MADRID 2014 ESMO congress

A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous Non-Small Cell Lung cancer (NSq-NSCLC) : LBA41_PR

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Disclosure

This study was funded by Sanofi-Aventis Korea Ltd.
(DOCET L 05478)

Dr. Y. Kim have received honoraria from
Lilly, Roche, Astra Zeneca, Sanofi-Aventis Korea,
Chong Kun Dang, and Hanmi.

ClinicalTrials.gov Identifier: NCT01282151

Background

Pemetrexed cisplatin is superior to gemcitabine cisplatin in Non-squamous NSCLC.

- Scagliotti GV, J Clin Oncol 2008;26:3543-51.

Docetaxel cisplatin is an active regimen for 1st line NSCLC.

- Schiller JH et al. N Engl J Med 2002;346:92-8

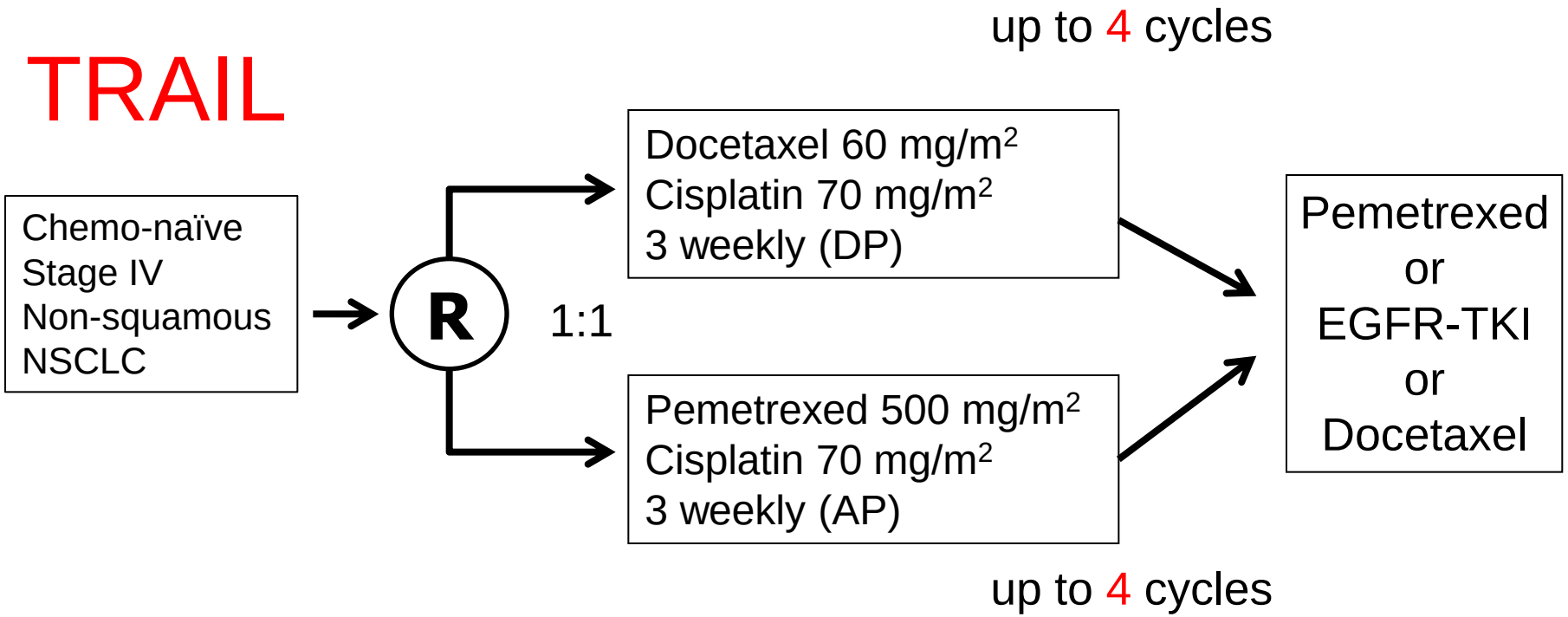
In Japan Docetaxel is used in 60mg/m^2/3 week dose.

- Kubota K, et al. J Clin Oncol 2004;22:254-61.

Docetaxel 60mg/m^2 + Cisplatin q3 week was not inferior to Docetaxel 75mg/m^2 + Cisplatin q3 week while showing lower toxicities.

- Kim KS. et al. Experimental and Therapeutic Medicine 2012;4(2):317-322

TRAIL


up to 4 cycles
Chemo-naïve
Stage IV
Non-squamous
NSCLC
R
1:1
Docetaxel 60 mg/m2
Cisplatin 70 mg/m2
3 weekly (DP)
Pemetrexed 500 mg/m2
Cisplatin 70 mg/m2
3 weekly (AP)
Pemetrexed
or
EGFR-TKI
or
Docetaxel
up to 4 cycles

Statistical analysis

Median PFS of Pem-Cis: 6.4 months in east Asian

- Yang CH, JTO 2010;5(5):688

compared to 5.3 months in all ethnic patients.

- Scagliotti GV, JCO 2008;26:3543.

Expected median PFS of Pem-Cis regimen = 6.4 months.
Non-inferiority margin = 1.5 months
Hazard ratio = 1.3
One sided significance level : 0.025, Power : 80%
N=281 * 2 = 562

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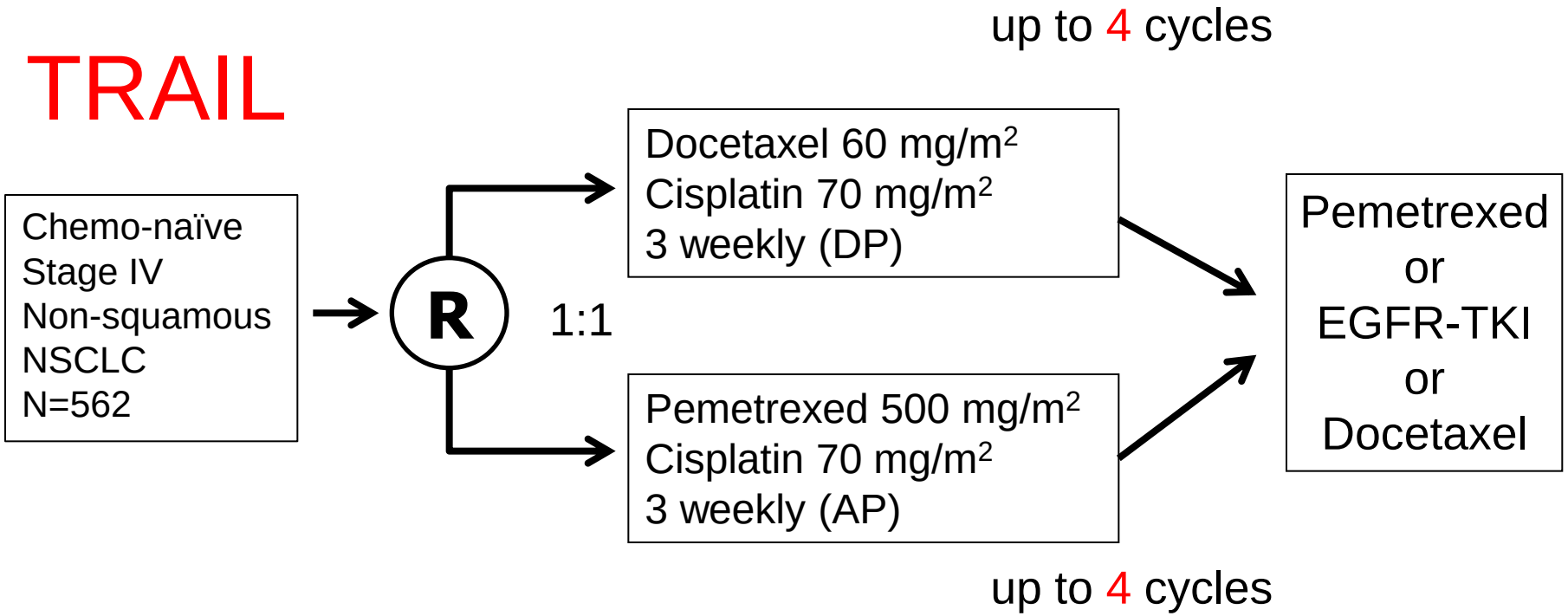


Stratification factors

ECOG 0-1 vs. 2
Sex M vs. F

Biomarkers

Genomic DNA
Paraffin Tissue
for available pts

Response evaluation
after 2 and 4 cycles
If not progressed,
f/u every 8~10 wks

Primary endpoint
•PFS

Secondary endpoints
•Response Rate
by RECIST v 1.1
•OS
•Safety

Inclusion Criteria

Age ≥ 18 years

ECOG Performance status: 0~2

Non-Squamous cell lung cancer

Stage IV or IIIB unable to receive curative radiation treatment or relapsed after Surgery or Radiation treatment

No prior Chemotherapy

Measurable leision according to RECIST version 1.1

Adequate marrow, hepatic and renal function

Exclusion Criteria

Activating EGFR mutation

Hypersensitivity to Taxanes

Serious comorbidity or poor medical conditions

Pregnancy or Lactating woman

Woman in child bearing age who refuses contraception

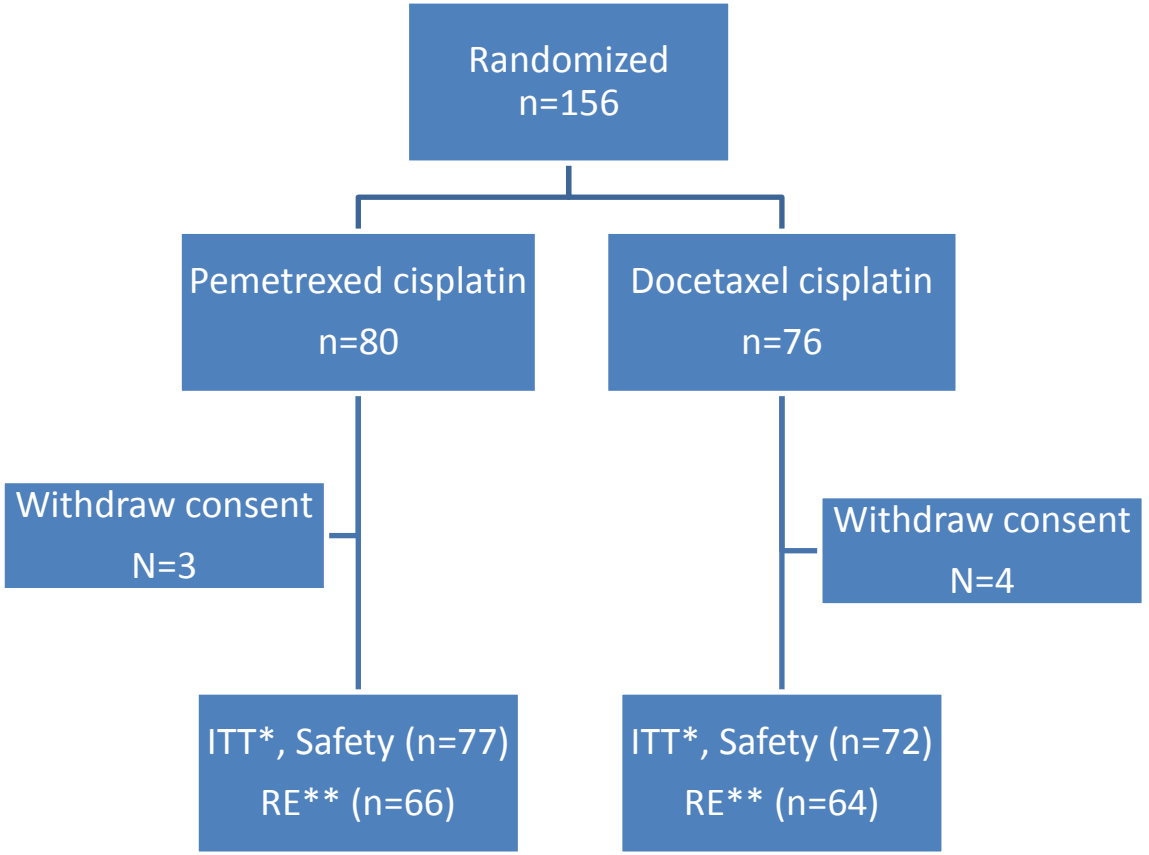
Motor or sensory peripheral neuropathy ≥ Grade 1

Other malignancy except cured basal cell carcinoma or uterine cervical carcinoma in situ

Recruitment

After 156 patients were randomized, from 2011 August to 2013 December, study team closed enrollment because of approval and use of maintenance pemetrexed treatment.

CONSORT Diagram



*ITT; intention to treat, **RE; response evaluable

Table 1. Comparison of characteristics of patients

	Pemetrexed/Cisplatin (n=77)	Docetaxel/Cisplatin (n=72)
Age, mean(SD)	63.0 ± 8.9	63.8 ± 9.8
Sex	53/24	50/22
ECOG PS (0/1/2)	14/55/8	17/48/7
Body mass index	23.1 ± 3.45	22.6 ± 2.68
Histology ADC/LCC/NSCLC	75/0/2	69/1/2
Stage (IIIB/IV)	5/72	3/69

Table 2. Comparison of treatment

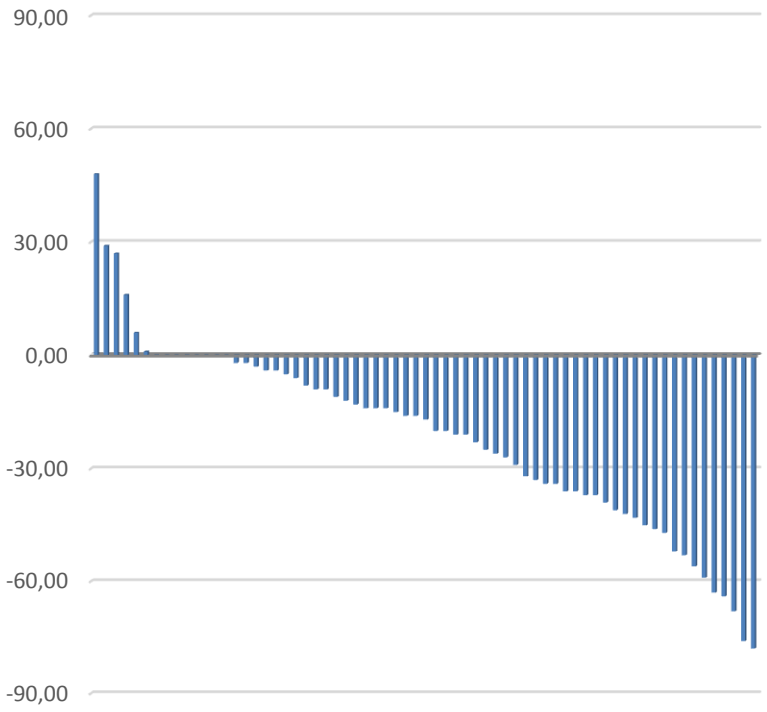
	Pemetrexed/Cisplatin (n=77)	Docetaxel/Cisplatin (n=72)
Cycles (1/2/3/4/6)	7/16/2/49/3	11/14/1/45/1
Cycles mean(range)	3.4 (1-6)	3.2 (1-6)
Total number of Cycles	259	228
Cycles delayed	17 (6.7%)	18 (7.9%)
Doses reduced	16 (6.3%)	21 (9.3%)
Relative dose-intensity (%)	97.6 ± 5.7	96.2 ± 6.9

Table 3. Comparison of adverse events.

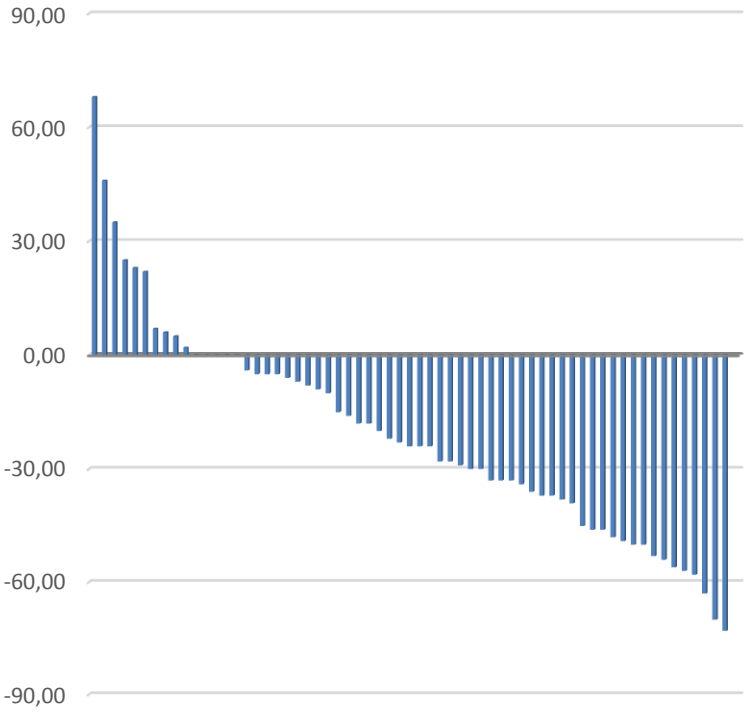
	Pemetrexed/Cisplatin (n=77)	Docetaxel/Cisplatin (n=72)
Neutropenia grade 3/4	1 (1.3%)	10 (13.9%) **
Febrile Neutropenia	1 (1.3%)	8 (11.1%) *
Anemia grade 1/2	1 (1.3%)	1 (1.4%)
AST/ALT increased gr 1/2	0	2 (2.8%)
Creatinine increased	1 (1.3%)	2 (2.8%)
Total number of SAE	24	42
Number of cases with SAE	17 (22.1%)	29 (40.3%) *
Fatal SAE	2	1

* $p<0.05$, ** $p<0.01$
Data survey in progress

Pemetrexed Cisplatin



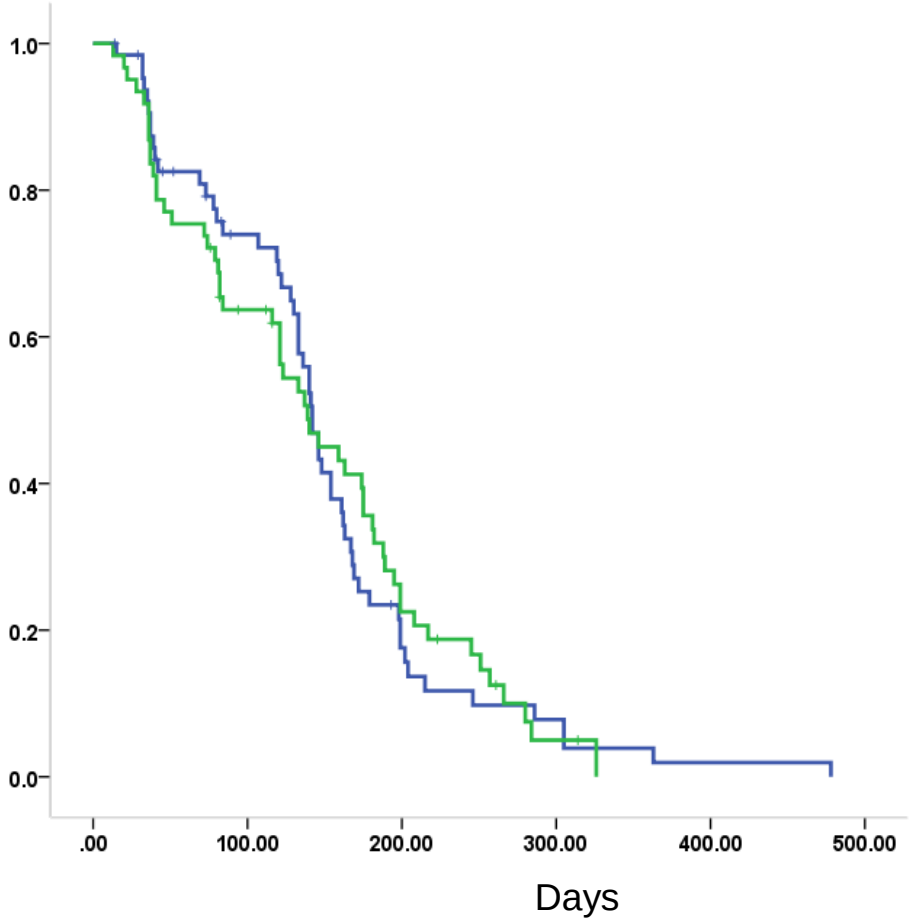
Docetaxel Cisplatin



24 / 33 / 10 / 10	PR / SD / PD / NE	**24 / 25 / 15 / 8**
31.2 (ITT*)	Response rate (%)	**33.3 (ITT*)**
35.8 (RE)**		**38.7 (RE**)**

*ITT; intention to treat, **RE; response evaluable

Progression Free Survival



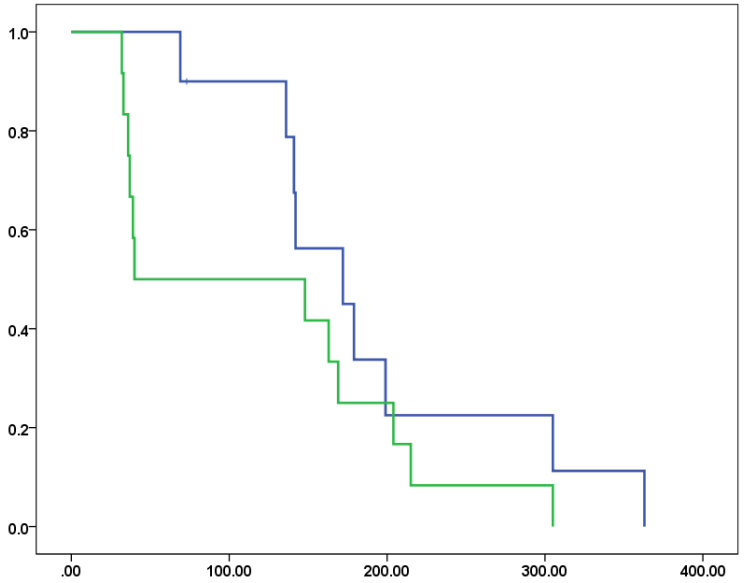
- Pem Cis: 4.7 m (4.4-5.1)
- Doc Cis: 4.6 m (3.7-5.6)

Log rank p > 0.05
HR=1.016 (0.737~1.400)

c.f. Median PFS of Pem Cis
6.4 m in east Asian
- JTO 5(5), 2010
5.3 m in all ethnic group.
- J Clin Oncol 2008;26.

Efficacy & PFS by TS expression in Pem-Cis arm

DAKO clone M3614	Thymidylate Synthase Low expressed	Thymidylate Synthase High expressed
Disease control (PR+SD)	11	8
Progressive disease	0	4



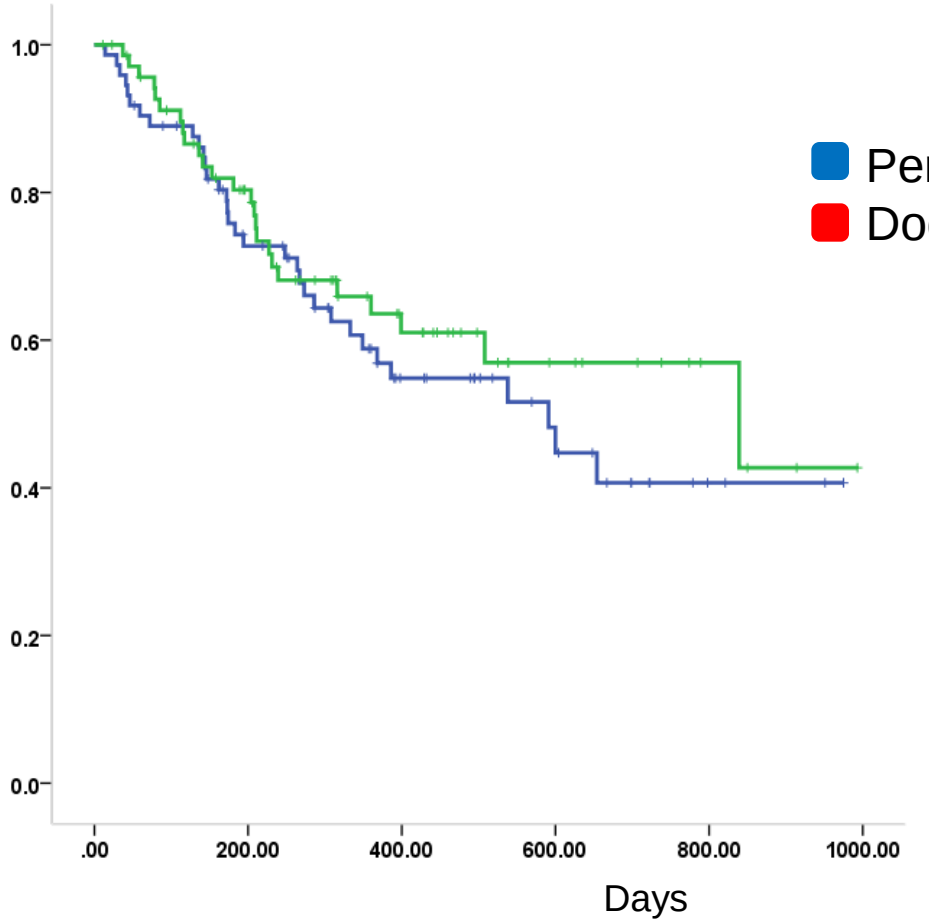
P=0.06

Progression Free Survival

TS Low: 5.7 m (2.8-8.6)
TS High: 1.3 m (0-7.5)

P=0.19

Overall Survival



Pem Cis: 19.7 (10.8-28.6)
Doc Cis: 28.0 (7.5-48.5)

c.f. Median OS of Pem Cis
21.2 m in east Asian
- JTO 5(5), 2010
11.0 m in all ethnic group.
- J Clin Oncol 2008;26.

Table 4. Treatment beyond First line study*.

	Pemetrexed/Cisplatin (n=77)	Docetaxel/Cisplatin (n=72)
Docetaxel	18 (23.4%)	
Pemetrexed		18 (25.0%)
EGFR-TKI	45 (58.4%)	33 (45.8%)
Gemcitabine	11 (14.3)	2 (2.8%)
Other chemotherapy	4 (5.2%)	4 (5.6%)

* Data survey in progress

Table 5. Comparison of Pem-Cis data in prior studies

	All ethnicity[1]	East Asian[2]	Pem-Carbo[3]	Paramount[4]	Author's trial
Number	862	67	128	359	77
Non-Squamous	71.7%	70.1%	100%	100%	100%
Age (median)	61.1	61.7	60.1	61	64.4
Sex (female)	29.8%	31.3%	42	44%	31.2%
Stage IV	76.2%	74.6%	84%	91%	93.5%
EGFR-TKI	24.9%	56.7%	Not reported	41.4%	58.4%
Cycles (median)	5	5-6	5-6	4+maintenance	3.57
Response rate	32.0% §	46.5% §	34.0	30%	36%
PFS	5.3m §	6.4m §	5.8m	6.9m	4.7m
OS	11.0m §	21.2m §	14.9m	16.9m	19.7m (premature)

1 JCO 2008;26:3543. 2 JTO 2010;5(5):688. 3 JTO 2011;6:1907
4. Lancet Oncol 2012;13:247, JCO 2013;31:2895. § in non-squamous patients

Conclusion

- In Non-Squamous NSCLC without driver mutations, Doc-Cis showed similar PFS and response rate, compared to Pem-Cis.
- More frequent adverse events and higher toxicities were observed in Doc-Cis arm.
- Numerically shorter PFS of both arms in this trial suggest that maintenance treatment should be considered unless disease progression is noted.

Acknowledgements

- We thanks the participating patients, their families, all investigators and research coordinators, at the following study institutions:
  - Chonnam National University Hwasun Hospital(YC Kim, KS Kim, IJ Oh, Choi YD), Kosin University(Jang TW), Dankook University(Kim YS), Yeungnam University(Lee KH, Shin KC), Keimyung University(Jung CY), Wonkwang University(Yang SH), Hanlym university(Jang SH), Inha university(Ryu JS), Kyungpook National University(Yoo SS), Yonsei university(Yong SJ), Konkuk university(Lee KY), Korea university(In KH), Pusan national university(Lee MK)
  - Sanofi-Aventis Korea Ltd.