

Pulmonary toxicity of anticancer drugs

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Conflicts of interest, G Meyer

- I have no conflict of interest related to this presentation

Pulmonary toxicity of targeted therapies

- Acute or subacute pneumonitis-ARDS
- Alveolar hemorrhage
- Hemoptysis
- Pleural effusion
- Pulmonary arterial hypertension
- Pulmonary embolism

Acute or subacute pneumonitis

- Gefitinib:
 - Incidence: 1% (Japan: 2%; US: 0,3%)
 - Lethality: 30%
- Erlotinib:
 - Incidence: 0.6% (Japan: 5%)
 - Lethality: 30%
- Sorafenib, Dasatinib, Sunitinib, Imatinib ..

Cohen MH. et al. *The Oncologist* 2003; 8: 303-6

Herbst RS. et al. *J Clin Oncol* 23: 5892-9.

Nakagawa K. et al. *J Thorac Oncol* 2012; 8: 1296-303

www.ema.europa.eu/docs/en_GB/.../WC500033994.pdf

Acute or subacute pneumonitis

- mTOR inhibitors: Everolimus, Temsirolimus
 - All grades: 11% (6% to 17%)
 - Grade 3-4: 3% (1% to 4%)
 - Incidence ratio: 19.0 (6.5 to 55.4)
 - Often asymptomatic
 - Low mortality rate

Acute or subacute pneumonitis

Risk-factors (Gefitinib)

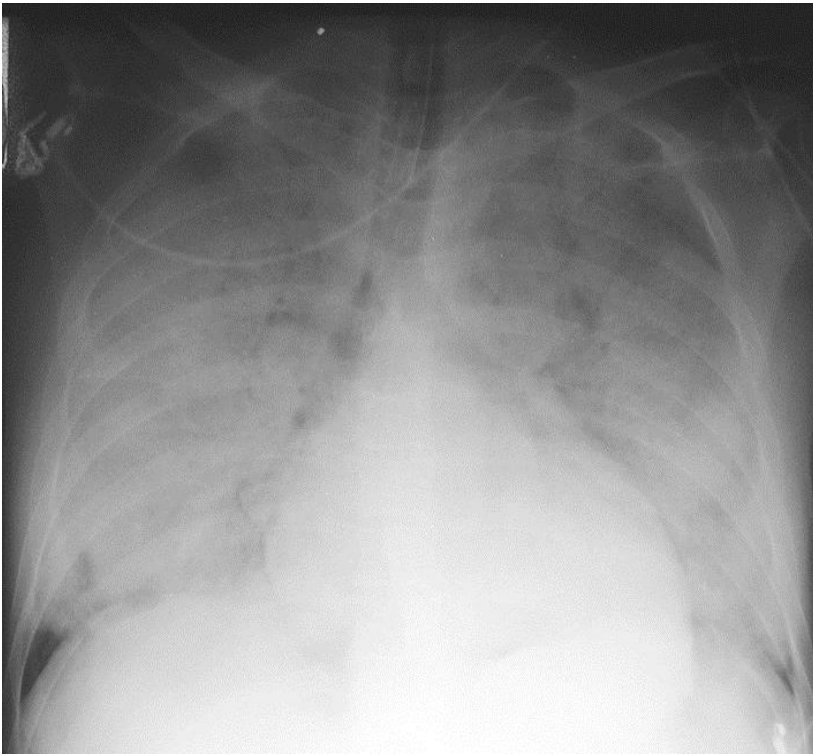
- older age
- poor WHO PS,
- smoking,
- short duration since diagnosis of cancer,
- reduced normal lung on CT scan,
- preexisting ILD,
- concurrent cardiac disease

Kudoh S et al. *Am J Respir Crit Care Med* 2008 ; 177 :1348–1357

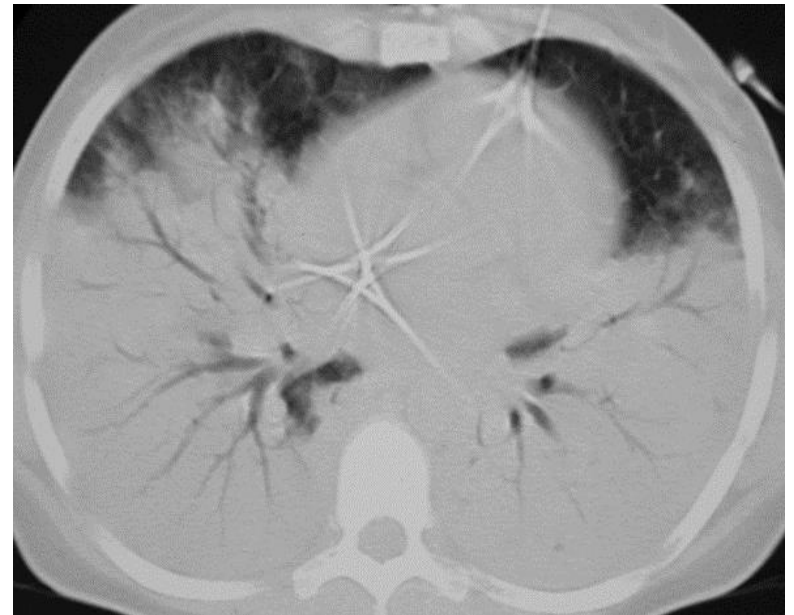
Acute or subacute pneumonitis

- Cough, dyspnea, fever
- Imaging patterns
 - Diffuse alveolar damage
 - Hypersensitivity pneumonia
 - Non Specific Interstitial Pneumonia (NSIP)
 - Acute eosinophilic pneumonia
 - Organizing pneumonia (OP)
- Lack of correlation between imaging pattern and pathological findings

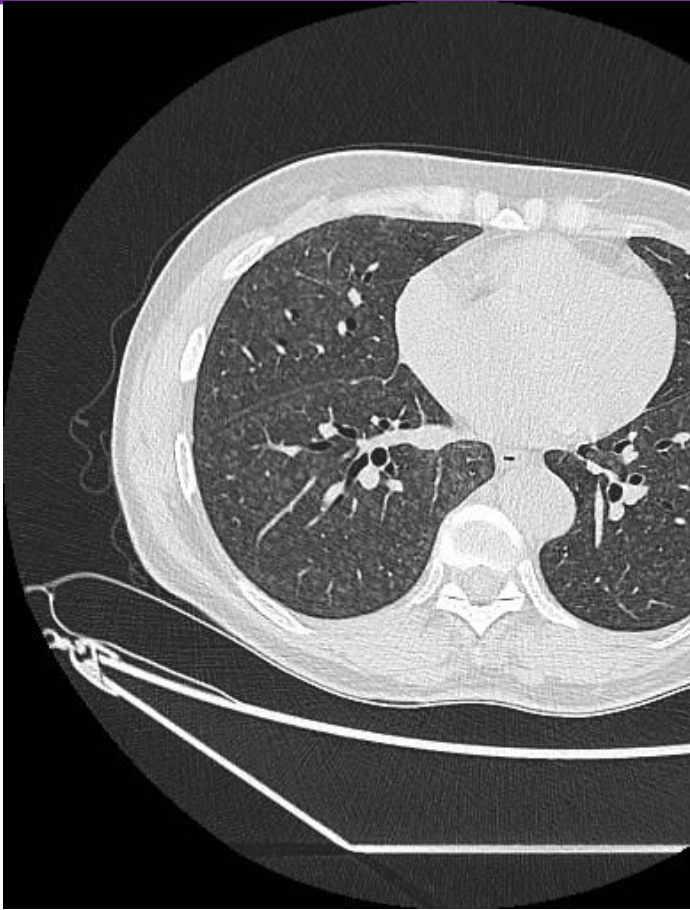
Diffuse alveolar damage/ARDS



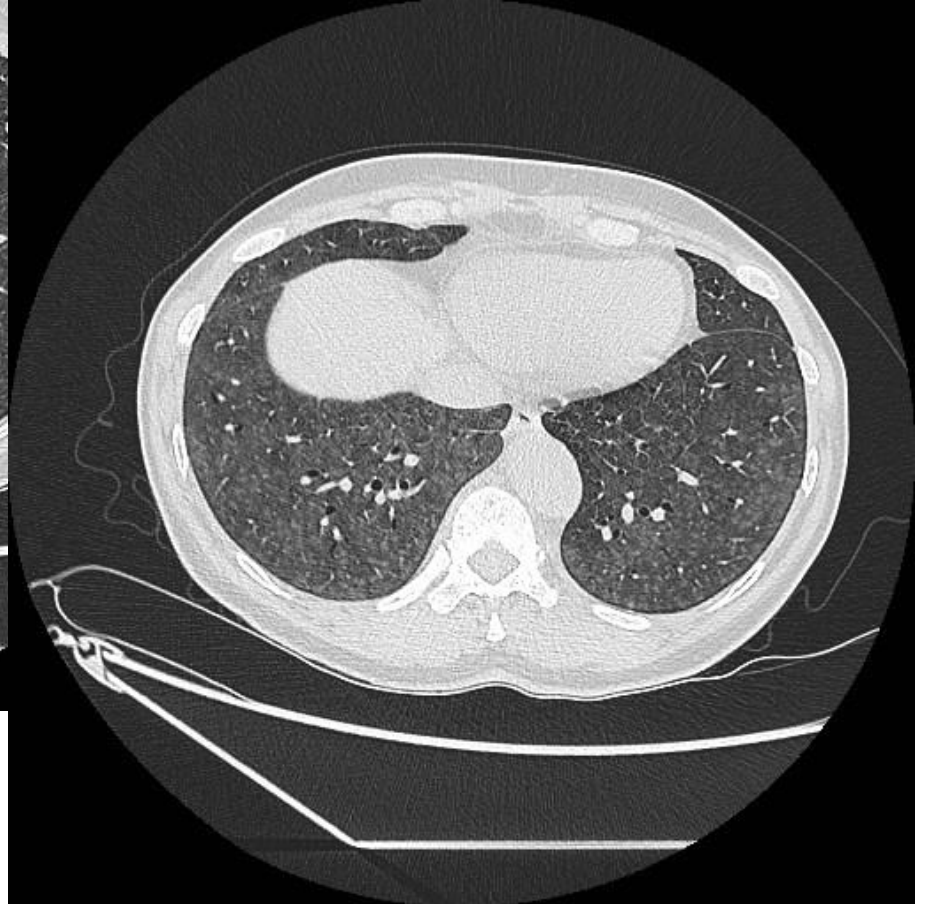
- Extensive airspace consolidation
- Posterior predominance



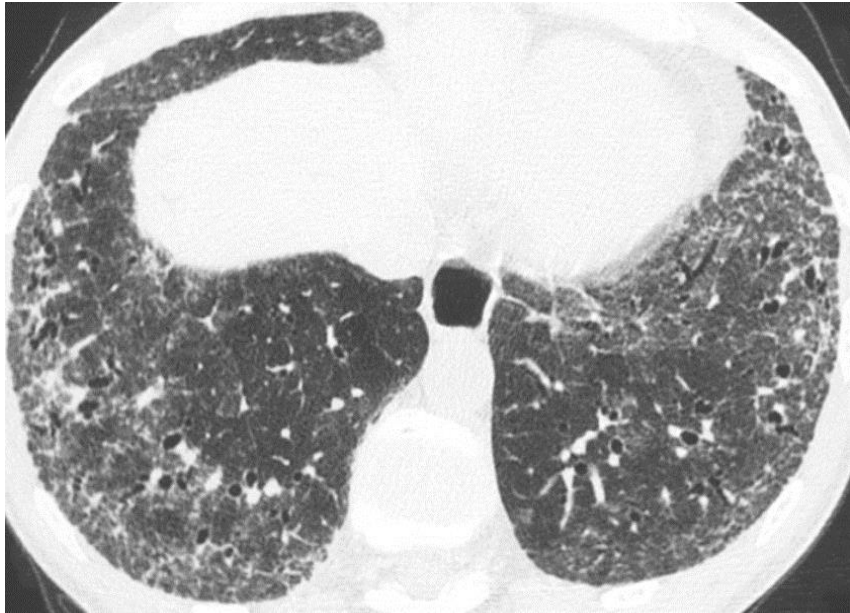
Hypersensitivity pneumonia



Peribronchiolar nodules



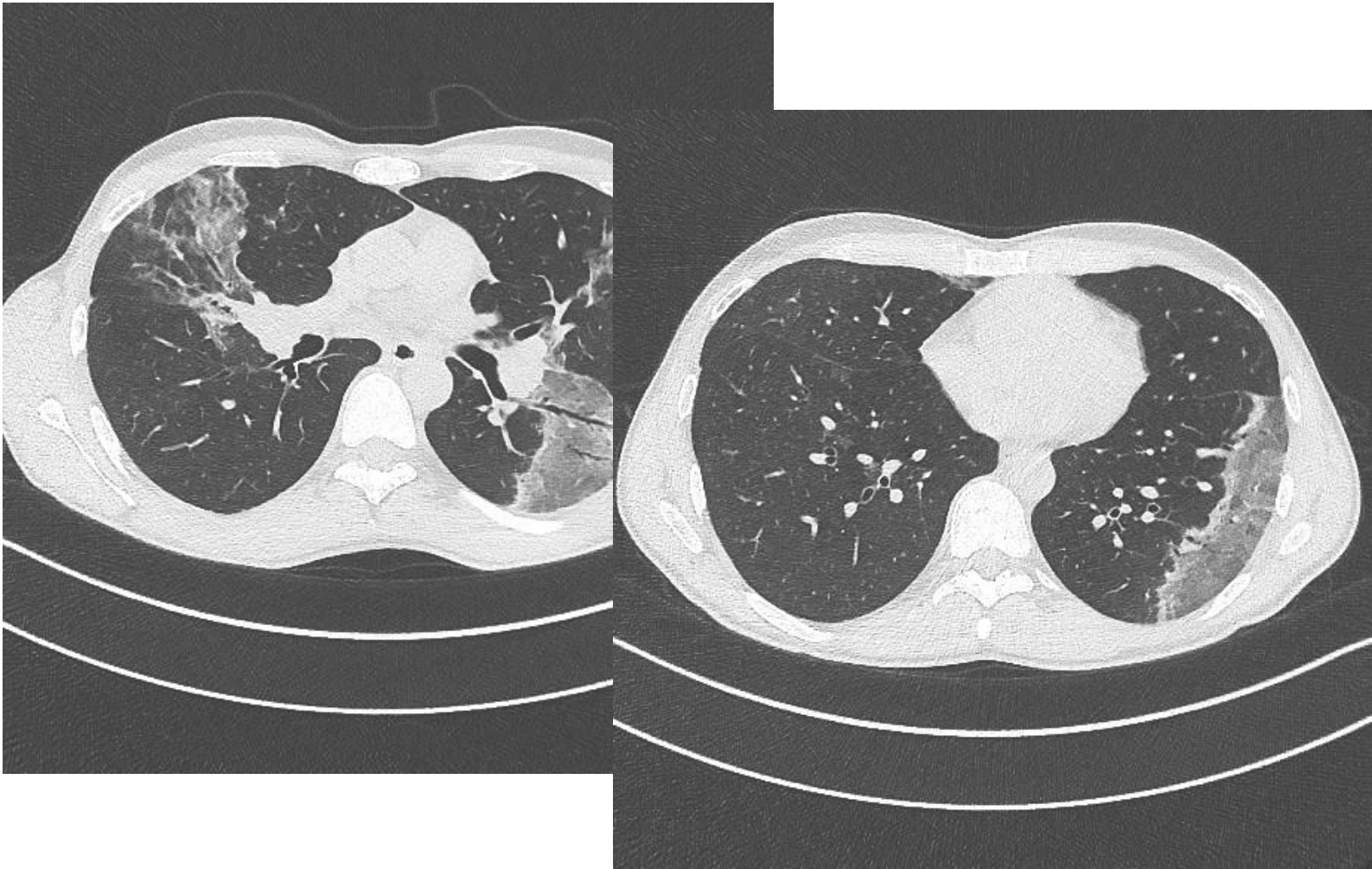
Non Specific Interstitial Pneumonia (NSIP)



Reticular peripheral pattern
Ground-glass attenuation
Traction Bronchiectasis



Acute eosinophilic pneumonia

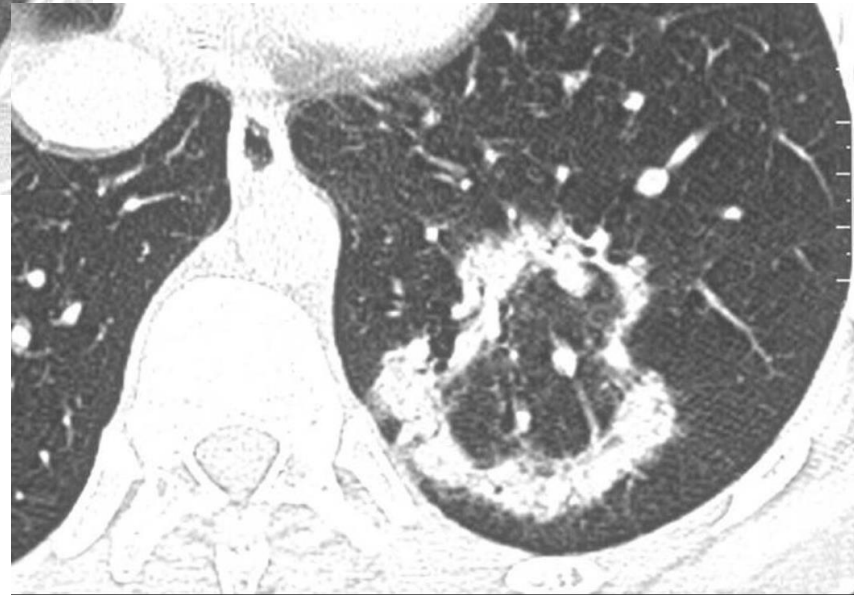


Peripheral ground-glass attenuation
Eosinophils in BAL

Organizing pneumonia (OP)



- Areas of consolidation
- Reversed halo sign: central ground-glass opacity surrounded by denser consolidation



Diagnosis of drug related pneumonitis

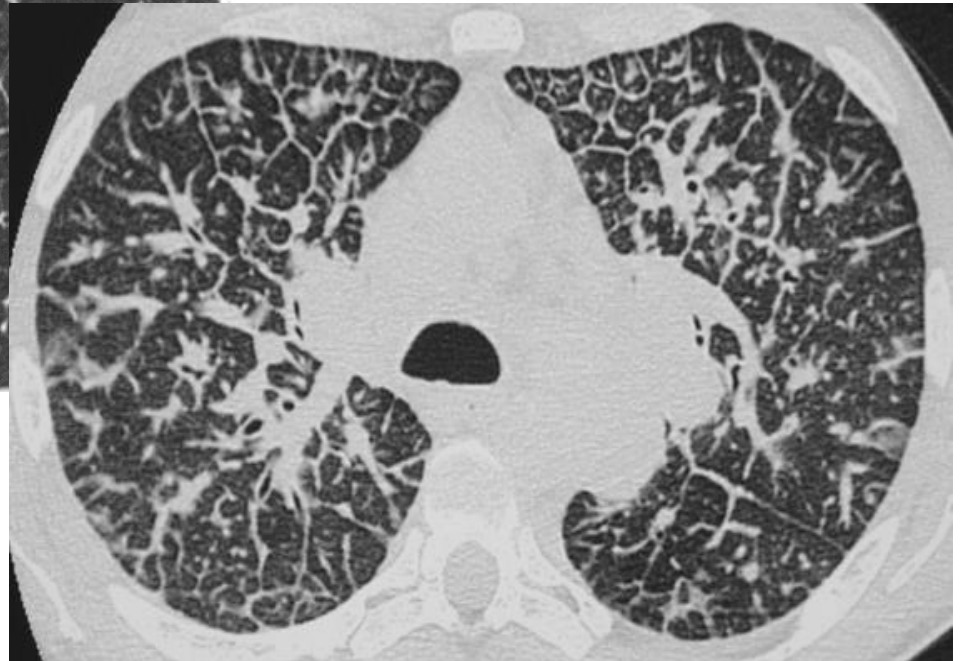
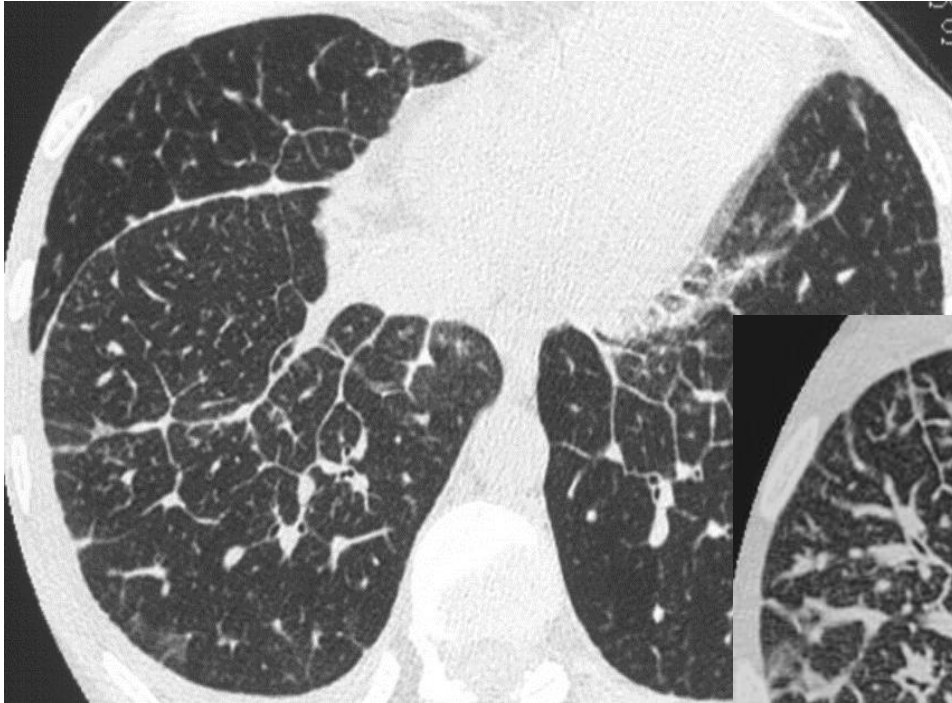
- Clinical and imaging findings are non-specific
- Rule-out other causes
 - Pneumonia
 - Cancer progression: carcinomatous lymphangitis

Diagnosis of drug related pneumonitis

- Rule-out other causes: **pneumonia**
 - Antibiotics usually started before first examination
 - Persisting symptoms despite antibiotics
 - Fibroscopy with bronchoalveolar lavage
 - No pathogens after search for bacterial species, *Pneumocystis Jirovecii*, *Aspergillus*, viruses
 - Lymphocytic alveolitis

Diagnosis of drug related pneumonitis

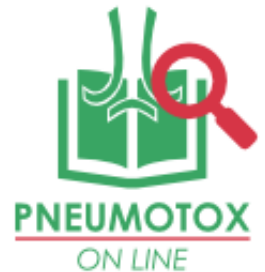
- Rule-out other causes: **lymphangitis**



- Irregular septal thickening
- Nodules

Diagnosis of drug related pneumonitis

- Clinical and most-often imaging findings are non-specific
- Rule-out other causes
 - Pneumonia
 - Cancer progression: carcinomatous lymphangitis
- Temporal relationship between administration of the drug and the onset of lung injury
 - Exposure to the drug before the onset of symptoms
- Known side-effect of the drug
 - Clinical and imaging findings already described



Pascal Foucher - Philippe Camus Dijon France

Treatment of drug related pneumonitis

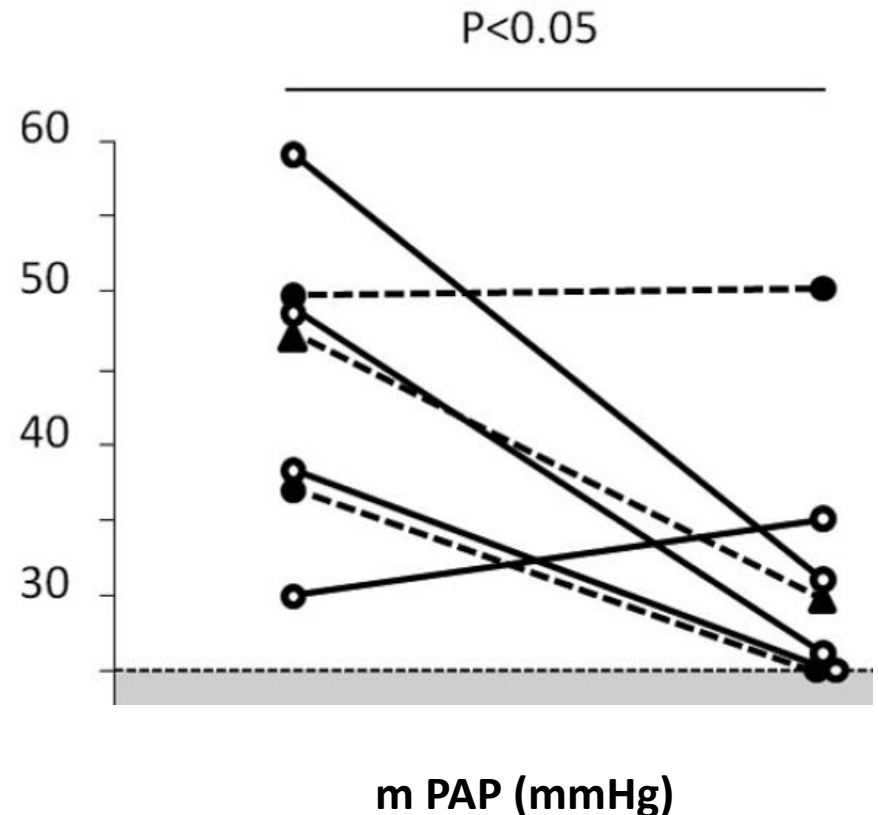
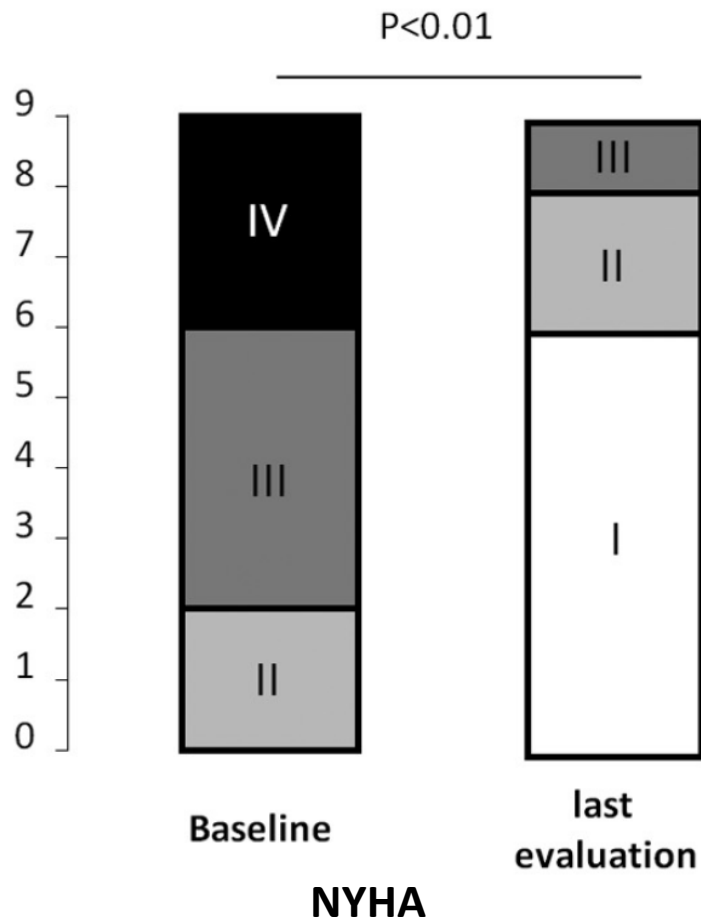
- Stop suspected drug if symptomatic
- Supportive care: oxygen, ventilation
- Severe cases: steroids (dosage? Duration?)
- Rechallenge?
 - 10 reported (7 reduced doses; 8 on steroids)
 - Gefitinib-gefitinib (n = 3)
 - Gefitinib- erlotinib (n = 5)
 - Erlotinib-erlotinib (n = 2)
 - 1 recurrence (not on steroids)

Pulmonary Arterial Hypertension

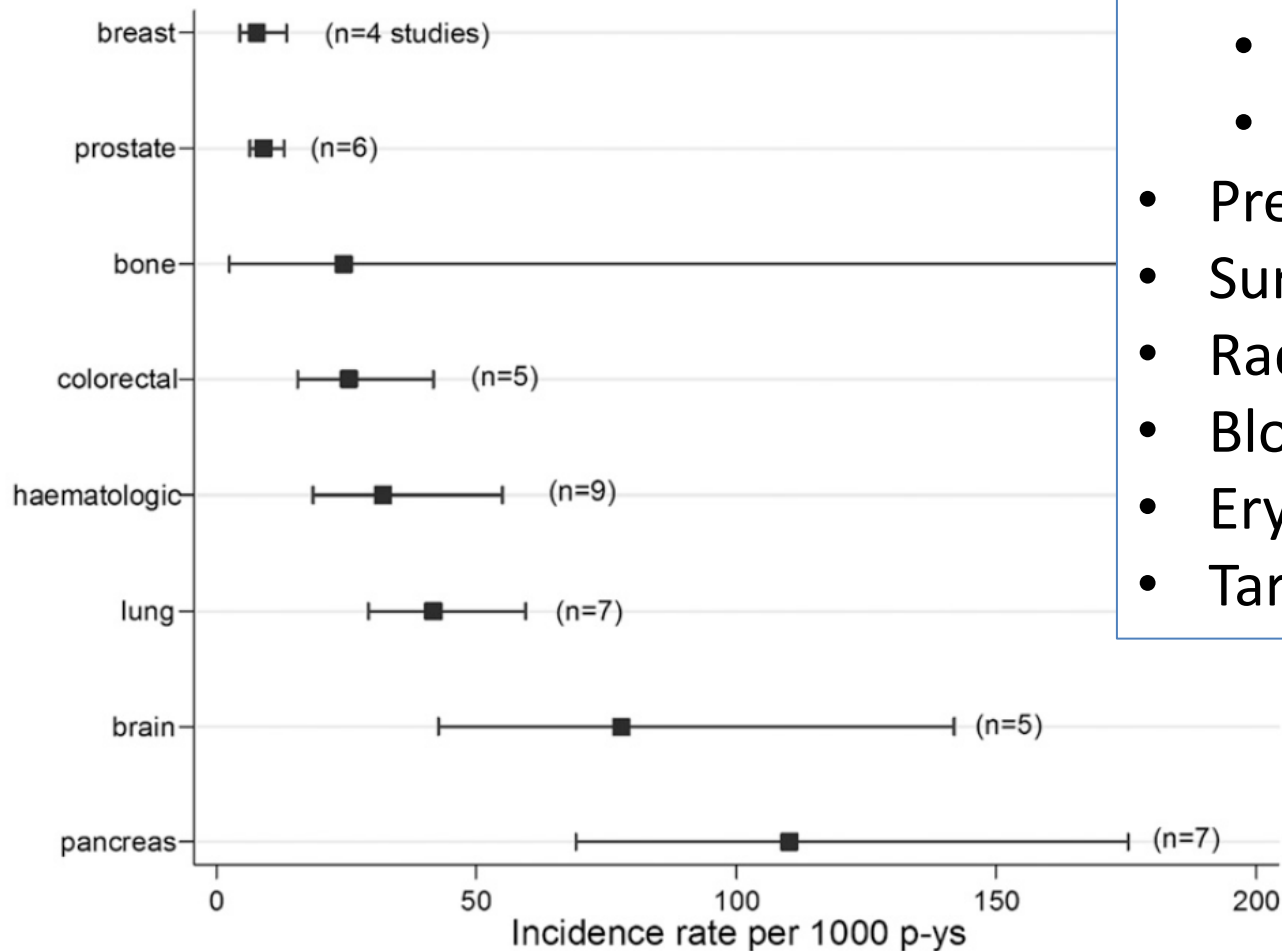
- Progressive onset of exertional dyspnea
- Clear chest sounds
- Normal Chest X-ray
- Echocardiography: Pulmonary hypertension
- Pulmonary embolism ruled out
- Right heart catheterization: m PAP > 25 mmHg

Pulmonary Arterial Hypertension

- Reported with Dasatinib (0.45% of chronically dasatinib-exposed patients)
- Partially reversible after drug discontinuation

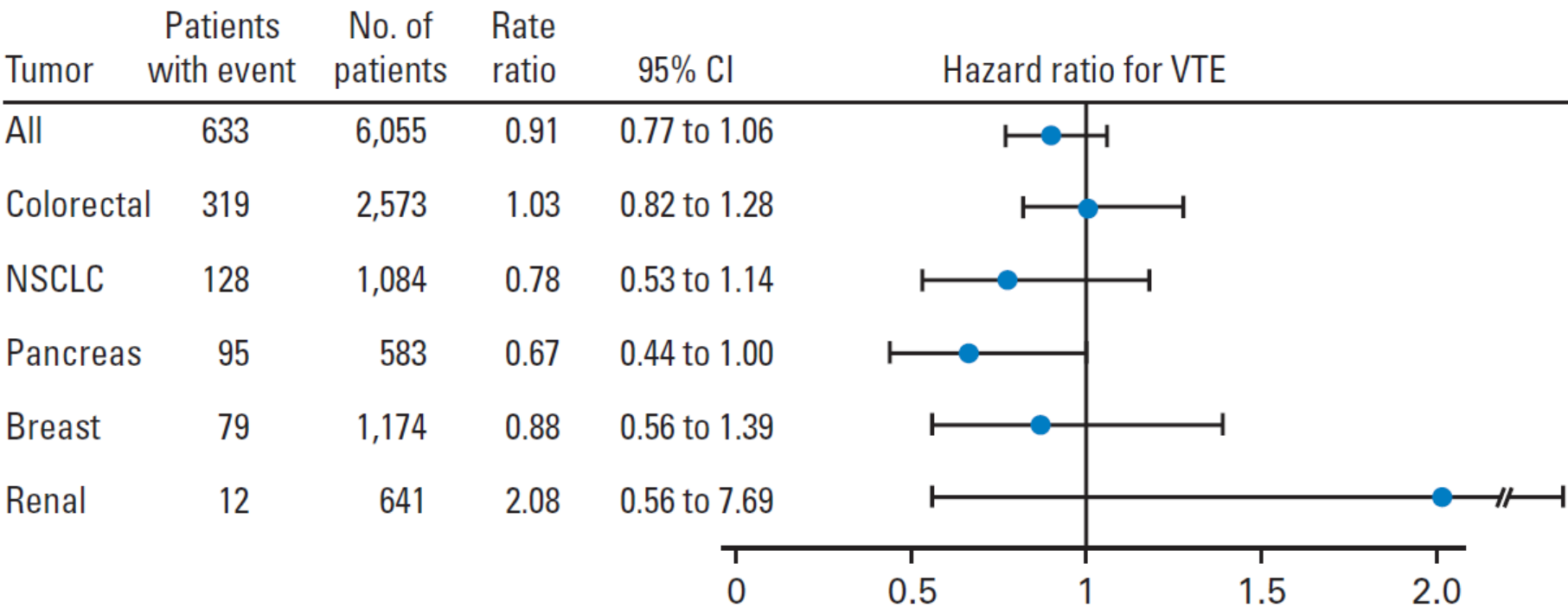


Pulmonary embolism



- Chemotherapy:
 - platin,
 - anthracyclins
- Prednisone
- Surgery
- Radiotherapy?
- Blood transfusion
- Erythropoietin
- Targeted therapies?

Bevacizumab and venous thromboembolism



Hurwitz H. et al. *J Clin Oncol* 2011; 29:1757-64.

Clinically unsuspected incidental PE



Incidental but symptomatic!

Symptom	n	%
Dyspnea	15	22.7
Heart rate > 75b/min	34	51.5
Chest pain	6	9.1
Haemoptysis	1	1.5
DVT symptoms	5	7.6
At least 1 symptom	51	77.3

DysPnEa

Sahut d'Izarn M. et al. *J Thromb Haemost.* 2012; 10: 2032-8