Multicenter randomized phase 2 trial of Gemcitabine - Platinum +/- Trastuzumab in advanced or metastatic urothelial carcinoma with HER2 overexpression

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Disclosure slide

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Introduction

- Urothelial carcinoma: 4th most common cancer among men
- 111,000 new cases and 40,000 deaths in 2011[1]
- Standard treatment in a metastatic setting:
  - ☞ Platinum + Gemcitabine chemotherapy[2]
- Median overall survival around 14 months

[1]Ferlay J et al. Eur J Cancer. 2010; 46(4):765-81. [2] Von der Maase et al. JCO 2005; 23:4602 - 8

The Human Epidermal growth Factor Receptor 2 (HER2) expression in Urothelial Carcinoma

- Incidence of HER2 over-expression (23-80%) and/or amplification (0-32%) remain uncertain[1-5]
- HER2: a TK receptor of the erb B family[6]
- Positive HER2 status is associated with disease progression and short survival[7].
- Trastuzumab is a monoclonal antibody targeted against HER2/neu receptor
- Trastuzumab can act synergistically with cisplatin with minimal additional side-effects suggesting it may be of value in the treatment of UC

1Marín AP, et al. J Cancer Res Clin Oncol. 2010;136:1915-20. 2Jimenez RE, et al. Clin Cancer Res. 2001;7:2440-7. 3Latif Z, et al. Br J Cancer. 2003 6; 89:1305-9. 4Coogan CL, et al. Urology. 2004 ;63:786-90. 5Caner V et al Pathol Oncol Res. 2008;14(3):261-6. 6 Tzahar E, et al. Mol Cell Biol. 1996; 16:5276-87. 7 Bolenz C, et al. BJU Int. 2010;106:1216-22.

Therapies with trastuzumab in UCs

Authors	Treatment	Design	Results
Amsellem-Ouazana D, *et al.* Ann Oncol. 2004;15:538	Paclitaxel + CarboPt + traztuzumab	2nd line Case report	Improve response and survival
Peyromaure M., *et al.* Eur Urology. 2005;48:771-8	Traztuzumab-based therapies	Report on 6 pts 1st, 2nd, and 3rd line	Partial disease regression in all cases
Salzberg M, et al. Eur J Cancer. 2006;42:2660-1.	Traztuzumab weekly	Report on 7 pts	1 SD for 19 weeks
Hussain M.H., *et al.* JCO. 2007;16:2218-24	Gemcitabin + Paclitaxel + CarboPt + traztuzumab	Phase II Multicenter	RR: 70, High cardiac toxicity rate (grade ≤2)

Hypothesis: could addition of trastuzumab to gemcitabin and platinum salt result in higher progression-free survival and clinical benefit?

Statistical Design

- Primary endpoint: Progression-Free Survival (radiological RECIST 1.0 or death)
- To detect 38% difference in median PFS (control = 6.5 months vs +trastuzumab = 9 months) with a power of 80 at 0.05 significance level (two-sided)
- Secondary endpoints: ORR, OS, Toxicity, Quality of life and evolution of serum HER2
- N=338 patients needed
- Stratification factors:
  - ECOG-PS: 0-1 vs 2
  - Setting: Advanced vs Metastatic disease

Treatment arms of the phase II randomize study

Arm A:

- **Gemcitabine: 1000 mg/m2 D1 & D8 every 21 D IV**
- ***If Creatinin clairance > 60 ml/min* :**
  - **Cisplatin = 70 mg/m², D1**
- ***If Creatinin clairance ≤ 60 ml/min* :**
  - **Carboplatin AUC 5, D1 every 21 D IV**

Arm B:

- **Same chemotherapy regimen with**
- **Herceptin® = loading dose (8 mg/Kg) then 6 mg/Kg IV every 21 D until progression**

- ***Treament for 6 cycles or PD --→ OFF treatment***

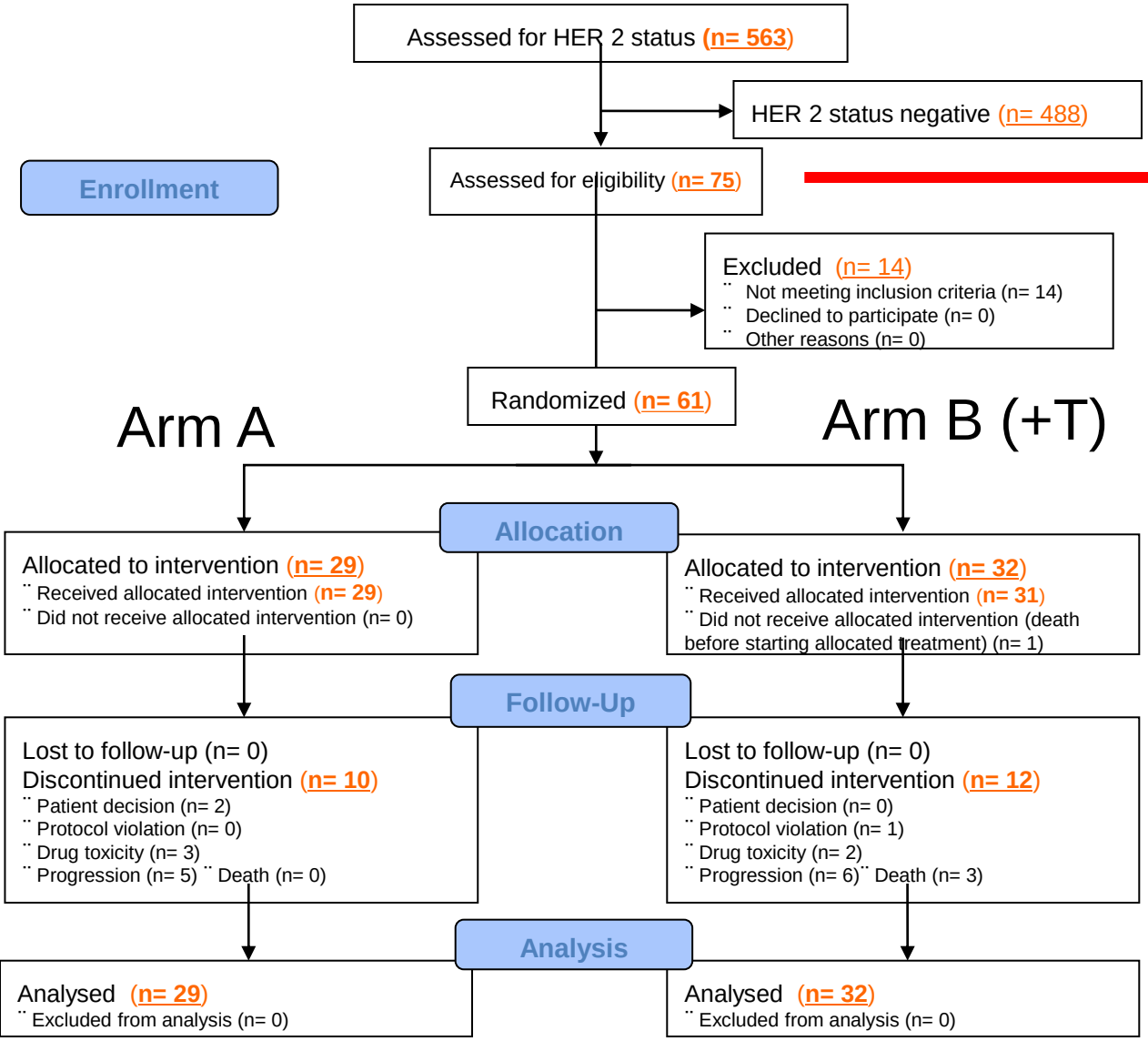
Key Eligibility criteria

- **Inclusion criteria**
  - Stage IV AJCC bladder Urothelial Carcinoma (Metastatic or T4b locally advanced unresectable)
  - Over-expression of HER2 upon IHC ("++ confirmed by FISH" or "+++")[1]
  - ECOG PS ≤ 2
  - Prior neo-adjuvant or adjuvant chemotherapy allowed if ≥ 6 months.
  - Normal biology parameters

- **Non-inclusion criteria**
  - Prior trastuzumab therapy
  - Heart failure, myocardial infarction, angina, significant valvular disease, or arrhythmias
  - CNS or meningeal metastasis
  - Any severe lung, liver or renal disease

1. Lae et al, Ann Oncol. 2010 Apr;21(4):815-9.

Methods



HER2 positive expression: 13.3%

Duration of study

- Recruitment : **Feb 2004 – Oct 2009 (slope: 10 pts per year)**
- Median follow-up **: 33.3 months (95CI: 32.8-37.3)**

Patients characteristics (n=61 pts)

Variables	Arm A (n=29 Pts)	Arm B+T[1] (n=32 Pts)
Mean Age (± SD); *years*	63.3(± 9.0)	62.1(± 10.3)
Gender Male; *n (%)*	27 (93.1)	27 (84.4)
ECOG – PS; *n (%)*		
0	11 (37.9)	12 (37.5)
1	13 (44.8)	14 (43.8)
2	5 (17.2)	6 (18.8)
Primary tumor (Bladder); *n (%)*	28 (96.6)	26 (81.3)
Metastatic Disease status; *n (%)*	25 (86.2)	25 (78.1)
Metastasis sites		
Bone; *n (%)*	5/28 (17.2)	7/32 (21.9)
Liver; *n (%)*	7/28 (24.1)	7/32 (21.9)
Lymph nodes; *n (%)*	21/28 (72.4)	25/32 (78.1)
Lung; *n (%)*	8/28 (27.6)	3/32 (9.4)
Visceral & bone; *n (%)*	19 (65.5)	16 (50.0)
HER2 status (IHC "++" + FISH"or +++")	1/28	1/31
Prior neo-/adjuvant chemotherapy; *n (%)*	6 (20.7)	12 (38.7)

[1] *T = trastuzumab*

Treatment Summary

	Arm A *n = 29 Pts*	Arm B (+ T[1]) *n = 32 Pts*
Creatinin clearance, mL/min		
< 60	**11 (37.9)**	**11 (34.3)**
≥ 60	**18 (62.1)**	**21 (65.6)**
Platinum regimens; *n (%)*		
Cisplatin based-CT	**15 (51.7)**	**17 (53.1)**
Carboplatin based-CT	**14 (48.3)**	**15 (46.9)**
Median chemotherapy cycles (range)	**6 (3 – 9)**	**8 (1 – 9)**
Median months on therapies (range)	**3.9 (1.6 – 6.5)**	**5.3 (0.2 – 14.5)**
Median months on maintenance trastuzumab therapy (range)	**-**	**10 (0.8-26.9)**
Median relative dose intensity (Range); (%)		
Gemcitabine	**0.79 (0.49-1.01)**	**0.77 (0.25-1.02)**
Platinum		
Cis	**0.96 (0.68-1.03)**	**1.00 (0.88-1.02)**
Carbo	**1.00 (0.81-1.14)**	**1.00 (0.69-1.19)**
Trastuzumab	**-**	**0.97 (0.57-2.04)**

Toxicity: Most common adverse events

Main toxicity (%)[2]	Arm A (n=29 Pts)		Arm B: + T[1] (n=32 Pts)	
	Gr 1&2	Gr 3&4	Gr 1&2	Gr 3&4
Nausea	72.4	-	54.8	3.2
Vomiting	24.1	-	35.5	3.2
Constipation	51.7	-	32.3	3.2
Diarrhea	27.6	3.4	48.1	3.2
Alopecia	17.2	-	12.9	-
Oedema	24.1	-	29	-
Anemia	55.2	41.4	61.3	38.3
Neutropenia	20.7	75.9	25.8	67.7
Febrile	3.4	-	3.2	6.5
Thrombocytopenia	41.4	48.3	45.2	38.7
Hypocalcemia	65.5	-	67.7	-

[1] *T = trastuzumab*

[2] *% of patients who presented at least one of the reported events*

Toxicity: Most common adverse events

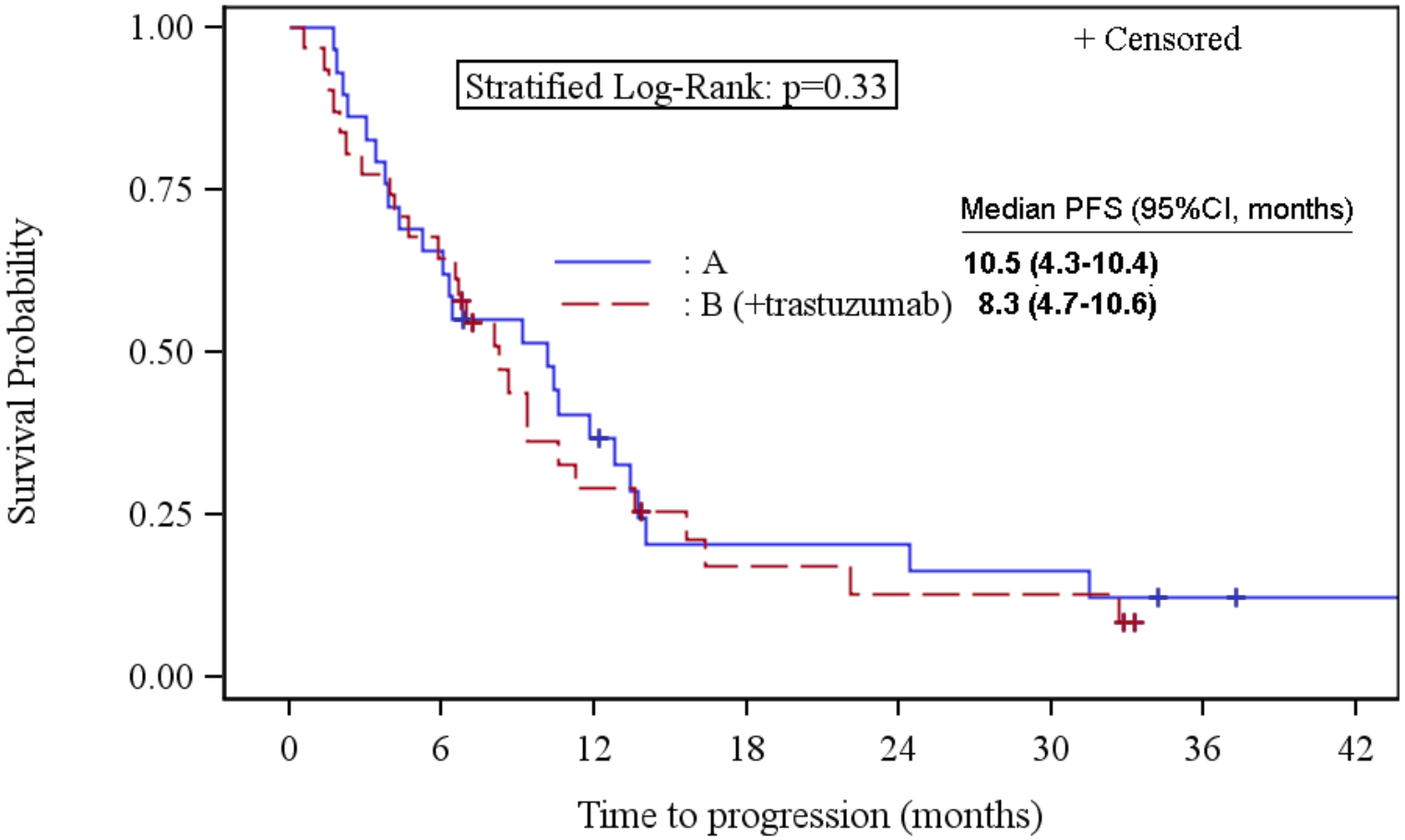
Main toxicity (%)[2]	Arm A (n=29 Pts)		Arm B: + T[1] (n=32 Pts)	
	Gr 1&2	Gr 3&4	Gr 1&2	Gr 3&4
Asthenia	44.8	3.4	28.1	3.2
Dyspnea (including exertional)	3.4	0	3.2	3.2
LVEF decreased	44.8	0	40.6	3.2
Rash	3.4	0	0	0
Gastro-intestinal disorders:				
- Abdominal pain	13.8	0	3.2	0
- Abdominal distention	0	0	3.2	0
- Subileus	3.4	0	0	0
- Unspecifed GI disorder	3.4	0	6.3	0

[1] *T = trastuzumab*

[2] *% of patients who presented at least one of the reported events*

[3] *LVEF : Left ventricular ejection fraction*

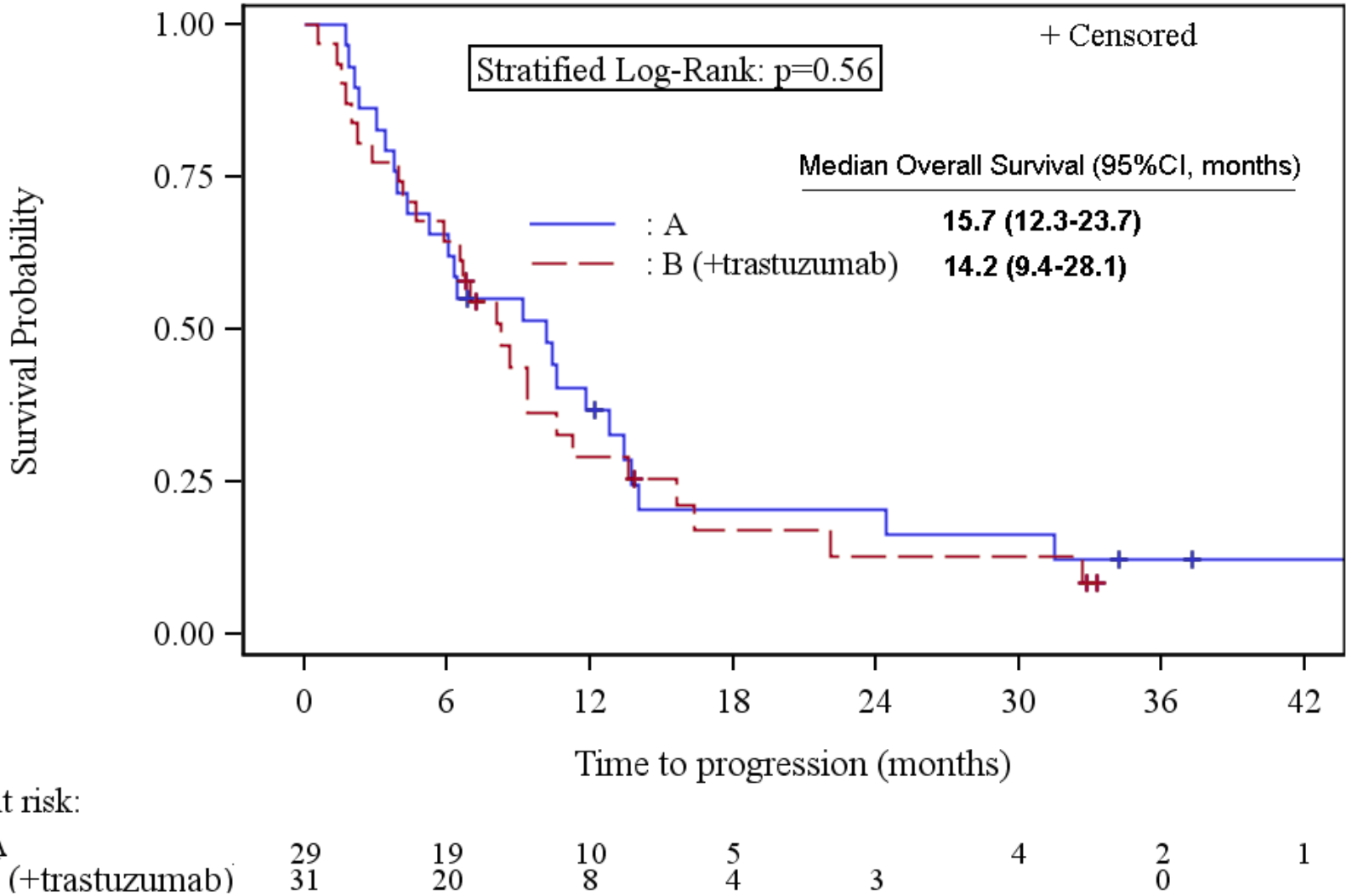
Progression-Free Survival (PFS)



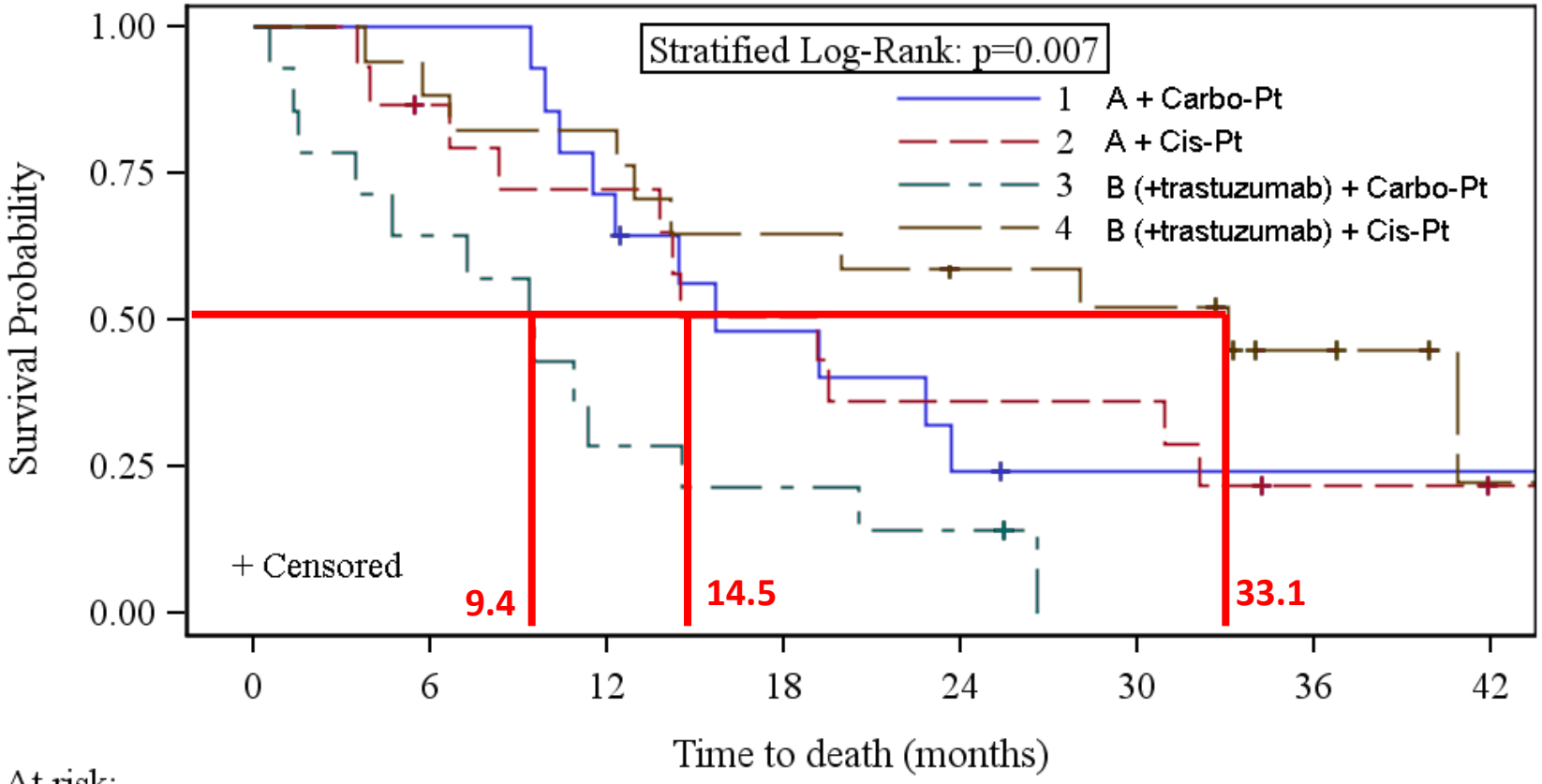
At risk:

A	29	19	10	5	4	2	1
B (+trastuzumab)	31	20	8	4	3	0	

Overall Survival (OS)



Descriptive Results: OS related to baseline platinum



At risk:

1	14		10	6	3	2		
2	15	12	10	7	5		2	1
3	14	9	4	3	2	0		
4	17	15	14	11	9	8	4	1

T = trastuzumab

Efficacy Summary

	Arm A *n = 29 Pts*	Arm B (+ T[1]) *n = 32 Pts*	p-value (2-sided)
Median PFS (Months); (95 IC)	**10.2** (5.3 – 13.4)	**8.3** (5.9 – 10.6)	0.69
cisplatin based-CT	6.4 (2.3 – 12.8)	10.6 (5.8 – 22.1)	
carboplatin based-CT	10.2 (3.9 – 24.4)	6.4 (1.5 – 8.6)	
Median OS (Months); (95 IC)	**15.7** (12.3 – 22.8)	**14.2** (9.5 – 28.1)	0.51
cisplatin based-CT	14.5 (6.7 – 30.9)	33.1 (12.4 – 50.0)	
carboplatin based-CT	15.7 (10.4 – 23.7)	9.4 (1.5 – 14.6)	
Objective response rate; *n(%)*			0.39
RC	**6** (20.7)	**7** (21.9)	
RP	**13** (44.8)	**10** (31.3)	
SD	**6** (20.7)	**7** (21.9)	
PD	**4** (13.8)	**4** (12.5)	

[1] *T = trastuzumab*

Quality of Life data

- **Baseline scores (median (range))**
  - *Global health status/QoL :*

    A (N=23) : 58 (8 - 100) B (N=19) : 58 (17 - 100) p=0.50
  - *Functioning scale :*

    A (N=25) : 84 (20 - 100) B (N=19) : 84 (49 - 100) p=0.68
  - *Symptoms scale* :

    A (N=21) : 20 (0 - 67) B (N=17) : 23 (3 - 44) p=0.92

- **Change from baseline (last questionnaire on treatment)**
  - *Global health status*/QoL:

    A (N=23) : **0** (-58 - +50) B (N=19) : **0** (-50 - +50) p=0.74
  - *Functioning scale* :

    A (N=25) : **0** (-47 - +69) B (N=19) : **0** (-31 - +9) p=0.69
  - *Symptoms scale* :

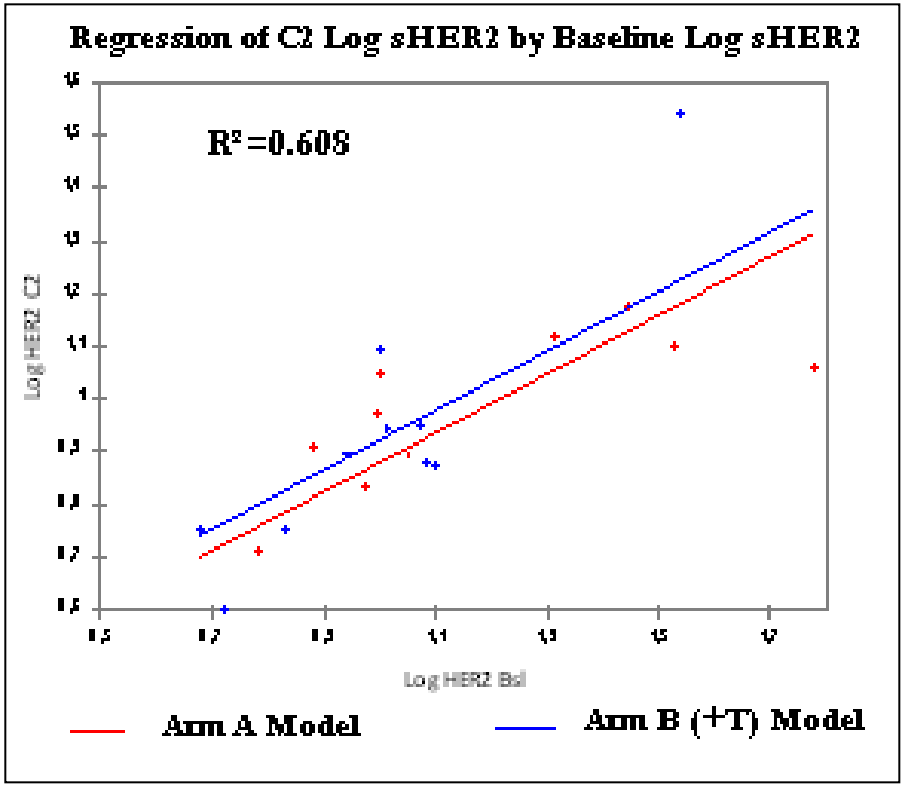
    A (N=21) : **0** (-51 - +51) B (N=17) : **0** (-26 - +28) p=0.71

↳ Arms were well balanced at baseline for QoL

↳ No impact of trastuzumab on QoL

Serum HER2 (sHER2) Predictive model

- Baseline sHER2 was strongly related to sHER2 level at C2 (Fisher=25.6, p<0.0001) whatever the treatment arm
- Baseline sHER2 was related to PFS (p=0.03, Cox regression with continuous covariate)



Predictive factors for PFS

- Main predictive factors (multivariate Cox regression):
  - PS-ECOG 0-1 vs 2: HR=3.66 (95CI:[1.72-7.78], p=0.0038)
  - Baseline sHER2: HR=1.012 (95CI:[1.001-1.023], (p=0.03)
  - Haemoglobin: NS (p=0.07)
  - Locally advanced vs Metastatic disease: NS (p=0.26)
  - LDH: NS (p=0.49)
  - Treatment arm A vs B(+trastuzumab): NS (p=0.49)
  - Platinum analog Cis vs Carbo: NS (p=0.77)
  - Creatinin clearance: NS (p=0.85)

Conclusions

- HER2 over-expression is rare (13.3%) in advanced and/or mUCs
- No difference was observed on ORR, PFS, OS and Quality of Live between CG +/- trastuzumab
- CG-trastuzumab was feasible - (with more febrile neutropenia, LVEF decreased and dyspnea)
- Baseline serum HER2 level was predictive of PFS whatever the treatment
- Trastuzumab could have a synergetic effect with cisplatinum leading to a longer OS

What is next?

- Clinical trials with HER2 targeting therapy in UC should be performed at an European level
- Should we propose a combination with trastuzumab to patient who could only receive cisplatium chemotherapy?
- Should we select patient based on baseline serum HER2?
- Should we use a more powerful drug: TDM-1?

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- Pathology Unit of Cochin Hospital (HER2 centralization)
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