A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small cell lung cancer patients. The NVALT-10 study

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on behalf of the NVALT Study Group

Disclosure information,

relations relevant to this session

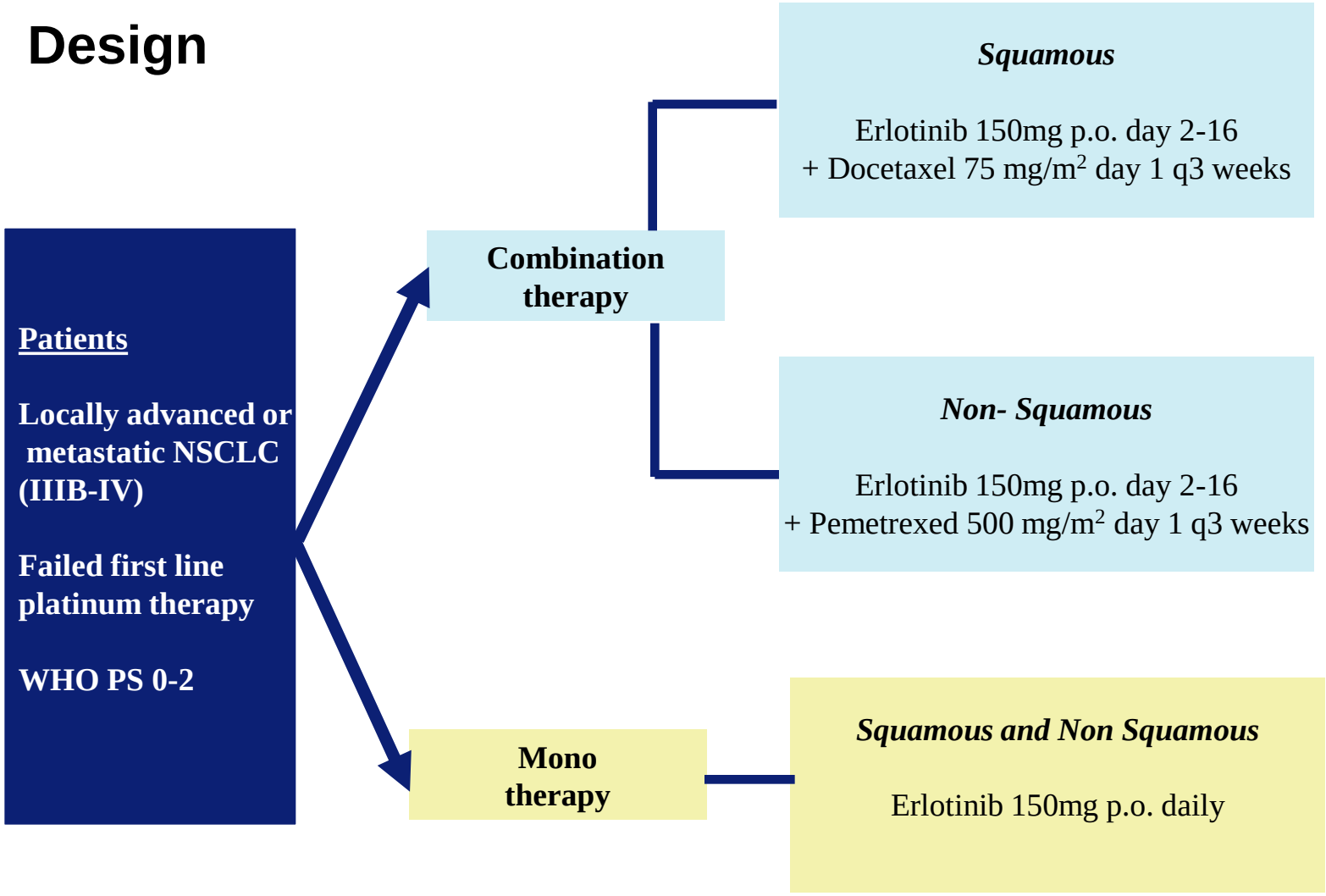
- Consultant: Roche; Eli-Lilly
- Research funding: Roche, Eli-Lilly

Background:

- Pemetrexed, docetaxel and erlotinib are approved single agent treatments for advanced NSCLC after platinum therapy failure
- NVALT showed carboplatin - pemetrexed combination therapy was superior to pemetrexed monotherapy in this setting[1]
- In preclinical models and exploratory trials pharmacodynamic separation EGFR-TKI and chemotherapy showed synergistic effects of both treatments[2,3]

[1]Smit EF et al , JCO 2010
[2]van Pawel J, ASCO 2011
[3]Giovanetti E, Mol Pharm, 2008

Design



Chemotherapy planned 4 cycles
Erlotinib until disease progression

Objectives

- Primary
  - To compare the progression free survival (PFS) of erlotinib monotherapy versus the combination therapy of erlotinib and chemotherapy

- Secondary
  - Overall survival (OS)
  - Response rate (RECIST 1.1)
  - Toxicity (NCIC-CTC grading system version 3.0)
  - Duration of respons

Statistical considerations

- **Assumptions**:
  - 80% power to detect (at alpha=0.05 two-sided log-rank test) a decrease of the hazard of progression in the combined arm of 33% (hazard ratio=0.67).

Stratification Factors

- WHO PS (0/1 or 2)
- Response to prior treatment (CR+PR or SD+PD)
- Treatment free interval after platinum (<6mths or >6mths)
- Histology (Squamous vs non squamous)

- **Subgroup analysis preplanned**
  - Squamous versus non-squamous

- **Accrual**
  - 230 patients, analysis after 190 events

Demographic Characteristics

		Erlotinib N= 115	Single agent + Erlotinib N= 116
Gender (%)	Male	75 (65)	73 (63)
	Female	40 (35)	43 (37)
Age (range)	Median (Range)	64 (38-81)	63 (40-82)
WHO PS	0/1	106 (92)	106 (91)
	2	9 (8)	9 (9)
Smoking status (%)	never	7 (6)	9 (8)
	smoker	35 (30)	29 (25)
	ex-smoker	63 (55)	68 (59)
	unknown	10 (9)	10 (9)

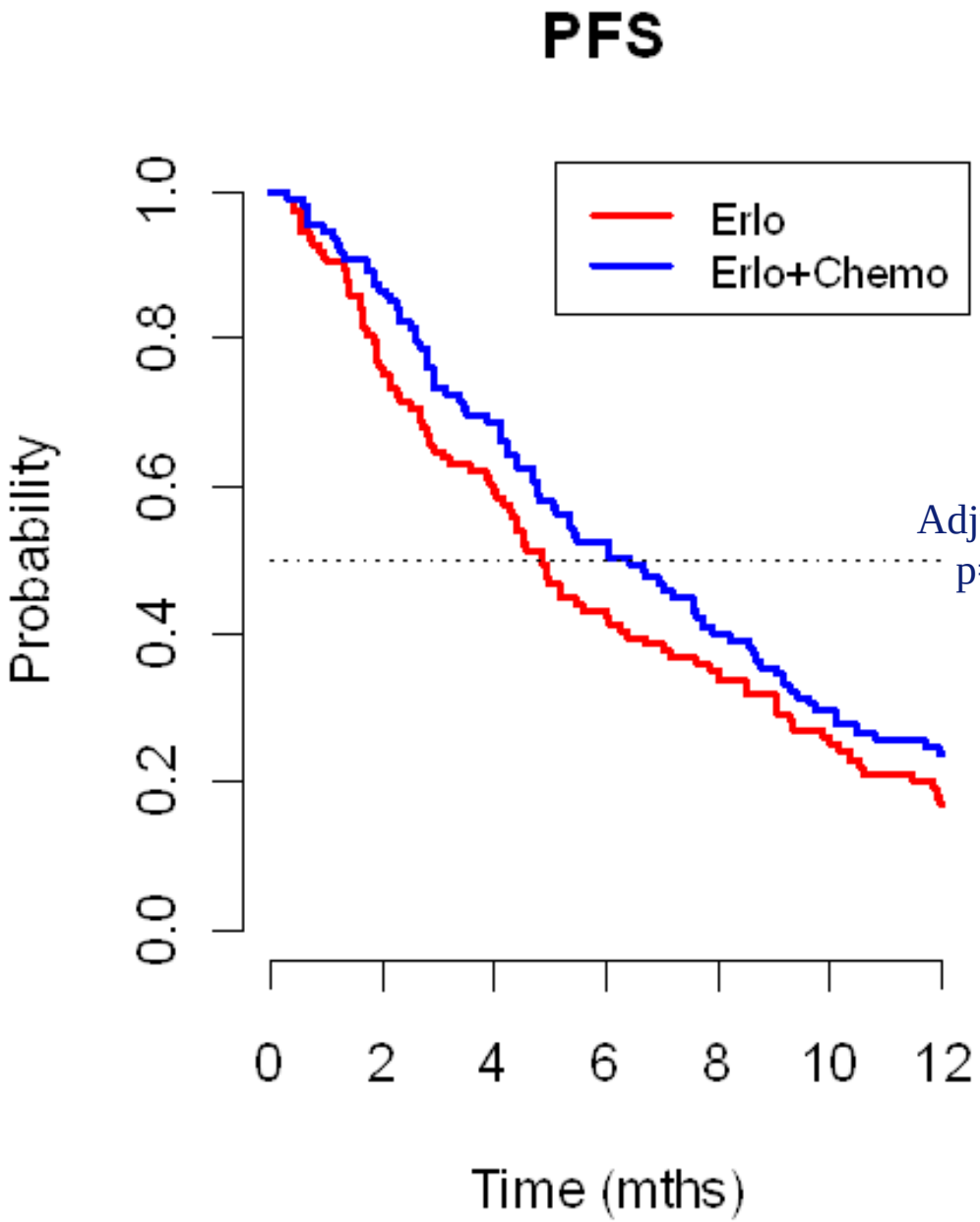
Disease Characteristics

		Erlotinib N= 115	Single agent + Erlotinib N= 116
Histology (%)	Adenocarcinoma	50 (43)	50 (43)
	Large cell	15 (13)	21 (18)
	Squamous cell	40 (35)	35 (30)
	Bronchoalveolar		1 (1)
	Other	6 (5)	4 (3)
	unknown	4 (3)	5 (4)
K-Ras (%)	not done	74 (64)	68 (59)
	Positive	4 (3)	9 (8)
	Negative	25 (22)	27 (23)
	Unknown	12 (10)	12 (10)
EGFR mutation (%)	not done	74 (64)	69 (59)
	positive	3 (3)	0 (0)
	negative	24 (21)	33 (28)
	unknown	14 (12)	14 (12)
Stage (%)	IIIb	28 (24)	22 (19)
	IV	86 (75)	94 (81)
	unknown	1 (1)	

Reasons for treatment discontinuation

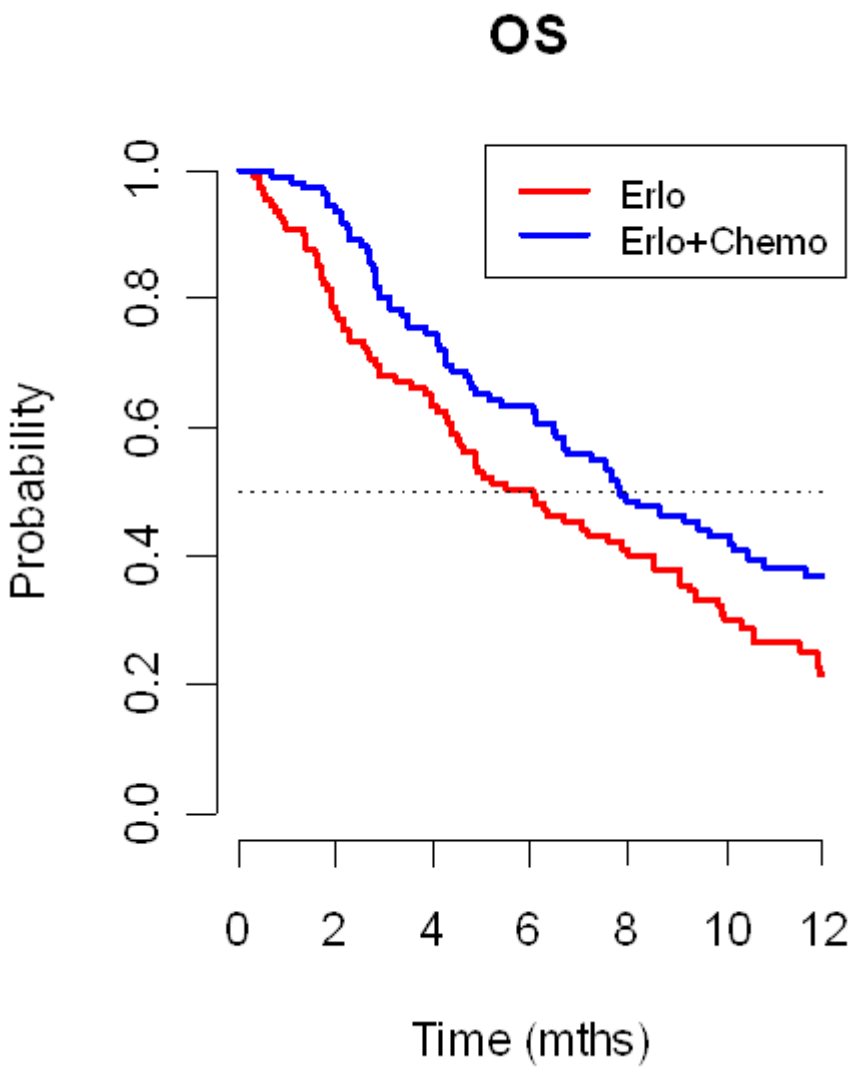
	Erlotinib N= 115	Single agent + Erlotinib N= 116
On study (%)	3 (3)	9 (8)
disease progression	76 (66)	60 (52)
clinical progression	10 (9)	9 (8)
death	10 (9)	7 (6)
adverse event	10 (9)	16 (14)
patient refusal	5 (4)	10 (9)
protocol violation		3 (3)
Other		1 (0.9)
Missing	4 (3)	10 (9)

Progression-Free Survival

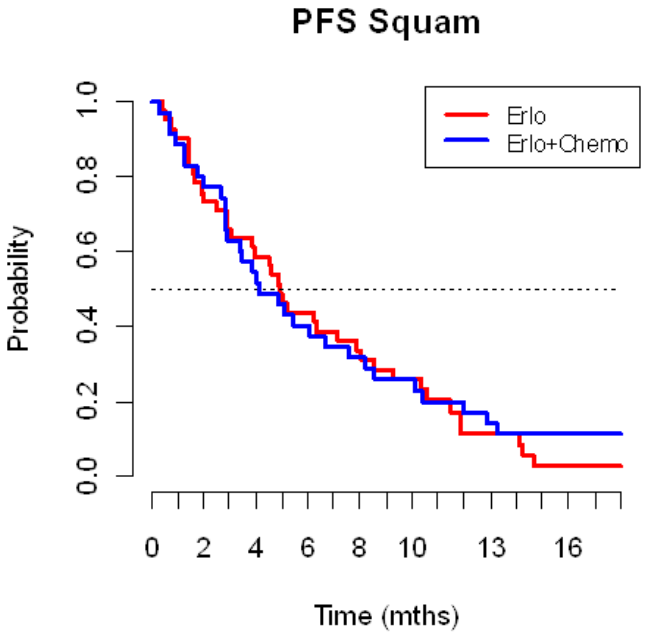


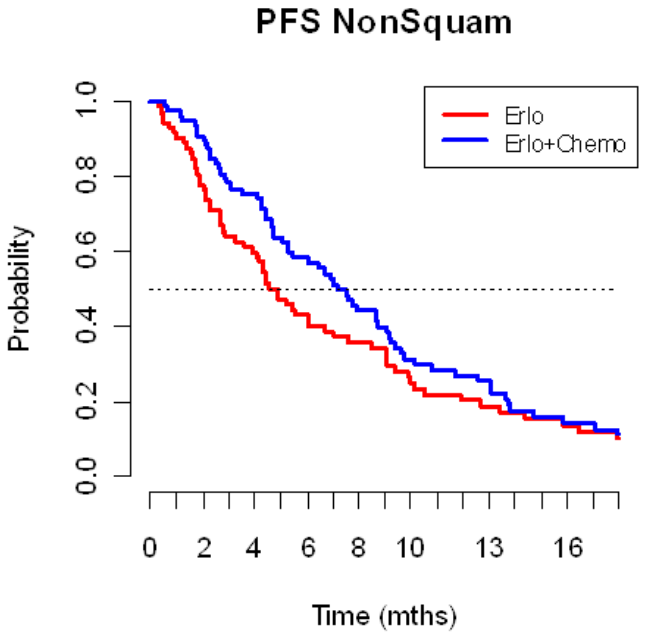
Adjusted for stratification factors:
p=0.09, HR=0.78 (0.59-1.04)

Overal Survival



Adjusted for stratification factors:
p=0.02, HR=0.67 (0.50 - 0.93)


PFS Squam
Erlo
Erlo+Chemo
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
13
16
Time (mths)


PFS NonSquam
Erlo
Erlo+Chemo
Probability
0.0
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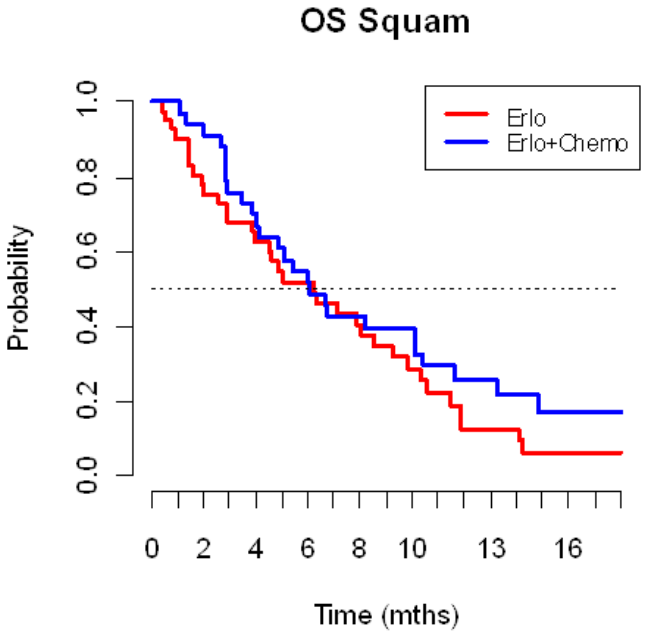
Time (mths)


OS Squam
Erlo
Erlo+Chemo
Probability
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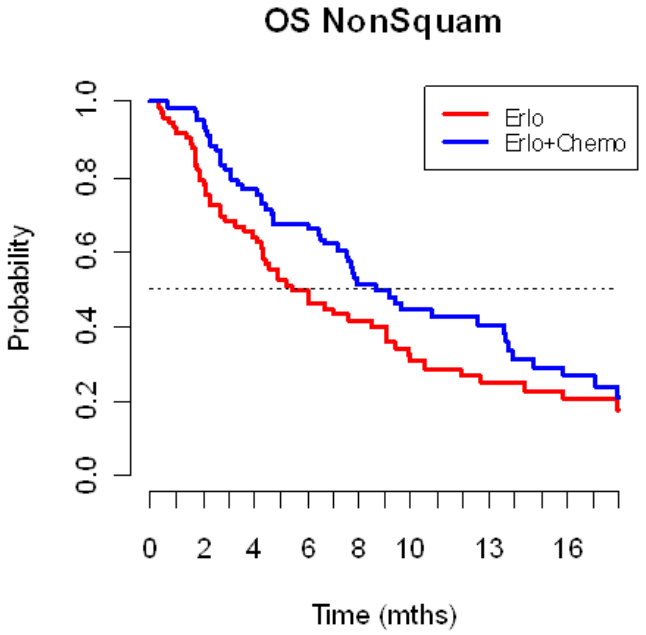
Time (mths)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13
16
Time (mths)

Results:

	All patients		Squamous		Non-squamous	
	Mono.	Comb.	Mono.	Comb.	Mono.	Comb.
PFS months Median (95% CI). P-value	4.9 (4.2-6.3)	6.1 (4.7-7.9) .09	4.9 (3.8 - 8.0)	4.1 (2.9 - 8.2) n.s.	4.9 (3.9 - 7.6)	7.0 (5.3 - 9.1) .10
OS months Median (95% CI). P-value	5.5 (4.5 - 8.5)	7.8 (6.5 - 10.4) .02	6.2 (4.5 - 9.8)	6.1 (4.1 - 11.7) n.s.	5.5 (4.3 - 9.4)	7.9 (6.7 - 13.7) .02

Best overall response

	Erlotinib N= 115	Single agent + Erlotinib N= 116
PR (%)	7 (6)	16 (14)
SD	36 (31)	43 (37)
PD	50 (43)	30 (26)
NE	20 (17)	24 (21)
Missing	2 (2)	3 (3)

Toxicity

	Erlotinib N= 113	Single agent + Erlotinib N= 114
Grade 3+ Toxicities (%)	**22 (19)**	**63 (55)**
Hemoglobin	**0**	**4%**
Leucocytes	**0**	**13%**
Neutrophils	**0**	**7%**
Platelets	**0**	**4%**
Fatigue	**5%**	**12%**
Rash	**7%**	**15%**
Diarrhea	**4%**	**10%**
Febrile neutropenia	**0**	**6%**
Infection	**0**	**4%**

Drug exposure

	Erlotinib N= 115	Single agent + Erlotinib N= 116
Did not start (%)	2 (2)	2 (2)
Erlotinib dose reduction (%)	10 (9)	19 (16)
chemo dose reduction(%)		8 (7)
Erlotinib cycles Median (range)	2.0 (0-29)	3.0 (0-39)
Cycles of chemotherapy(%)		
0		5 (4)
1		56 (22)
2		23 (20)
3		8 (7)
4		54 (47)

Treatment after disease progression

	Erlotinib N= 115	Single agent + Erlotinib N= 116
3rd line treatment	48 (42%)	45 (39%)

Summary:

- In non-squamous histology, combination therapy pemetrexed and erlotinib increases PFS and OS compared to erlotinib monotherapy.
- In squamous histology, combination therapy docetaxel and erlotinib did not increase efficacy compared to erlotinib monotherapy.
- Combination therapy increases toxicity. Safety profiles were consistent with existing data and suggest an increased erlotinib level during pemetrexed combination.

Ackowledgements

- We thank the patients and their families who participated in the trial

- We also thank all NVALT investigators, nurses, data managers, and support staff.