



smile

BioMILD & SMILE trials

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DISCLOSURES

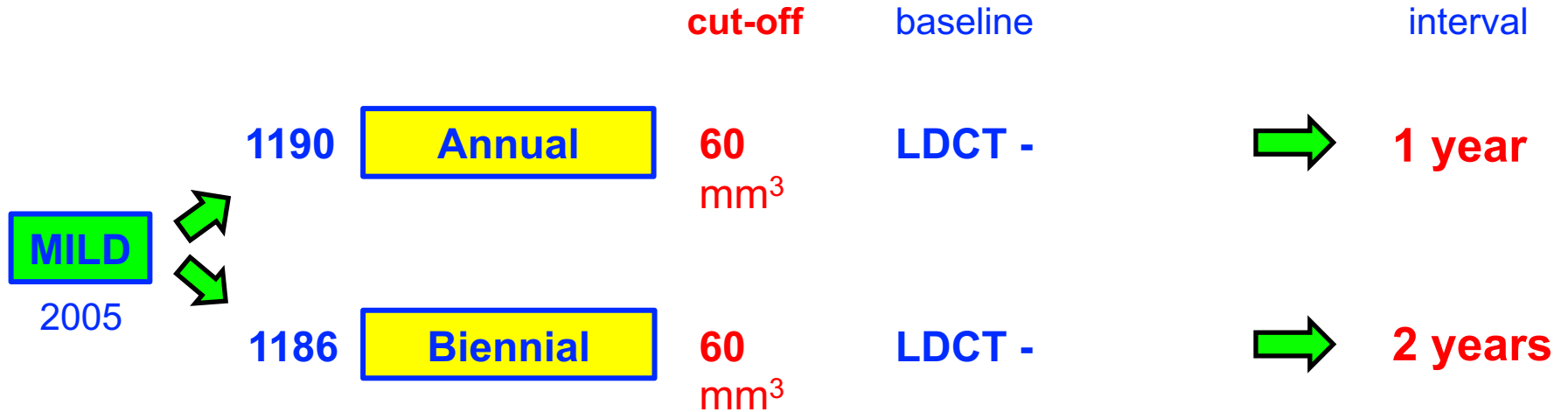
- no commercial interest
- microRNA signature classifiers patent
(not on the market)

INTM screening strategy: **target individual risk**

- **baseline LDCT -** longer screening intervals
- **non invasive ADC** active surveillance of SSNs
- **different biologic risk** blood miRNA signature
- **stop active smoking** anti-tobacco therapy

MILD screening intervals

2005





ELSEVIER

MILD trial

journal homepage: www.ejancer.com

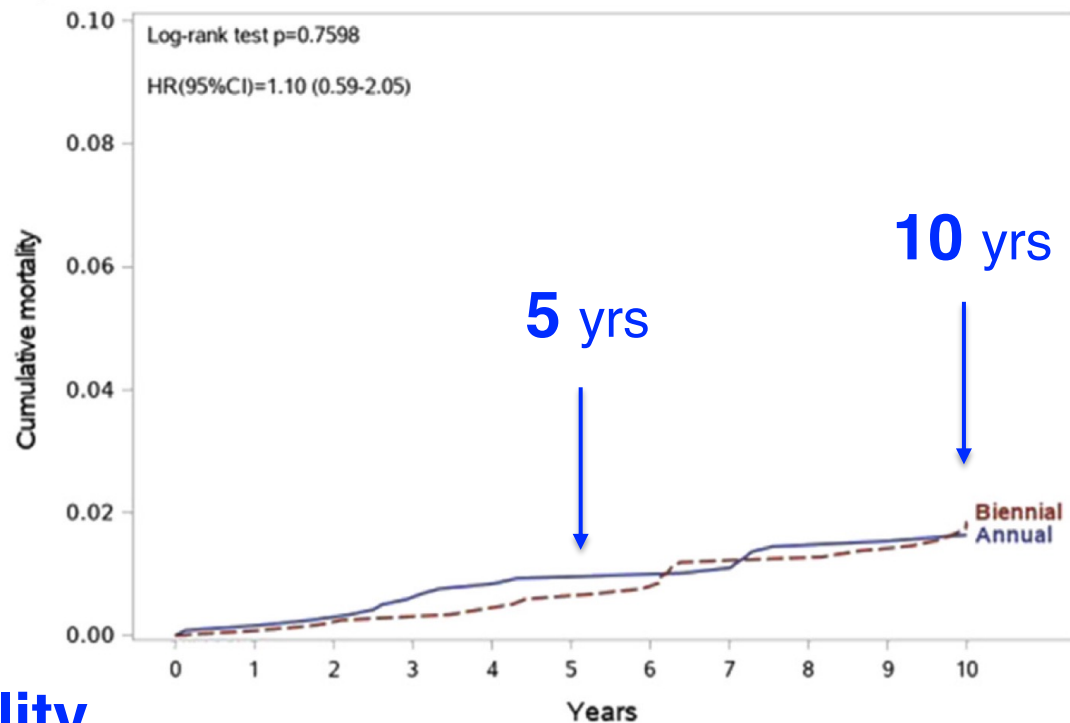
Original Research

Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening

**no difference in LC mortality
between annual and biennial LDCT
at 10 years follow-up**

A)

Lung cancer mortality



blood microRNA for LDCT screening development of a signature classifier (MSC)

TRAINING SET

Pilot trial: 1035 subjects

↳ 38 LC within 5 years

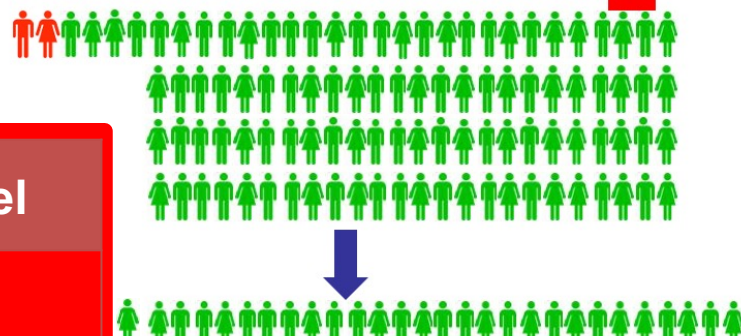


Ratios
between 24
microRNAs

VALIDATION SET

MILD trial: 4099 subjects

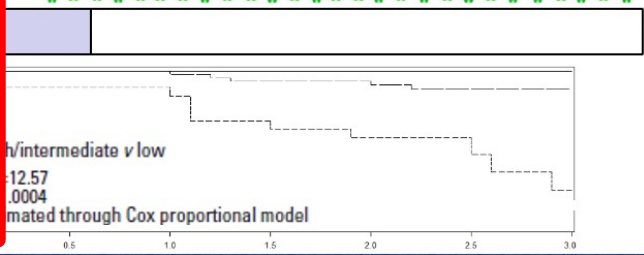
↳ 85 LC within 5 years



Vs.



BioMILD	Risk level
pos	High
	Intermediate
neg	Low



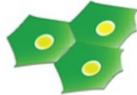
origin of the 24 INTM blood microRNAs

Lung cancer



Cluster miR-17-92
miR-21
miR-106a
miR-320
miR-660

Endothelial



miR-126

Fibroblasts



miR-145
miR-221

Skeletal MC



cluster miR-17-92
miR-106a
miR-133a
miR-221

Smooth MC



miR-320

miR-28-3p
miR-145

Lymphocytes



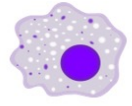
miR-92a
miR-101
miR-30b

Monocytes



miR-197
miR-660

Macrophages



miR-19b
miR-21
miR-140-5p
miR-197
miR-660

Granulocytes



miR-19b
miR-140-5p
miR-142-3p
miR-148a
miR-486-5p

Platelets



miR-17
miR-28-3p
miR-126
miR-145
miR-486-5p
miR-451

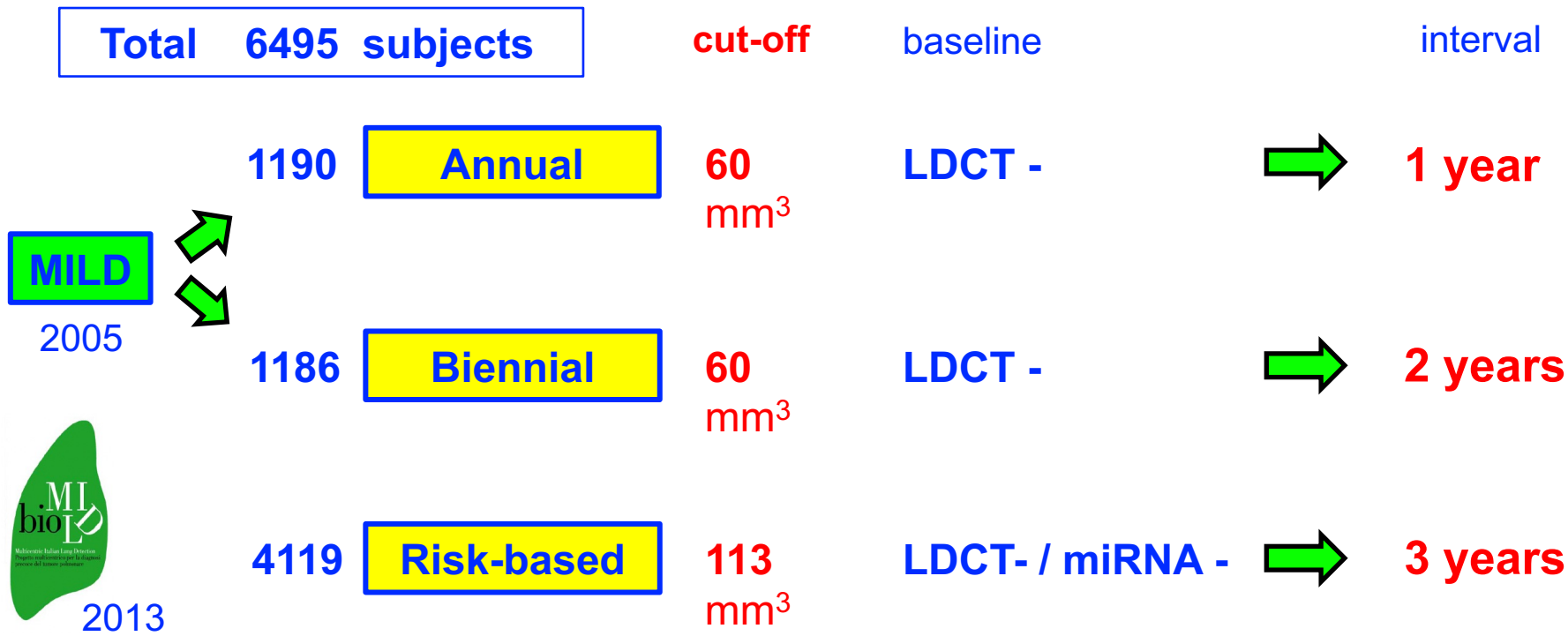
Hematopoietic:

miR-16
miR-140-3p

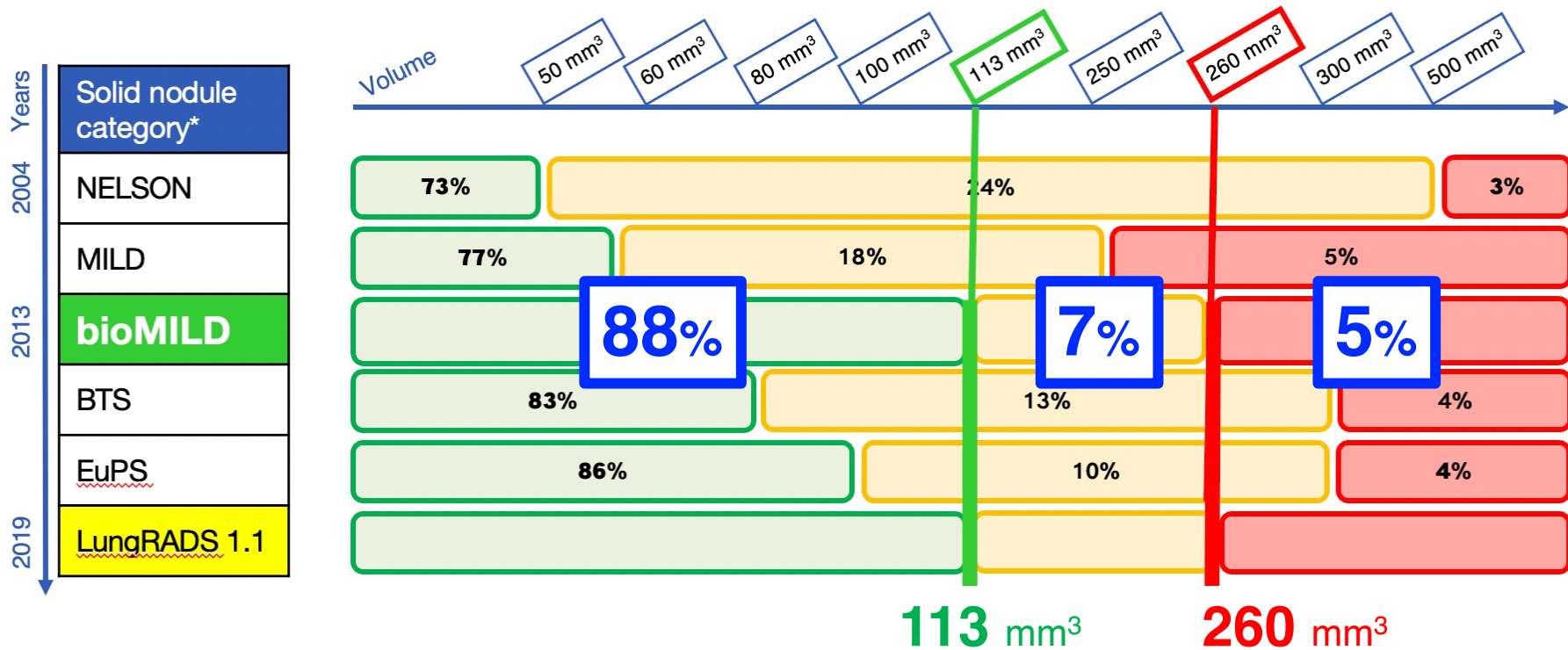
©

less than 20% from LC cells

MILD vs. BioMILD screening intervals



Baseline volumetric LDCT cut-off intervals



2013

BioMILD trial: AIMS

- evaluate the utility of blood microRNA and LDCT for prediction of individual LC risk
- assess the feasibility and safety of **3-year screening interval** in subjects with double negative baseline LDCT and microRNA
- reveal **potential damage** of 3-year LDCT interval: stage I LC, resection rates, interval cancer





Risk outcome

2neg

1pos

2pos

LDCT

miRNA

0-112 mm³
negative

AND

low

≥ 113 mm³
Ind / pos

OR

Interm / high

≥ 113 mm³
Ind / pos

AND

Interm / high

2384 **58%**

1526 **37%**

209 **5%**

average # LDCTs

2,0

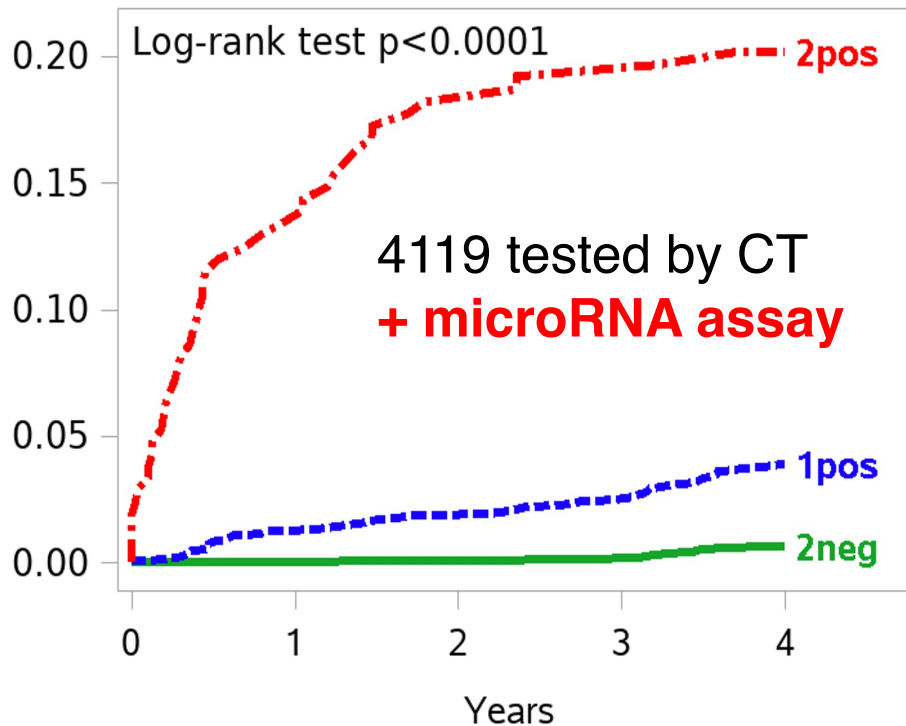
3,2

3,5





Lung cancer incidence



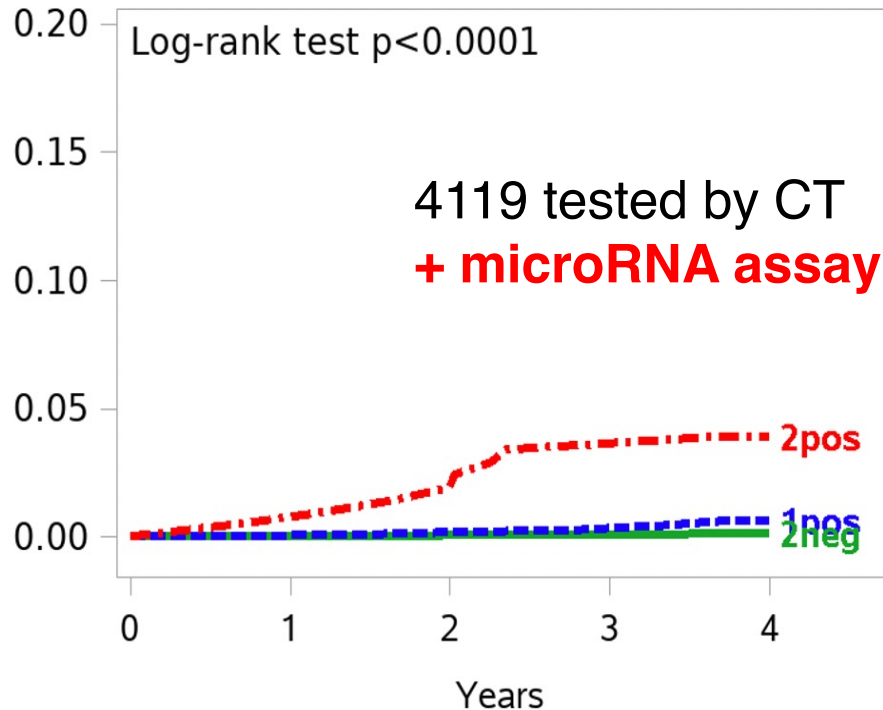
	Lung Cancer incidence HR* (95%CI)
2neg	1.00 (ref.)
1pos	5.96 (3.38-10.52)
2pos	36.64 (20.31-66.11)

* Adjusted for age, sex and pack-years.

Log-rank test 2neg vs. 1pos	<0.0001
Log-rank test 1pos vs. 2pos	<0.0001



Lung cancer mortality



Lung Cancer mortality HR* (95%CI)	
2neg	1.00 (ref.)
1pos	4.67 (1.26-17.24)
2pos	32.24 (8.55-121.60)

* Adjusted for age, sex and pack-years.

Log-rank test 2neg vs. 1pos	0.0103
Log-rank test 1pos vs. 2pos	<0.0001



Active surveillance of subsolid nodules (225 subjects)



Subsolid nodules (SSNs)	2neg 33*	1pos 135	2pos 57
SSN % at baseline	1.4%	8.8%	27.3%
LC from SSN	0	7	0
LC deaths from SSN	0	0	0

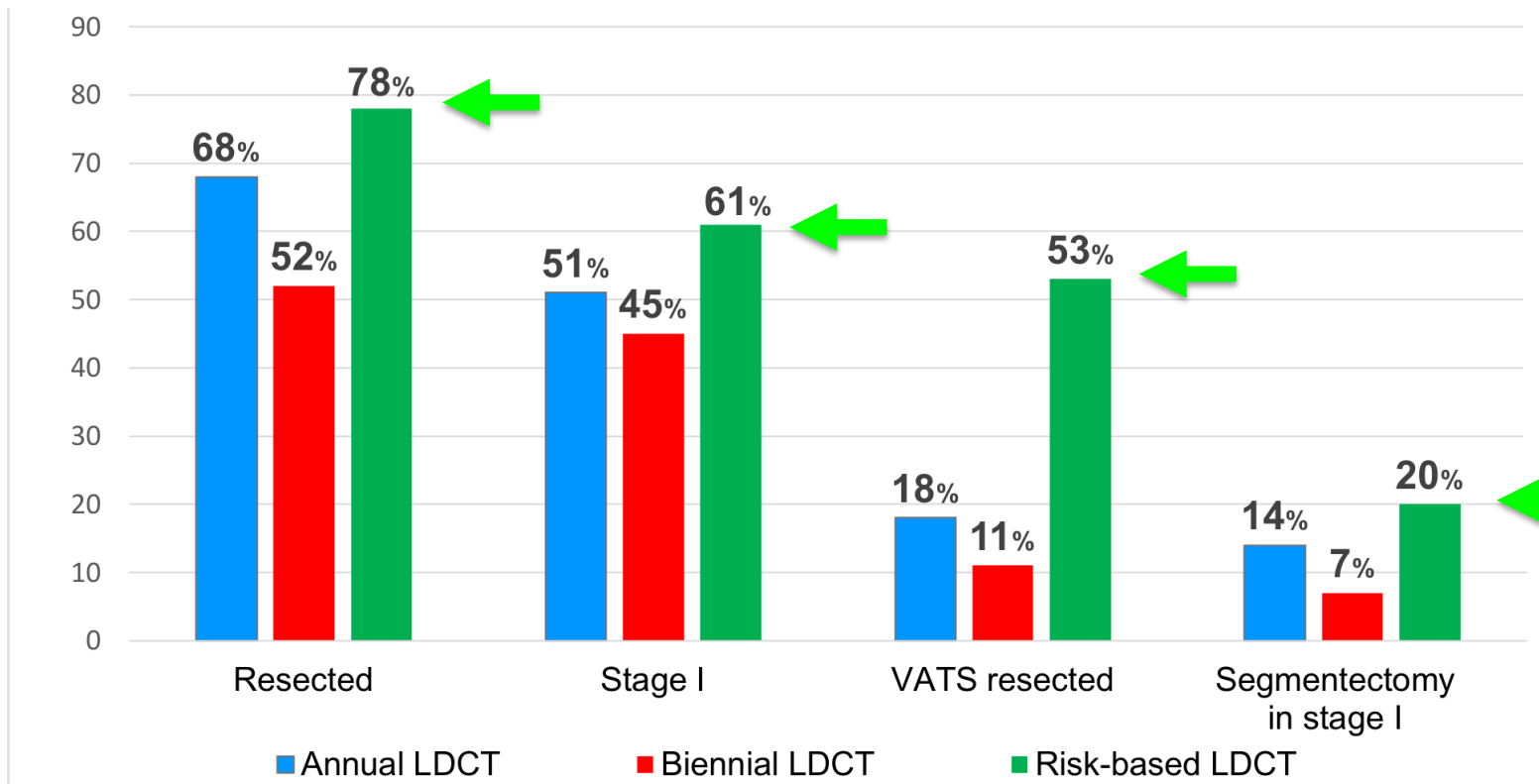
5.4%

3%

* SSN < 5 mm

no LC deaths from SSN site

surgical outcome by screening intervals



BioMILD results: April 2021 update

- median follow-up of 5.3 years
- safety of 3-year interval for LDCT- / MSC-
- no increase of high stage or unresectable LC
- risk prediction confirmed at 5 years
- added value of miRNA on LCRAT and PLCOm2012
- final results have been **submitted for publication**

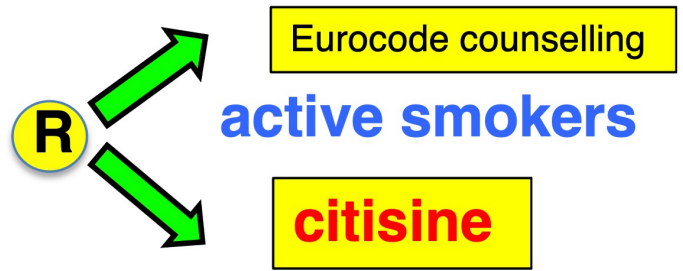




2019

ultra-low-dose LDCT
Screening and
Multiple **I**ntervention
on **L**ung **E**pidemics

Population:
55-75 yrs-old
current / ex-smokers
≥ 30 pack / years



2 x 2 factorial design



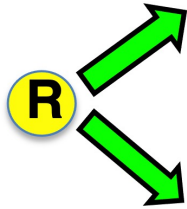


- natural origin (**Cytisus laburnum**)

- used in Est Europa since 1960

Citisine

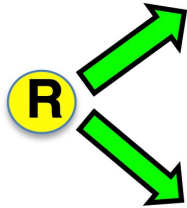
- partial agonist of **$\alpha 4\beta 2$ nicotine receptors**
- excellent tolerability



> 30% CO-confirmed quitters at **12 months**

citisine

primary end-points



> 30% decrease of blood CRP at **24 months**

cardioASA + diet + exercise



Trial status

04 / 2021

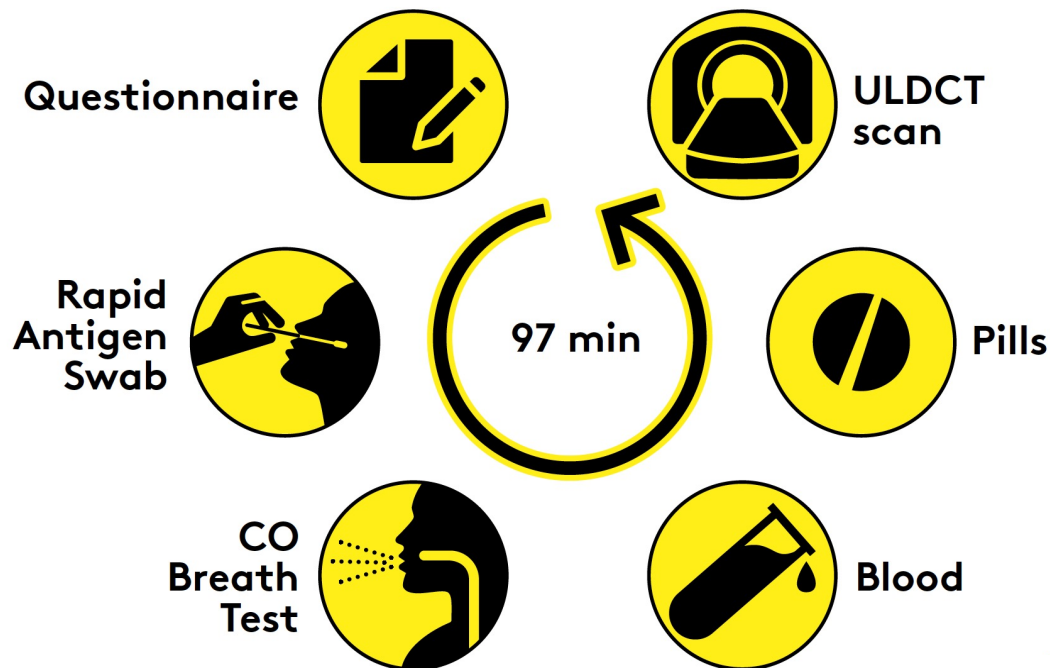
- LDCT screening started in July 2019
- of 2,000 planned subjects, 1114 were randomised
- accrual was stopped in March 2020 **due to Covid-19**
- 978 subjects had received baseline LDCT
- study re-started in October 2020 **with swab protection**
- 739 (76%) received 12-months LDCT control
- Citisine efficacy analysis is planned by September 2021



FEASIBILITY AND SAFETY OF LUNG CANCER SCREENING AND PREVENTION DURING COVID-19 PANDEMIC

SARS-COV-2 ANTIGEN RAPID TEST CE IVD

Lateral flow immunochromatographic assay for the qualitative detection of SARS-CoV-2 antigen from nasopharyngeal swab specimen.





BioMILD & SMILE: **take home message**

- **targeted screening** intervals after baseline are safe
- **overtreatment** can be limited by SSNs surveillance
- LDCT + prevention is feasible to **reduce all-cause mortality**
- added value of **miRNA assay** is ready to be tested by RCT
- LDCT screening was feasible during **Covid-19** pandemic