Hermes project: implementing *EGFR* mutation analysis in clincal care in Antwerp

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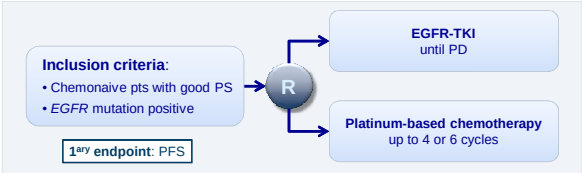
1st line EGFR-TKI *vs* chemotherapy in *EGFR* mutation positive NSCLC



Trial	N	Ethnicity	EGFR-TKI	Chemotherapy
IPASS (subgroup)	261	asian	Gefitinib	Carbo + Pacli (6x)
WJTOG3405	172	asian	Gefitinib	Cis + Doc (6x)
NEJ002	228	asian	Gefitinib	Carbo + Pacli (6x)
OPTIMAL	165	asian	Erlotinib	Carbo + Gemci (4x)
EURTAC	174	caucasian	Erlotinib	Cis/Carbo + Doc/Gemci (4x)

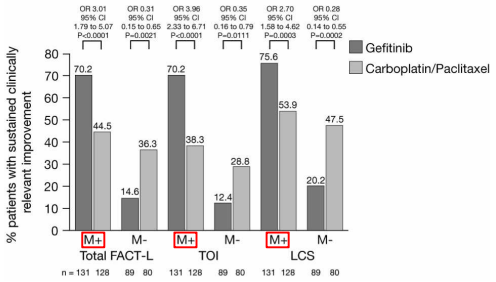
1st line EGFR-TKI *vs* chemotherapy in *EGFR* mutation positive NSCLC

Trial	RR *	PFS *	HR PFS *
IPASS (subgroup) [1]	71% *vs* 47%	9.6 m *vs* 6.3 m	0.48
WJTOG3405 [2]	62% *vs* 31%	9.2 m *vs* 6.3 m	0.49
NEJ002 [3]	74% *vs* 31%	10.8 m *vs* 5.4 m	0.30
OPTIMAL [4]	83% *vs* 36%	14.7 m *vs* 4.6 m	0.16
EURTAC [5]	58% *vs* 15%	9.7 m *vs* 5.2 m	0.37

* all *P* <0.05

1. Mok et al. *NEJM* 2009; vol 361:947-57.
2. Mitsudomi ea. *Lancet Oncol* 2010; vol 11: 121-128.
3. Inoue et al. *J Clin Oncol* 2011; vol 29 (suppl): abstr 7519.
4. Zhou et al. *J Clin Oncol* 2011; vol 29 (suppl): 7520.
5. Rosell et al. *J Clin Oncol* 2011; vol 29 (suppl): 7503.

IPASS: QoL and Symptom Improvement Rates by *EGFR* Mutation Status



Mok et al. *NEJM* 2009; 361:947-57.

EGFR-TKI as 1st-line treatment for NSCLC with activating *EGFR* mutations?

Pro	Contra
Improved progression free survival	Logistics of EGFR mutation analysis
Improved response rate	*No improved overall survival*
Improved QoL and symptom control	
Favourable toxicity profile	
Following 1st line chemotherapy ±1/3 of pts receive no further treatment	

→ **gefitinib is the new standard of care for the 1st-line treatment for NSCLC with activating *EGFR* mutations!**

Hermes project

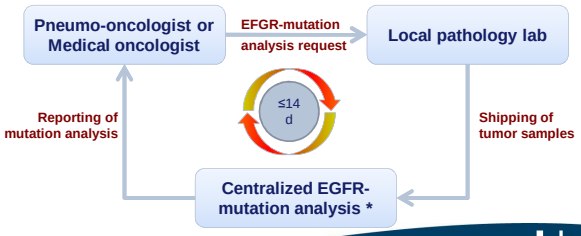
Aims:

- to establish a "regional network" for the analysis of molecular tumor markers (i.e. EGFR mutation status)
- to optimize the logistics of such a network for molecular tumor analysis:
  - Ideally the results should be available in all patients within 2 weeks of the analysis request.
- to obtain an epidemiologic description of the molecular tumor characteristics (i.e. EGFR mutation status) in Antwerp

Hermes project

Aim:

- to establish a "regional network" for the analysis of molecular tumor markers (i.e. EGFR mutation status)
- to optimize the logistics of such a network for molecular tumor analysis

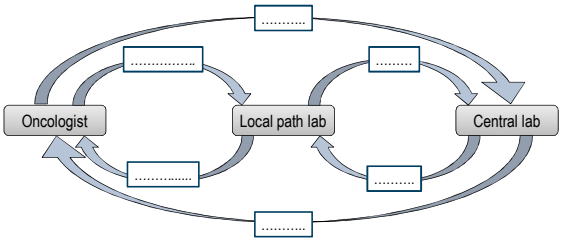


Hermes project

Primary endpoints:

- time to get the mutation analysis results
  - time from oncologist to local pathology
  - time from local pathology to molecular analysis lab
  - time from molecular analysis lab to oncologist

Hermes project: median time (range) of each step



Hermes project

Primary endpoints:

- time to get the mutation analysis results
  - time from oncologist to local pathology
  - time from local pathology to molecular analysis lab
  - time from molecular analysis lab to oncologist

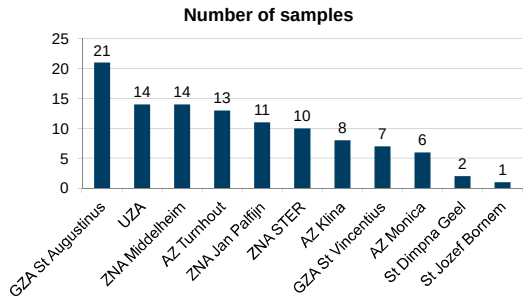
Secondary endpoints:

- epidemiologic description of the molecular tumor characteristics (I;e. EGFR mutation status) in Antwerp
- "exploratory analysis" of the relationship between the pulmonary function and incidence of EGFR mutation

Hermes project: patient characteristics

Age (n 107)	
Median (range)	65 yr (44-90 yr)
Gender (n 107)	
Male	68 (64%)
Female	39 (36%)
Ethnicity (n 106)	
Caucasian	104 (97%)
Asian	1 (1%)
North African	1 (1%)
Smoking status (n 106)	
Smoker	45 (42%)
Ex-smoker	49 (46%)
Never smoker	13 (12%)
Performance status (n 97)	
PS 0	38 (39%)
PS 1	50 (52%)
PS 2	9 (9%)

Hermes project: participating hospitals



Hermes project: biopsy characteristics

Tumor biospy type (n 107)	
Cytology	8
Percutaneous needle biopsy	20
EUS FNA	1
EBUS TBNA	6
Bronchoscopic biopsy	33
Mediastinoscopic biopsy	6
Surgical biopsy	33

Pleural fluid	4		
Bronchoscopy	3		
Pericardial fluid	1		

Lung	9	LN	1
Bone	3	Adrenal	1
Liver	3	Muscle	1
Skin	2		

Lung	20	Adrenal	1
Pleura	5	Breast	1
LN	2	Brain	1
Skin	2	NOS	1

Hermes project: tumor characteristics

Tumor Histology (n 104)	
Adenocarcinoma	84
Large cell carcinoma	1
NSCLC NOS	5
Squamous cell carcinoma	13
Small cell carcinoma	1
***EGFR* mutation analysis** (n 107)	
EGFR wild type	95
EGFR activating mutation	7
EGFR analysis not possible	5

Bronchial biopsy	2
Lung resection	1
Bone biopsy	1
Cytology	1

Hermes project: tumor characteristics

EGFR mutations (n 7)	
Exon 19 deletion	6
Exon 21 L858R mutation	1

Gender	N	Incidence
Male	4	6%
Female	3	8%
Smoking status		
Smoker	2	4%
Ex-smoker	3	6%
Never	2	15%
Ethnicity		
Caucasian	6	6%
Asian	1	
Histology		
AdenoCA	7	8%

Biopsy type	
Surgical lung resection	2
Bronchoscopic lung biopsy	1
Surgical pleural biopsy	1
Bone biopsy (spirotoom 10G)	1
TTNA	1
Bronchial aspirate (cytology)	1

Of all *EGFR*-mutations found in this project 57% occurred in men and 71% occurred in (ex-)smokers

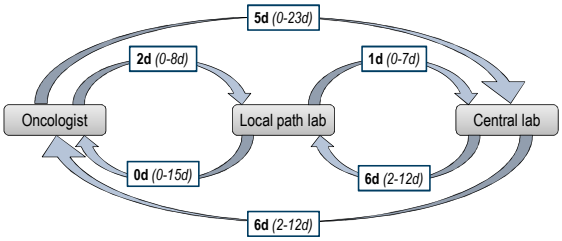
Hermes project: *EGFR*-mutations in non-asians with non-squamous carcinoma (N89)

EGFR mutations (n 6)	
Exon 19 deletion	5
Exon 21 L858R mutation	1

Gender	N	Incidence
Male (n 56)	4	7%
Female (n 33)	2	6%
Smoking status		
Smoker (n 39)	2	5%
Ex-smoker (n 39)	3	8%
Never (n 10)	1	10%

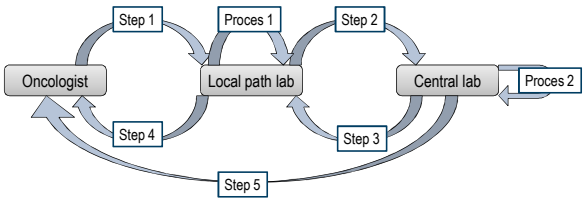
Of all *EGFR*-mutations found in caucasians with non-squamous carcinoma: 67% occurred in men and 83% occurred in (ex-)smokers

Hermes project: median time (range) of each step

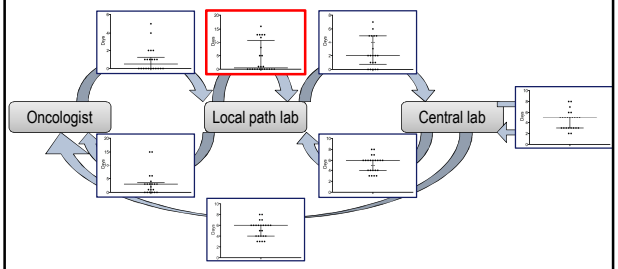


Total processing time	median	mean	range
result via local path lab	10 d	12 d	3-37 d
result via central lab	9 d	11 d	3-29 d

Hermes project: interdepartemental communication steps & intradepartemental processing steps

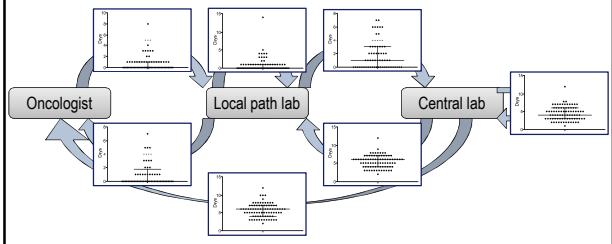


Hermes project:
processing times in 1st two months of project (n 24)



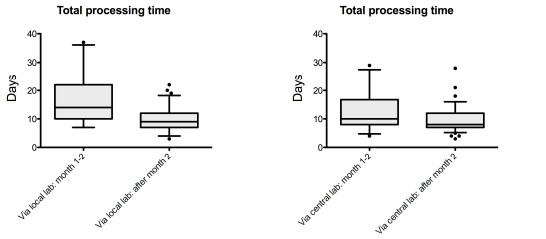
Total processing time	median	25-75 %	range
result via local path lab	14 d	10-22 d	7-37 d
result via central lab	10 d	8-17 d	4-29 d

Hermes project:
processing times after 1st two months of project (n 83)



Total processing time	median	25-75 %	range
result via local path lab	9 d	7-12 d	2-22 d
result via central lab	8 d	7-12 d	3-28 d

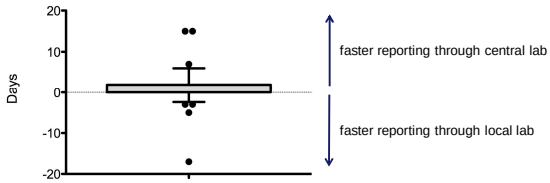
Hermes project:
processing times before and after 1st two months



Total time local lab	median	25-75 %
1st two months	14 d	10-22 d
After 1st two months	9 d	7-12 d

Total time central lab	median	25-75 %
1st two months	10 d	8-17 d
After 1st two months	8 d	7-12 d

Hermes project:
difference between local and central lab reporting



EGFR Gene Alterations in a Norwegian Cohort of Lung Cancer Patients Selected for Surgery

EGFR mutations: in 18/240 or 7.5% of samples	
Exon 18 G719X mutation	1
Exon 19 deletion	8
Exon 20 insertion	3
Exon 21 L858R mutation	5
Exon 21 L861Q mutation	1

Gender	
Male	4 (22%)
Female	14 (78%)
Smoking history	
Ever-smoker	8 (44%)
Never smoker	10 (56%)
Histology	
Adenocarcinoma	14 (78%)
Squamous cell	2 (11%)
BAC	2 (11%)

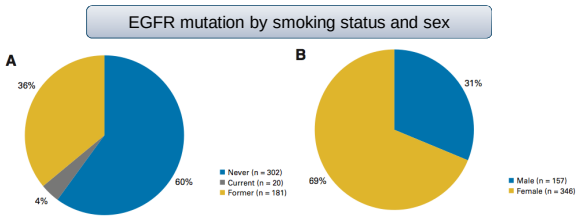
Helland et al. *J Thorac Oncol* 2011;6: 947–950 .

Incidence of *EGFR* Exon 19 deletions and L858R in lung adenocarcinomas from men and smokers

- 2,142 samples were tested.
- *EGFR* mutations were found in:
  - 6% of tumors from current smokers
  - 15% of tumors from former smokers
  - 52% of tumors from never smokers
  - 19% of tumors from men
  - 26% of tumors from women

D'Angelo et al. *J Clin Oncol* 2011; 29: 2066–2070.

Incidence of *EGFR* Exon 19 deletions and L858R in lung adenocarcinomas from men and smokers



→ If only women who were never smokers were tested, 57% of all *EGFR* mutations would be missed

D'Angelo et al. *J Clin Oncol* 2011; 29: 2066–2070.

Incidence of *EGFR* Exon 19 deletions and L858R in lung adenocarcinomas from men and smokers

Table 1. Incidence of *EGFR* Mutations by Cigarette Smoking History

Smoking History	Stage I-IIIA			Stage IIIB/IV			All Stages				
	No. with Mutations	Total No. of Tumors	%	No. with Mutations	Total No. of Tumors	%	No. with Mutations	Total No. of Tumors	%	95% CI	*P*
Never	131	228	57	171	352	49	302	580	52	48 to 56	< .001 $\chi^2_{(df=2)} = 314$
Former	83	714	12	98	504	19	181	1,218	15	13 to 17	
Current	4	143	3	16	201	8	20	344	6	4 to 9	

Table 2. Incidence of *EGFR* Mutations by Pack-Years of Cigarettes Smoked

Pack-Years	Stage I-IIIA			Stage IIIB/IV			All Stages			
	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI
Never smokers	131	228	57	171	352	49	302	580	52	48 to 56
1 to 5	22	57	39	20	68	29	42	125	34	25 to 43
6 to 10	11	47	23	29	69	42	40	116	34	26 to 44
11 to 15	10	59	17	9	49	18	19	108	18	11 to 26
16-25	13	129	10	13	110	12	26	239	11	7 to 16
26 to 50	16	294	5	27	246	11	43	540	8	6 to 11
51 to 75	10	148	7	11	95	12	21	243	9	5 to 13
> 75	3	116	3	4	66	6	7	183	4	2 to 8
P (trend test)	< .001 $\chi^2_{(df=1)} = 129$			< .001 $\chi^2_{(df=1)} = 90.2$			< .001 $\chi^2_{(df=1)} = 224$			

Table 3. Incidence of *EGFR* Mutations by Sex

Sex	Stage I-IIIA			Stage IIIB/IV			All Stages				
	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI	*P*
Female	161	690	23	185	625	30	346	1,315	26	24 to 29	< .001 $\chi^2_{(df=1)} = 15.2$
Male	57	395	14	100	432	23	157	827	19	16 to 22	
Total	218	1,085	20	285	1,057	27	503	2,142	23	22 to 25	

D'Angelo et al. *J Clin Oncol* 2011; 29: 2066–2070.

Incidence of *EGFR* Exon 19 deletions and L858R in lung adenocarcinomas from men and smokers

Table 4. Incidence of *EGFR* Mutations by Cigarette Smoking History and Sex

Smoking History and Sex	Stage I-IIIA			Stage IIIB/IV			All Stages				
	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	No. With Mutations	Total No. of Tumors	%	95% CI	*P**
Never smokers											
Female	101	176	57	116	222	52	217	398	55	49 to 59	.15
Male	30	52	57	55	130	42	85	182	47	39 to 54	$\chi^2_{(df=1)} = 2.12$
Total	131	228	57	171	322	53	302	580	52	48 to 56	
Smokers											
Female	60	514	12	68	403	17	129	917	14	12 to 16	.073
Male	27	343	8	45	302	15	72	645	11	9 to 14	$\chi^2_{(df=1)} = 3.21$
Total	87	857	10	114	705	16	201	1,562	13	11 to 15	

*P value was adjusted for stage.

Table 5. Patients Tested and *EGFR* Mutations Missed Under Different Testing Strategies

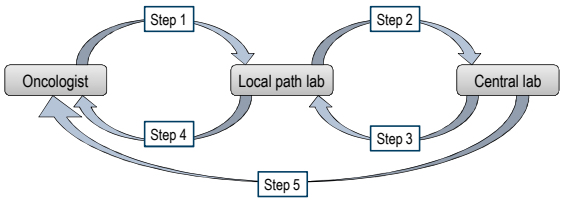
Population Tested	Patients Tested		*EGFR* Mutations Detected		*EGFR* Mutations Missed	
	No.	%	No.	%	No.	%
Women only	1,315	61	346	69	157	31
Never smokers only	580	27	302	60	201	40
Never smoking women	398	19	217	43	286	57
All patients	2,142	100	503	100	0	0

D'Angelo et al. *J Clin Oncol* 2011; 29: 2066–2070.

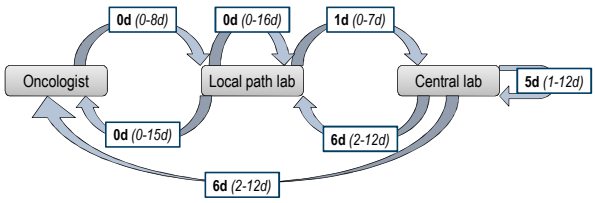
BESLUIT

- Snelle implementatie van EGFR mutatie testing met gemiddeld na 14 dagen resultaat.
- EGFR mutatie testen bij alle non-squamous onafhankelijk van het geslacht en rokerstatus.

Hermes project



Hermes project:
interdepartemental communication steps & intradepartemental processing steps



Total processing time	median	mean	range
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result via central lab	9 d	11 d	3-29 d

Hermes project: tumor characteristics

EGFR mutations (n 7)	
Exon 19 deletion	6
Exon 21 L858R mutation	1

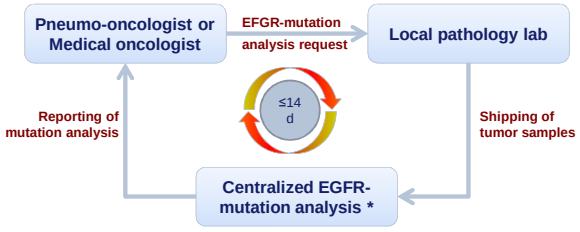
Gender	
Male	4
Female	3
Smoking history	
Smoker	2
Ex-smoker	3
Never smoker	2
Ethnicity	
Caucasian	6
Asian	1
Histology	
Adenocarcinoma	7

Biopsy type	
Lung resection	2
Bronchoscopic biopsy	1
Pleural biopsy	1
Bone biopsy	1
TTNA	1
Unknown	1

Hermes project: tumor characteristic:

Tumor biospy type (n 107)	
Cytology	8
Percutaneous needle biopsy	20
EUS FNA	1
EBUS TBNA	6
Bronchoscopic biopsy	33
Mediastinoscopic biopsy	6
Surgical biopsy	33
Tumor Histology (n 104)	
Adenocarcinoma	84
Large cell carcinoma	1
NSCLC NOS	5
Squamous cell carcinoma	13
Small cell carcinoma	1

Hermes project



EGFR Gene Alterations in a Norwegian Cohort of Lung Cancer Patients Selected for Surgery

- *EGFR*-mutation detected in 18/240 or 7.5% of samples

TABLE 2. Mutations Identified by the TheraScreen Mutation Kit and by dHPLC and Sequencing

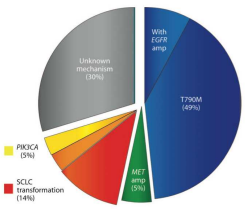
Sample Number	Mutation TheraScreen	dHPLC + Sequencing	Gender	Age (yr)	Pack-Years	Histology
T48	L858R	Leu858Arg; ex21	F	75	0	AC
T59	L858R	Leu858Arg; ex21	F	76	0	AC
T62	Deletion	c.2240_2257del18; p.Leu747_Pro753delinSer; ex19	F	66	0	AC
T73	Deletion	c.2235_2249del15; p.Glu746_Ala750del; ex19	F	56	10	AC
T97	Insertions	Neg	F	63	33	SCC
T104	Insertions	9BP insertion; ex20	F	75	5	AC
T107	Insertions	c.2297_2235_dup9; p.Ala767_Val 769dup; ex20	F	70	0	BAC
T148	L858R	Leu858Arg; ex21	M	71	0	AC
T169	L858R	Not done	M	81	24.5	AC
T175	Deletion	c.2235_2249del15; p.Glu746_Ala750del; ex19	M	65	1.3	AC
T189	Deletion	c.2240_2257del18; p.Leu747_Pro753delinSer; ex19	F	51	9	SCC
T194	Deletion	c.2240_2257del18; p.Leu747_Pro753delinSer; ex19	F	70	0	AC
T195	Deletion	Neg	M	66	24.7	AC
T208	Deletion	c.2236_2250del15; p.Glu746_Ala750del; ex19	F	65	0	BAC
T231	Deletion	c.2235_2249del15; p.Glu746_Ala750del; ex19	F	73	0	AC
T249	G719X	c.2126A > C; p.Glu709Ala; ex18, c.2155G > T; p.Gly719Cys; ex18, -2 mutations	F	62	30	AC
T261	L858R	Leu858Arg; ex21	F	48	2.5	AC
T266	L861Q	Neg	F	67	39	AC

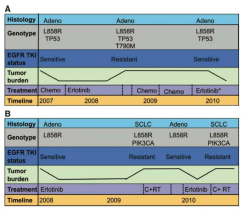
AC, adenocarcinoma; SCC, squamous cell carcinoma; BAC, bronchoalveolar carcinoma.

Helland et al. *J Thorac Oncol* 2011;6: 947–950 .

Genotypic and Histological Evolution of NSCLCs Acquiring Resistance to EGFR Inhibitors

- All drug-resistant tumors retained their original activating EGFR mutations
- In 10% of patients, serial biopsies revealed that genetic mechanisms of resistance were lost in the absence of the continued selective pressure of EGFR inhibitor treatment, and such cancers were sensitive to a second round of treatment with EGFR inhibitors.





Sequist et al. *Science Translational Medicine* 2011; vol. 3: 75ra26.