Persistent cough and shortness of breath: red flags

Dr Mary O’Brien, Consultant Medical Oncologist and Head of the Lung Unit

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Be Clear On Cancer

I’ll tackle it soon

Been coughing for 3 weeks? Tell your doctor.

Had a cough for more than 3 weeks? Has it changed? Or are you coughing up small spots of blood? If you’ve any of these symptoms, then visit your doctors and ask for a simple chest X-ray now. It may be something more than just a cough. The sooner it is diagnosed, the sooner – and easier – it can be treated.

If you’ve been coughing for 3 weeks or more, don’t make excuses, make an appointment with your doctors today.

www.3weekcough.org

WE’RE WAITING, YOU SHOULDN’T

NHS
Which of the following are associated with an increased risk of developing lung cancer? (select all that apply)

A. Smoking
B. Family history
C. Asbestos exposure
D. Diagnosis of COPD
E. Age
F. History of pneumonia
G. Cannabis use
H. Thoracic Radiotherapy
I. Exposure to Radon
Symptoms of lung cancer

- Cough ✗
- Haemoptysis ✗
- Dyspnoea ✗
- Weight loss ✔
- Chest pain ✗
- Shoulder pain ✗
- (Fatigue) ✔
- Hoarse voice ✗
- Symptoms of metastatic disease e.g. back pain, headaches etc ✗
Diagnosis of COPD

- 70 year old male
- Known diagnosis of COPD on inhalers for six years
- 54 pack year smoking history
- Christmas develops a worsening cough, productive of white sputum
- Seeks GP advice in January and is prescribed a course of oral antibiotics for a LRTI
- February- no improvement in cough. Spirometry repeated and prescribed tiotropium and with initial improvement
- March, presents again and further course of antibiotics and carbocisteine prescribed
- April 2014 referred to respiratory physician for management of COPD and admitted to hospital
Introduction

RED FLAG – UK stats
Delayed and late diagnosis leads to:
Patient dissatisfaction
– smokers and never smokers

SCREENING
NODULES

CHEQUERED FLAG – endgame
Operable disease
Progress – EGFR, ALK PDLI antibodies.
Lung cancer costs the UK almost twice as much as any other cancer
56 deaths per 100,000/yr UK
25% before retirement age

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cost per Year</th>
<th>Cost per Individual/Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>£2.4 billion</td>
<td>£9071</td>
</tr>
<tr>
<td>Bowel</td>
<td>£1.5</td>
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<tr>
<td>Prostate</td>
<td>£0.8</td>
<td>£1584</td>
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</table>

Total cancer cost in UK is £15.8 bn

Costs include:
premature deaths - 25% before retirement/time of work 50%
healthcare costs 35%
unpaid costs to friends and families 15%

157,000 11-15 yrs old start smoking/yr

Dr Jose Leal, University of Oxford, NCRI Liverpool Nov 2012
Health systems

The lost tribe – poor socio economic conditions
Health systems

Smoking habits
Health systems

Smoking cessation – ban public places, plain packing, increase cost
Screening a target population
Smoking and lung cancer; which of the following are true? (select all that apply)

A. The total number of cigarettes smoked in a lifetime is more important that the number of years.

B. The risk increases substantially after 40 years of smoking

C. After 10 years of stopping smoking, the risk of lung cancer is the same as a never smoker

D. Stopping smoking at any age reduces the risk of developing lung cancer

E. Starting smoking under the age of 20 is associated with a higher risk of developing lung cancer
The Royal Marsden

## Health systems

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Lung ca</th>
<th>Deaths</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>126m</td>
<td>70,000</td>
<td>52,000</td>
<td>25/100,000</td>
</tr>
<tr>
<td>UK</td>
<td>64m</td>
<td>43,000</td>
<td>35,000</td>
<td>30/100,000</td>
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</table>
4.1. Consultations with doctors

4.1.1. Number of doctor consultations per capita, 2011 (or nearest year)

4.2. MRI units, 2011 (or nearest year)

<table>
<thead>
<tr>
<th>Country</th>
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<th>Outside hospital</th>
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<td>Italy</td>
<td>21.3</td>
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</tr>
<tr>
<td>Greece</td>
<td>22.6</td>
<td></td>
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1. Equipment outside hospital not included.
2. Only equipment eligible for public reimbursement.

StatLink http://dx.doi.org/10.1787/888932917256

4.2.2. CT scanners, 2011 (or nearest year)

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StatLink http://dx.doi.org/10.1787/888932917256
Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2)

Claudia Allemani, PhD, Hannah K Weir, PhD, Helena Carreira, MPH, Rhea Harewood, MSc, Devon Spika, MSc, Xiao-Si Wang, PhD, Finian Bannon, PhD, Jane V Ahn, MSc, Christopher J Johnson, MPH, Audrey Bonaventure, MD, Rafael Marcos-Gragera, PhD, Charles Stiller, MSc, Prof Gulnar Azevedo e Silva, MD, Wan-Qing Chen, PhD, Prof Olufemi J Ogunbiyi, FWACP, Bernard Rachet, FFPH, Matthew J Soeborg, PhD, Hui You, MAAppStats, Tomohiro Matsuda, PhD, Prof Magdalena Bielska-Lasota, MD, Hans Storm, MD, Prof Thomas C Tucker, PhD, Prof Michel P Coleman, FFPH

The Lancet
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DOI: 10.1016/S0140-6736(14)62038-9

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Low coverage

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**Figure 3**

Liver and lung cancer remain lethal in all nations: for both cancers, 5-year survival is below 20% everywhere in Europe, in the range 15–19% in North America, and as low as 7–9% in Mongolia and Thailand.

<table>
<thead>
<tr>
<th>Country</th>
<th>Survival Rate</th>
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<td>NZ</td>
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<td>Portugal</td>
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<td>Ireland</td>
<td>12.9%</td>
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<tr>
<td>France</td>
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<tr>
<td>Australia</td>
<td>15%</td>
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<td>Canada</td>
<td>17.3%</td>
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<tr>
<td>US</td>
<td>18.7%</td>
</tr>
</tbody>
</table>
UK survival figures 2013 – LUCADA database

Figure 18
Survival curve for all lung cancer (2013)

Proportion still alive

Days

All lung cancer

Median Survival: 232 days

Figure 19
Survival curves by Stage for all NSCLC (2013)

Proportion still alive

Days

Stage I
Stage II
Stage III
Stage IV
All NSCLC
All lung cancer

Median survival: Stage 1 – not reached; Stage 2 – not reached; Stage 3 = 293 days; Stage 4 = 100 days
Variation in survival by network

Source: NLCA 2011 annual report
Male lung cancer mortality is decreasing
Lung cancer survival is improving

NCIN, 2013
Family History, Shoulder Pain and Current Smoker

- 50 year old woman develops left sided shoulder pain in May
- Current smoker with a 70 pack year history
- Started smoking aged 10
- Sister diagnosed with lung cancer 18 months earlier
- Treated with analgesia with little improvement. Shoulder radiograph is normal
- Referred to musculoskeletal service
Pancoast Tumour
Family History

– Overall a 51% increase in risk for a first degree relative
– Risk is higher if that relative is a sibling 82% increase in risk
RP – never smoker with a cough, not breathless
Definition of a never smoker – 100 cigarettes in lifetime

Light smoker – 10 pack years

One packet/day for 1 year = 1 PKY

10 cigs/day for 20 yrs is 10 PKY

ADVISE NO 1:
speak in Pack years – as this gives the risk.

ADVISE NO 2:
duration since stop smoking > 20 yrs is good
Pharmacy triggered referral project

- To increase awareness of the signs and symptoms of lung cancer and lung disease (pharmacist/patients)
- To promote healthy lifestyles by signposting to local smoking cessation services
- To facilitate early diagnosis of COPD and lung cancer, direct referral pathway from community pharmacy into secondary care respiratory services
- Support reductions in the inequalities gap between the more and less affluent parts of South West London
Phase 2 – confirm pilot

Hypothesis from pilot:
There are patients who do not access GP over a 6 month period, 50 at-risk patients referred for investigation a 20% incidence of undetected airways disease requiring further investigation. (1 in 5 patients)

Increase in coverage and duration:
– 4 boroughs- Croydon, Wandsworth, Sutton & Merton
– 43 pharmacies
– October 2012-March 2013
Pharmacy project

- Pharmacist shows concern for patients buying cough medicine or antibiotics
- 35 patients referred
- New diagnosis in 17/22 include: COPD, lung cancer, pneumonia, asthma,
- 20 patients referred to smoking cessation by pharmacy
- Minimal cost impact
- Repeated in second study
NLST - 56,000 people

- 20% reduction in lung cancer mortality
- 356/1056 lung cancer deaths in CT group
- 443/663 lung cancer deaths in CXR group

- 25% false positives
- 42% of invasive procedures were benign
- Patients anxiety and cost
- Prevention is better than cure

*N Engl J Med 2011 Aug 4*
<table>
<thead>
<tr>
<th>Study</th>
<th>Start date</th>
<th>Status</th>
<th>Inclusion</th>
<th>Study design</th>
<th>Participant/ proposed</th>
<th>Test positive rate</th>
<th>Test positive rate in screening arm</th>
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<tbody>
<tr>
<td>NLST*</td>
<td>2002</td>
<td>Final results</td>
<td>Age 55-74, ≥ 30 PY</td>
<td>LDCT at baseline, year 1 and 2 Vs CXR</td>
<td>53,454</td>
<td>24.1%</td>
<td>0.9%</td>
</tr>
<tr>
<td>LSS</td>
<td>2000</td>
<td>Final results</td>
<td>Age 55-74, ≥ 30 PY</td>
<td>LDCT at baseline and year 1Vs CXR</td>
<td>3,318</td>
<td>20.5% at baseline, 25.8% at 1 year</td>
<td>1.8% at baseline, 0.6% at 1 year</td>
</tr>
<tr>
<td>*MILD</td>
<td>2005</td>
<td>Recruiting</td>
<td>Age 50 – 75, &gt; 20 PY</td>
<td>LDCT annually or 2 yearly for 10 years Vs Usual care</td>
<td>5000</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>ITALUNG</td>
<td>2004</td>
<td>Screening rounds completed</td>
<td>Age 55-69, ≥20 PY</td>
<td>LDCT baseline and annually for 4 years Vs Usual care</td>
<td>3,206</td>
<td>30%</td>
<td>1.5%</td>
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<tr>
<td>DANTE</td>
<td>2001</td>
<td>Screening rounds completed</td>
<td>Age 60-74, Male, ≥20 PY</td>
<td>LDCT baseline and annually for 4 years Vs Usual care baseline CXR only</td>
<td>2,472</td>
<td>15.6 % at baseline, 17.7% at year 3</td>
<td>2.19% at baseline, 4.7% at year 3</td>
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<tr>
<td>DLCST</td>
<td>2004</td>
<td>Screening rounds completed,</td>
<td>Age 50-70, ≥20 PY</td>
<td>LDCT baseline and annually for 4 years Vs Usual care</td>
<td>4,104</td>
<td>8.7%</td>
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<td>NELSON</td>
<td>2003</td>
<td>Screening rounds completed</td>
<td>Age 50-70, &gt;15 cigarettes/day &gt; 35 years, or &gt; 10 cigarettes/day for &gt; 30 years</td>
<td>LDCT at baseline, year 1 and year 3 Vs. Usual care</td>
<td>16,000</td>
<td>2.6% at baseline, 1.8% at year 1</td>
<td>0.9% at baseline, 0.5% at year 1</td>
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<td>LUSI</td>
<td>2007</td>
<td>Recruiting</td>
<td>Age 50-69 heavy smoking history</td>
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<td>4,000</td>
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<tr>
<td>UKLST</td>
<td>2011</td>
<td>Recruiting</td>
<td>5% risk of lung cancer based on the LLP risk model</td>
<td>Single LDCT Vs, Usual care</td>
<td>32,000 (initial 4,000 in pilot)</td>
<td>NA</td>
<td>NA</td>
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*primary end point 20% reduction in lung cancer mortality in screened (95% CI 6.8 - 26.7; p=0.004). Stage shift with less stage IV 356/443 deaths from 1060/941 detected lung cancers in LDCT/CXR groups.
## Screening figures

<table>
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<th></th>
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<th>Europe</th>
<th>UK</th>
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<td>Population</td>
<td>300m</td>
<td>731m</td>
<td>62m</td>
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<td>L saved/yr</td>
<td>12,000</td>
<td>67,000</td>
<td>3-5000</td>
<td>3-400</td>
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</table>

### UK deaths
- From lung ca: 36,000
- 20% decrease: 3000
- 20% decrease: 600
Screening population
5% risk at 5 years - LLP

55-74 years – smokers/non smokers <10 years

40 pk/yr
30pk/yr + 1 of below

FEV1 abnormal/COPD/emphysema/asbestos
FHx – 1st degree relative
Previous malignancy – including lung cancer
Pneumonia
Evolution of NSCLC - first line - testing is with us already

NSCLC as one disease

First-targeted tx
- ALK
- EGFR

Histology-Based Subtyping

Adenocarcinoma

Squamous Cell Cancer

Mutations found in 54% (280/516) of tumors completely tested (95% CI: 50% to 59%)

- Referral to appropriate biomarker-driven clinical trial based on patient-specific analysis
EGFR-directed therapy

EGF  
TGFα  
Amphiregulin  
β-cellulin  
HB-EGF  

Heregulins  

NRG2  
NRG3  
Heregulins  
β-cellulin  

Tyrosine kinase domain

mutation

erbB-1  
HER1  
EGFR  

erbB-2  
HER2  
neu  

erbB-3  
HER3  

erbB-4  
HER4
Presenting with metastatic disease

- 73 year old female, never smoker presents to her GP with an episode of suddenly being unable to speak; this resolved after a few minutes
- She is referred to the TIA service and undergoes further investigation.
Risk Factors for the Development of Lung Cancer

1. Smoking ✗
2. Family history ✗
3. Asbestos exposure ✗
4. Diagnosis of COPD ✗
5. Age ✔
6. History of pneumonia ✗
Symptoms of lung cancer

- Cough ×
- Haemoptysis ×
- Dyspnoea ×
- Weight loss ×
- Chest pain ×
- Shoulder pain ×
- (Fatigue) ×
- Hoarse voice ×
- Symptoms of metastatic disease e.g. back pain, headaches etc ×
Signs of Lung Cancer

- Finger Clubbing ✗
- Supraclavicular lymphadenopathy ✗
- Chest Signs- pleural effusion, fixed wheeze ✗
- Evidence of metastatic disease-e.g. hepatomegaly, subcutaneous ‘lumps’ ✗
- Hoarse Voice ✗
**T cell mediated immune rejection of tumours**

**Therapeutic intervention**

- **Tumour vaccine**
- **Presentation of tumour-specific/associated Ag**

**Activation of Tumour-specific T cells**
- CD137
- CD28
- IL-2
- IL-15

**Co-stimulatory T cell Signals**
- Agonists
  - CD137
  - CD28
  - IL-2
  - IL-15

**Negative Regulatory signals (immune check-points)**
- Antagonists
  - CTLA-4
  - PD1
  - B7-1

**Other immunosuppressive factors environment**
- T regulatory cells
- Myeloid suppressor cells
- IL-10, TGFβ
PD-1 as a Target in Cancer Therapy

Activated T Cell
Initial immune response

Tumor or APC

Cytokines
Proliferation
Activation

CD28
CD80
CD86

Exhausted T Cell
Persistent antigen stimulation

Tumor or APC

CD28
CD80
CD86

PD-1
PD-L1

Nivolumab
Pembrolizumab
Pidelizumab
Atezolizumab
Durvalumab
Avelumab


Slide credit: clinicaloptions.com
Select immune-related adverse reactions

- hypophysitis
- thyroiditis
- adrenal insufficiency
- enterocolitis
- dermatitis
- pneumonitis
- hepatitis
- pancreatitis
- motor & sensory neuropathies
- arthritis
**Treatment-Related AEs With Incidence ≥2% In the Treated Population**

**Potentially Immune Related**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>7.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>3.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2.0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Skin</td>
<td>0.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Colitis</td>
<td>0.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>0.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Myasthenic syndrome</td>
<td>0.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

*Potentially immune-mediated AEs are presented regardless of investigator-designated attribution.

The following potentially immune-related AEs were not observed in any patients: adrenal insufficiency, hepatic, myocarditis, myositis, neuropathy, pancreatitis, pericarditis, renal, thyroiditis, type 1 diabetes mellitus, and uveitis.

Analysis cut-off date: August 29, 2014.
## Differences in Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Targeted</th>
<th>Immuno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anaemia</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Fatigue</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Rash</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Nausea</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vomiting</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALOPECIA</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

We cannot predict any of these toxicities – no biomarker
# Differences in Toxicities

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Targeted</th>
<th>IRAE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-12 weeks</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>After Tx</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Predictable</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Dose dependent</strong></td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cumulative</strong></td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
General toxicity principles

*Grade toxicity – be objective*

Withhold tx until toxicity resolves to G 0-1.
Support the patient – anti diarr, O2, T4 etc
Treat the symptom
Use steroids for all potential IrAEs
Stop treatment if toxicity 12 + weeks
or still steroid dependent
Permanently discontinue for renal tox, eye, heart, recurrent tox
Others symptoms/conditions for which a CXR should be considered include:

- new diagnosis or being followed up with chronic obstructive pulmonary disease (COPD) with changing symptoms
- symptoms of lower respiratory infection requiring a second course of antibiotics
- non-specific symptoms in a patient who has not previously visited their GP but has now attended on at least two occasions.
**Message NO 1:**
speak in Pack years – as this gives the risk.

**Message NO 2:**
duration since stop smoking > 20 yrs is good

**Message No 3:**
nodules need to be followed up

**Message No 4:**
screening works

**Message No 5:**
ever smokers, young, women, get lung cancer

**Message No 6:**
new treatments – new toxicities