Discussion PD 421-424

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Disclosure slide

- Consultancy: Eli Lilly
- Advisory Boards: Astra Zeneca, Boehringer Ingelheim, Bayer, Cellgene, Novartis, Clovis, Roche-Genentech, Pfizer, BMS.
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- Stock Options: None

- I will not discuss off label use or promote non-registered drugs

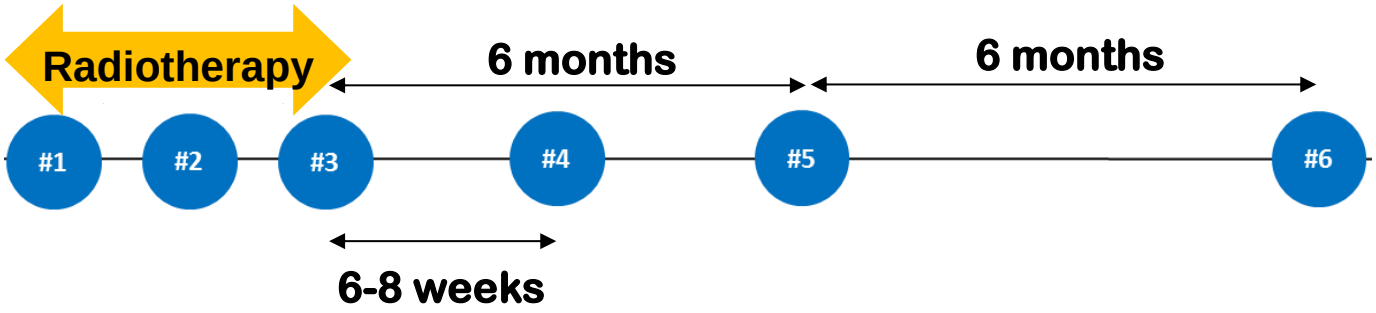
- PD 421: prospective monitoring of lung function tests with CO and NO diffusion during high dose thoracic radiotherapy for lung cancer: CONORT study – C. Fontaine-Delaruelle

What was done and why?

- Serial measurement of DLCO and DLNO as a measure for membrane (Dm) or cappillary volume (Vc) after various delivery methods of high dose TRT in early (?) stage NSCLC

- LF tests in high dose RT alone showed no change in volumes (FEV1, FVC).
- Changes in diffusion capacity not well studied

Materials &Methods

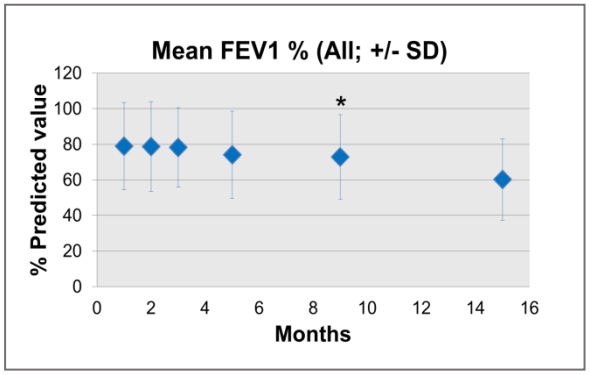


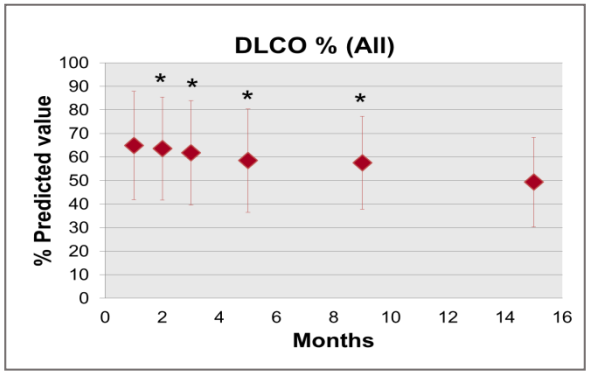
- Observational prospective monocentric study since February 2014.
- **Inclusion criteria** :
  - Patients with thoracic radiotherapy
  - Patients consent
- Achievement of 6 pulmonary function tests including double assessment of NO and CO diffusing capacities before, during and after RT

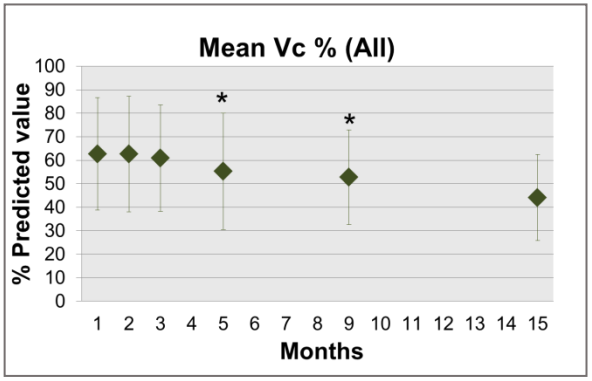
Results

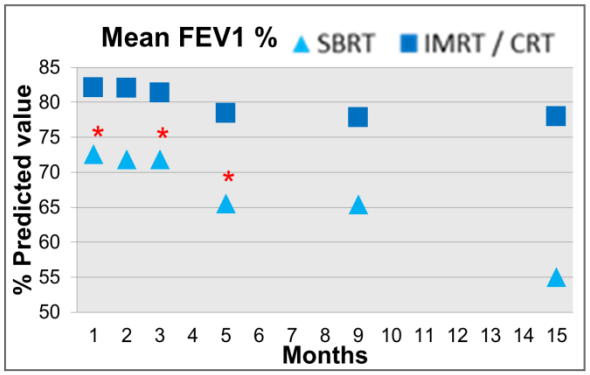
		SBRT		IMRT / CRT		All	
		n (31)	% (SD)	n (60)	% (SD)	n (91)	% (SD)
Sex	Male	21	68%	44	73%	**65**	**71%**
Age (moy, SD)		71 (9)		68 (11)		**69**	
Tabacco	Never	6	19%	6	10%	**12**	**13%**
	Former	21	68%	39	66%	**60**	**67%**
	Current	4	13%	14	24%	**18**	**20%**
PS 0/1		27	87%	54	90%	**81**	**89%**
Total dose (Gy)		59.87		62.20		**61.40**	

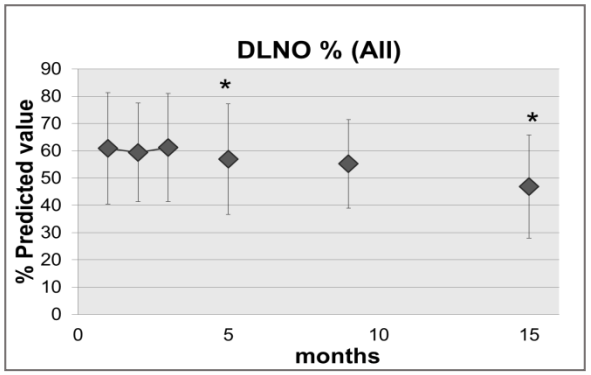
Tumor size? Stage? PTV/GTV?

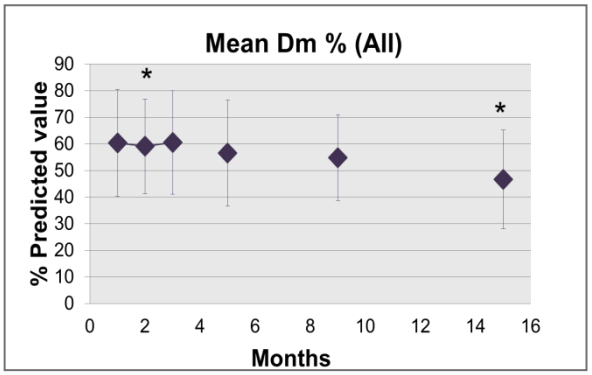












p < 0.05 compared to baseline * p < 0.05 between two groups
Vc : Volume of capillaries **Dm : Diffusion of membrane**

Figure 4 – PFT evolution during and after thoracic radiotherapy

Conclusion

- **Lung volumes are not significantly affected by thoracic RT, but lung diffusion decreased, both by membrane alteration and by capillary alteration.**

- The diffusion capacity decreases until one year after radiotherapy completion (non-significant results, probably due to the patient cohort size.

- These results must be analyzed with caution in the absence of control arm. Furthermore, the potential clinical impact is not yet assessed.

- The study completion is planned for early 2016.

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A recent paper on LF tests in SABR for Lung Cancer

TABLE 2. Mean Pulmonary Function Test Results for All Patients After Stereotactic Body Radiotherapy

PFT Parameter	TLC	FVC	FVC %Predicted	FEV1	FEV1 %Predicted	FEV1/FVC	Corrected DLCO	DLCO/VA
Baseline	5.67	2.53	83.56	1.51	67.0%	0.59	12.23	3.01
6 weeks	5.62	2.51	83.42	1.46	66.0%	0.59	11.95	3.02
Relative Δ from baseline	1.1%	−0.3%	−0.3%	1.0%	0.1%	1.6%	3.1%	0.3%
3 months	5.60	2.56	84.9	1.43	65.58%	0.57	14.18	2.92
Relative Δ from baseline	−0.4%	0.5%	0.4%	2.5%	3.0%	2.2%	−0.7%	−2.0%
6 months	5.50	2.48	96.6	1.39	66.88%	0.59	12.26	3.07
Relative Δ from baseline	−0.8%	1.4%	0%	5.7%	5.1%	4.6%	−2.1%	0.5%
9 months	5.55	2.48	83.52	1.42	66.67%	0.60	11.74	2.98
Relative Δ from baseline	−1.2%	−2.5%	−1.6%	0.3%	0.9%	3.3%	−6.1%*	−0.5%
12 months	5.57	2.51	84.7	1.36	63.78%	0.56	11.48	2.95
Relative Δ from baseline	−3.6%*	−5.7%*	−4.6%*	−4.1%*	−3.3%	1.9%	−5.2%*	−2.3%
24 months	5.43	2.31	81.3	1.28	63.1%	0.57	12.77	3.36
Relative Δ from baseline	−2.2%	−8.9%*	−5.2%	−7.6%*	−4.1%	1.6%	−11.3%	2.4%

FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; DLCO/VA, diffusing capacity for carbon monoxide divided by alveolar volume; TLC, total lung capacity; FVC, forced vital capacity; FEV1/FVC, forced expiratory volume in 1 second divided by forced vital capacity; Δ, change.

*$p < 0.05$.

Grills et al. J. Thor. Oncol. 2015

Comments

- Test method
  - Reproducibility
  - Variability
  - Physiological decline
- Is DLCO the best measurement for
  - Risk stratification/Patient outcome?
  - Functional capacity

Reproducibility of LF measurements

Table 4—*Change in Percentage of Accuracy in FEV_1 and DLCO Between Time Points

Instrument	Δ Day 0–30, %	Δ Day 30–60, %	Δ Day 60–90, %	Overall, %
Collins				
FEV_1	−0.01	−0.43‡	0.46†	0.02
DLCO	−1.50†	−0.70	−1.70†	−3.9†
Morgan				
FEV_1	−0.53†	−0.22†	0.62†	−0.13
DLCO	4.20	8.90†	4.90	18.0†
SensorMedics				
FEV_1	1.53†	−0.49†	−0.19	0.85†
DLCO	0.00	1.40	−0.10	1.30
Jaeger				
FEV_1	−0.55	1.52†	−2.72†	−1.75†
DLCO	1.90	2.50	16.50†	20.9†
MedicalGraphics				
FEV_1	−0.83†	−0.55†	−0.08	−1.46†
DLCO	0.90	−3.40	−14.70†	−17.2†

*Percent accuracy = ([observed − target]/target) × 100; Overall = sum of time point differences in accuracy.
†$p < 0.008$.

Jensen et al. Chest 2007

Fysiological annual decline in LF

		mean	SD
All (n=4727)	FVC [ml]	-24.9	40.3
	FEV_1 [ml]	-35.4	29.8
	FEV_1/FVC %†	-0.4	0.5
	FEF_{25-75} [ml/s]	-70.8	64.5
Never smokers (n=2213)	FVC [ml]	-22.4	38.0
	FEV_1 [ml]	-32.6	28.8
	FEV_1/FVC %†	-0.4	0.5
	FEF_{25-75} [ml/s]	-67.1	62.9

† FEV_1 as a percentage of FVC

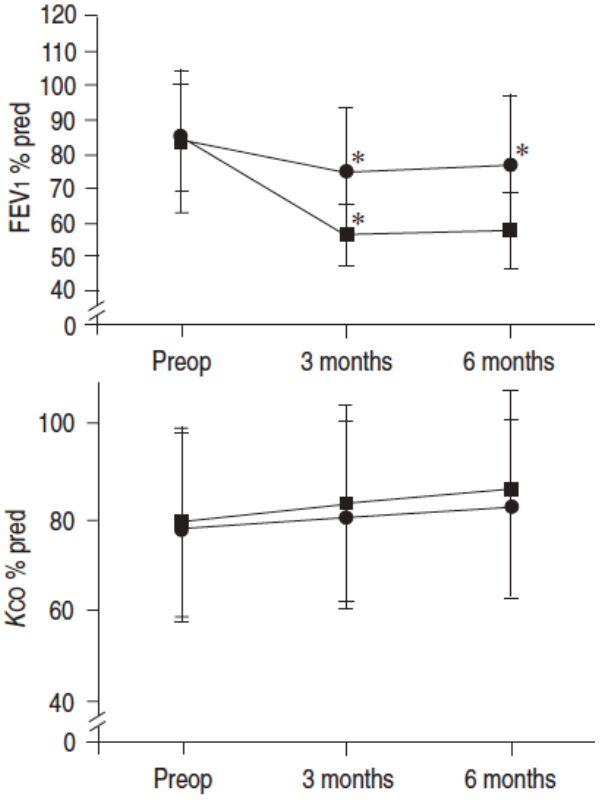
Downs et al. New Eng J. Med. 2007

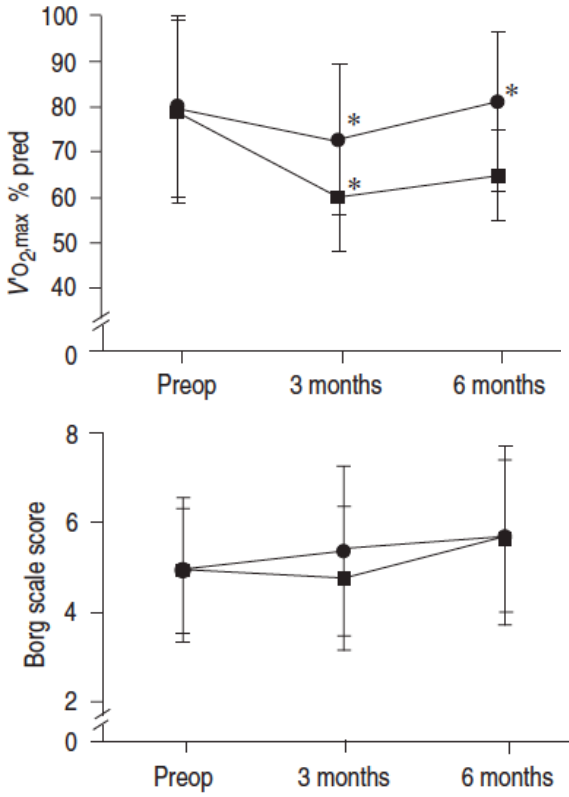
Risk stratification

- No single lung function test predicts for early morbidity or mortality
  - Contrary to surgery

- Lower FEV1 and DLCO predict for lower median and overall survival times
  - Comorbidity

Is LF the best measure for functional capacity after TRT?





	Group	Preop (n=64)	3 months (n=64)	6 months (n=64)
Exhaustion	L	10 (22)	6 (13)	12 (26)
	P	1 (5)	1 (6)	3 (17)
Dyspnoea	L	7 (15)	8 (17)	9 (20)
	P	4 (22)	11 (61)*$	9 (50)*$
Muscle fatigue	L	24 (52)	25 (54)	21 (46)
	P	10 (56)	4 (22)*$	2 (11)*$
Other	L	5 (11)	7 (15)	4 (9)
	P	3 (17)	2 (11)	4 (22)

Bolliger et al. Eur. Resp. J. 1996

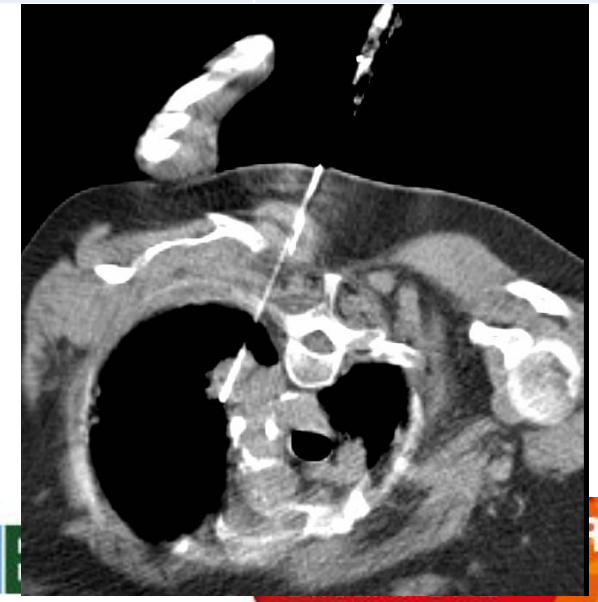
- PD 421: prospective monitoring of lung function tests with CO and NO diffusion during high dose thoracic radiotherapy for lung cancer: CONORT study – C. Fontaine-Delaruelle
- PD 422: Determining the prevalence of EGFR mutations in Asian and Russian patients with advanced AC and non-AC histology – IGNITE study. Chinese subgroup. C. Shi et al.

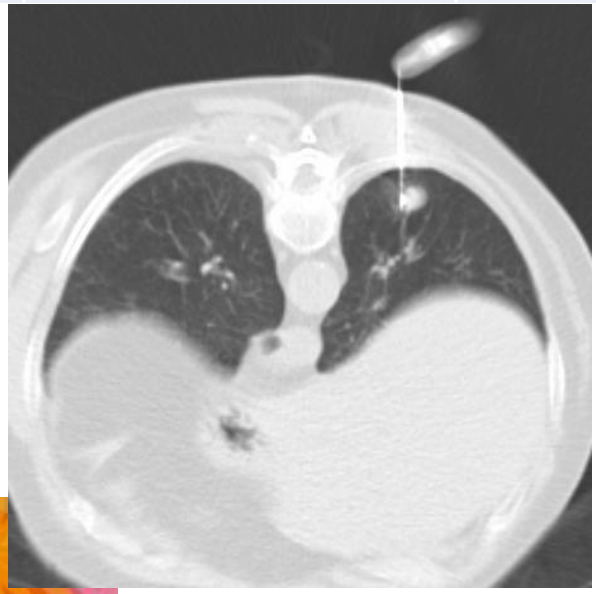
Why the interest in circulating biomarkers?

- Lung tumors frequently inaccessable.
- Tumor biopsies high failure rate in procuring sufficient DNA (10%-30%??)
- Blood (Urine!) samples easy to obtain, low complication rate, repeated sampling possible

Obtaining tumor biopsy specimen by transthoracic route

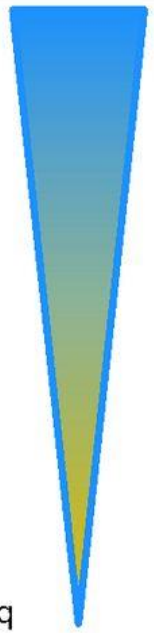
Author	No. Procedures	Adequate tissue	Complication
Tam 2014	179 PTCNB	82.9%	15.3%
Cheung 2010	47 PTCNB	NA	12.8%
Solomon 2010	18 PTCNB	89%	16.6%
Swischuk 1998	651 FNA	94%	26.9%





Methodologies to detect ctDNA

Technique	Sensitivity	Optimal Application
Sanger sequencing	> 10%	Tumor tissue
Pyrosequencing	10%	Tumor tissue
Next-generation seqeuncing	2%	Tumor tissue
Quantative PCR	1%	Tumor tissue
ARMS	0.10%	Tumor tissue
BEAMing, PAP, Digital PCR, TAM-Seq	0.01% or lower	ctDNA, rare variants in tumor tissue

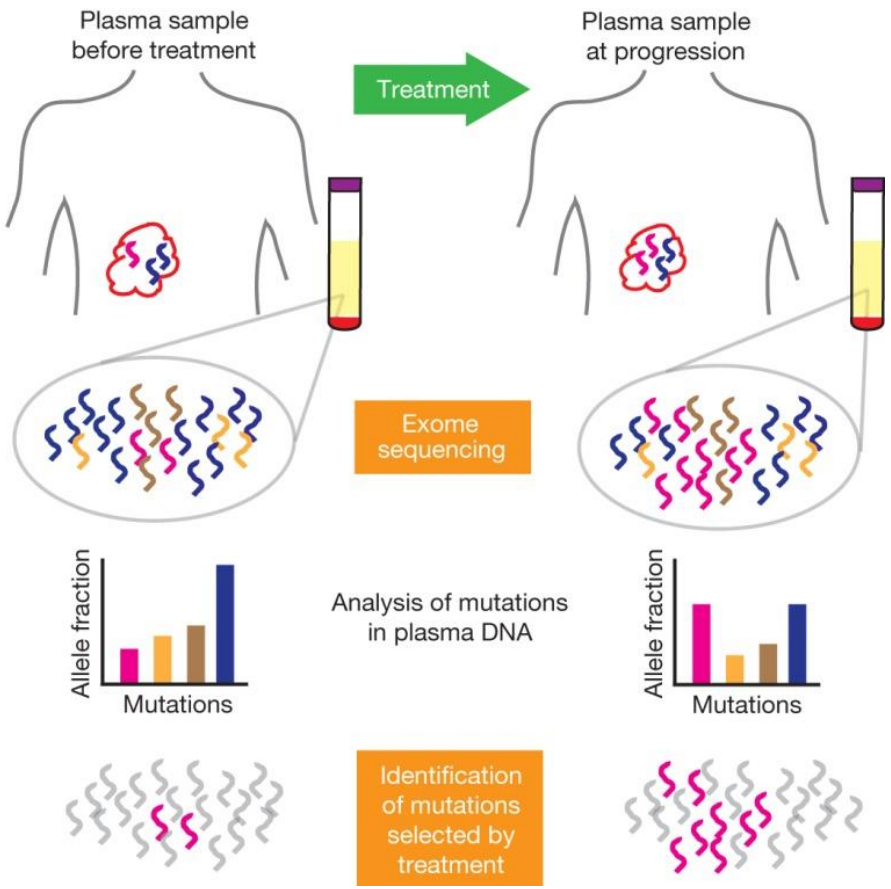


Diaz Jr et al. J. Clin. Oncol. 2014

What applications in the clinic?

- Diagnosis and prediction
  - EGFR mutation, Alk rearrangement, Immunotherapy
- Follow up after curative treatment
  - Stratification for adjuvant therapy
- Detection of resistance to systemic treatment
  - EGFR T790M,

Treatment associated changes in ctDNA



Murtaza et al. Nature 2013

ctDNA EGFR-T790M b/a treatment with EGFR TKI's

	ARMS		D-PCR		*P*
T790M	No.	%	No.	%	
Pre-TKI (n=103)	6	5.8	32	31.1	<0.001
Post-TKI (n=135)	34	25.2	58	43	0.001

Wang et al. PlosOne 2015

Study design

Patients were enrolled from China (n=1458), Russia (n=972), Indonesia (n=302),Taiwan (n=271), Singapore (n=102), Thailand (n=94), Australia (n=71), South Korea (n=62) and Malaysia (n=50)

Patients

- Patients with newly diagnosed, locally advanced / metastatic chemotherapy-naïve NSCLC not suitable for curative treatment (including surgery and chemoradiotherapy) *or*
- Recurrent disease after surgical resection with / without adjuvant chemotherapy

Objectives

To determine

- *EGFR* mutation frequency (ADC and non-ADC histology) [primary endpoint]
- Concordance between *EGFR* mutation status obtained via tissue / cytology and blood (plasma)-based testing
- Correlations between *EGFR* mutation status and demographic data / disease status
- *EGFR* mutation testing practices
- Treatment decisions following *EGFR* mutation testing

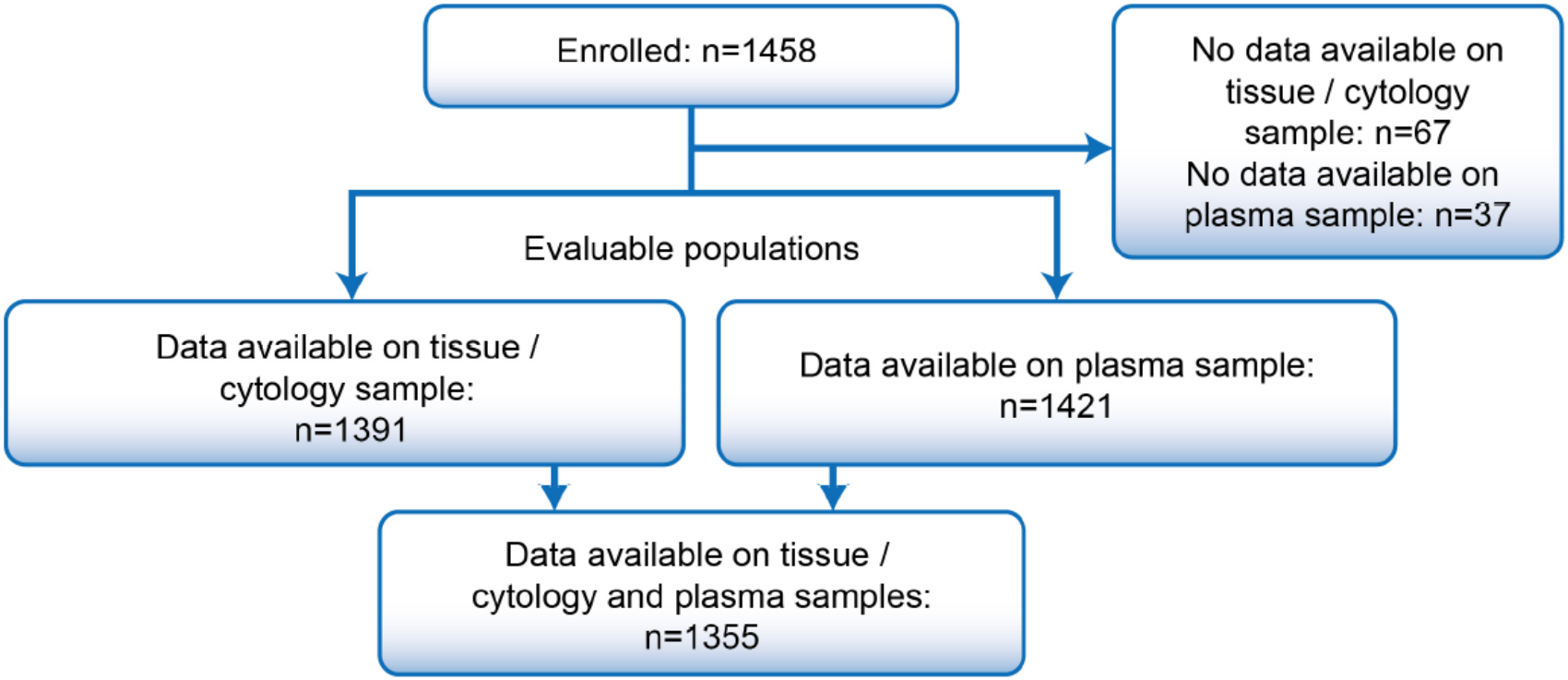
Statistical analysis

- Sample size: 2500 patients from AsiaPac / 1000 patients from Russia needed to be tested to give similar precision of ADC and non-ADC mutation frequency estimate
- Descriptive summary statistics described *EGFR* mutation frequency, sampling / mutation testing methodologies and treatment decisions
- Concordance rate of *EGFR* mutation status between matched tissue / cytology and plasma samples, pooled test sensitivity, specificity, PPV and NPV; exact 2-sided 95% CIs
- Correlation between EGFR mutation status and demographic / disease data analysed with multivariate logistic regression model of *EGFR* mutation status at baseline

ence interval; NPV, negati ictive value; PPV, positive predictive value; WHO, World Health Organization
opulations (all patients with known tumour

Results

First patient enrolled: 27 February 2013; last patient last visit: 25 August 2014



Results

EGFR mutation status concordance

Matched tissue / cytology and plasma samples

China (N=1355)		
Concordance	n/N (%)	1051/1355 (77.6)
	95% CI	75.2, 79.8
Sensitivity	n/N (%)	267/548 (48.7)
	95% CI	44.5,53.0
Specificity	n/N (%)	784/807 (97.1)
	95% CI	95.8,98.2
PPV	n/N (%)	267/290 (92.1)
	95% CI	88.3,94.9
NPV	n/N (%)	784/1065 (73.6)
	95% CI	70.9, 76.2

ctDNA EGFR mut testing

Author	No. Samples	No. EGFR+	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Young 2009	35	15	92	100		
Rosell 2009	164	97	59	100		
Liu 2012	40	27	67	100		
Goto 2012	86	22	43	100	100	55
Douillard 2014	652	105	66	100	99	94
Mok 2015	241	105	75	96	94	95
ASSESS Reck 2015	1162	189	46	97	78	90
This study	1458	566	48	97	92	74

ctDNA EGFR mut testing Ready for prime time?

- Of clinical value when insufficient tumor DNA available at diagnosis
  - PPV
  - Method matters

- More studies needed to establish it's value during therapy

- PD 421: prospective monitoring of lung function tests with CO and NO diffusion during high dose thoracic radiotherapy for lung cancer: CONORT study – C. Fontaine-Delaruelle
- PD 422: Determining the prevalence of EGFR mutations in Asian and Russian patients with advanced AC and non-AC histology – IGNITE study. Chinese subgroup. C. Shi et al.
- PD 423: A prospective phase III study of three weekly versus weekly paclitaxel as second line therapy in advanced non small cell lung cancer. Akil Kaphoor et al

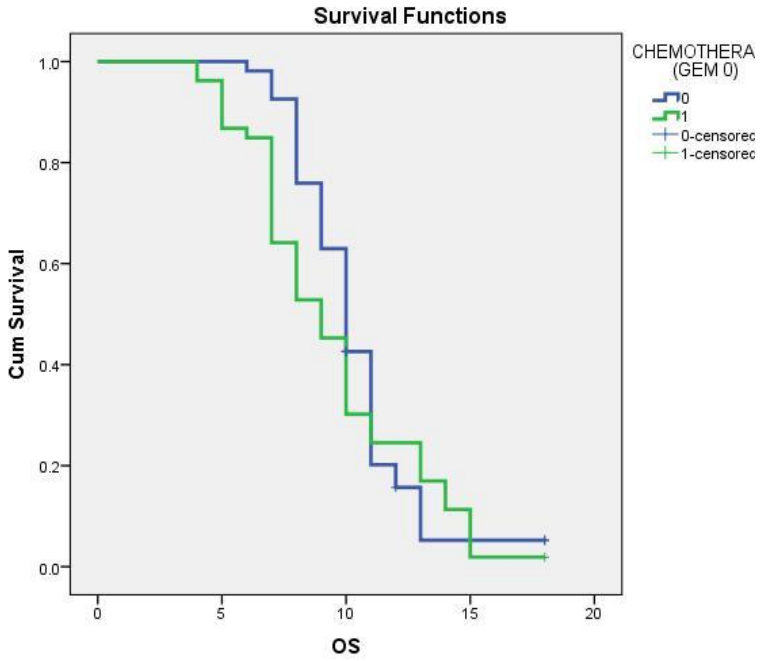
What was done and why?

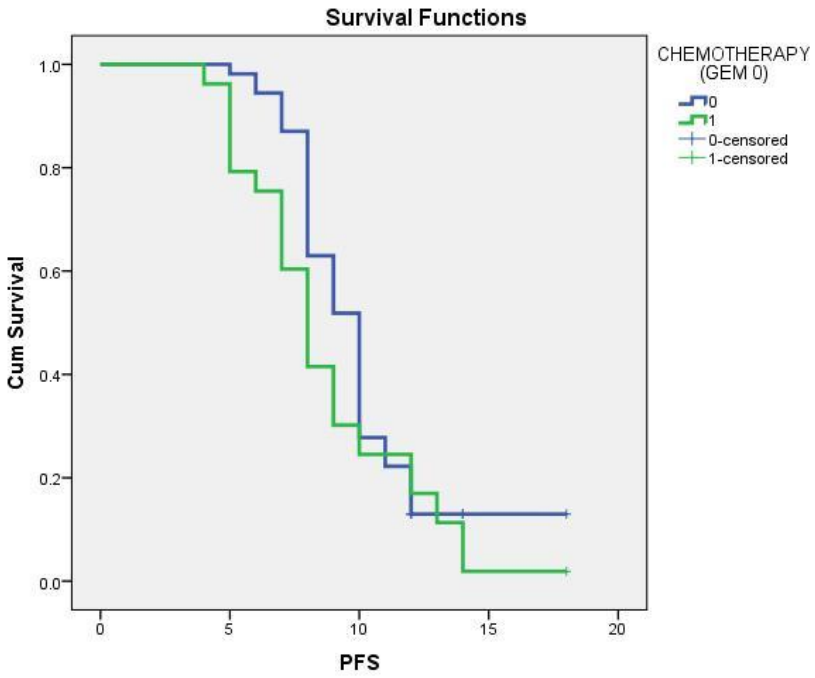
- To evaluate the efficacy of three weekly versus weekly paclitaxel as second line therapy in previously treated patients of advanced non small cell lung cancer (NSCLC) in patient population.

- Weekly paclitaxel is associated with less hematological toxicity and peripheral neuropathy
- Well studied in combination with carboplatin in 1st line
- Less data in second line setting

Patient Characteristics

Characteristics	Category	n=109	%
Age (Median)	-	59 years	
Sex	Male	86	78.8
	Female	23	21.2
ECOG status	0-1	73	66.9
	2	36	33.1
Ever Smoker	Weekly Pacli	35/55	63.6
	3-weekly Pacli	38 /54	70.4
Histology	Sq Cell Ca	28	25.6
	AdenoCa	73	66.9
Stage of disease	IIIB	32	29.4
	IV	77	70.6





Median OS was for three weekly paclitaxel versus weekly paclitaxel 6.8 vs. 7.6 months (HR, 1.19; 95% CI, 0.79 to 1.29; P=0.47)

Median PFS for three weekly paclitaxel versus weekly paclitaxel was 3.1 vs. 4.3 months (HR, 1.42; 95% CI: 1.07-1.75; P=0.03)

How does this result compare to exisiting literature?

Response	All patients	Subgroup 1	2	3
Total patients	62	16	28	18
Median no. of weekly P treatments (range)	8 (1–32)	8 (2–32)	8 (2–32)	7 (1–22)
Best response to weekly P: No. (%)				
PR	5 (8)	0 (0)	5 (18)	0 (0)
SD	23 (37)	7 (44)	10 (35)	6 (33)
PD	28 (45)	7 (44)	10 (35)	11 (61)
Unknown[a]	6 (10)	2 (12)	3 (11)	1 (6)

Median OS 5.2 months
1 & 2 yr survival 20%, 10%

Socinski et al, Cancer 2002

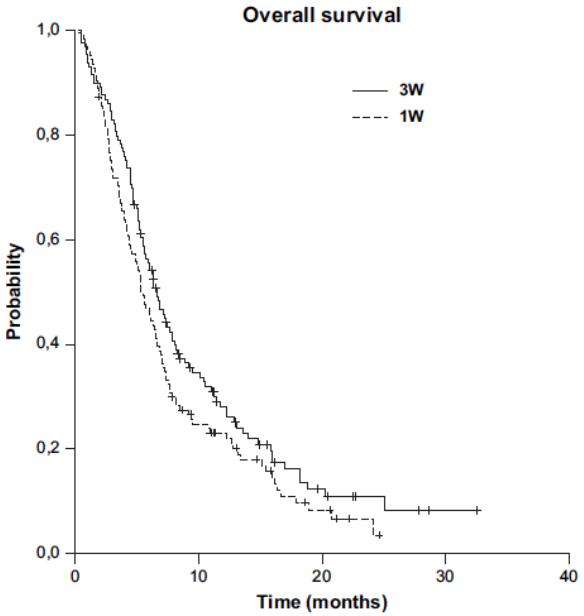


Figure 2 Median survival by treatment arm. Three-weekly arm: 105

Median OS weekly 5.4 months, 3 weekly 6.6 months

Camps et al Ann Oncol 2006

Conclusion

Weekly paclitaxel demonstrated better PFS in comparison to conventional three weekly paclitaxel as second line therapy in patients with advanced non small cell lung cancer with acceptable toxicity profile.

- Equally important is the finding that OS was not different.

Comments

- No information on
  - Sample size calculation
  - Toxicities (!) other than hematological toxicity and diarrhea (which was lower in the weekly arm)

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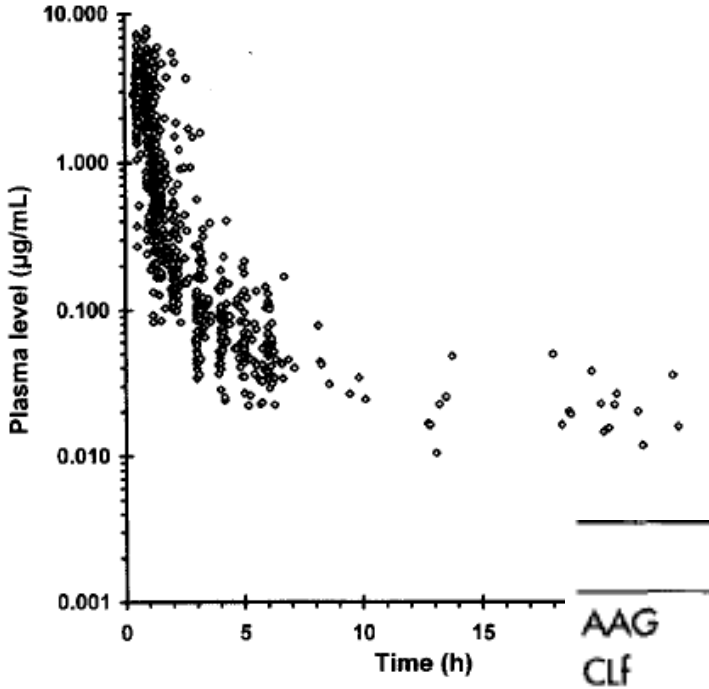
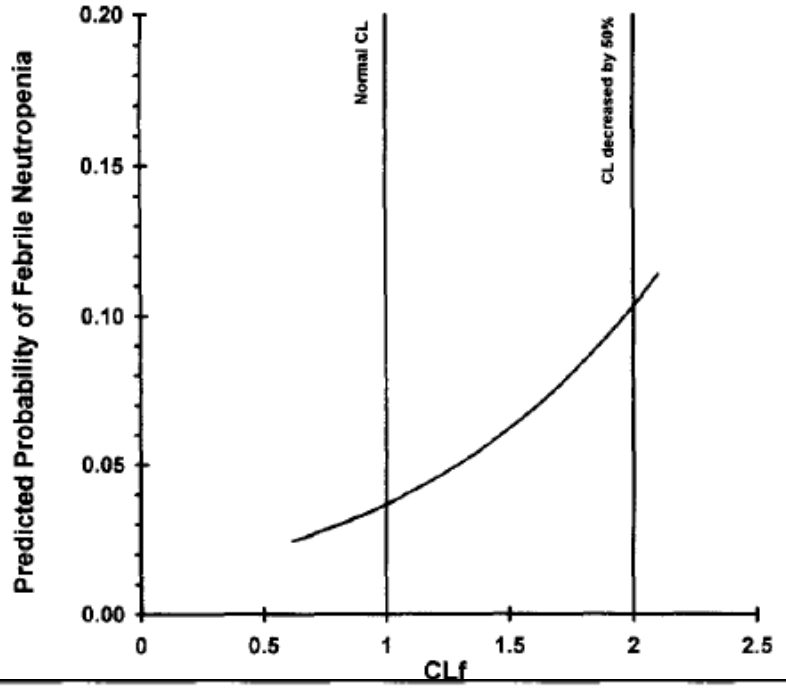
- PD 423: A prospective phase III study of three weekly versus weekly paclitaxel as second line therapy in advanced non small cell lung cancer. Akil Kaphoor et al
- PD 424: Individualization of docetaxel in advanced NSCLC based on PK-guided dosing strategy. Ma et al.

What was done and why?

- BSA dosing of Docetaxel is associated with a high variability in PK parameters, notably AUC
- AUC is highly correlated with hematological toxicity
- In the Asian population the “standard” dose of 75 mg/msq is associated with higher toxicity as compared to Caucasians

Docetaxel Pk/PD

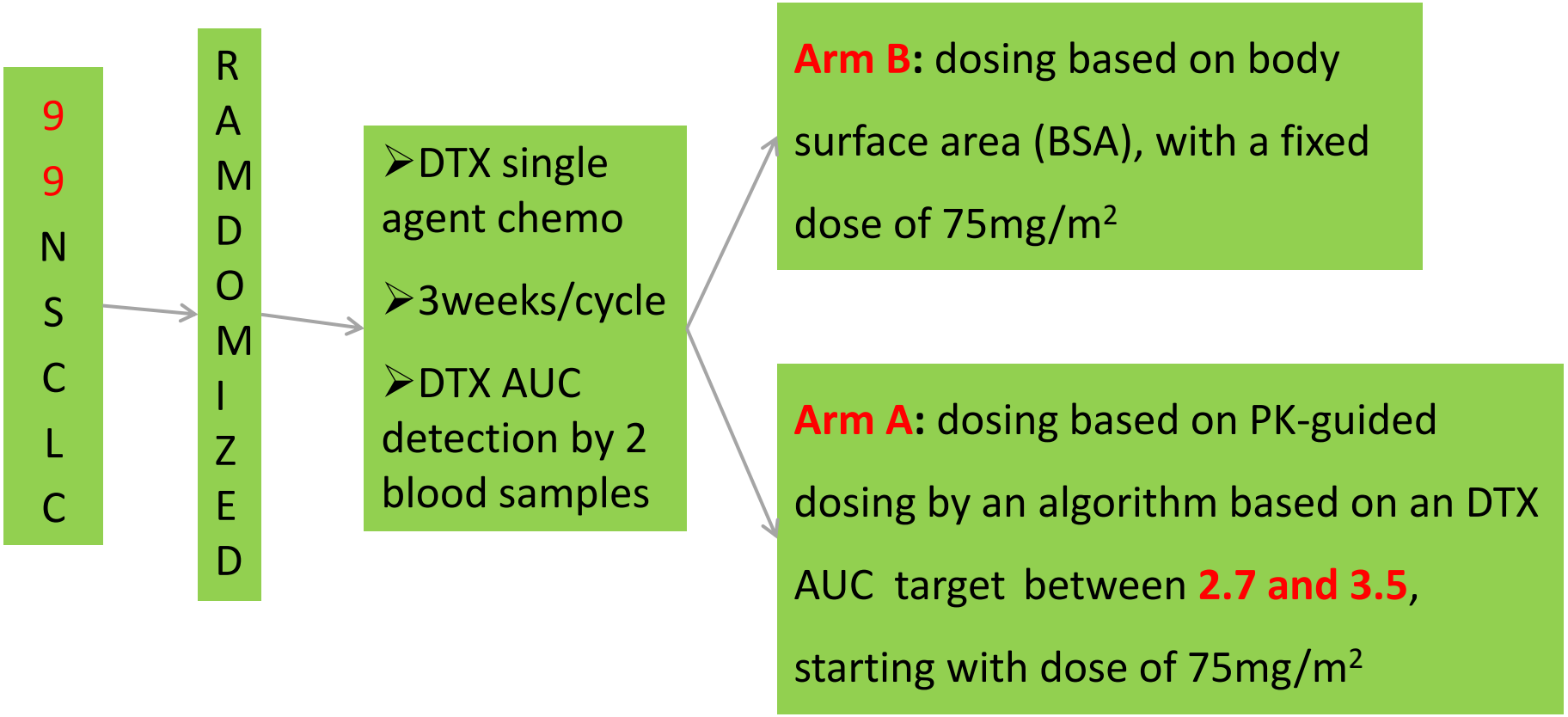




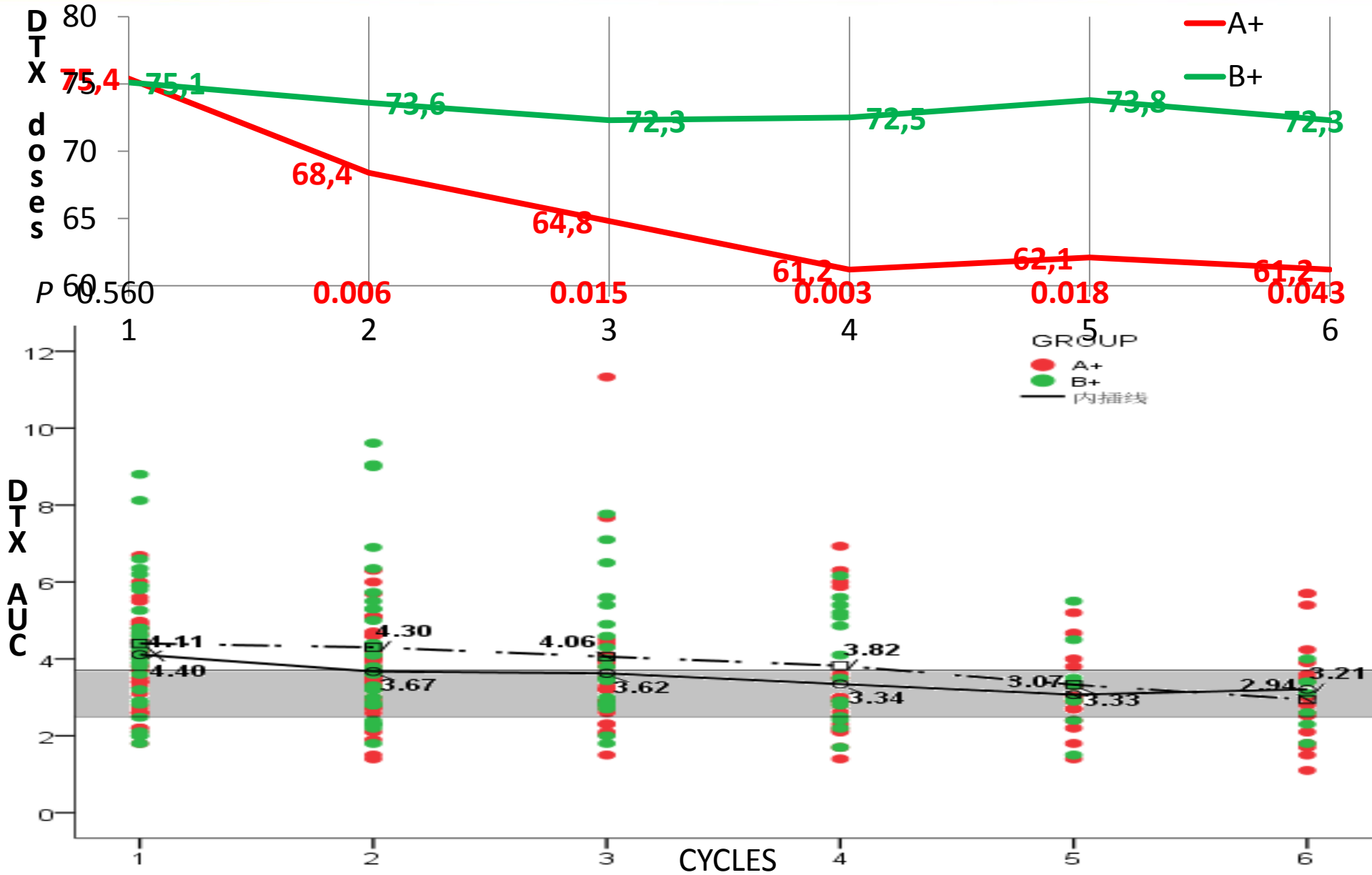
Predictor	P	Odds Ratio	95% CI
AAG	<.0001	0.17	0.10-0.29
CLf	<.0001	4.26	2.46-7.39
Baseline count	.0002	0.84	0.77-0.92
No. of previous regimens	.0002	1.72	1.30-2.29

Bruno et al J. Clin. Oncol. 1998

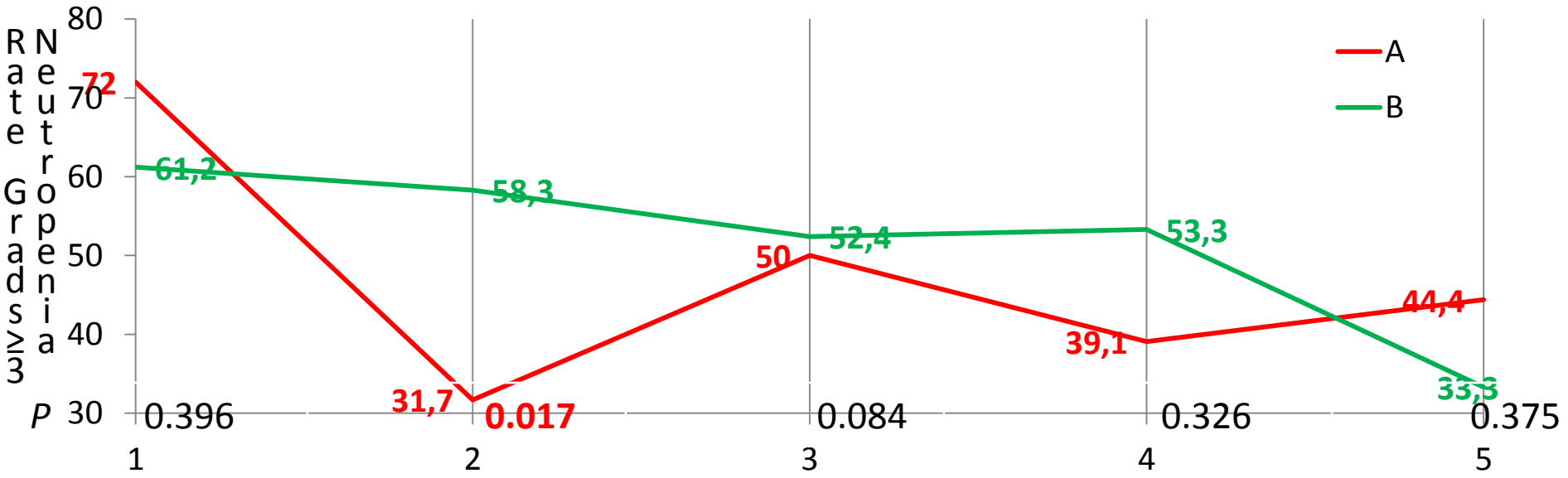
OBJECTIVES: optimization of an individual's doses based on exposure measures may improve DTX safety and efficacy.



PK-guided dosing could positively reduce the DTX doses and adjust the DTX AUC into optimal target.



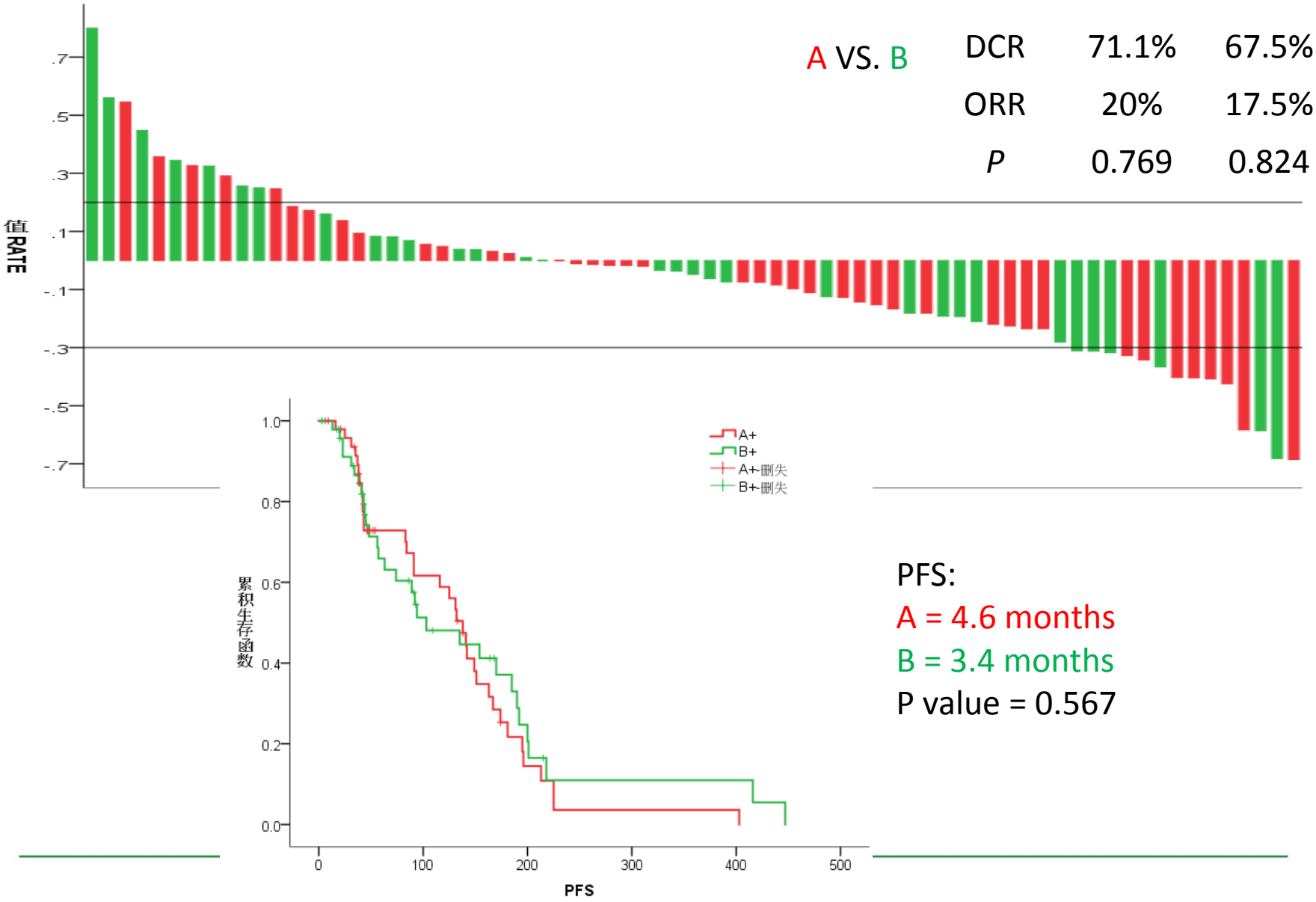
PK-guided dosing could positively relief the DTX related neutropenia



NEU		0 - 2	3 - 4	NA	TOTAL	*P*-value
2nd - 6th	A	53 (42%)	48 (38.4%)	24	125	0.001
	B	16 (18%)	43 (48.9%)	29	88	

No differences were found in ORR and PFS between BSA group and PK group

A VS. B		
DCR	71.1%	67.5%
ORR	20%	17.5%
P	0.769	0.824



PFS:

A = 4.6 months

B = 3.4 months

P value = 0.567

Comment

- No information was provided on the PK sampling
- No information on the analytical method
- Randomization? Power calculation?

Has docetaxel TDM a role in clinical management of NSCLC patients

- Labour intensive strategy
- (probably) not applicable in community practice
- Dose reduction
  - Docetaxel dose 60 mg/sqm East Asia
- May be mandated in the face of unexpected toxicity in the curative setting

Thanks

- To the ESMO to invite me to Singapore
- To the authors for sharing their slides and poster
- You for your attention