ASCO 2014: Induction and Adjuvant Treatment in Locally Advanced Head and Neck Cancer-New Insights, Old Challenges

EMORY
WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

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September 6, 2014

Treatment Goals

- Induction chemotherapy (ICT)
  - Initial tumor shrinkage may allow for improved locoregional control, decrease radiation dose, reduce radiation field
  - Reduce risk of relapse leading to improved survival
  - Select for biologically favorable tumor
- Adjuvant chemotherapy
  - Reduce risk of tumor relapse (locoregionally or distantly) leading to improved survival

Challenges with Induction or Adjuvant Treatment

- **Induction**
  - Delay definitely local therapy
  - Up to 10-15% patients may not receive local treatment
  - May result in accelerated tumor repopulation, reducing efficacy of radiotherapy –RT duration > 8 w was an independent prognostic factor for survival in Tax 324 (Sher IJROBP 2011)
- **Adjuvant**
  - Poor compliance
- **Both**
  - Prolonged course of treatment
  - Increased cost
  - May lead to more acute & late toxicity

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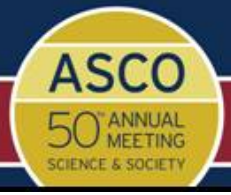
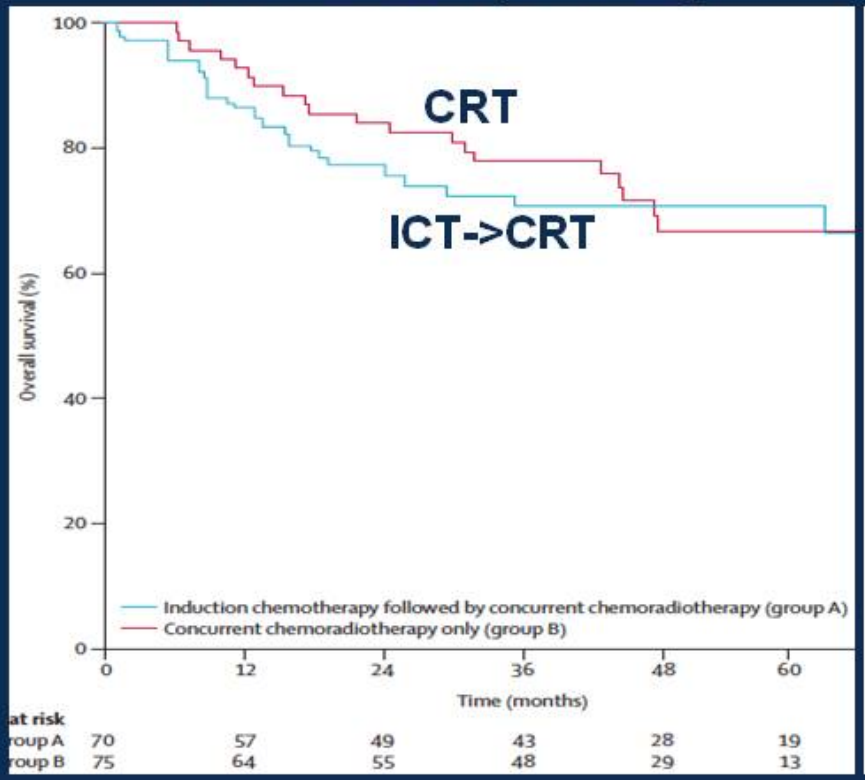
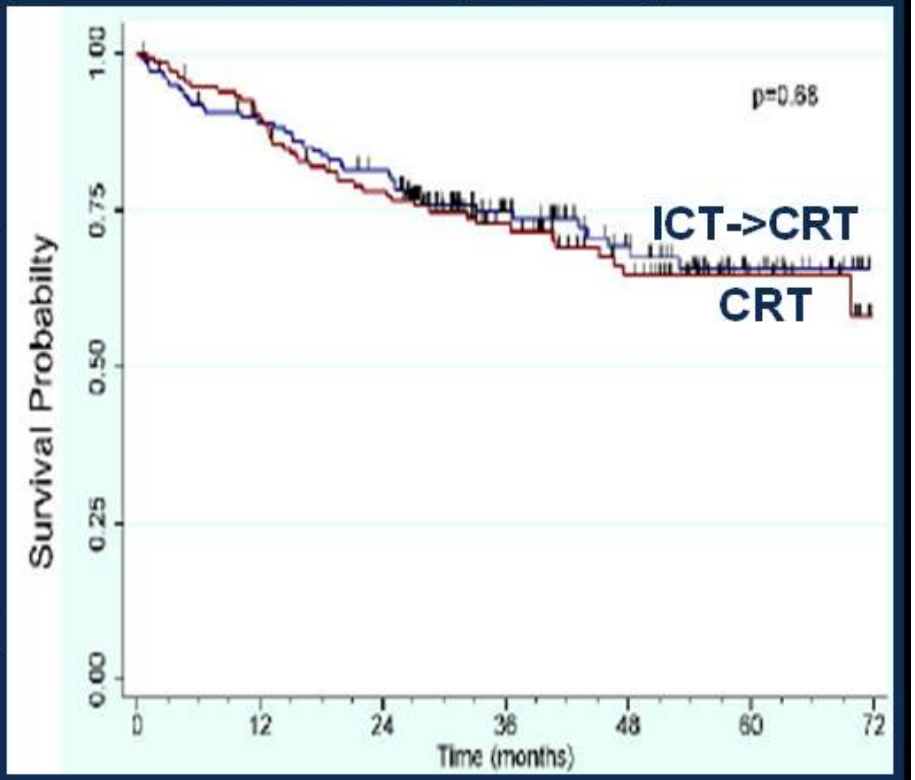


ICT vs. CRT

PARADIGM (N=145)



DeCIDE (N=285)



- Are these studies underpowered to detect an advantage for ICT?
- Which patient population would benefit the most from ICT?

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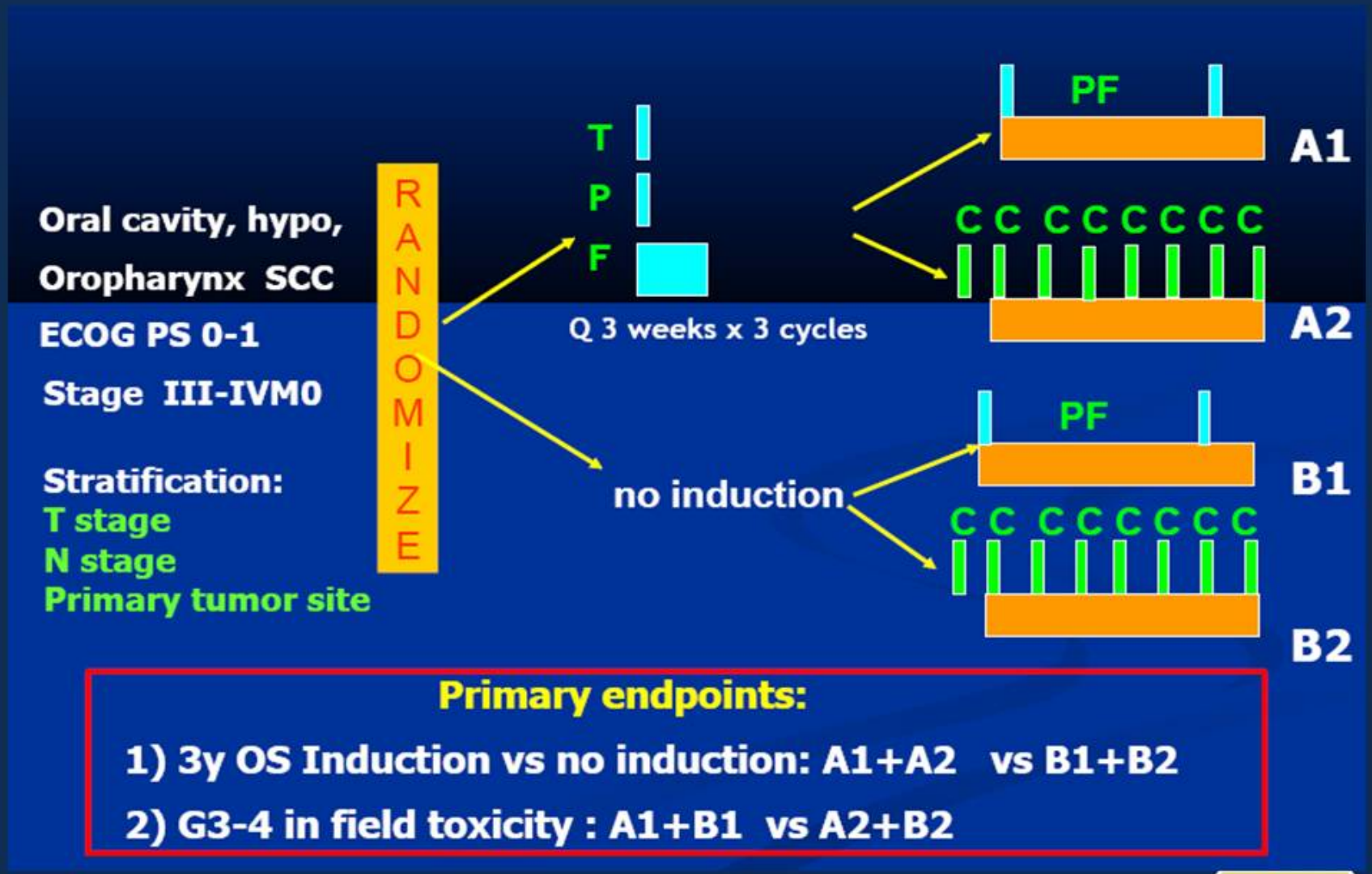
PHASE III PART: 2 X 2 FACTORIAL DESIGN



Primary endpoints:

1) 3y OS Induction vs no induction: A1+A2 vs B1+B2

2) G3-4 in field toxicity : A1+B1 vs A2+B2

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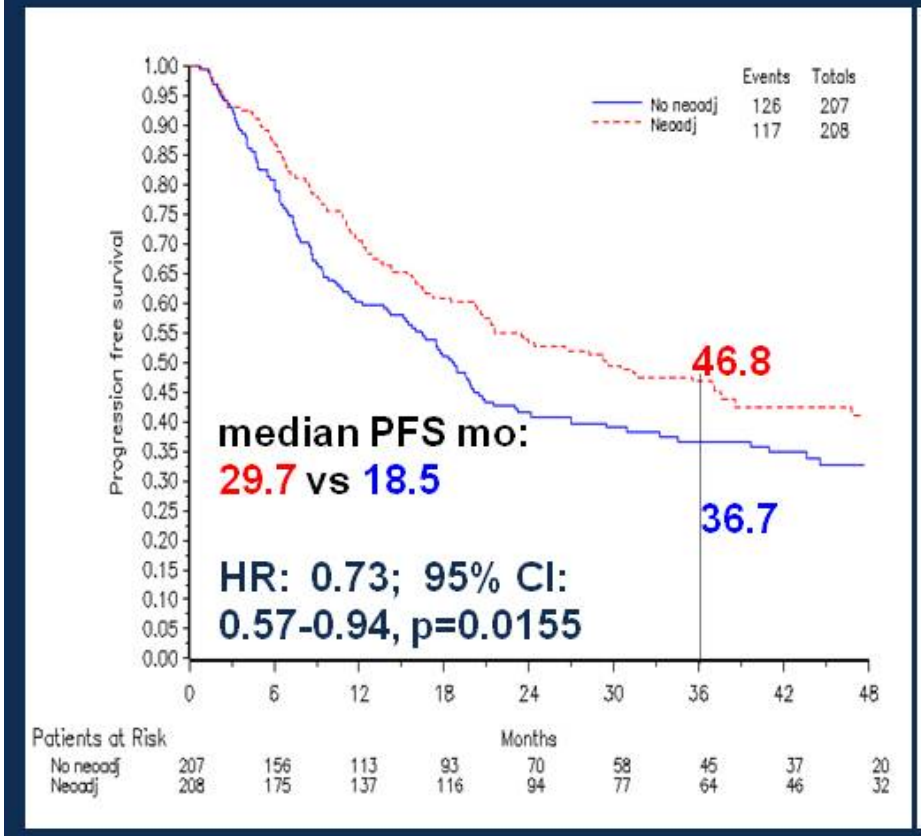
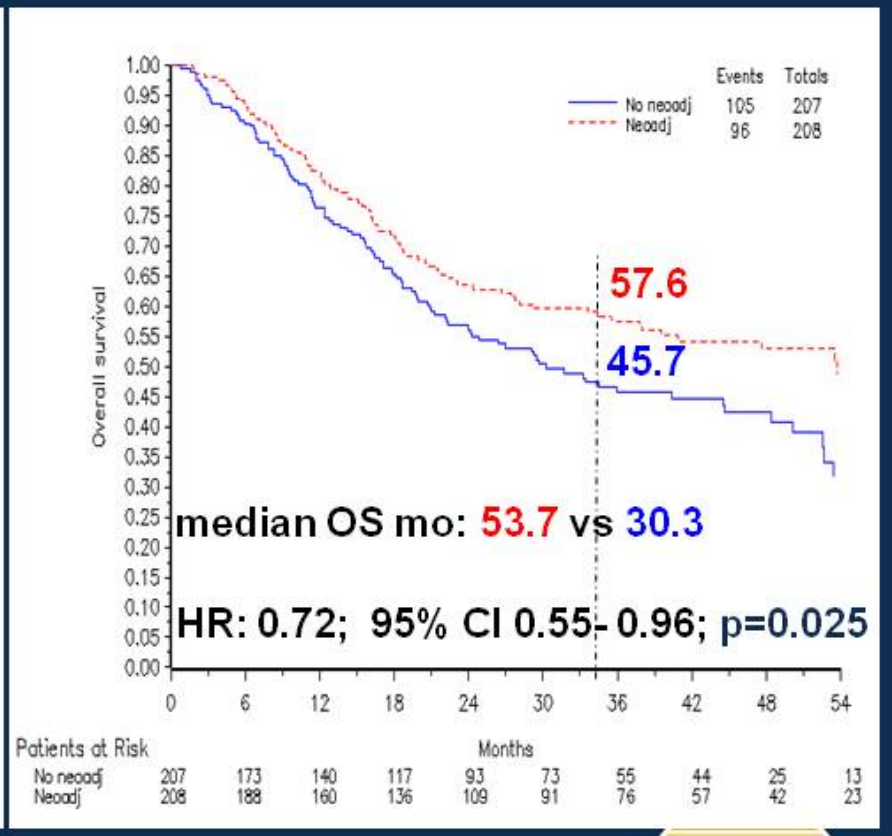
Survival Results

Progression-Free Survival



Overall Survival



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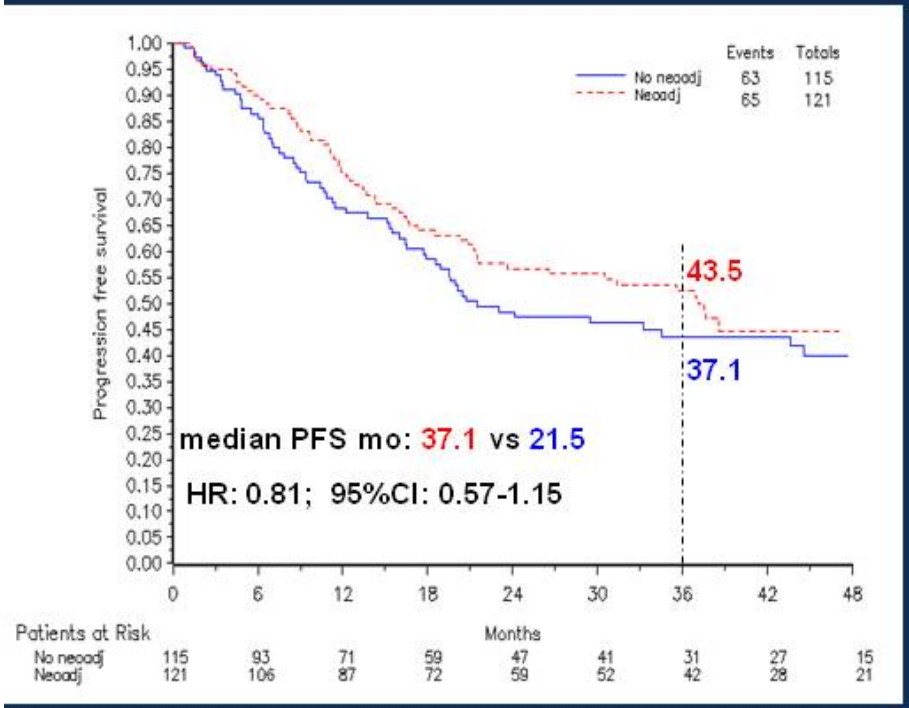
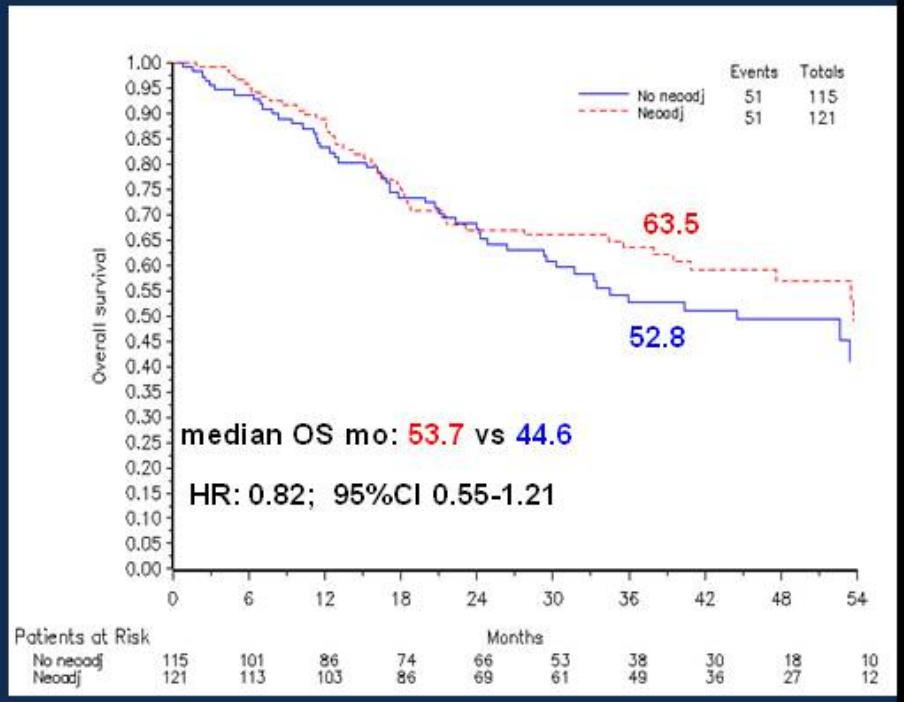
Oropharynx cancer: PFS and OS (unplanned)

Progression-Free Survival



Overall Survival



***HPV status analysis in progress**

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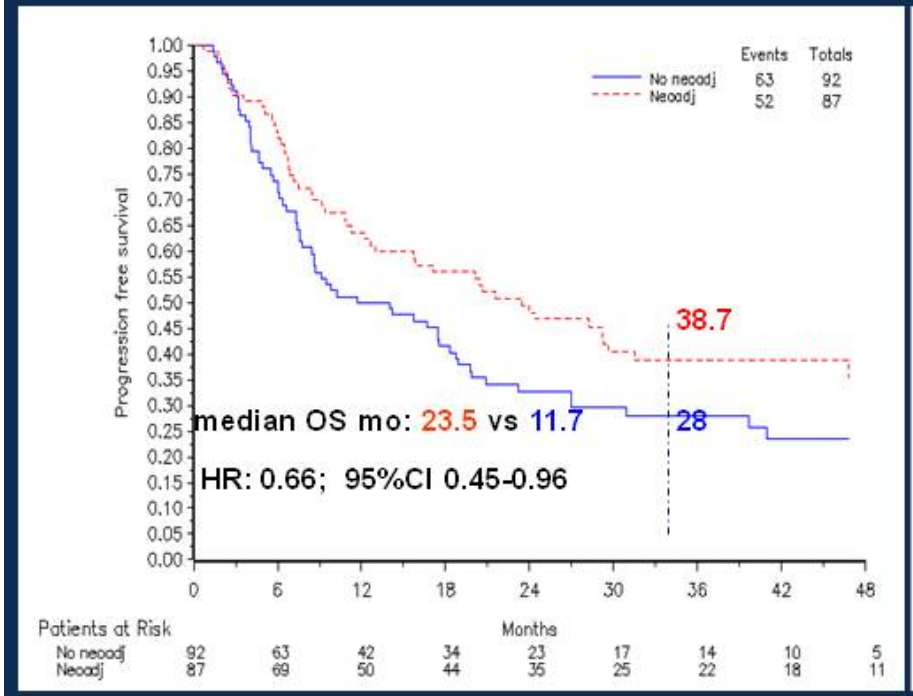
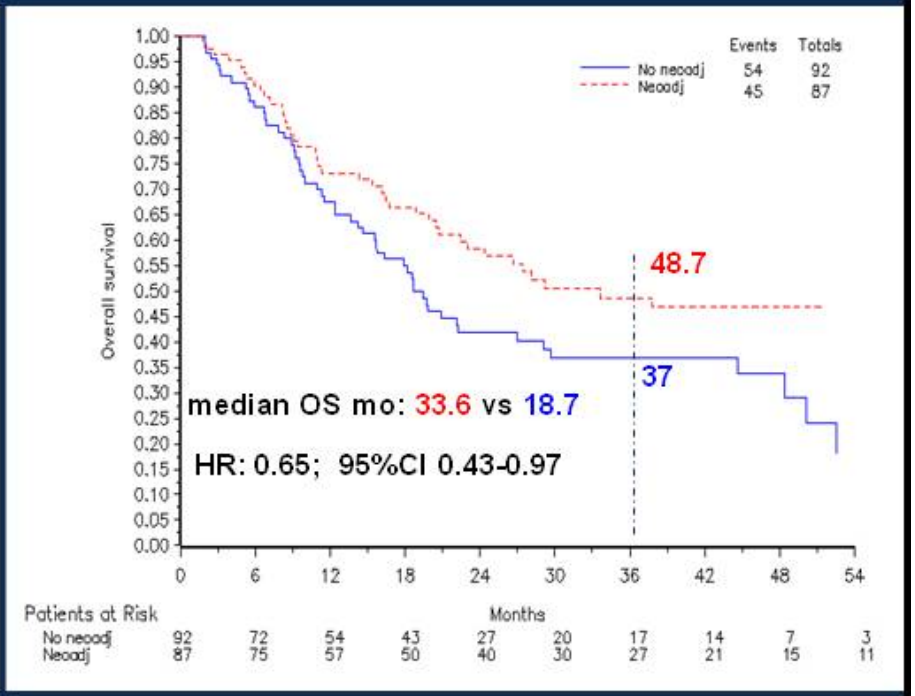
Non OPC: PFS and OS (unplanned)

Progression-Free Survival



Overall Survival



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OS Subgroup Analysis (Unplanned) Cox Model

Study Arms	patients	events	HR	95% CI
TPF → CRT	129	69	0.80	0.56 – 1.15
CRT	129	62		
TPF → cet/RT	79	27	0.57	0.34 – 0.93
cet/RT	78	43		

- 415 patients
- 4 arms
- 6 possible comparison
- unplanned
- hypothesis generator
- random effect?

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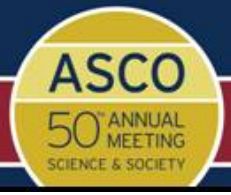

Questions Pertained to the Italian Study

- Is the benefit for ICT seen primarily in HPV(-) tumor? Need analysis
- Is the benefit for ICT the same for each concomitant regimen? May be not
- Why are the PFS & OS results of this study lower than other published studies? Is it HPV? Is it smoking? Is it something else?

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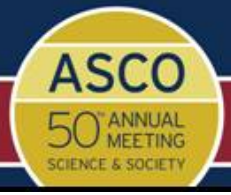

What can we conclude about ICT?

- Its benefit in non-OPC need to be validated in a larger study using one single concomitant regimen.
- RT quality assurance needs to be addressed, especially in the era of high complexity IMRT.
- Additional analysis on pattern of failure is important to determine the contribution ICT
- This trial has revived interest in ICT but has not definitely proven its role in HNC

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Rationale for using Induction Chemotherapy to Decrease RT Dose

- Induction chemotherapy with Paclitaxel & Carboplatin in E2399 resulted in high RR (82%) & 2y OS (95%) in HPV+ OPC
- Cetuximab added to a platinum/taxane regimen has been associated with higher CR rate
- Induction chemotherapy allowed for successful RT dose reduction in HD & NHL
- Can triple drug induction chemotherapy be used to decrease RT dose in HPV+ OPC

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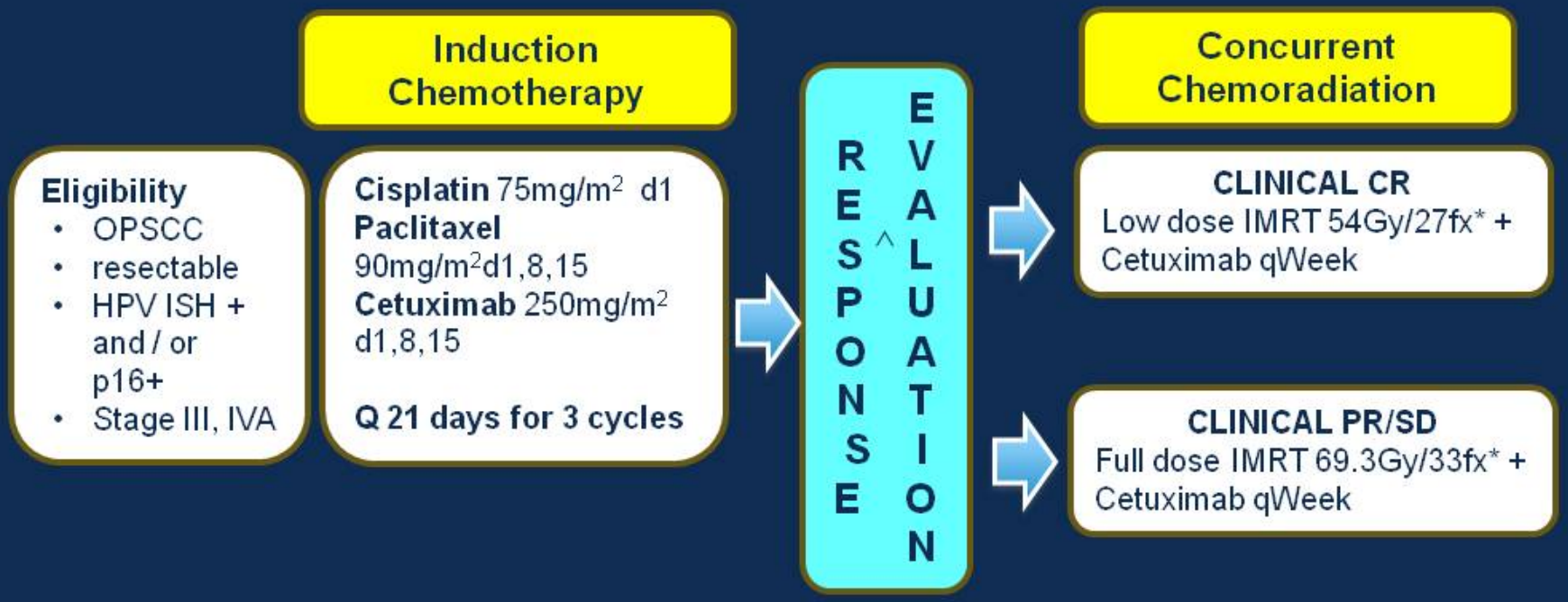
ECOG 1308: Phase II Schema



IMRT margins for primary: 1.0 to 1.5cm around gross dz
Nodal margin: 1cm margin minimum

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Endpoint: 2yr PFS and OS

Cohort (n)	2 year PFS (90% CI)	2 year OS
All low dose pts (62)	0.80 (0.70, 0.88)	0.93 (0.85, 0.97)
T4a (7)	0.54 (0.19, 0.79)	0.86 (0.45, 0.97)
Non-T4a (55)	0.84 (0.73, 0.91)	0.94 (0.86, 0.98)
N2c (19)	0.77 (0.56, 0.89)	0.95 (0.76, 0.99)
Non-N2c (43)	0.82 (0.69, 0.90)	0.93 (0.82, 0.97)
Smoker >10pk-yrs (22)	0.57 (0.35, 0.73)	0.86 (0.67, 0.94)
Smoker ≤10pk-yrs (40)	0.92 (0.81, 0.97)	0.97 (0.87, 0.995)
Smoker ≤10k-yrs, <T4, N2c (27)	0.96 (0.82, 0.99)	0.96 (0.82, 0.99)
All high-dose pts (15)*	0.65 (0.41, 0.82)	0.87 (0.63. 0.96)

* 3 high-dose pts did not go on to receive RT

Good risk HPV+ Tumors may do Well with RT Alone

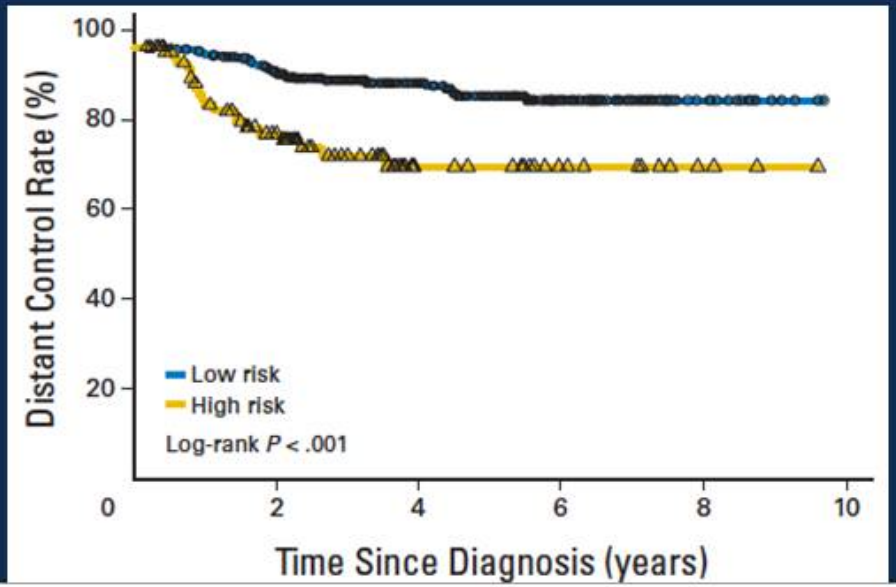

Table 4. Pattern of Failure in HPV-Positive Low-Risk Category

Cohort	T1	T2	T3	N0-N2a	N2b	N2c
Distant control rate at 3 years, %						
RT alone	95	92	85	97	89	73
95% CI	82 to 99	81 to 96	68 to 93	89 to 99	75 to 95	47 to 88
CRT	88	97	94	88	98	92
95% CI	68 to 96	87 to 99	79 to 98	66 to 96	90 to 99	77 to 97
P	.29	.09	.28	.07	**.03**	**.02**

Presented by: O'sullivan B et al, JCO 31:543, 2013 PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

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Questions to address in good risk HPV+ patients

- What is the best strategy to decrease treatment while minimizing late toxicity in these patients (induction chemo -> reduced RT dose, surgery -> reduced RT dose, RT alone, low dose CRT)?
- What is the best way to measure long-term function and late toxicity in these patients?
- What is the best way to address the cost of treatment and toxicity in these patients?

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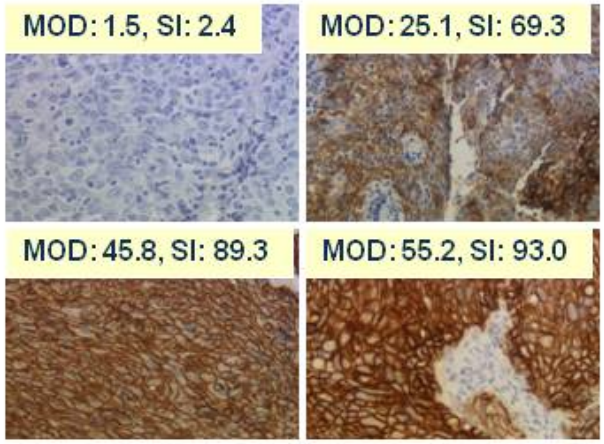
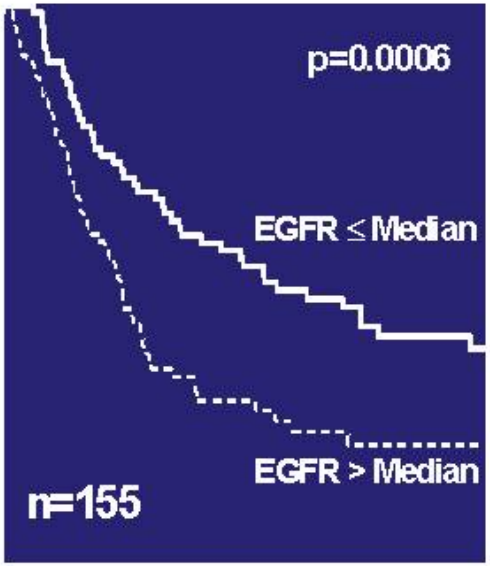
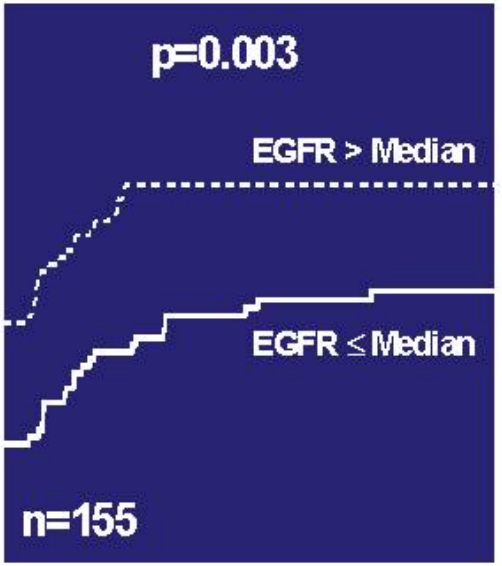
EGFR Tumor Expression & Outcomes



Overall Survival



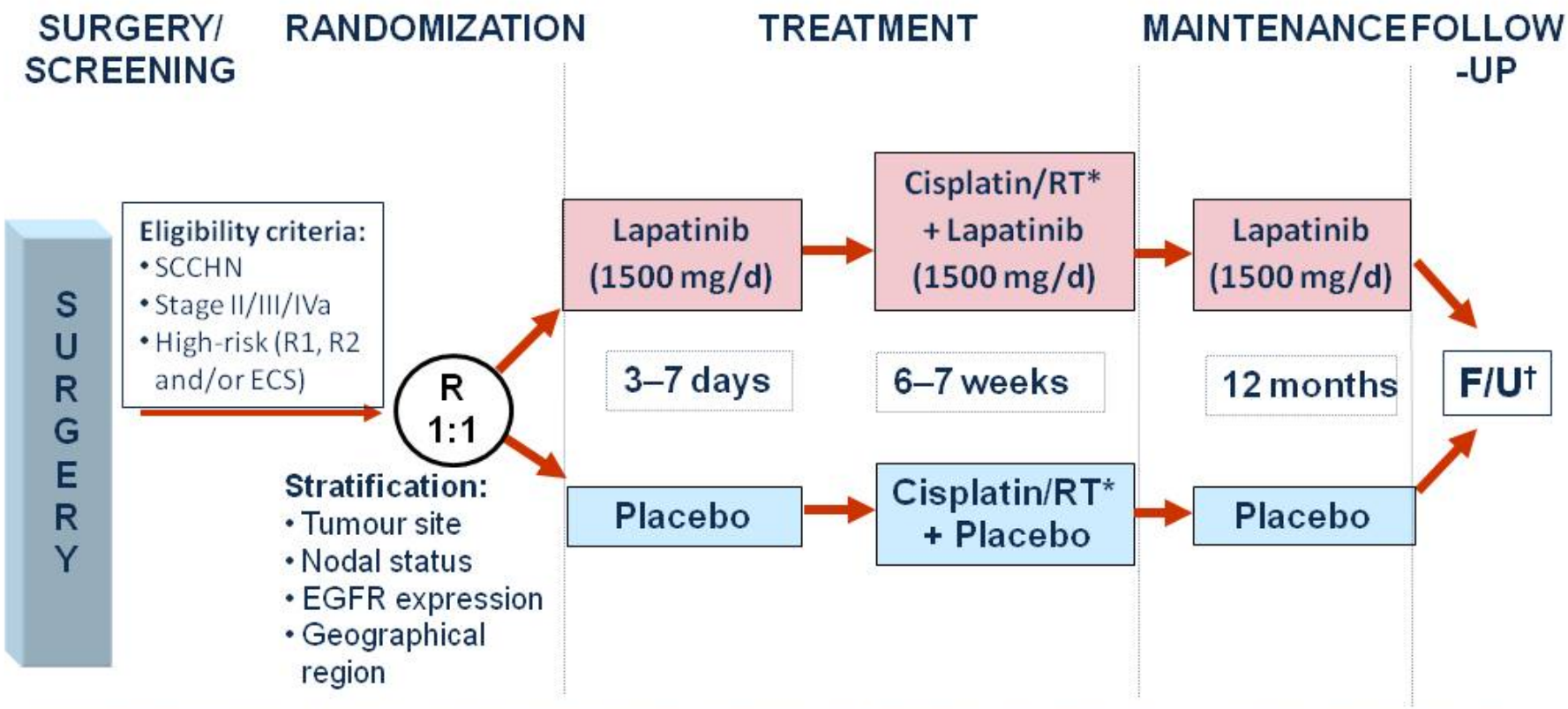
Locoregional Relapse



Ang et al., Cancer Research 62: 7350, 2002

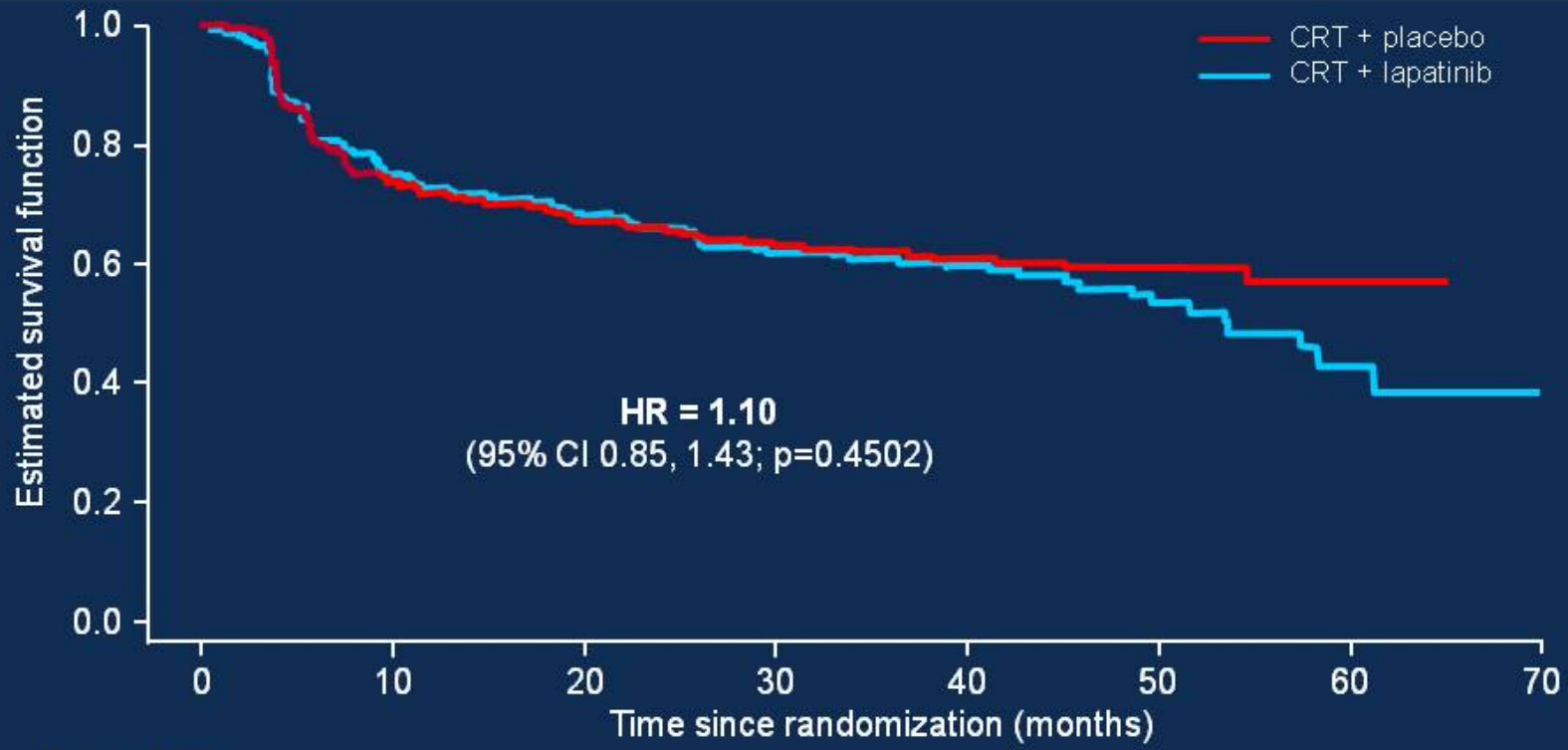
Study Design

Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of lapatinib combined with chemoradiotherapy, before administration as a maintenance monotherapy for 1 year, in patients with resected SCCHN



*Cisplatin 100 mg/m² on Days 1, 22 and 43; RT 2Gy/day, 5 days/week † Patients were followed up every 4 months for 2 years and then every 6 months until withdrawal from the study, or death, whichever occurred first.
ECS, extracapsular spread; F/U, follow-up; RT, radiotherapy; RTQA, Radiotherapy Quality Assurance; SCCHN, squamous cell carcinoma of the head and neck

Primary endpoint: IRC-assessed DFS (ITT population)



- Median DFS (95% CI): Placebo arm, NR (54.6, NR); lapatinib arm, 53.6 (45.8, NR)
- Investigator-assessed DFS: HR = 1.03 (95% CI 0.81,1.30; p=0.8208)

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DFS, disease-free survival; HR, hazard ratio; ITT, intent to treat; IRC, independent review committee; NR, not reached

Discussion

- Results consistent with prior studies showing EGFR TKI has less activity than cetuximab in unselected HNSCC
- Will Lapatinib be more active when combined with CRT in definitive setting?
- Will adjuvant TKI targeting the HER pathway be more active in selected high risk population?

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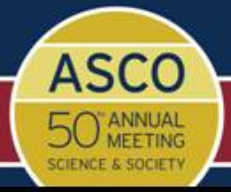

ASCO 2014: Another option for refractory thyroid cancer

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September 6, 2014

A phase 3, multicenter, randomized, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with ^{131}I-refractory differentiated thyroid cancer (SELECT)

Martin Schlumberger,[1] Makoto Tahara,[2] Lori J. Wirth,[3] Bruce Robinson,[4] Marcia S. Brose,[5] Rossella Elisei,[6] Corina E. Dutcus,[7] Begoña de las Heras,[8] Junming Zhu,[7] Mouhammed Amir Habra,[9] Kate Newbold,[10] Manisha H. Shah,[11] Ana O. Hoff,[12] Andrew G. Gianoukakis,[13] Naomi Kiyota,[14] Matthew H. Taylor,[15] Sung-Bae Kim,[16] Monika K. Krzyzanowska,[17] Steven I. Sherman[9]

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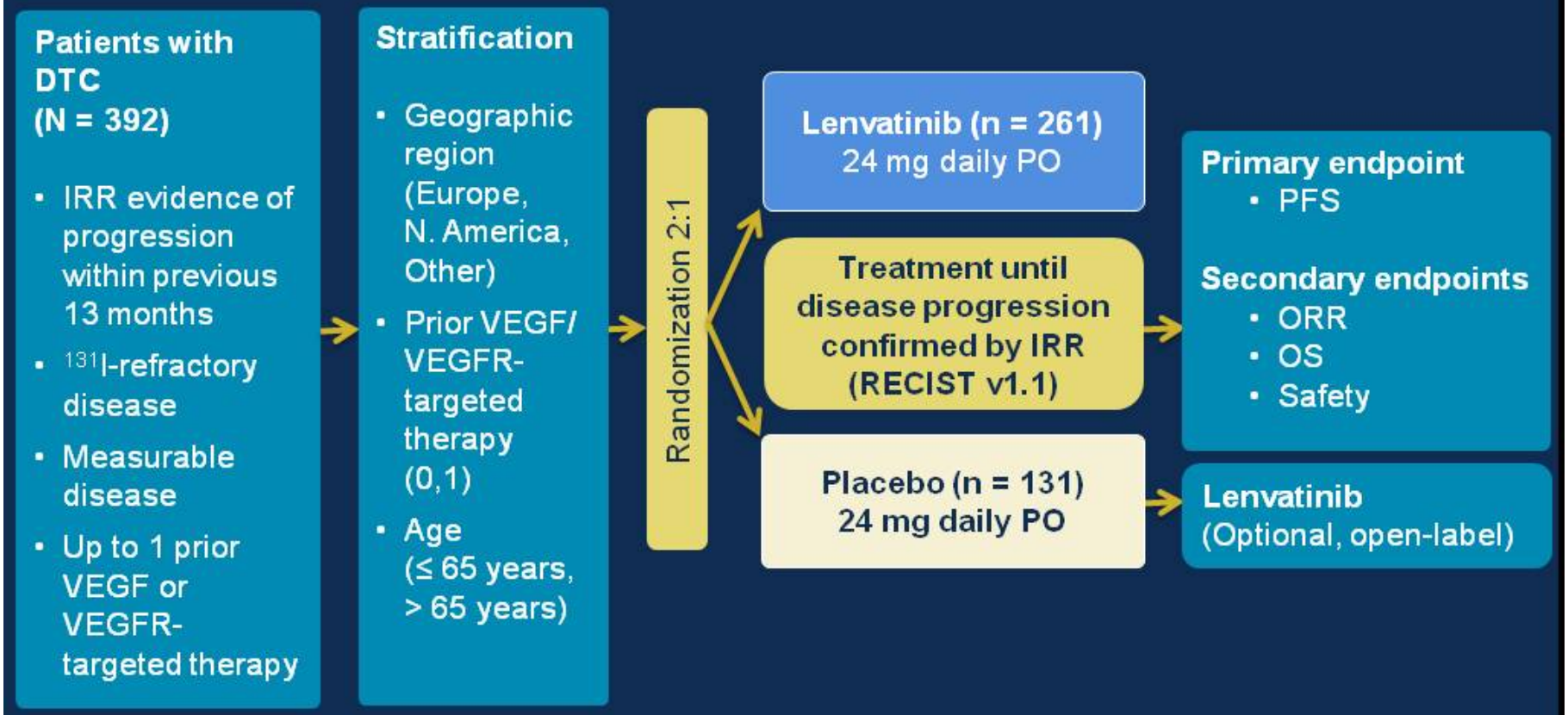
Study 303: Study Schema

Global, randomized, double-blind, phase 3 trial



DTC, differentiated thyroid cancer; 131I, radioiodine; IRR, independent radiologic review, ORR, objective response rate; OS, overall survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors.

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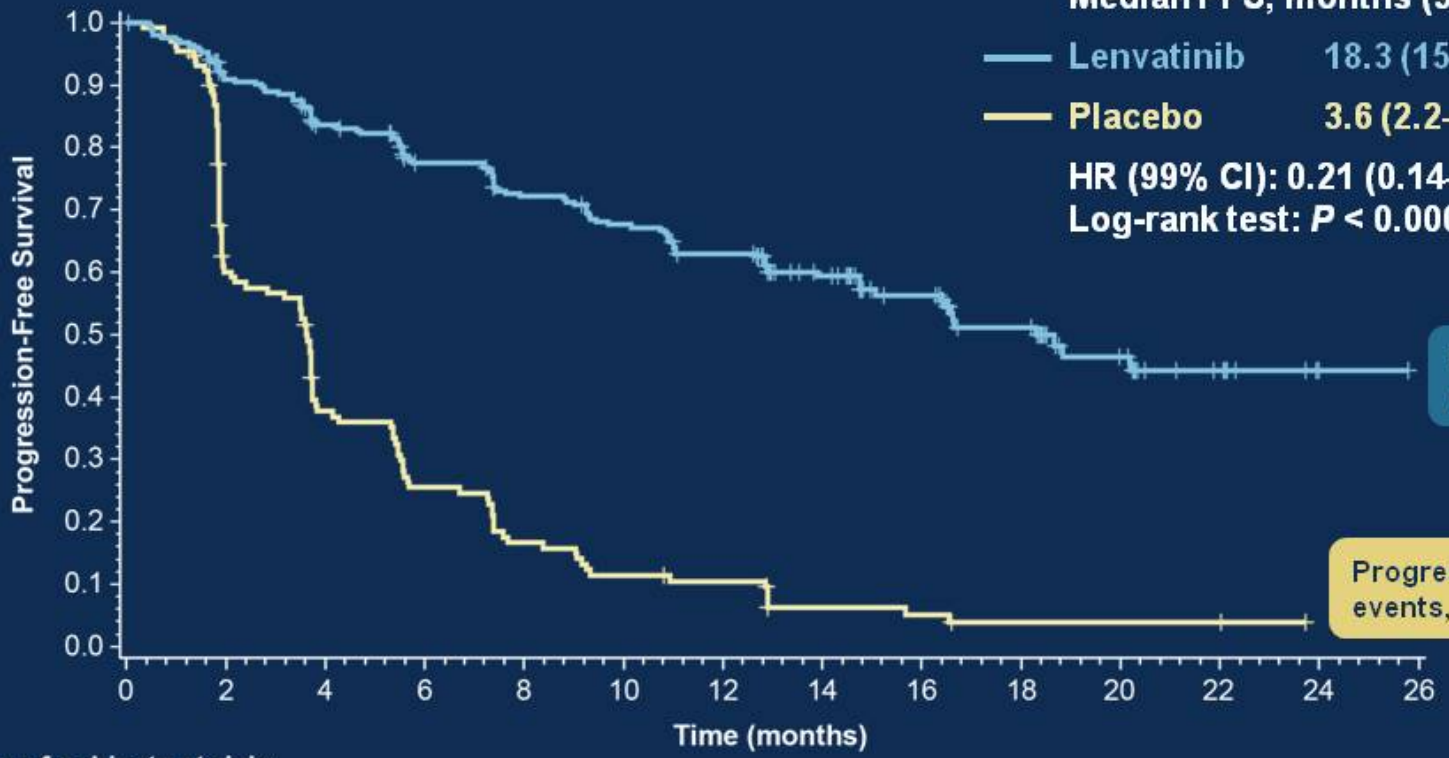
Primary Endpoint: Kaplan-Meier Estimate of PFS



Number of subjects at risk:

Lenvatinib	261	225	198	176	159	148	136	92	66	44	24	11	3	0
Placebo	131	71	43	29	19	13	11	5	4	2	2	2	0	0

CI, confidence interval; HR, hazard ratio; NR, not reached.

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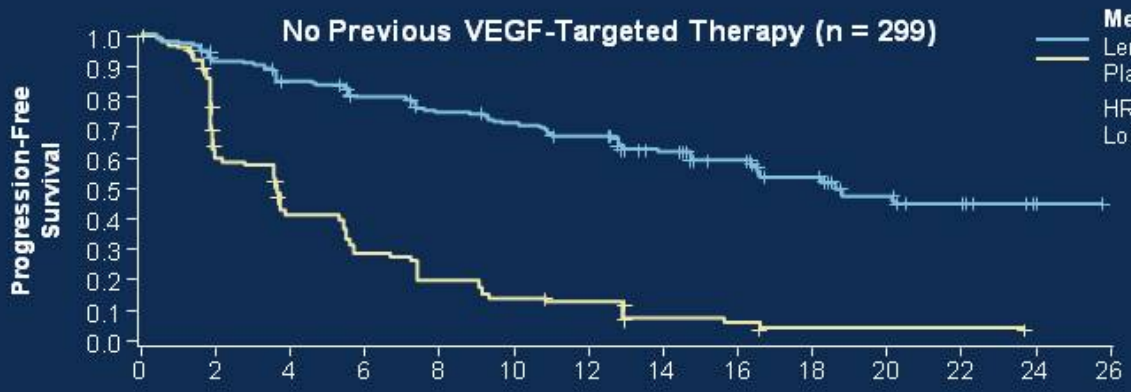
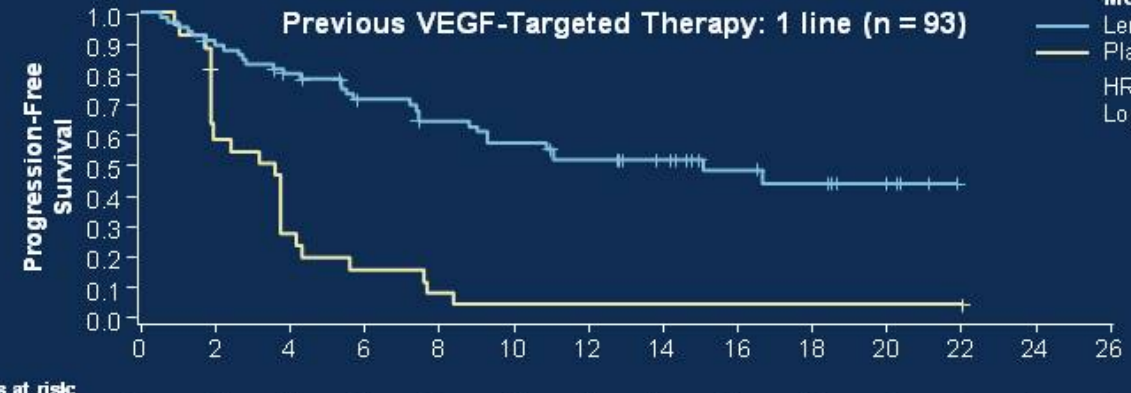
PFS by Previous VEGF-Targeted Therapy



Number of subjects at risk

Lenvatinib	195	167	148	135	123	116	108	72	52	34	20	11	3	0
Placebo	104	56	36	25	17	12	10	4	3	1	1	1	0	0



Number of subjects at risk

Lenvatinib	66	58	50	41	36	32	28	20	14	10	4	0	0	0
Placebo	27	15	7	4	2	1	1	1	1	1	1	1	0	0

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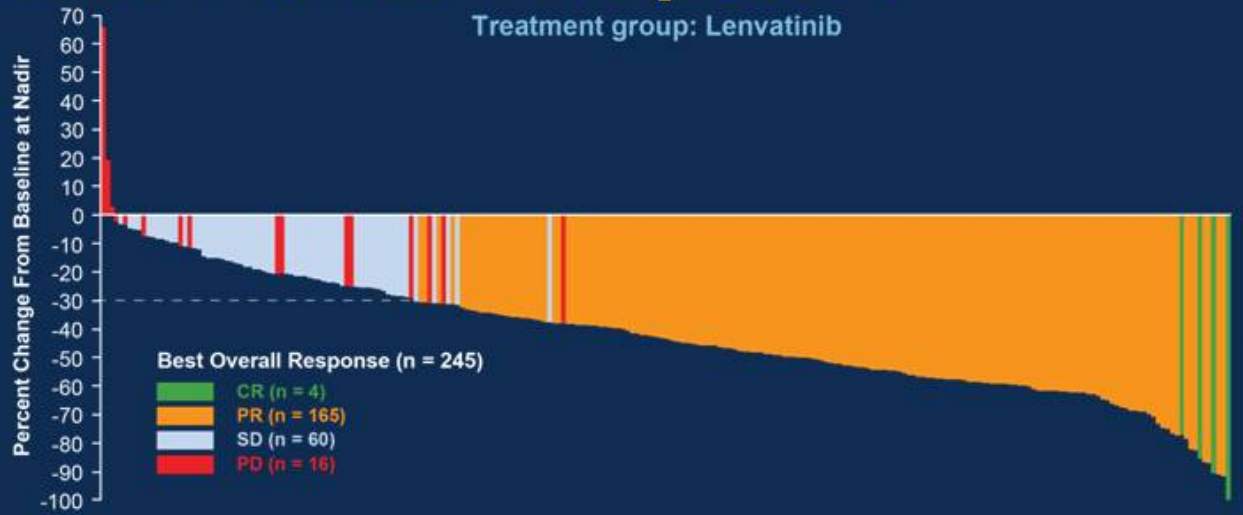
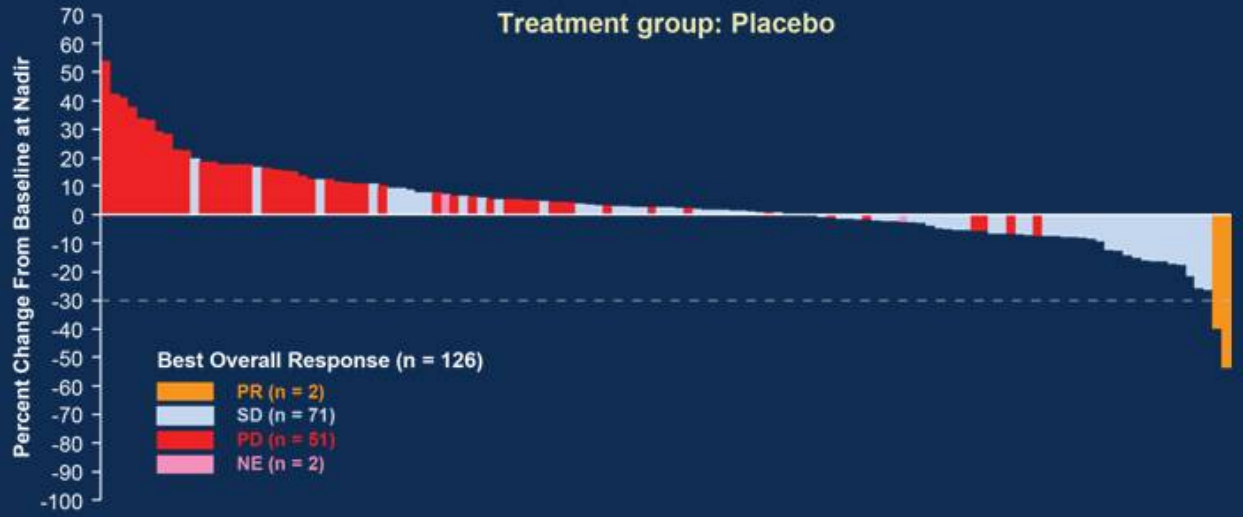
Best Tumor Response



Median tumor shrinkage for responders (range): -52% (-100%, -30%)



Median tumor shrinkage for all patients (range): +2% (-53%, +54%)

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

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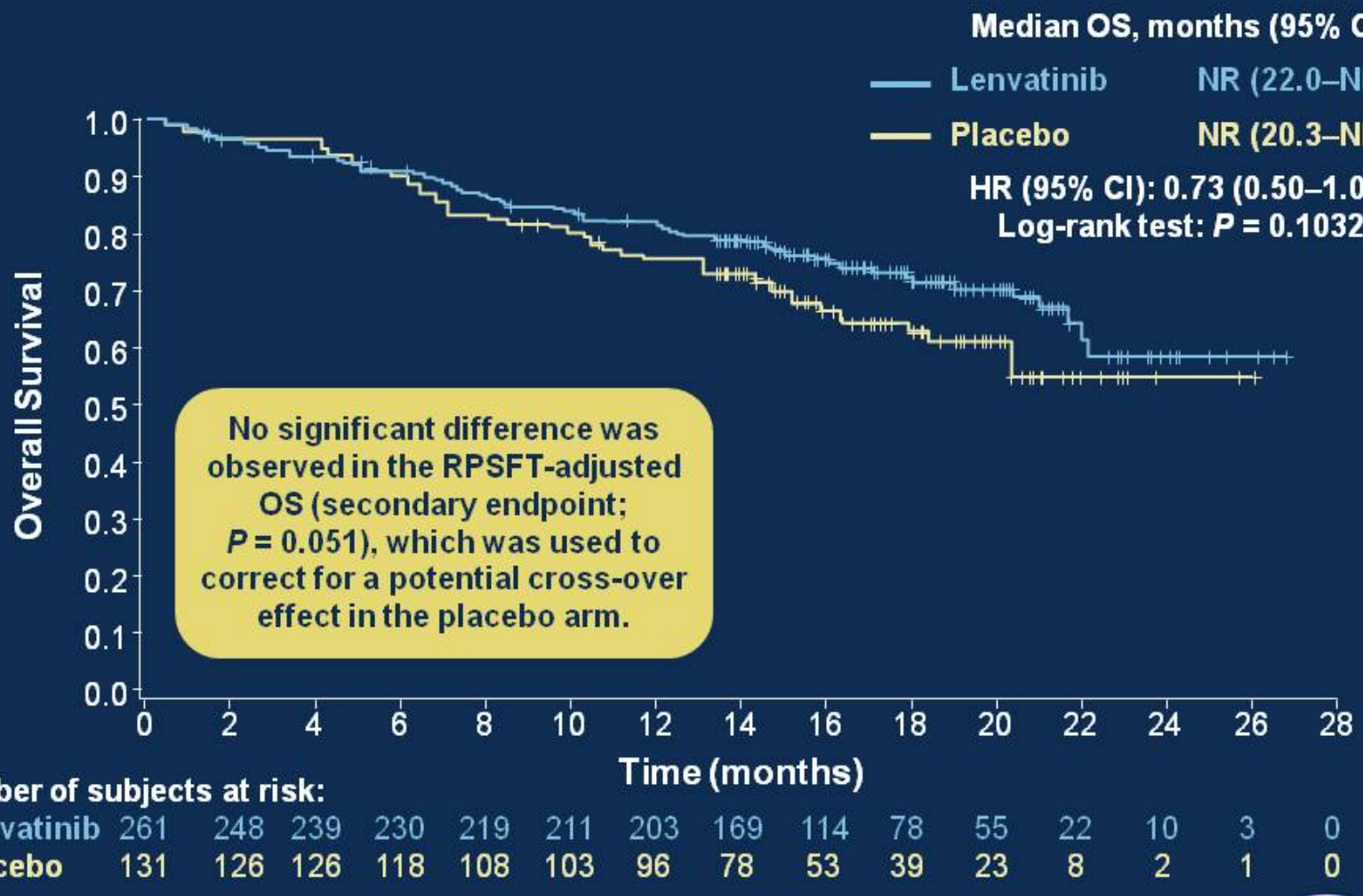
Overall Survival, ITT population



Number of subjects at risk:

Lenvatinib	261	248	239	230	219	211	203	169	114	78	55	22	10	3	0
Placebo	131	126	126	118	108	103	96	78	53	39	23	8	2	1	0

ITT, intent-to-treat; RPSFT, rank-preserving structural failure time.

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TEAEs of Special Interest

Adverse Event, %	Lenvatinib (n = 261)		Placebo (n = 131)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hypertension [a]	73	44	15	4
Proteinuria	32	10	3	0
Venous TEs	5	4	5	2
Arterial TEs	5	3	2	1
Renal failure [b]	4	2	1	1
Hepatic failure	0.4	0.4	0	0
PRES	0.4	0	0	0

[a] Includes 'hypertension' and 'blood pressure increased'.
[b] Includes 'renal failure' and 'renal failure acute'.
PRES, posterior reversible encephalopathy syndrome; TE, thromboembolic event; TEAEs, treatment-emergent adverse events.

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Conclusions

- In patients with RR-DTC, lenvatinib significantly prolonged median PFS by 14.7 months compared with placebo:
  - Lenvatinib median PFS: 18.3 months (95% CI 15.1–NR)
  - Placebo median PFS: 3.6 months (95% CI 2.2–3.7)
    - HR 0.21 (99% CI, 0.14–0.31)
- Response rates for lenvatinib and placebo, respectively, were:
  - ORR: 65% vs 2% (with CR: 2% vs 0%)
  - The median time to objective response for lenvatinib was 2.0 months (95% CI, 1.9–3.5 months)
  - The median duration of response for lenvatinib has not been reached
    - 75% of responders had an objective response >9.4 months
- Toxicities of therapy, although considerable, were managed with dose modification and medication

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