Immunomodulatory therapy in NSCLC: a year into clinical practice

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Disclosure

JRG is a paid advisor to and speaker for *AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Dako, Diaceutics, Lilly & Co, Merck, Sharp and Dohme, Novartis, Pfizer and Roche*

Pathology report 2007

SPECIMEN
TISSUE FROM MASS IN LEFT UPPER PULMONARY LOBE

MACROSCOPIC DESCRIPTION
Cores of white tissue measuring up to 12mm

MICROSCOPY
These are cores of fibrotic pulmonary parenchyma infiltrated by a morphologically poorly differentiated non-small cell carcinoma with no features diagnostic of either squamous or adenocarcinoma.

Immunochemistry reveals strong, diffuse nuclear expression of TTF-1, but not of p40.

The features are of an adenocarcinoma of pulmonary origin.

Pathology report 2017

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PREDICTIVE PROFILING

EGFR GENE MUTATIONS
Epidermal growth factor (EGFR) mutation analysis has been performed to determine suitability of this patient's non-small cell lung cancer (NSCLC) for treatment with tyrosine kinase inhibitors (TKIs).

Analysis was done using RT-PCR (Scorpions/ARMS methodology , Qiagen Therascreen EGFR kit). The Therascreen kit detects the following 29 somatic mutations:

Exon 18: G719X
The kit detects, but does not distinguish between, any from the following 3 mutations;
G719A (c.2156?G>A p.G719A)
G719S (c. 2155G>S p.G719S)
G719C (c.2155G>C p.G719C)
Exon 19: deletions
The kit detects, but does not distinguish between, any from a total of 19 deletions;
Exon 20: T790M
Exon 20: S768I
Exon 20 - insertions
The kit detects, but does not distinguish between, any from the following 3 mutations;

c.2307_2308ins9 p.V769_D770insASV
c.2319_2320insCAC p.H773_V774insH
c.2319_2311insGGT p.D770_N771insG
Exon 21: L858R (c.2573T>G p.L858R)
Exon 21: L861Q (c.2582T>A p.L861Q)

Test sensitivity
The limit of sensitivity is stated to be 1% mutated EGFR alleles in a wild-type background

Results
NO MUTATIONS IN THE EGFR GENE HAVE BEEN DETECTED

Conclusion
This patient is unlikely to respond to TKIs active against NSCLCs with sensitising mutations in the EGFR gene.

Any remaining DNA from this patient's sample will be stored in the laboratory archives.

ALK GENE REARRANGEMENT
Immunochemistry using the Ventana system and Roche D5F3 antibody has been performed to detect the **ALK fusion protein**.

STRONG, GRANULAR EXPRESSION OF THE PROTEIN IS DETECTED. Such expression correlates with rearrangement of the ALK gene and indicates that this patient is likely to respond to TKIs active against NSCLCs with this genetic abnormality

PD-L1 EXPRESSION
Expression of PD-L1 has been sought by immunochemistry using the Dako 22C3 antibody as a guide to the likely sensitivity of the tumour to pembrolizumab.

Expression of PD-L1 is as follows:
Neoplastic cells: Overall expression (TPS) **60%** (strong 30%, moderate 30%)
Immune cells: Overall expression 10% (weak 10%)

Adult patients who: either (1) are previously untreated and have a PD-L1 expression TPS of ≥50% or more or (2) have received at least one prior chemotherapy regimen and have a PD-L1expression TPS of 1% or more are eligible for treatment with pembrolizumab for locally advanced or metastatic non-small cell carcinoma (NSCLC) on the NHS. Patients whose tumours have EGFR mutations or ALK rearrangement should also have received therapy targeted against these genetic abnormalities prior to receiving pembrolizumab.

Tailored therapy for NSCLC

- **Therapies dependent on morphology**
  - **Antifolate**
    - **pemetrexed (Alimta)**
  - **Anti-VEGFA monoclonal antibody**
    - **bevacizumab (Avastin)**
- **Therapies dependent on genetic aberrations**
  - **Small molecule tyrosine kinase inhibitors (TKIs)**
    - **erlotinib (Tarceva), gefitinib (Iressa), afatinib (Giotrif), osimertinib (Tagrisso) crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa)**
- **Therapies dependent on protein expression**
  - **Anti-PD-1 and PD-L1 monoclonal antibodies**
    - **nivolumab (Opdivo), pembrolizumab (Keytruda), atezolizumab (Tecentriq), durvalumab (Imfinzi), avelumab (Bavencio)**
  - **Anti-EGFR monoclonal antibody**
    - **necitumumab (Portrazza)**

Predictive profiling of NSCLC

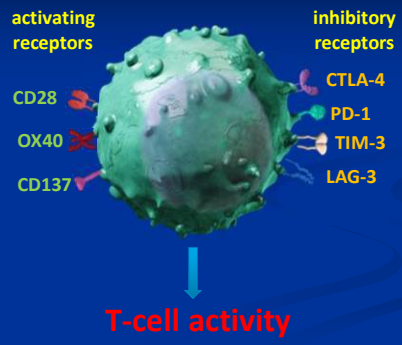
- **EGFR gene mutations**
  - **~12%**
- **ALK gene rearrangement**
  - **<5%**
- **PD-L1 protein expression**
  - **depends on 'cut-off'**

A challenge!

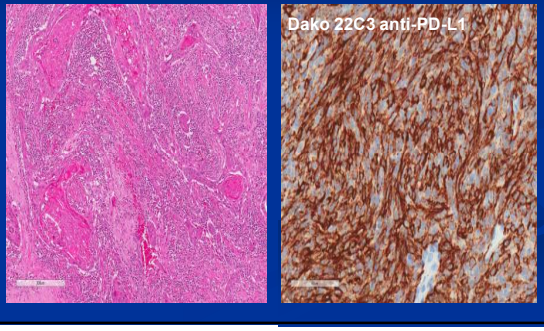
That's not me!

Porifera; the sponges

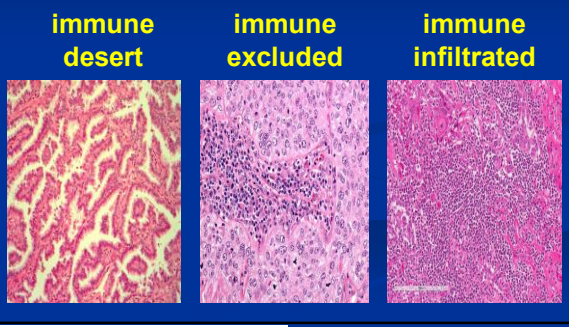
Immune checkpoints



PD-L1 expression confers protection



Patterns of immune cell infiltration



Questions about PD-L1 expression

- Which system can be used to detect it?
- How can it be determined accurately?
- Which specimens are appropriate?
- When should it be assessed?
- Are there other (better) biomarkers?

Multiple tests for PD-L1 expression

	Pembrolizumab Merck, Sharp & Dohme	Nivolumab Bristol-Myers Squibb	Durvalumab AstraZeneca	Atezolizumab Roche/ Genentech
DRUG TARGET	PD-1	PD-1	PD-L1	PD-L1
ANTIBODY FOR DETECTION	Dako 22C3	Dako 28-8	Roche SP263	Roche SP142
RELEVANT EXPRESSION	Surface of tumour cells	Surface of tumour cells	Surface of tumour cells	Surface of tumour cells and immune cells
CRITERIA FOR ôPOSITIVITYö	Ó1% orÓ50% expression	Ó1% expression	Ó25% expression	TC expression 0-3: <1, 1-4, 5-49, Ó50; % of tumour infiltrated by PD-L1+ve ICs 0-3: <1, 1-4, 5-9, Ó10

Relationship between tests

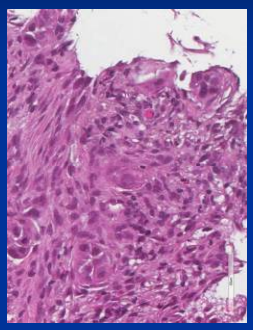
- Inter-observer concordance comparable for all tests, but much higher when assessing expression by tumour cells than by immune cells
- Dako 28-8, Dako 22C3 and Ventana SP263 closely similar: strong expression on tumour cells, but weaker expression by immune cells
- Ventana SP142: strong expression on immune cells, but delineate fewer tumour cells

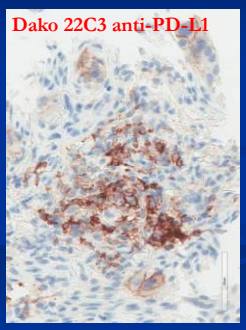
Scheel *et al.*, Mod Pathol 2016, 29: 1165-72; Neuman *et al.*, J Thorac Oncol 2016, 11:1863-1868; Hirsch *et al.*, J Thorac Oncol 2017, 12: 208-222; Ratcliffe *et al.*, Clin Cancer Res 2017, DOI: 10.1158/1078-0432.CCR-16-2375; Rimm *et al.*, JAMA Oncol 2017, DOI: 10.1001/jamaoncol.2017.0013

Relationship between tests

	Pembrolizumab, Nivolumab, Durvalumab	Atezolizumab
DRUG TARGET	PD-1, PD-1, PD-L1	PD-L1
ANTIBODY FOR DETECTION	Dako 22C3, Dako 28-8 or Ventana SP263	Roche SP142
RELEVANT EXPRESSION	Surface of tumour cells	Surface of tumour cells and immune cells
CRITERIA FOR ôPOSITIVITYö	Variable ëcut-offsíaccording to drug	TC expression 0-3: <1, 1-4, 5-49, Ó50; % of tumour infiltrated by PD-L1+ve ICs 0-3: <1, 1-4, 5-9, Ó10

Interpretation





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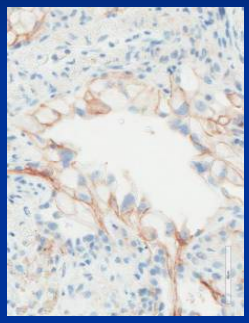

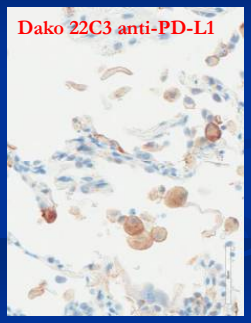

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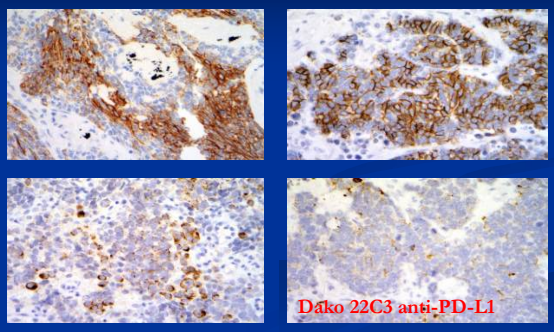

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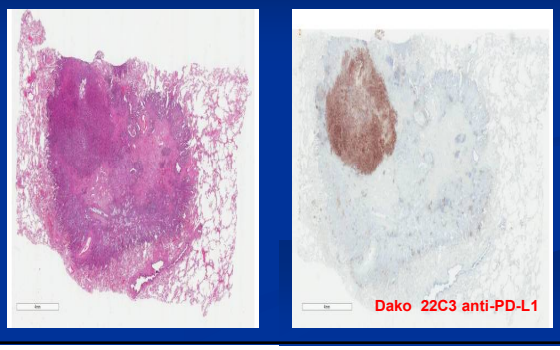
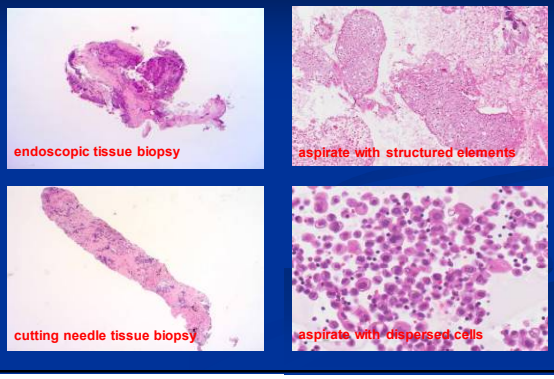
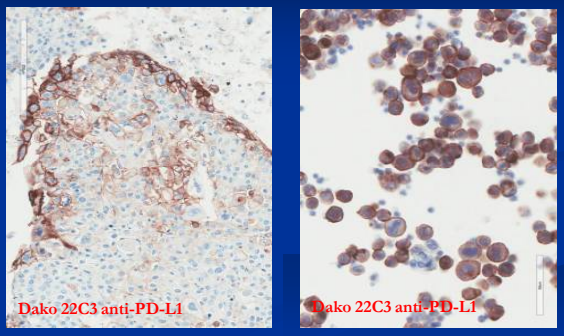


Suitable specimens



'Cytology' specimens



What and when to test: automatic (reflex) testing?

ADVANTAGES

- Saves time
- Provides clinicians with comprehensive information
- Permits 'forward planning'
- Aids integration of information
- Establishes principle that predictive profiling is routine

DISADVANTAGES

- Costs more
- Information may be inappropriate to immediate management
- Information may be inappropriate when disease relapses

The future

- Mutational load
- Immune environment

Have a nice day!