Poster Discussion (1022-1023)

37th ESMO Congress
Vienna, Austria
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Disclosure slide

- Advisory Board (Merck KGaA)

First-line therapy for R/M

- The backbone of treatment for R/M HNSCC is palliative systemic therapy with standard chemotherapeutic agents and inhibitors of Epidermal Growth Factor Receptor (EGFR)*
- Despite the use of third generation chemotherapeutic agents and targeted therapy, the median overall survival for patients with R/M HNSCC remains less that 1 year
- Novel therapeutic strategies are needed, and enrollment in clinical trials should be encouraged

*Vermorken et al: N Engl J Med 2008; 359:1116-1127

First-line chemotherapy for R/M HNSCC

- No specific platinum chemotherapy regimen is clearly superior in the treatment of R/M HNSCC
- The most promising single agents on the basis of phase II data are docetaxel, paclitaxel and pemetrexed
- Pemetrexed and cisplatin did not prove superior to cisplatin alone in terms of response rate (RR), Progression-free (PFS) and Overall Survival (OS) in a randomized phase III study*.Of note, however, preplanned subset analysis of patients with oropharynx cancer and patients with good performance status (PS) had superior PFS and OS with the addition of pemetrexed compared with cisplatin alone

***Urba et al: Cancer. 2012;20 March**

1022PD

Phase II Study of Pemetrexed, Cisplatin and Cetuximab in Advanced Squamous Cell Carcinoma of the Head and Neck

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Study Design

- Phase II, open-label, single-arm study
- Patients with recurrent and/or metastatic SCCHN

N = 65

Study Treatment

Pemetrexed 500 mg/m²
Cisplatin 75 mg/m² D1 Q 21 d
Cetuximab 250 mg/m² weekly
(Cetuximab loading dose = 400 mg/m²)
x ≤6 Cycles

Optional maintenance after a minimum of 4 cycles of triplet

Pemetrexed 500 mg/m² q 21 d

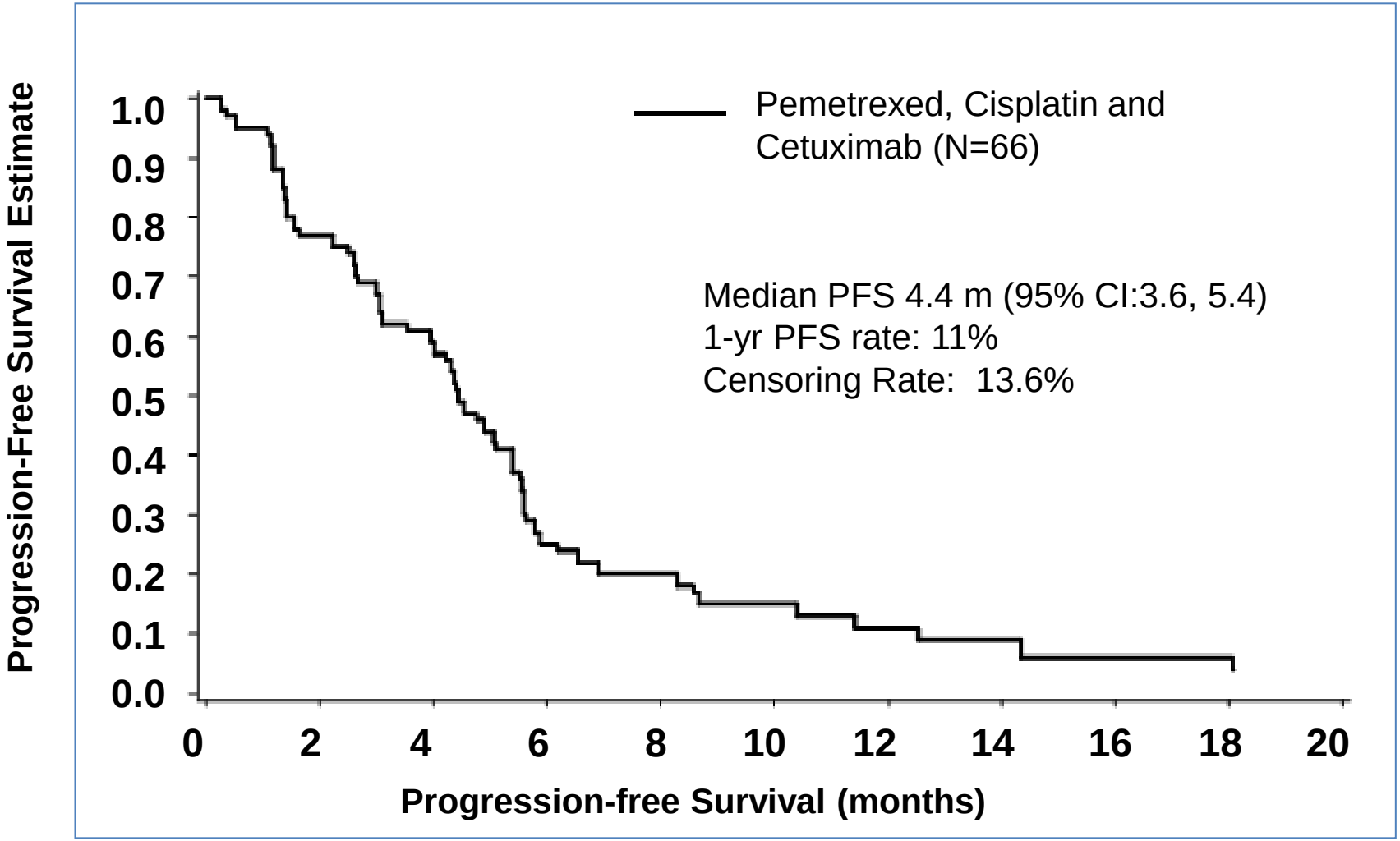
Cetuximab 250 mg/m² weekly

Folic acid , vit.amin B_{12} and dexamethasone given for prophylaxis ; ciprofloxacin (or equivalent) d2-12 during triple therapy (protocol amendment after 35 patients) ,diphenhydramine (or equivalent) before cetuximab

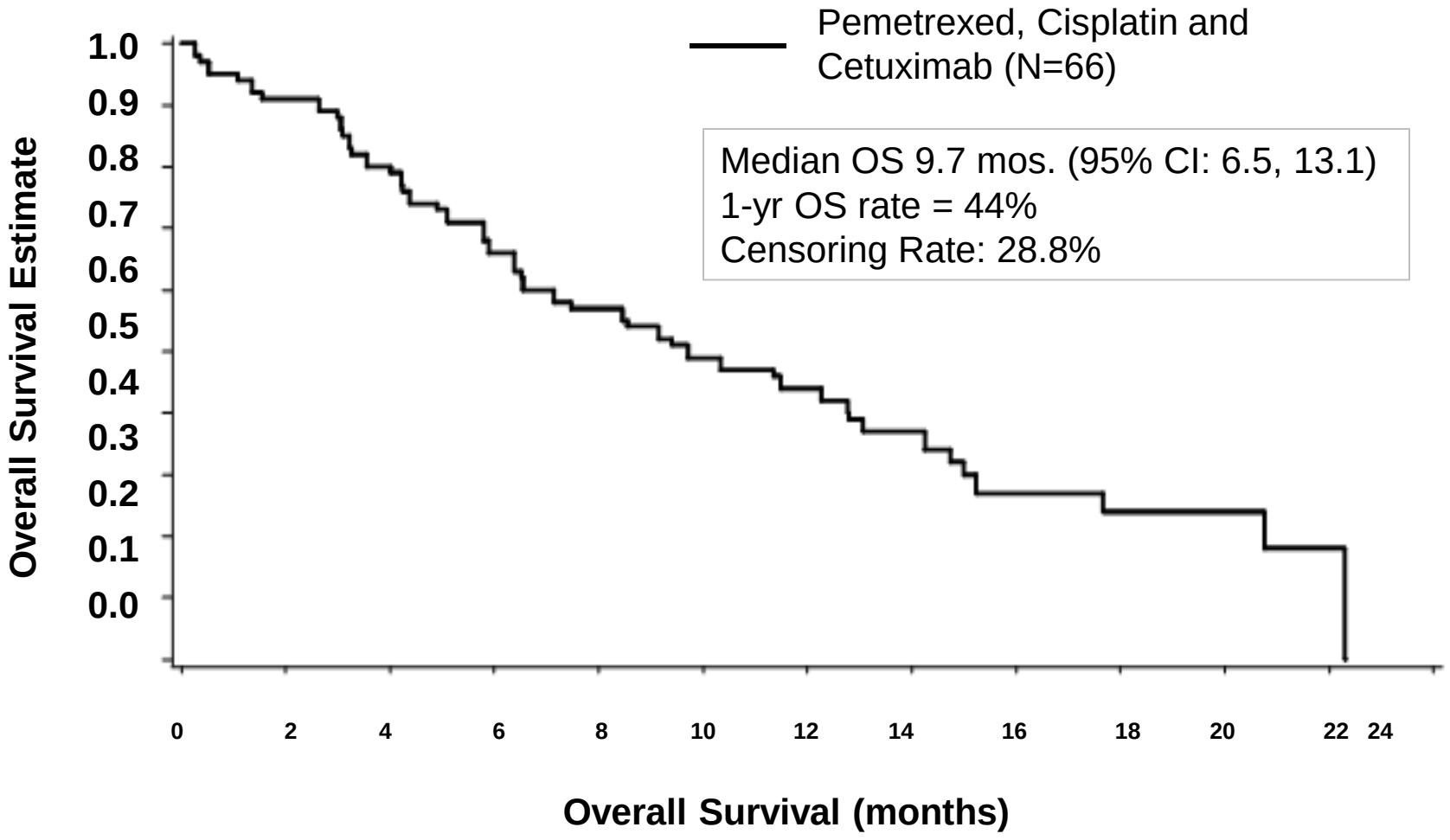
Study Population:

- ECOG Performance Status 0/1
- At least 6 months since last chemotherapy
- No more than 1 prior systemic therapy for loco-regional primary disease and no prior systemic therapy for recurrent/metastatic disease

Progression-free Survival



Overall Survival



Selected Grade 3/4 AEs Related to Study Drug in ≥ 10% of Patients

Adverse Events	Grade 3 n (%)	Grade 4 n (%)
N = 66		
Leukopenia	14 (21.2)	9 (13.6)
Fatigue	14 (21.2)	2 (3.0)
Neutropenia	12 (18.2)	10 (15.2)
Hypomagnesemia	5 (7.6)	2 (3.0)
Anorexia	7 (10.6)	1 (1.5)
Any Infection	4 (6.1)	3 (4.5)

Treatment-Related Safety Events

Treatment- Related Deaths	N = 66	n	(%)
Within Triplet and Maintenance Phase		5	(7.6)
Unknown		1	(1.5)
Septic shock and respiratory failure		1	(1.5)
Aspiration pneumonia leading to respiratory failure		2	(3.0)
Sepsis, tumor emboli and respiratory failure		1	(1.5)

CONCLUSIONS

- Efficacy results were consistent with current standard treatment for R/M-SCCHN, but the prespecified goal of a median PFS of 5.5 months was not met.
- Most toxicities were grade 1/2. Most frequently observed grade 3/4 toxicities were:
    - Leukopenia 35%
    - Neutropenia 33%
    - Hypomagnesemia 11%
- Correlative analysis for translational data with clinical outcomes is pending

Temsirolimus is active in refractory squamous cell carcinoma of the Head and Neck (SCCHN) failing platinum-based chemotherapy and cetuximab: efficacy and toxicity data from the phase II TEMHEAD study

V. Grünwald, U. Keilholz, A. Boehm, O. Guntinas-Lichius, B. Hennemann, H.J. Schmoll, P. Ivanyi, A. Zörner, A. Zapf, T.C. Gauler

Targeting mTOR Pathway

- The PI3K/AKT/mTOR pathway is frequently activated in HNSCC
- 74% of HNSCC contain genetic alterations of PI3K/AKT/mTOR pathway (PI3KCA mutations, PTEN loss etc)*
- Targeting mTOR pathway appears a rational therapeutic strategy

- ***Morris LG PNAs Nov 2011**

Study design

- **Design:** Single arm, open-label phase II trial
- **Primary endpoint:** progression free survival rate at 12 weeks (PFR_{12wks}) >20%.
- **Patients:** advanced/metastatic SCCHN with failure of platinum and cetuximab therapy
- **Treatment:** Temsirolimus 25 mg wkly. i.v. until disease progression or unacceptable toxicity
- **Disposition:** 12 of 40 pts. (30%) completed the 12 weeks interval.

Best response according to RECIST 1.0

	n	%
CR	**0**	**0**
PR	**0**	**0**
SD	**19**	**55.9**
PD	**10**	**29.4**
NE	**1**	**2.9**

4 missing (11.8%) of 34 assessable patients

Clinical efficacy of temsirolimus

	days	%	CI95%
PFR_{12wks}	-	40	25-55%
OS_{12wks}	-	66	49-79%
mPFS	56	-	36-113d
mOS	152	-	76-256d

PFR: Progression -free survival rate
mPFS: median PFS
mOS: median OS

Most common Adverse Events

(all-causality in >10% of patients)

N=40	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Fatigue	19 (47.5)	3 (7.5)	1 (2.5)
Anemia	10 (25.0)	6 (15.0)	2 (5.0)
Nausea	8 (20.0)	0	0
Pneumonia	8 (20.0)	3 (7.5)	1 (2.5)
Dyspnea	7 (17.5)	1 (2.5)	0
Vomiting	7 (17.5)	0	0
Infection	6 (15.0)	2 (5.0)	0
Weight loss	6 (15.0)	0	0
Rash	6 (15.0)	0	0
Pruritus	5 (12.5)	0	0
Facial edema	5 (12.5)	0	0
Diarrhea	5 (12.5)	0	0
Stomatitis	5 (12.5)	0	0

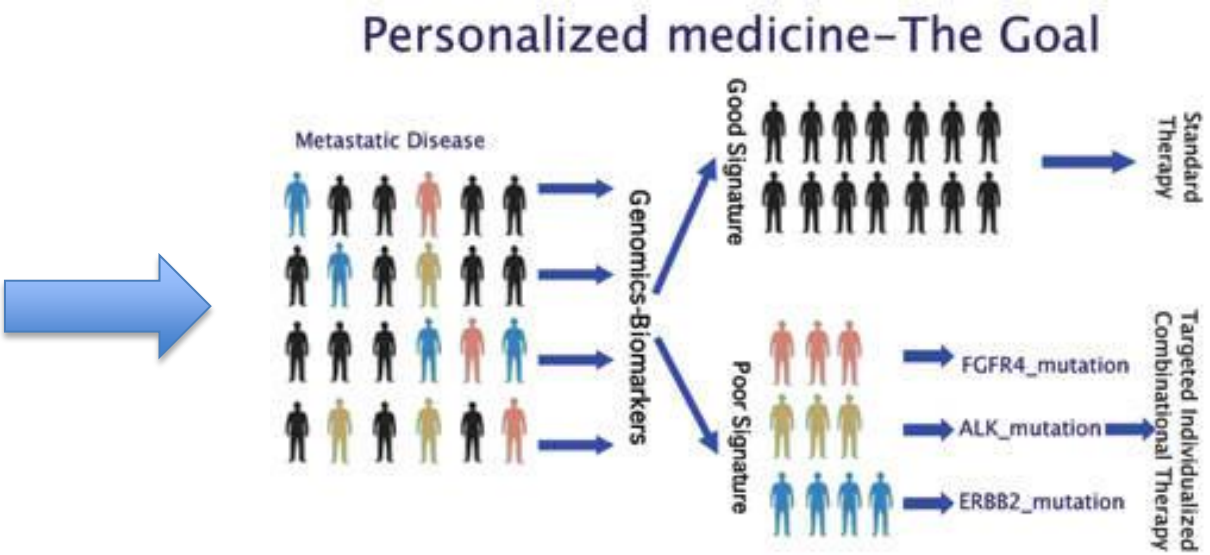
Conclusions

- Temsirolimus shows clinical efficacy with a median PFS of 56 days
- Duration of PFS is within expectations for effective regimens in refractory disease
  - cetuximab TTP 70d (2.3 mo.)
  - docetaxel and cetuximab PFS 3.1 mo.
- Further exploration of mTOR inhibitors in SCCHN is warranted

Vermorken et al. J Clin Oncol 2007;25:2171–7. Knödler et al. Oncology 2012, in press

The future

Randomized phase II biomarker trial design, which, after completion, recommends the type of phase III trial to be used for the definitive testing of the therapy and the biomarker



Thank you