75% of cases occur sporadically, 25% are hereditary[3,4]
  - Up to 65% of sporadic cases have somatic RET mutations[3]
  - >95% of hereditary cases have germline RET mutations[4]
- Hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2) pathways have been implicated in the pathogenesis of MTC[5,6]

Cabozantinib

- A potent oral targeted therapy that inhibits MET, VEGFR2, and RET[1]
- Clinical activity observed in MTC patients in Phase 1[2]



Phase 3 Study Design (EXAM)



Key Eligibility Criteria and Assessments

Key Eligibility Criteria:

- Locally advanced or metastatic MTC
- Documented RECIST progressive disease (PD) within 14 months of screening as confirmed by an independent radiology committee (IRC)
- Measurable disease per RECIST 1.0 required in ≥ 90% patients
- No limit on prior therapy

Assessments:

- Tumor assessment (CT and/or MRI) at baseline and every 12 weeks, bone scan at baseline
- Scans evaluated by blinded IRC for primary analyses of progression-free survival (PFS) and objective response rate (ORR)
- Safety: adverse events (AE; CTCAE 3.0) and laboratory monitoring at least every 4 weeks
- RET mutation status centrally analyzed in blood and tumor samples

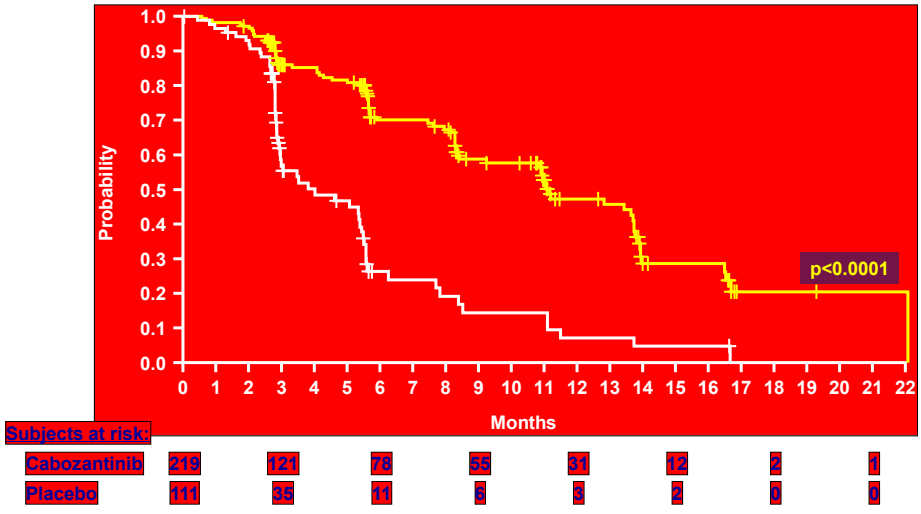
Subject Disposition

Cabozantinib n=219		Placebo n=111	
Continuing treatment	45%	Continuing treatment	13%
Discontinued treatment	55%	Discontinued treatment	87%
Did not receive treatment	2%	Did not receive treatment	2%
PD	26%	PD	60%
AE	16%	AE	8%
Death	5%	Death	5%
Subject request	4%	Subject request	12%
Investigator decision	1%	Investigator decision	0%
Other	1%	Other	0%
Included in ITT analysis n=219		Included in ITT analysis n=111	
Included in safety analysis n=214		Included in safety analysis n=109	

Baseline Patient Characteristics

		Cabozantinib n=219	Placebo n=111
Median age (y)		54	54
Male (%)		69	63
Race (%)	White	90	89
ECOG (%)	0 -1	95	90
	2	4	10
Measurable disease per RECIST (%)		95	94
Prior systemic therapy (%)		37	42
Prior TKI exposure (%)			
	Yes	20	22
	Unknown	2	1
	No	78	78
RET mutation status (%)			
	Positive	46	52
	Unknown	40	39
	Negative	14	9
Bone metastases at baseline (%)		51	51

Progression Free Survival by IRC (Primary Endpoint)



Summary of PFS Analyses: IRC vs Investigator Assessment

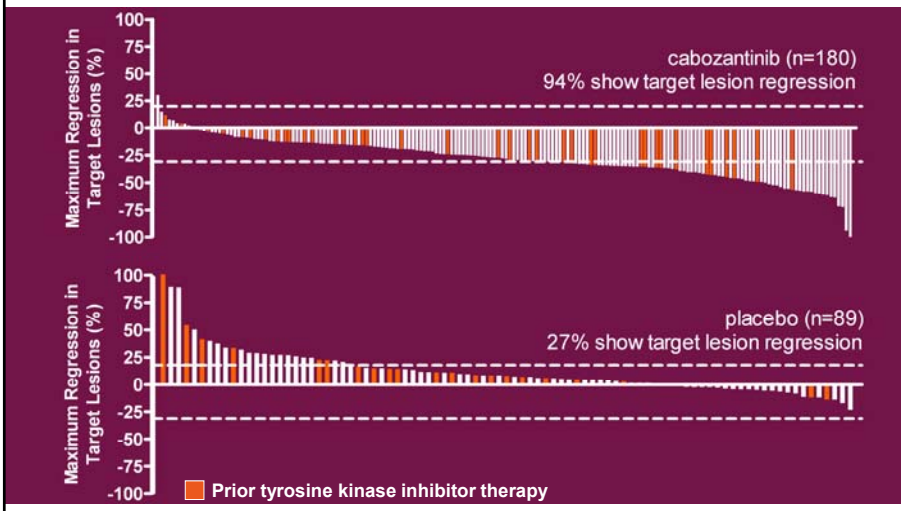
	Radiographic Assessment	
	IRC	Investigator
PFS (months)	11.2 vs 4.0	13.8 vs 3.1
HR* (95% CI)	0.28 (0.19-0.40)	0.29 (0.21-0.42)
p-value**	<0.0001	<0.0001

All pre-specified sensitivity analyses were consistent with the primary analysis

Secondary Endpoints

- Objective Response Rate per IRC
  - Cabozantinib 28% vs placebo 0%, *p*<0.0001
  - Median duration of response, 14.6 months
- Overall Survival: interim data are not mature
  - Final analysis to be conducted after 217 events
  - Pre-specified interim analysis 15 June 2011
    - 96 (44%) of the required events had occurred
    - No difference in OS observed at the time of the interim analysis

Maximum Regression in Target Lesions from Baseline by IRC



Most Frequent Adverse Events (>25% Incidence)

	Cabozantinib (N=214)		Placebo (N=109)	
Median Duration of Exposure	6.7 months		3.4 months	
Adverse Event[a]	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Diarrhea	135 (63)	34 (16)	36 (33)	2 (2)
Hand foot skin reaction	107 (50)	27 (13)	2 (2)	-
Decreased weight	102 (48)	10 (5)	11 (10)	-
Decreased appetite	98 (46)	10 (5)	17 (16)	1 (1)
Nausea	92 (43)	3 (1)	23 (21)	-
Fatigue	87 (41)	20 (9)	31 (28)	3 (3)
Dysgeusia	73 (34)	1 (0.5)	6 (6)	-
Hair color changes	72 (34)	1 (0.5)	1 (1)	-
Hypertension[b]	70 (33)	18 (8)	5 (5)	1 (1)
Stomatitis	62 (29)	4 (2)	3 (3)	-
Constipation	57 (27)	-	6 (6)	-

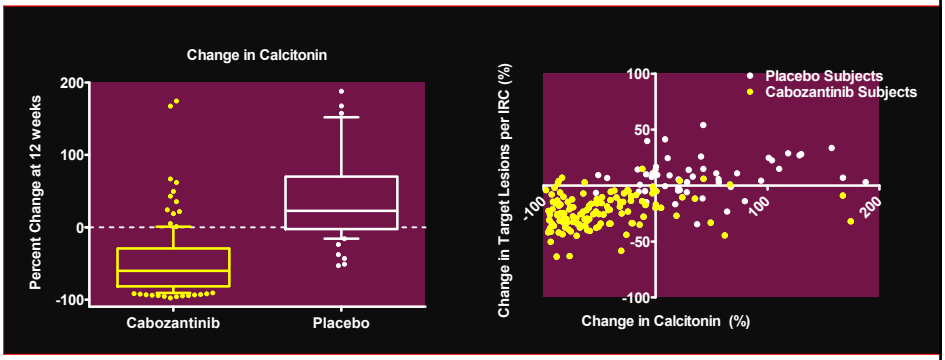
AEs* Commonly Associated with VEGF Pathway Inhibition

	Cabozantinib N=214		Placebo N=109	
Adverse Event	All n (%)	Grade ≥ 3 n (%)	All n (%)	Grade ≥ 3 n (%)
Hypertension	70 (33)	18 (8)	5 (5)	1 (0.9)
Hemorrhage	54 (25)	7 (3)	17 (16)	1 (0.9)
Venous thrombosis	12 (6)	8 (4)	3 (3)	2 (2)
GI perforation	7 (3)	7(3)	0	0
Non-GI fistula	8 (4)	4 (2)	0	0

Overall deaths for any reason were balanced between treatment arms
Deaths within 30 days of treatment cessation for reasons other than PD
- 5.6% in the cabozantinib arm vs 2.8% in the placebo arm
  - 1.9% in the cabozantinib arm from causes typically associated with VEGF inhibition (4 patients including 3 cases of fistula formation and 1 hemorrhage)

*** ≥ Grade 3 with >1% incidence in either arm**

Correlation Between Changes in Calcitonin and Target Lesions



- Mean calcitonin levels decreased by 45% in the cabozantinib arm but increased by 57% in the placebo arm during the first three months
- Similar effects were seen with CEA

Conclusions

- EXAM is the first randomized phase 3 study in MTC patients with IRC confirmed radiographic progressive disease
- Unmet medical need of this population is documented by the short PFS in the placebo arm
- Cabozantinib treatment resulted in clinically meaningful and statistically significant prolongation of PFS in this setting
  - Median PFS: 11.2 vs 4.0 months [HR 0.28, p <0.0001]
  - 1 year PFS rate: 47.3% vs 7.2%
  - PFS benefit observed across all pre-specified subgroups
- Cabozantinib treatment leads to durable tumor responses
  - ORR: 28% vs 0% (p <0.0001); median duration of response = 14.6 months
- Serum calcitonin and CEA decrease with tumor shrinkage
- AEs are generally manageable, allowing treatment with cabozantinib for extended periods of time
- Cabozantinib is an important new treatment option for MTC patients

Head and Neck Cancer Post ASCO 2012: Three steps backward, one leap forward

- DeCIDE and Paradigm, two phase III trials of induction chemotherapy vs. concurrent therapy, failed to show evidence in support of induction.
- Only RTOG has the capacity to run adequately powered Phase III trials in this setting to determine whether a role exists for induction chemotherapy in locally advanced, high risk HNSCC.
- Panatumimab failed to replicate the benefit of cetuximab in advanced HNSCC.
- Approaches targeting RET with Cabozantinib for Medullary Thyroid Cancer look promising and are likely to enhance treatment of advanced diseases.