Quantification of cell-free DNA as a prognostic marker in advanced NSCLC

Anneli Dowler Nygaard, M.D.
Karen-Lise G. Spindler M.D. Ph.d, Niels Pallisgaard Ph.d,
Rikke F. Andersen Ph.d, Anders Jakobsen M.D. DMSc.

Vejle Hospital
Denmark

VIENNA 2012 ESMO congress

www.esmo2012.org

Disclosures

No conflicts of interest to declare

Introduction

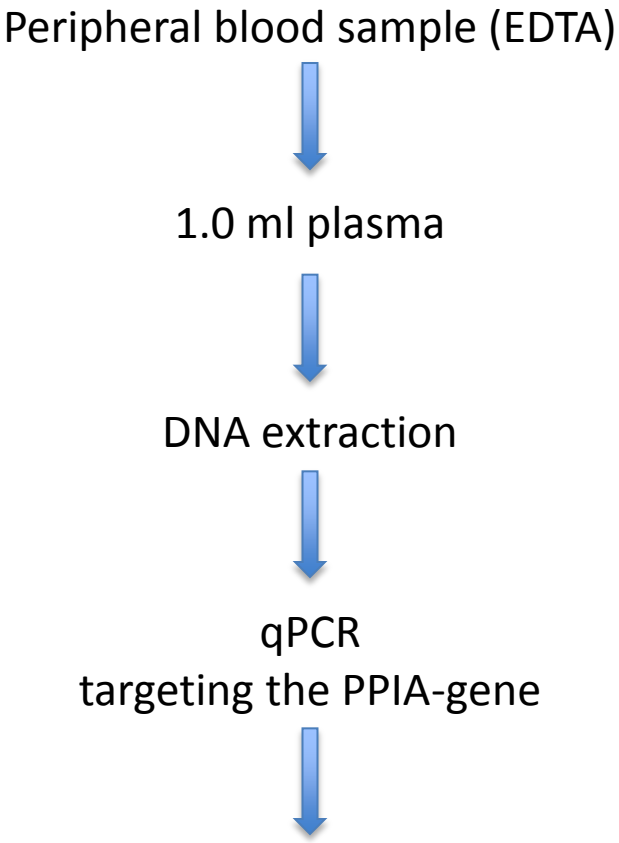
- Cell-free DNA (cfDNA)
  - DNA circulating in the blood-stream
  - Normal cells, tumour cells, tumour surrounding tissue
  - Increased level under malignant conditions
    - Quantification
    - Qualification (tumour-specific mutations)
- ”Liquid biopsy”

Aim

To investigate the **prognostic** value of the **baseline level** of **cfDNA**, in patients with newly diagnosed, **advanced NSCLC**.

Material and Methods

- Prospective marker trial
- Newly diagnosed, histopathologically confirmed NSCLC
- Candidates for 1.st line chemotherapy
  - Carboplatin AUC5 iv day 1 every three weeks
  - Vinorelbine 30 mg/m^2 iv day 1 every three weeks and 60 mg/m^2 po day 8 every three weeks
- Pre-treatment blood-sample
- Primary end-point : Overall Survival (OS)
  - Secondary end-point: Progression Free Survival (PFS)

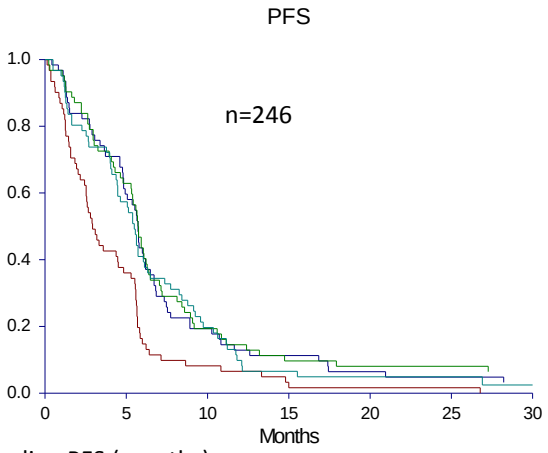

Peripheral blood sample (EDTA)
1.0 ml plasma
DNA extraction
qPCR
targeting the PPIA-gene
Level of cfDNA in the sample
(alleles/ml)

Patient characteristics		Number (n=246)	Percent (100)
Age			
	Median (range)	66 (40-80)	
Gender			
	Male	151	61
	Female	95	39
Histology			
	Adenocarcinoma	150	61
	Squamous Cell Carcinoma	75	31
	Large Cell Carcinoma	8	3
	Other	13	5
Stage			
	II	2	1
	III	60	24
	IV	184	75
Metastatic sites			
	0	116	47
	1-2	118	48
	>2	12	5
ECOG performance status at baseline			
	0	89	36
	1	125	51
	2	32	13
LDH at baseline			
	Normal	140	61
	Elevated	91	39
Smoking history			
	Active or former	234	97
	Never	8	3
Number of cycles			
	Median (range)	4 (1-6)	
Radiotherapy			
	None	192	78
	Palliative	39	16
	Curative	15	6

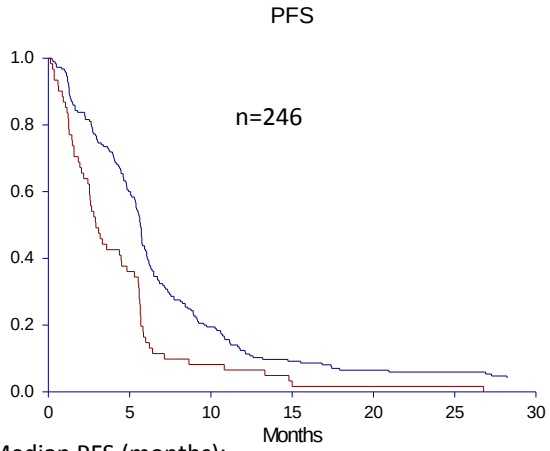
Survival analyses

Median OS:	Median PFS:
(all patients)	*(all patients)*
8.9 months	5.4 months
20 patients were censored	7 patients were censored

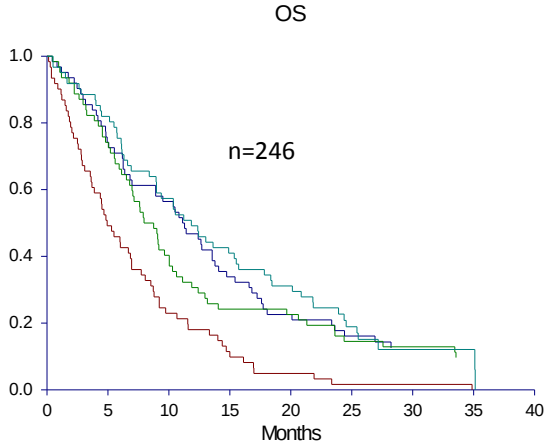
Quartiles → Upper 75th percentile



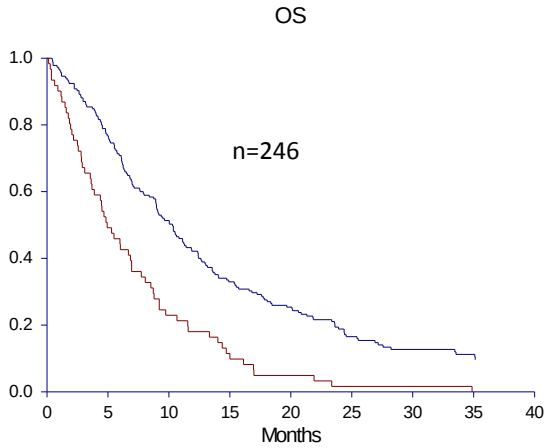
Median PFS (months):
<25%: 5.5 (4.5-6.1); 25-50%: 5.7 (4.8-6.1);
50- 75%: 5.7 (5.3-6.2); >75%: 2.9 (2.5-4.5). p=0.0004



Median PFS (months):
<75%: 5.7 (5.4-5.8); >75%: 2.9 (2.5-4.5).
HR: 1.83 (1.29-2.59), p<0.0001



Median OS (months):
<25%: 11.8 (9.0-15.4); 25-50%: 11.1 (7.0-13.6); 50- 75%:
8.0 (6.8-9.6); >75%: 4.9 (3.7-6.8). p<0.0001



Median OS (months):
<75%: 10.3 (8.9-11.4); >75%: 4.9 (3.7-6.8)
HR: 2.11 (1.47-3.05), p<0.0001

Variables	PFS		OS	
	Risk Ratio (95% CI)	p-value	Risk Ratio (95% CI)	p-value
Plasma cfDNA <75% >75%	1.64 (1.20-2.23)	0.0019	1.89 (1.37-2.60)	0.0001
PS 0-1 2	1.92 (1.29-2.85)	0.0013	1.77 (1.18-2.64)	0.0056
Histology Adenocarcinoma Other NSCLC	0.76 (0.58-1.01)	0.06	0.79 (0.59-1.06)	0.12
Stage 3 4	1.03 (0.91-1.17)	0.64	0.97 (0.85-1.10)	0.62
Distant metastases No Yes	1.35 (0.97-1.86)	0.07	1.46 (1.04-2.04)	0.03
LDH baseline Normal Elevated	1.24 (0.93-1.63)	0.14	1.41 (1.05-1.88)	0.02
All variables were dichotomised. The Risk Ratio refers to moving from the reference group to the other group.				

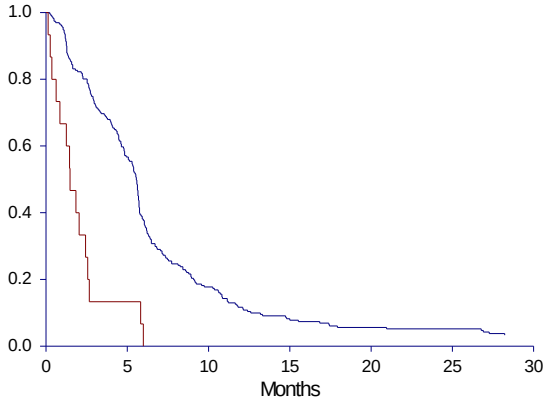
Subgroup analyses

Subgroup of patients with Performance status 2 and cfDNA above the 75th percentile

”High risk group”

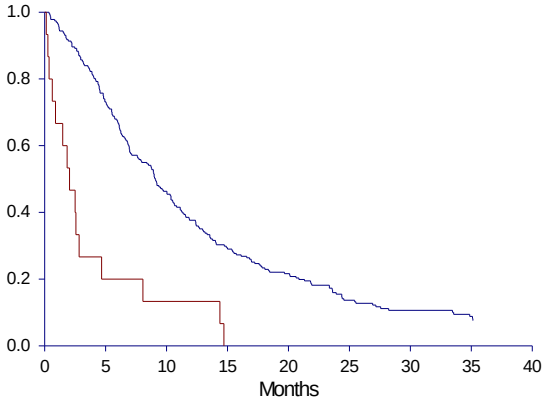
n=15

PFS



Median PFS (months):
High risk group: 1.5 (0.9-2.0)
All other patients: 5.6 (5.1-5.7)
HR: 4.00 (1.48-10.84)
p<0.0001

OS



Median OS (months):
High risk group: 2.0 (0.9-2.6)
All other patients: 9.1 (7.6-10.4)
HR: 3.62 (1.40-9.33)
p<0.0001

Conclusion

- cfDNA seems to hold a prognostic value in patients with NSCLC, treated with standard chemotherapy.
- Combining level of cfDNA and PS may identify a group of patients who do not benefit from treatment – best supportive care?
- Further investigation and validation.

Thank you for your attention!