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Randomized Phase II Study of MEHD7945A vs Cetuximab in ≥2nd-line Recurrent/Metastatic Squamous Cell Carcinoma of the Head & Neck Progressive on/after Platinum-based Chemotherapy

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- XW is an employee and shareholder of Roche
- AK is an employee and shareholder of Roche
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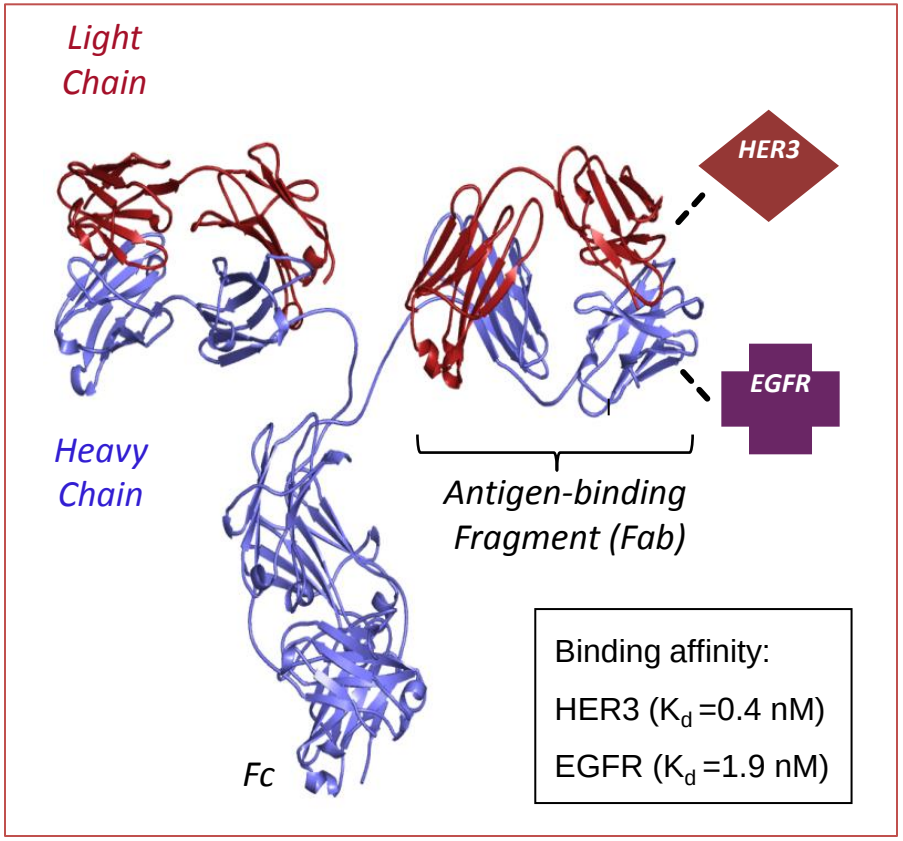
- BM is an employee and shareholder of Roche
- AP is an employee and a shareholder of Roche
- JV is a consultant for Genentech, Inc.

Anti-HER3/EGFR Dual-Action Fab: MEHD7945A "Duligotuzumab"



- Affinity-matured, humanized IgG1
- Dual binding specificity:
  - Each antibody arm (Fab) can bind to either EGFR or HER3 with high affinity
  - Simultaneously blocks ligand-binding to EGFR and HER3
- Inhibits signaling by all major ligand-dependent HER-family dimers
- Mediates ADCC

Schaefer et al., Cancer Cell, 2011.

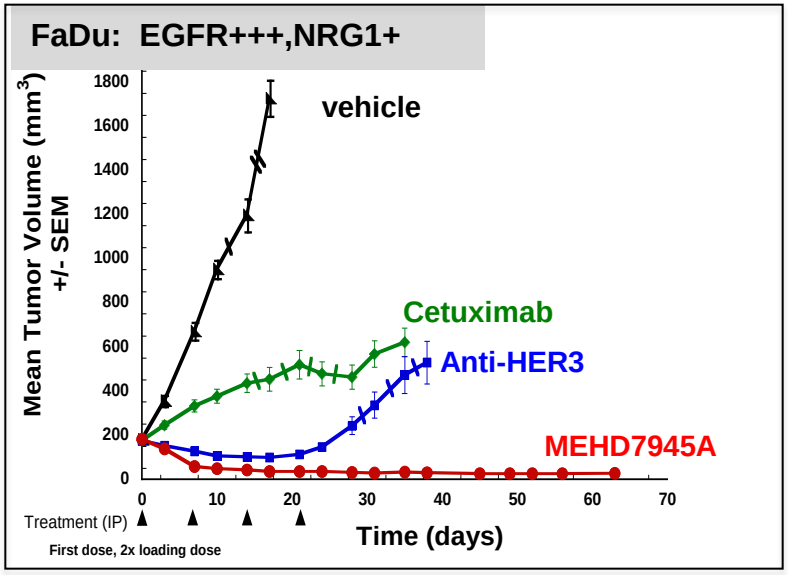
Dual Inhibition of EGFR & HER3: Rational therapeutic strategy in SCCHN

- EGFR inhibition in SCCHN clinically validated

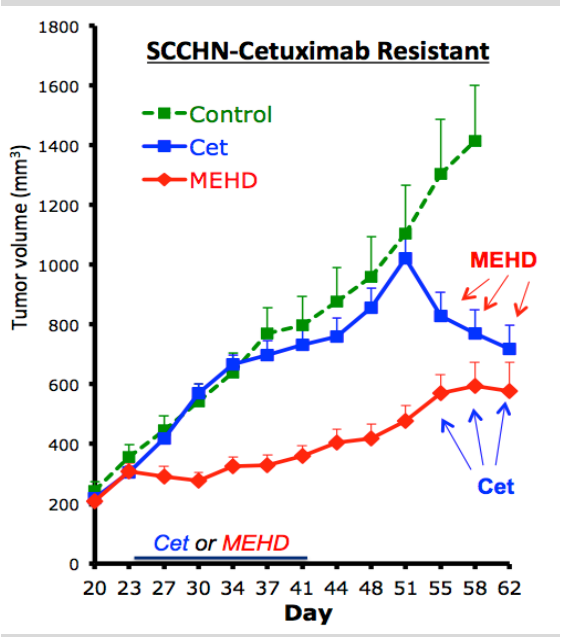
  (Vermorken JB, JCO 2007 & NEJM 2008; Bonner JA, NEJM 2006 & Lancet 2010)

- MEHD7945A exhibits superior preclinical activity compared to mono-specific anti-HER antibodies, with strongest activity in SCCHN models

  (Schaefer G, Cancer Cell 2011)



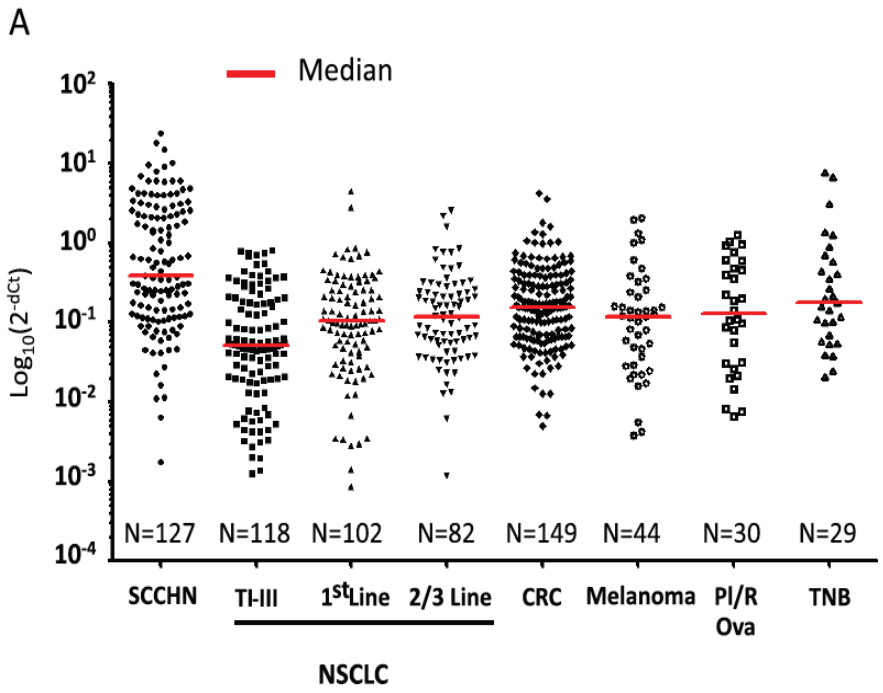
- HER3 activation associated with de novo and acquired resistance to anti-EGFR therapy in SCCHN models; MEHD7945A active in cetuximab resistant models *(Wilson T, Cancer Cell 2011; Huang S, Cancer Res 2013)*



Biomarker Hypothesis: Expression of the HER3 ligand NRG1 in tumors may select for benefit by dual inhibition of EGFR/HER3

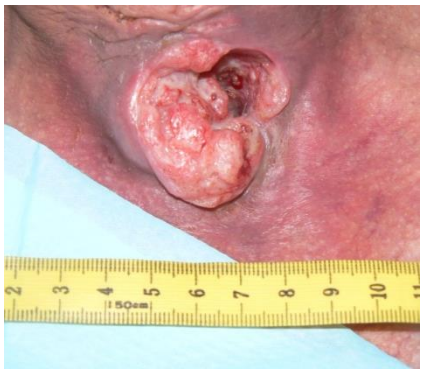
NRG1 expression elevated in clinical SCCHN tumor samples in comparison to other indications

(Shames et al., PLosOne 2013)

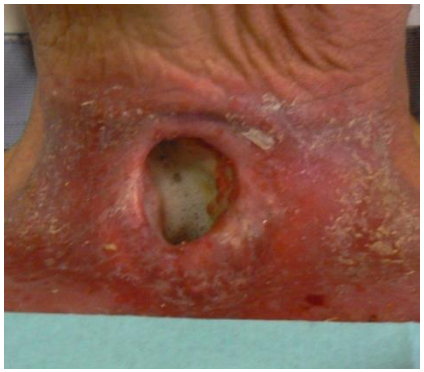


Durable responses in Ph 1a: 2 HPV-neg SCCHN patients with high tumor NRG1

(Cervantes A et al, J Clin Oncol 30, 2012 [suppl. Abstr 2568])



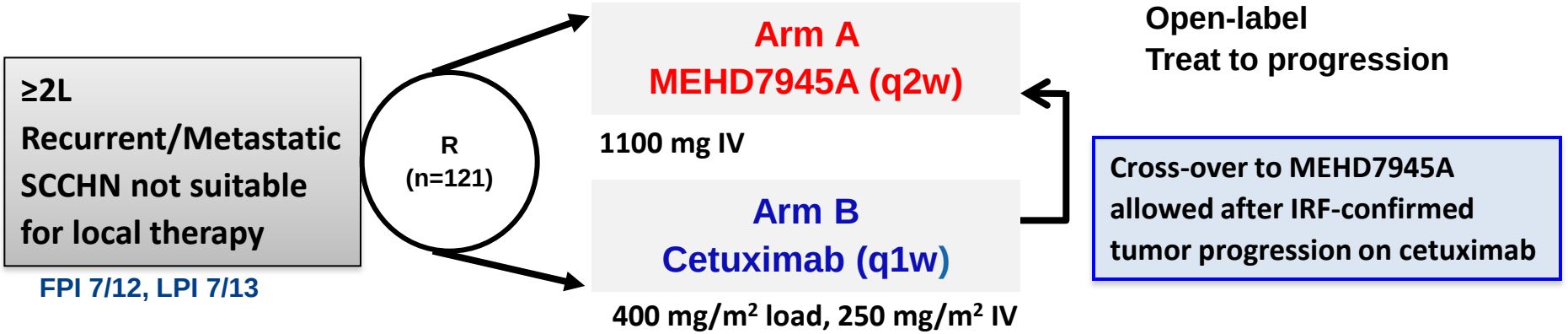
Baseline



C5D1 (after 4 doses, 8 weeks)

Cetuximab-Relapsed SCCHN of the Larynx, sustained regression for >2.5 years on MEHD7945A 14 mg/kg q2w

Phase II MEHD7945A vs Cetuximab in ≥2nd-line Recurrent/Metastatic SCCHN (MEHGAN)



Key eligibility	Stratification factors	1° objective	2° objectives
• Histologically confirmed recurrent or metastatic (R/M) SCCHN • Progressive disease on/after platinum based chemotherapy for R/M disease • Not suitable for local therapy, e.g. relapsed incurable SCCHN • No prior anti-EGFR therapy • ECOG 0-2 • Measurable disease by RECIST 1.1 • Archival or fresh tissue available • Life expectancy ≥12 weeks	• ECOG 0/1 vs 2 • Time to platinum failure (≤ 2 months vs >2 months)	**PFS** •All randomized patients •Biomarker positive patients (high NRG1 by qRT-PCR)	• OS • ORR • Safety/ tolerability Arm A only: • PK; ATA

MEHGAN Study: Conduct & Analysis Population

Study conduct:
- 36 sites in 11 countries[1]
- 12 months enrollment duration

Analysis population
- Data cut-off March 20, 2014
- All randomized patients followed for a minimum of 8.4 months

121 Randomized[2]
59 MEHD7945A
62 cetuximab[2]

120 Safety Evaluable
107 biomarker evaluable
[20 crossover patients[3]]

102 PFS events
73 OS events

11 pts remain on study [4]

1. 33 US, 88 ex-US (21 ROM, 17 FRA, 11 GBR, 10 AUS, 10 ESP, 7 BUL, 7 HUN, 3 GER, 1 BEL and 1 ITA)
2. One patient randomized twice in error
3. 20 crossover pts received at least one dose of MEHD
4. 5 cetuximab, 2 MEHD, 4 crossover

Key Baseline Characteristics

		MEHD7945A (*n* = 59)	Cetuximab (*n* = 62)	All Patients (*n* = 121)
Age (years)	**Median (range)**	62.0 (29 – 80)	62.0 (28 - 84)	62.0 (28 – 84)
Sex	**Male**	55 (93%)	46 (75%)	101 (84%)
Race	**White**	47 (80%)	45 (74%)	92 (77%)
Tobacco use history	**Never**	12 (20%)	8 (13%)	20 (17%)
ECOG PS	**0/1**	50 (85%)	52 (85%)	102 (85%)
Time to PD since last platinum-based chemo	**≤ 2 months**	31 (53%)	34 (55%)	65 (54%)
Site of primary tumor	**Oral cavity**	15 (25%)	20 (32%)	35 (29%)
	Oropharynx	16 (27%)	20 (32%)	36 (30%)
	Larynx	11 (19%)	8 (13%)	19 (16%)
	Hypopharynx	6 (10%)	6 (10%)	12 (10%)
	Unknown primary site	4(7%)	2 (3%)	6 (5%)
HPV (qRT-PCR assay)	**Positive**	10 (17%)	15 (24%)	25 (21%)
Prior therapies, n (%)	**Radiation Therapy**	52 (88%)	52 (84%)	104 (86%)
# Chemotherapy prior to study *	**1**	37 (63%)	31 (50%)	68 (56%)
	≥2	22 (37%)	30 (49%)	52 (43%)
Extent of disease at baseline	**Locoregional recurrence only**	4 (7%)	13 (21%)	17 (14%)

* 26 patients enrolled in 1L R/M setting, without significant impact on efficacy results

Adverse Events Reported in ≥ 15% of Patients Regardless of Attribution

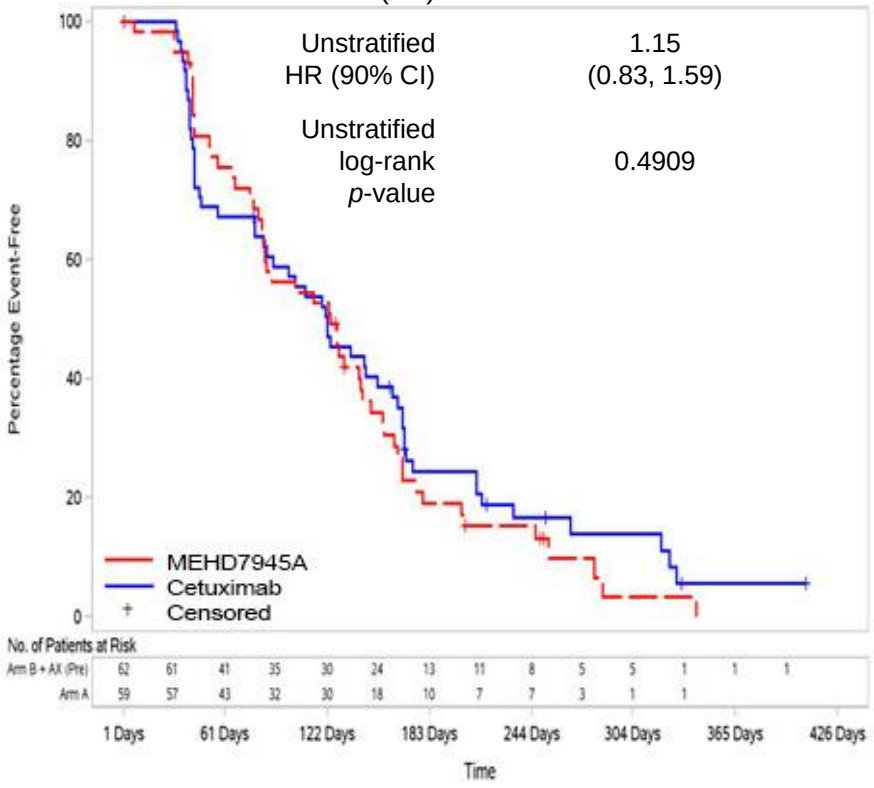
MedDRA Preferred Term	MEHD7945A (*n* = 59)		Cetuximab (*n* = 61)	
	Any Grade	≥ G3	Any Grade	≥ G3
All	58 (98.3%)	36 (61.)%)	59 (96.7)	31 (50.8%)
RASH & related MedDRA terms #	29 (49.2%)	-	40 (65.6%)	3 (4.9%)
INFECTIONS (SOC) #	33 (55.9%)	13 (22.0%)	26 (42.6%)	7 (11.5%)
DIARRHOEA	25 (42.4%)	2 (3.4%)	14 (23.0%)	-
FATIGUE	19 (32.2%)	2 (3.4%)	18 (29.5%)	1 (1.6%)
NAUSEA	13 (22.0%)	-	18 (29.5%)	-
HYPOMAGNESAEMIA	12 (20.3%)	1 (1.7%)	15 (24.6%)	3 (4.9)
VOMITING	12 (20.3%)	-	11 (18.0%)	-
PYREXIA *	15 (25.4%)	-	6 (9.8%)	-
HEADACHE *	15 (25.4%)	-	5 (8.2%)	-
PARONYCHIA	13 (22.0%)	-	6 (9.8%)	-
SKIN FISSURES	11 (18.6%)	-	8 (13.1%)	1 (1.6%)
DECREASED APPETITE	10 (16.9%)	1 (1.7%)	10 (16.4%)	1 (1.6%)
MUCOSAL INFLAMMATION	13 (22.0%)	-	4 (6.6%)	-
WEIGHT DECREASED	6 (10.2%)	-	11 (18.0%)	1 (1.6%)
CONSTIPATION	9 (15.3%)	-	7 (11.5%)	-
DRY SKIN	8 (13.6%)	-	10 (16.4%)	-
DYSPNOEA	7 (11.9%)	1 (1.7%)	11 (18.0%)	4 (6.6%)

- IRR symptoms, # includes multiple preferred terms
- Numerical imbalance in infections and non-PD deaths (no consistent etiology)

MEHD7945A vs Cetuximab in ITT population: Comparable Anti-Tumor Activity

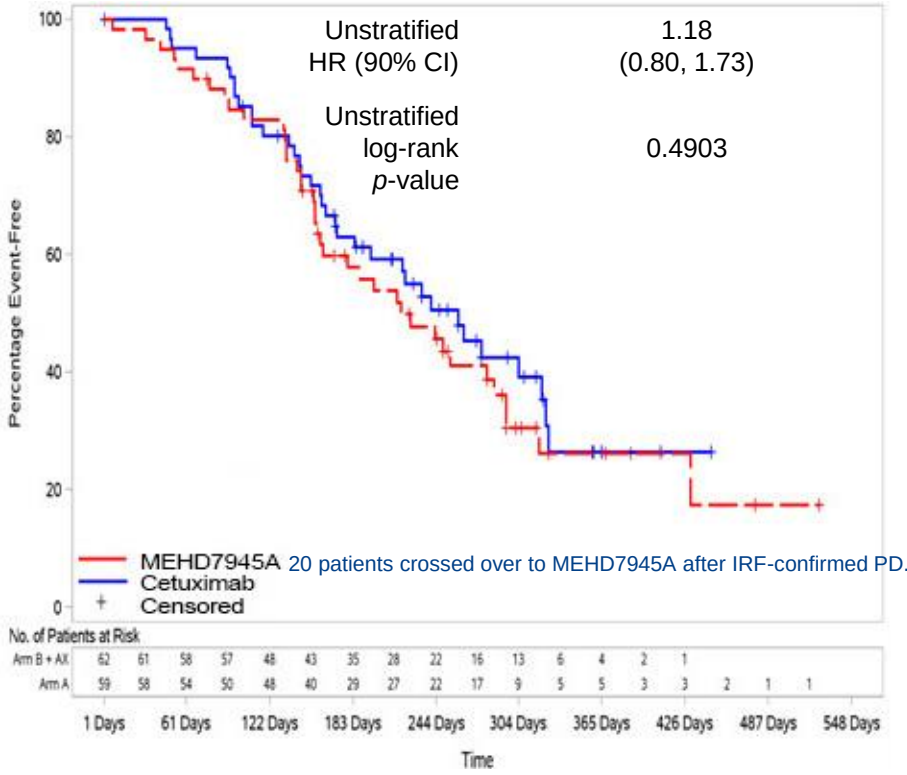
PFS

	MEHD7945A (*n* = 59)	Cetuximab (*n* = 62)
No. of events	52	53
Median (mo)	4.1	4.0
Unstratified HR (90% CI)	1.15 (0.83, 1.59)	
Unstratified log-rank *p*-value	0.4909	



OS

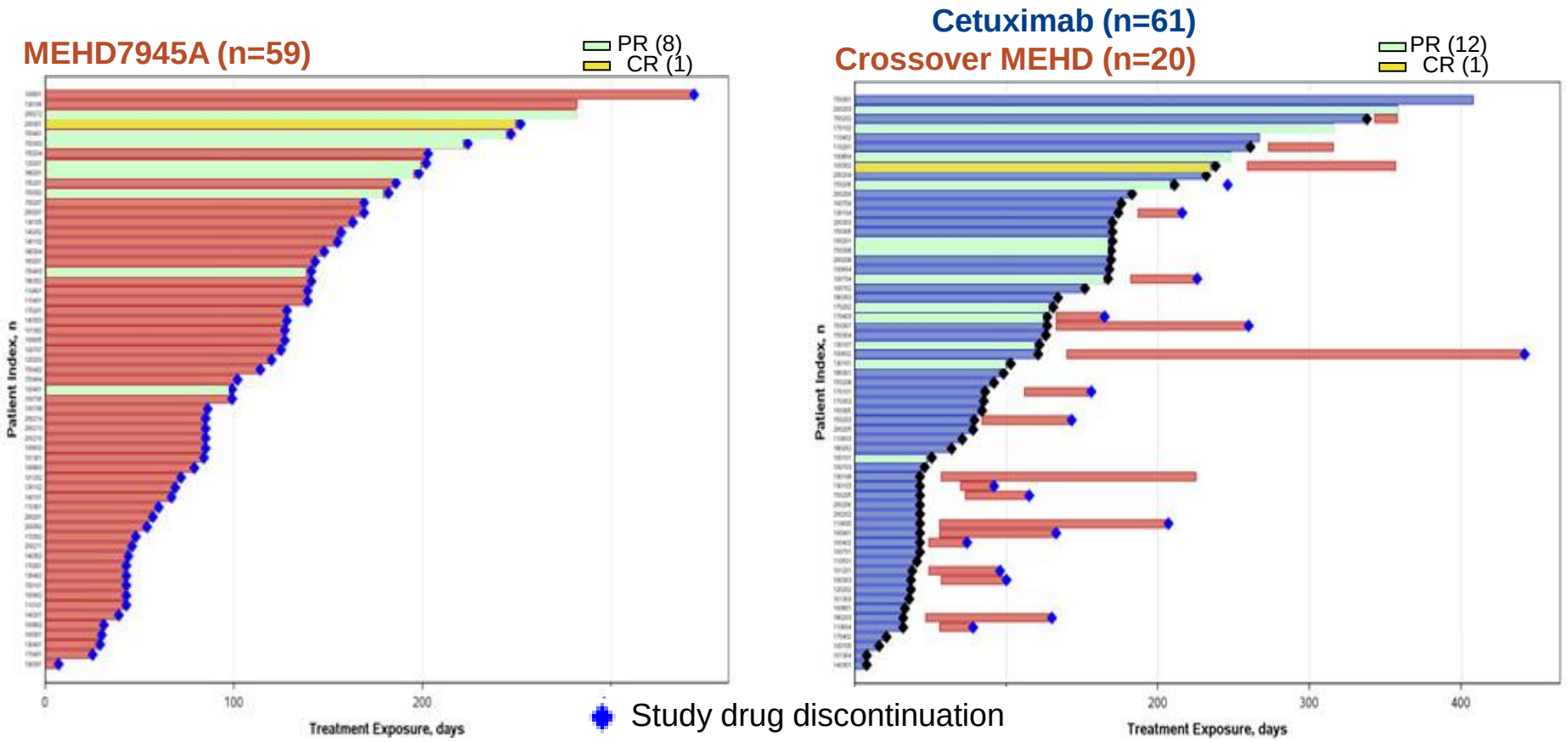
	MEHD7945A (*n* = 59)	Cetuximab (*n* = 62)
No. of events	38	35
Median (mo)	7.2	8.5
Unstratified HR (90% CI)	1.18 (0.80, 1.73)	
Unstratified log-rank *p*-value	0.4903	



20 patients crossed over to MEHD7945A after IRF-confirmed PD.

PFS and OS Subgroup Analysis by patient and disease characteristics and stratification factors did not show benefit for MEHD over cetuximab

ORR and Treatment Duration for Primary Treatment Arms and Crossover Patients



Objective response and treatment duration are comparable

- ORR 11.9% (7 pts) MEHD vs 14.5% (9 pts) Cetuximab
- Median time to disease progression 4.6 (MEHD) vs 4.1 (cetuximab)

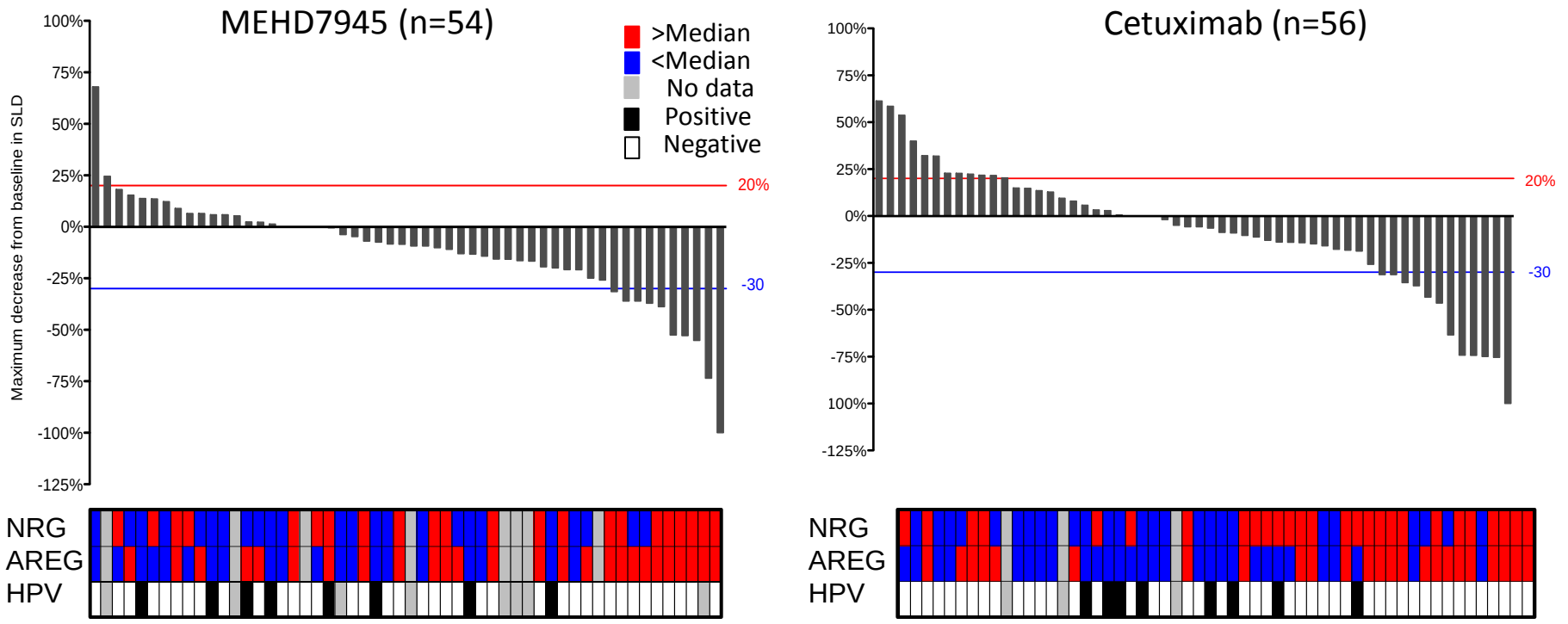
Limited evidence of activity in crossover patients (n=20)

- No objective responses, 7 SD (4 active); superseding prior time on cetuximab in 5 pts

MEHD7945A vs Cetuximab: Responsiveness Relative to Key Biomarkers

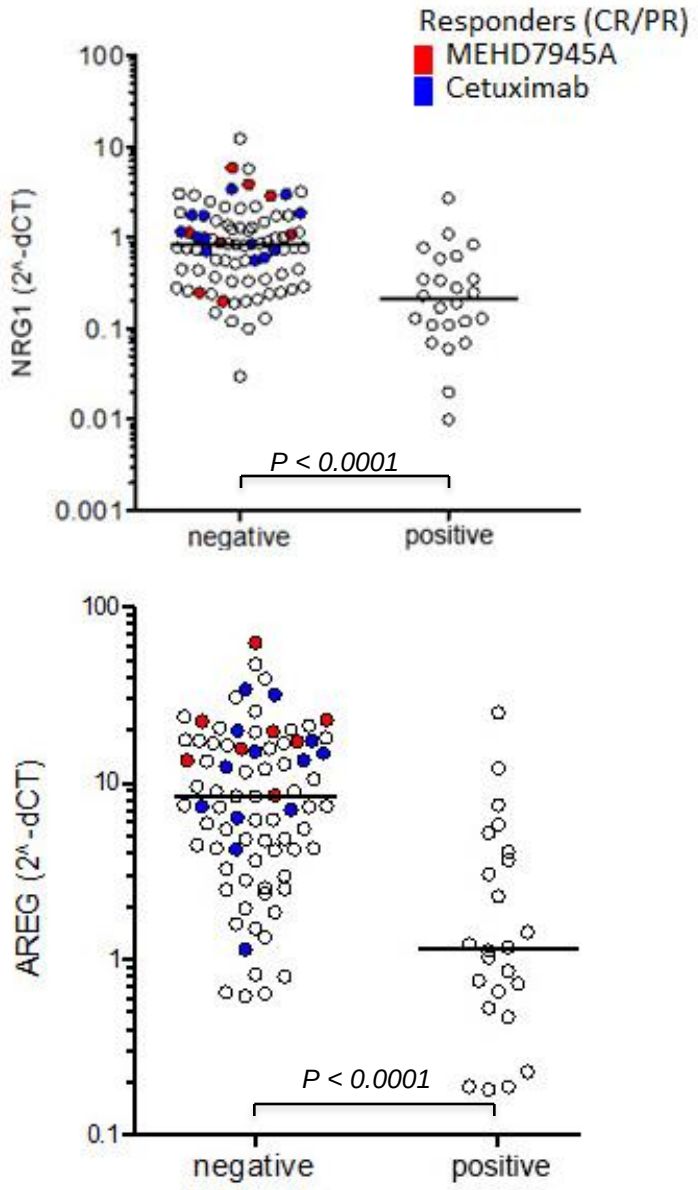
- Baseline NRG1 expression: cut-off analysis performed using quartiles
- Range of expression comparable to that in Phase 1a (including responders)

Best change in Target lesion SLD



- Elevated NRG1 expression did not appear to predict for response to MEHD or against response to cetuximab
- NRG1 and EGFR ligands (AREG=Amphiregulin) trend towards co-expression
- Fewer patients with best response of PD on MEHD, however, no difference in PFS

HER family ligand expression generally higher in HPV (-), no Responses in HPV (+)



- HPV (+) SCCHN may be a biologically and clinically distinct subset from HPV (-) with differential activity to EGFR inhibition
  - Leemans CR et.al. Nat Reviews Cancer 2011
  - Hayes DN et.al. JCO 2013
  - Seiwert TY et.al. 2014 13: 3310
  - Vermorken JB et.al. Lancet 2013 & Ann Oncol 2014

Phase 2 findings:

- HPV (+): 25/109 evaluable tumor samples
- **HPV (-) samples tend to have higher NRG1 and EGFR ligand expression**
- **No responses with either MEHD or cetuximab in HPV (+) patients**

Summary

- **Dual inhibition of HER3 & EGFR by single-agent MEHD7945A** demonstrated activity comparable, but **not superior, to single-agent cetuximab** in ≥2L R/M SCCHN
  - **Response rates and PFS similar**
    - High NRG1 expression in tumor (primary biomarker hypothesis) did not enhance for MEHD efficacy
    - Responses to both MEHD and cetuximab associated with higher AREG expression

- **Safety profile largely similar to cetuximab**
    - **Higher GI toxicity (predominantly G1/2 diarrhea and mucosal inflammation),** consistent with other regimens targeting multiple HER receptors
    - Overall skin toxicity comparable though less rash
    - Frequency and severity of infusion related reactions comparable (symptoms differ)

- Ongoing studies in combination with chemotherapy in 2L mCRC and 1L R/M SCCHN *(see Poster 989D, Sept 28, 2014; 1-2 pm, Bilboa Room)* and with cobimetinib (MEK inhibitor) in KRAS-mutant tumors)

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