# Workshop 5:
# Update on Diagnostic Techniques in Cancer Medicine

Canadian CTG: New Investigator Clinical Trials Course
10 August, 2017

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# Workshop Objectives

At the end of this workshop, participants will be able to:

- List the characteristics of an effective diagnostic for the selection of a cancer treatment,
- Describe the challenges of developing effective diagnostics in cancer medicine,
- Develop strategies to collaborate with pathology/laboratory medicine to design clinical trials incorporating companion diagnostics.

# Before and During the Workshop

- Before: Review this presentation, and included references. Prepare to discuss questions raised in this presentation.

- During: The workshop will include an interactive discussion of these case studies, with additional didactic materials and references.

# Disclosure

- No relevant conflicts to declare.

# Overview

- Diagnostics are Important – A Cautionary Tale from a Now-Established Biomarker

- Case Study 1: Diagnostic(s) for Cancer Immunotherapy
- Case Study 2: A Diagnostic for Ovarian Cancer Targeted Therapy
- Case Study 3: Multiple Mutation Analysis for Lung Cancer Targeted Therapy

- Diagnostic Techniques in Clinical Trials – Hints and Tips

# “A Cautionary Tale” (Case Study 0)

The New England Journal of Medicine



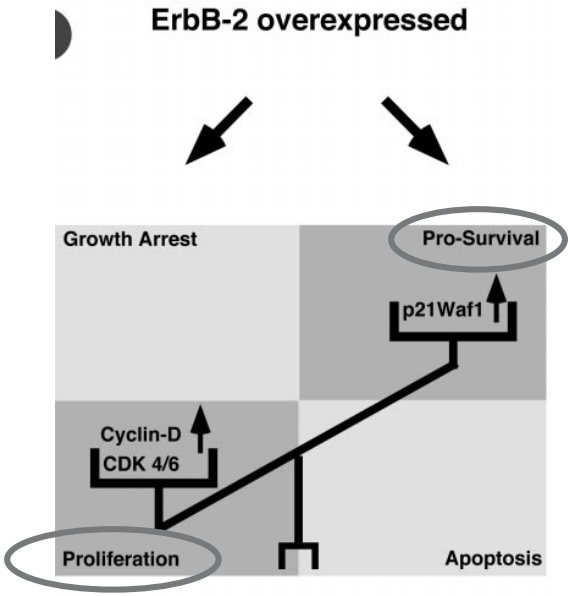
VOLUME 344 MARCH 15, 2001 NUMBER 11

## USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

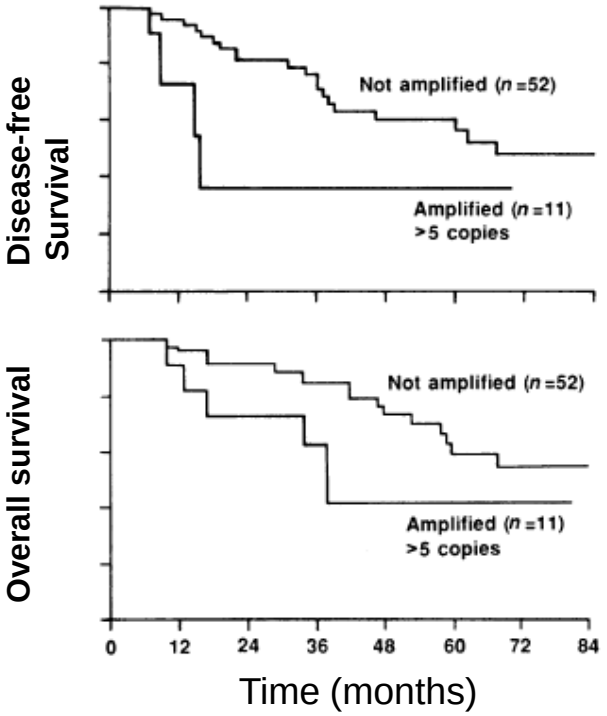
DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

- Questions for Discussion:
  a) What was the definition of “overexpresses HER2”?
  b) What was the scientific basis of this definition?
  c) How was the diagnostic for HER2 overexpression validated?

# HER2: Human Epidermal Growth Factor Receptor 2




Importance in human breast cancer first shown in 1987




Slamon et al., Science 1987
(HER2 assessment by Southern blotting)

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# HER2 Adjuvant Trials:
# What Diagnostics Were Used?

| Trial | IHC | ISH |
|---|---|---|
| NSABP B31 (n=2119) | **Positive =3+ (≥10% strong)** | FISH ratio ≥ 2 if IHC 2+ |
| NCCTG 9831 (n=3505) | **Positive =3+ (≥10% strong)** | FISH ratio ≥ 2 if IHC 2+ |
| HERA (n=5081) | **Positive =3+ (unspecified)** | FISH ratio ≥ 2 if IHC 2+ |
| BCIRG 006 (n=3222) | Not used | FISH ratio ≥ 2 |
| Finnish Trial (n=232 in HER+ arm) | All IHC 2+ or 3+ were confirmed by ISH | Single Probe CISH HER2 copies ≥ 6 in >50% of cells* |

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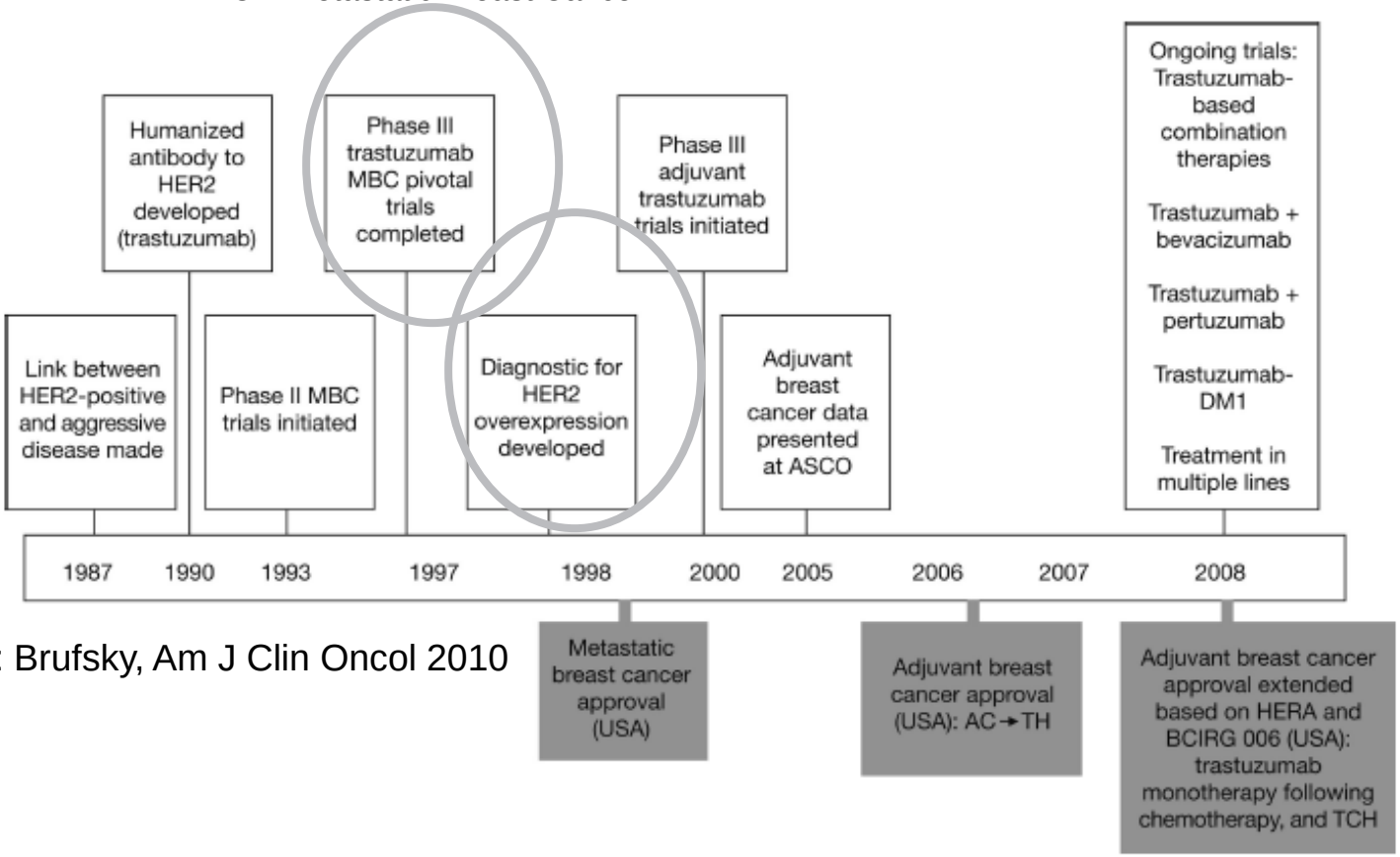
*** FinHer: If HER2 copies between 4 and 6, additional CEP17 probe used to assess for ratio ≥ 2.0**

# The Evolution of HER2 Diagnostics

MBC = Metastatic Breast Cancer




Reviewed in: Brufsky, Am J Clin Oncol 2010

# “HER2 Positive”:

Before 2007; after 2013

- Positive (3+):
  **>10%** of cells with strong membranous staining
- Positive:
  HER2/CEP17 ratio **> 2.0** (or HER2 >6)

2007 to 2013

- Positive (3+):
  **>30%** of cells with strong membranous staining
- Positive:
  HER2/CEP17 ratio **> 2.2** (or HER2 >6)

Take Home Point:
Design of the original trials shaped eventual practice for both diagnostics and therapeutics.
Because of how this drug was originally tested, we don’t know (and may never know) the best way to test for it.

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*Wolff et al., Arch Pathol Lab Med.* 2007;131:18–43

# Case Study 1: Diagnostic(s) for Cancer Immunotherapy

## Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

*Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon*

Lancet 2016;387:1540-50

- Questions for Discussion:
  a) What is the definition of “PD-L1-positive”?
  b) What is the scientific basis of this diagnostic approach?
  c) How might you design a trial to determine the patient population most likely to respond to drugs such as pembrolizumab?

# PD-L1 and Immune Checkpoints

- PD-L1 contributes to a tumour immune microenvironment that inhibits T-cell function.
- Targeting PD-L1 enhances the host immune response.
- Does PD-L1 protein expression level make sense as a biomarker?

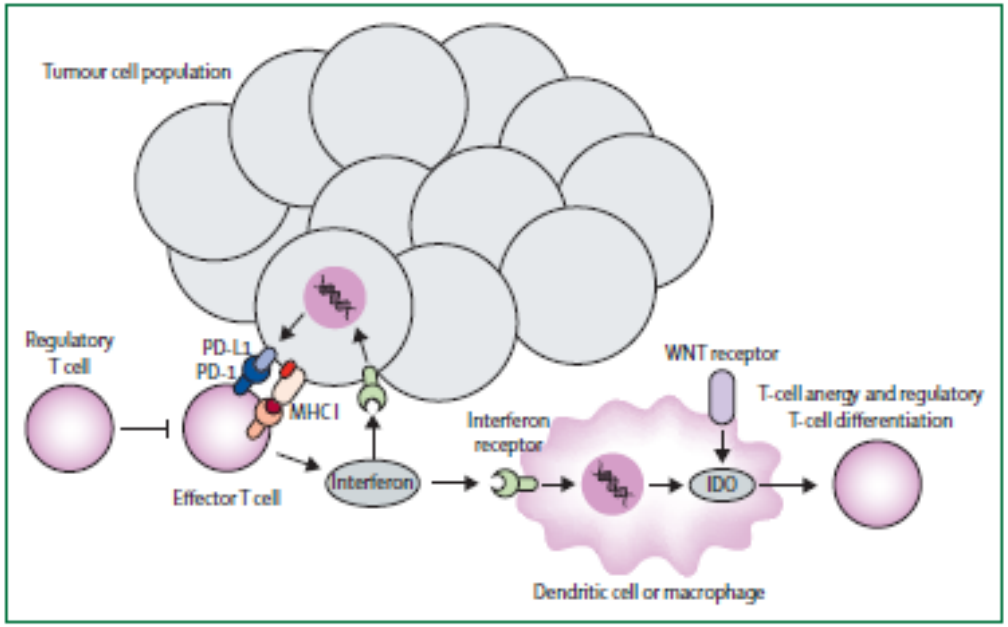
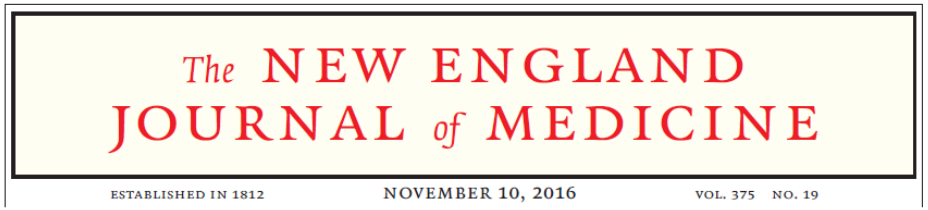



***Figure:*** **Immune response in the tumour microenvironment**
After an immune response directed against tumour cells, immune tolerance can develop in the tumour microenvironment. Various mechanisms have been described including upregulation of tumour cell PD-L1 and dendritic cell and macrophage IDO expression in response to interferon γ signalling, upregulation of additional checkpoints (eg, LAG3), and enhanced regulatory T-cell function. These events serve both as potential therapeutic targets and predictive biomarkers. MHC I=major histocompatibility complex I.

Gibney et al, Lancet Oncol 2016;16:e542

# PD-L1: A Tale of 2 Trials




Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

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References: Reck et al, NEJM 2016:375
Herbst et al, Lancet 2016;387

# PD-L1: A Tale of 2 Trials

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

## Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

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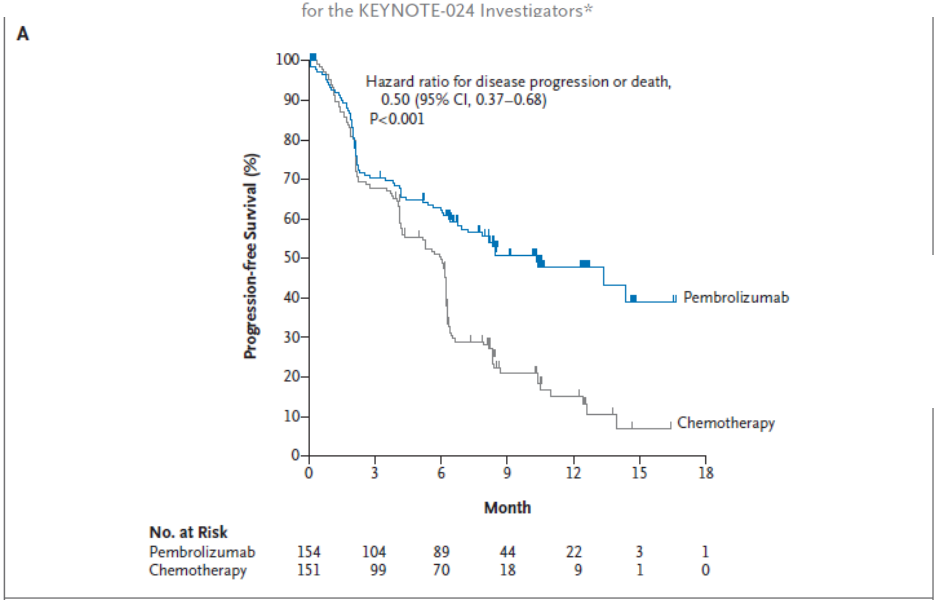


- In untreated metastatic EGFR-and-ALK-negative NSCLC, pembrolizumab vs. chemo.
- At least 50% PD-L1 IHC expression was an inclusion criterion. (Remind you of anything?)

This study led to the following FDA approval for pembrolizumab:

- patients with metastatic NSCLC whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC. (1.2)

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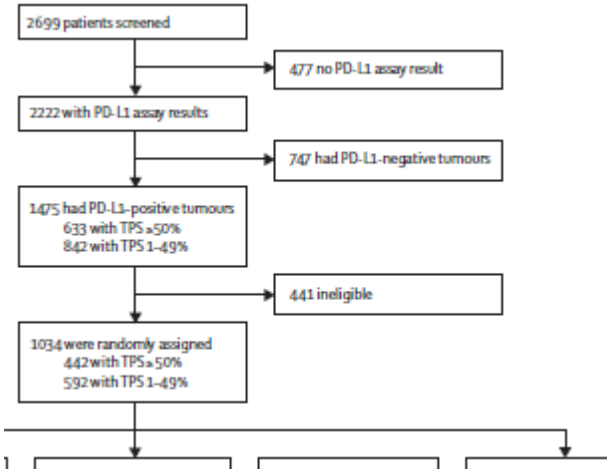
Reference: Reck et al, NEJM 2016:375

# PD-L1: A Tale of 2 Trials




- PD-L1 IHC score of 1% was used as an inclusion criterion, but <u>stratified as part of the analysis</u>.
- This was to decide maintenance therapy for previously-treated metastatic NSCLC.
- Led to the following FDA approval for pembrolizumab:

- patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA. (1.2)

**Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial**

*Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon*

Reference: Herbst et al, Lancet 2016;387

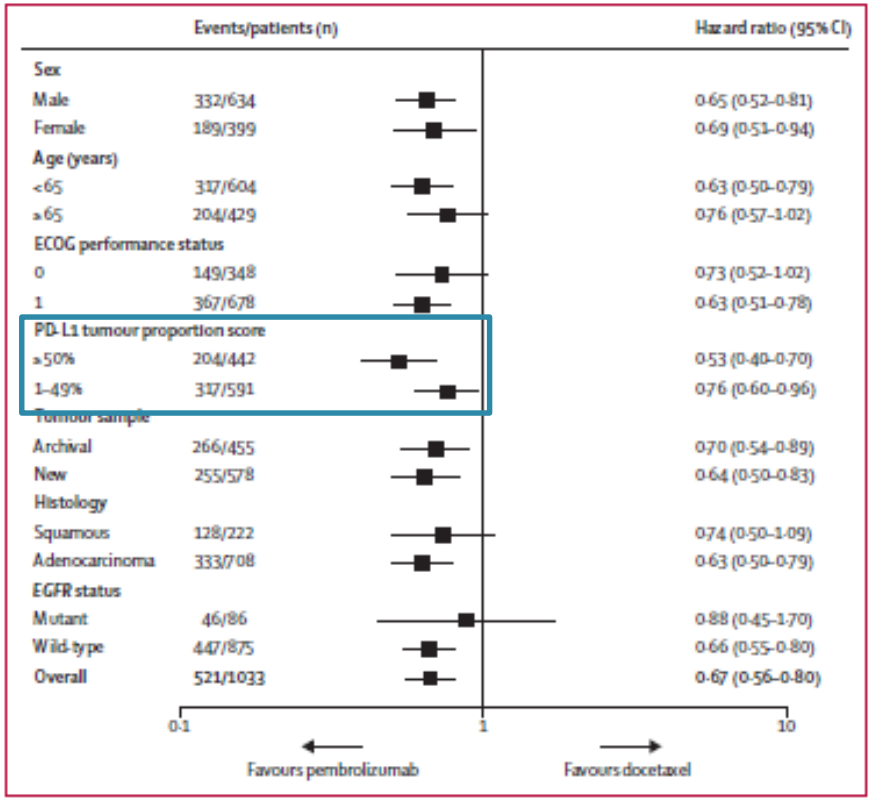



***Figure 3*: Subgroup analysis of overall survival**
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

# PD-L1 and Immune Checkpoints: Diagnostic Strategies

| | Details of approach | Malignancies studied | Improved clinical outcome association |
|---|---|---|---|
| PD-L1 | Immunohistochemistry-based assessment of the proportion of PD-L1-positive tumour cells, immune cells, or both | Multiple tumour types | Positive PD-L1 tumour status |
| Tumour-infiltrating lymphocyte | Immunohistochemistry-based assessment of T cells at invasive tumour margin or tumour parenchyma | Melanoma; multiple tumour types | Increased CD8+ tumour-infiltrating lymphocyte density |
| T-cell receptor clonality | Involves next-generation sequencing of T-cell receptor β chain | Melanoma | Restricted, clonal T-cell receptor β chain |
| Mutational burden | Whole or targeted exome sequencing to assess non-synonymous somatic mutations | Melanoma, NSCLC, bladder cancer | High mutational count |
| Neoantigen burden | Predicted neoantigens derived from whole-exome sequencing data | Melanoma, NSCLC | High neoantigen count |
| Immune gene signatures | Assessment of gene expression from the tumour microenvironment using an automated platform | Melanoma | Interferon γ or T-cell inflamed profile |
| Multiplex immunohistochemistry | Direct assessment of multiple protein markers on tumour cells and immune cells, including spatial relationships | Multiple tumour types | Physical interaction with PD-1-positive and PD-L1-positive cells; others likely to be determined |

PD-L1=programmed death-ligand 1. NSCLC=non-small-cell lung cancer. PD-1=programmed death-1.

**Table: Leading tumour biomarker strategies under development for checkpoint immunotherapy**

Gibney et al, Lancet Oncol 2016;16:e542

- For Diagnostics: The most informative strategy will require prospective tissue collection, along with retrospective multi-modality testing.

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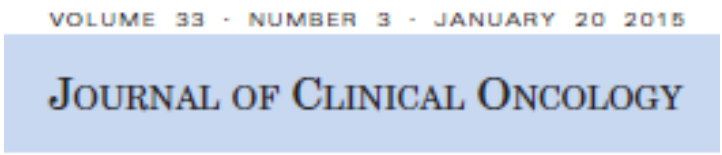
# Case Study 2: A Diagnostic for Ovarian Cancer Targeted Therapy

## Part 1


Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Marja Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D., Mark J. O'Connor, Ph.D., Alan Ashworth, Ph.D., James Carmichael, M.D., Stan B. Kaye, M.D., Jan H.M. Schellens, M.D., Ph.D., and Johann S. de Bono, M.D., Ph.D.




Olaparib Monotherapy in Patients With Advanced Cancer and a Germline *BRCA1/2* Mutation

*Bella Kaufman, Ronnie Shapira-Frommer, Rita K. Schmutzler, M. William Audeh, Michael Friedlander, Judith Balmaña, Gillian Mitchell, Georgeta Fried, Salomon M. Stemmer, Ayala Hubert, Ora Rosengarten, Mariana Steiner, Niklas Loman, Karin Bowen, Anitra Fielding, and Susan M. Domchek*

- Question for Discussion:
  a) These studies led to FDA-approval for olaparib. What is the FDA-approved diagnostic?
  b) Can an independent laboratory develop a test for BRCA-mutation status?

# Case Study 2: A Diagnostic for Ovarian Cancer Targeted Therapy

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

## Part 1

**Patients and Methods**

This multicenter phase II study enrolled individuals with a germline *BRCA1/2* mutation and recurrent cancer. Eligibility included ovarian cancer resistant to prior platinum; breast cancer with ≥ three chemotherapy regimens for metastatic disease; pancreatic cancer with prior gemcitabine treatment; or prostate cancer with progression on hormonal and one systemic therapy. Olaparib was administered at 400 mg twice per day. The primary efficacy end point was tumor response rate.

The FDA Label was based on the subcohort of ovarian cancer patients. (Results on Next Slide.)

There are several limitations to this study. There was no central laboratory or central review of mutational status before enrollment. However, the vast majority of patients (265 [89%] of 298) carried truncating mutations, including 158 (53%) who carried one of the Ashkenazi Jewish founder mutations (and one patient carried two). Of the remaining patients, 17 carried missense mutations. Although it can be more difficult to establish the deleterious nature of missense mutations (and there is no universal standard for classification at this time), six missense mutations were *BRCA1* C61G (clearly established pathogenic founder mutation). Thus, we feel that the chance of misclassification of mutation status is low.

A companion diagnostic was not included in this study, but evaluated separately in a retrospective “bridging study”.

# Case Study 2: A Diagnostic for Ovarian Cancer Targeted Therapy

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

## 14 CLINICAL STUDIES

The efficacy of Lynparza was investigated in a single-arm study in patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced cancers (Study 1). A total of 137 patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza at a dose of 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST v1.1.

The median age of the patients was 58 years, the majority were Caucasian (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious, germline *BRCA* mutation status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the companion diagnostic BRACAnalysis CDx™, which is FDA approved for selection of patients for Lynparza treatment.

Efficacy results from Study 1 are summarized in Table 5.

**Table 5 Overall Response and Duration of Response in Patients with *gBRCA*-mutated Advanced Ovarian Cancer Who Received 3 or More Prior Lines of Chemotherapy in Study 1**

| | N=137 |
|---|---|
| Objective Response Rate (95% CI) | 34% (26, 42) |
| Complete Response | 2% |
| Partial Response | 32% |
| Median DOR in months (95% CI) | 7.9 (5.6, 9.6) |

# Case 2: Summary of Part 1

- The “FDA-approved” companion diagnostic becomes a de facto “gold standard”, sometimes without full justification.
- A significant limitation arises when insufficient tissue is available for retrospective analysis.
- When “positive status” is an eligibility criterion, it is difficult to confirm what happens when you treat “test-negative” patients.

# Case Study 2: A Diagnostic for Ovarian Cancer Targeted Therapy

## Part 2

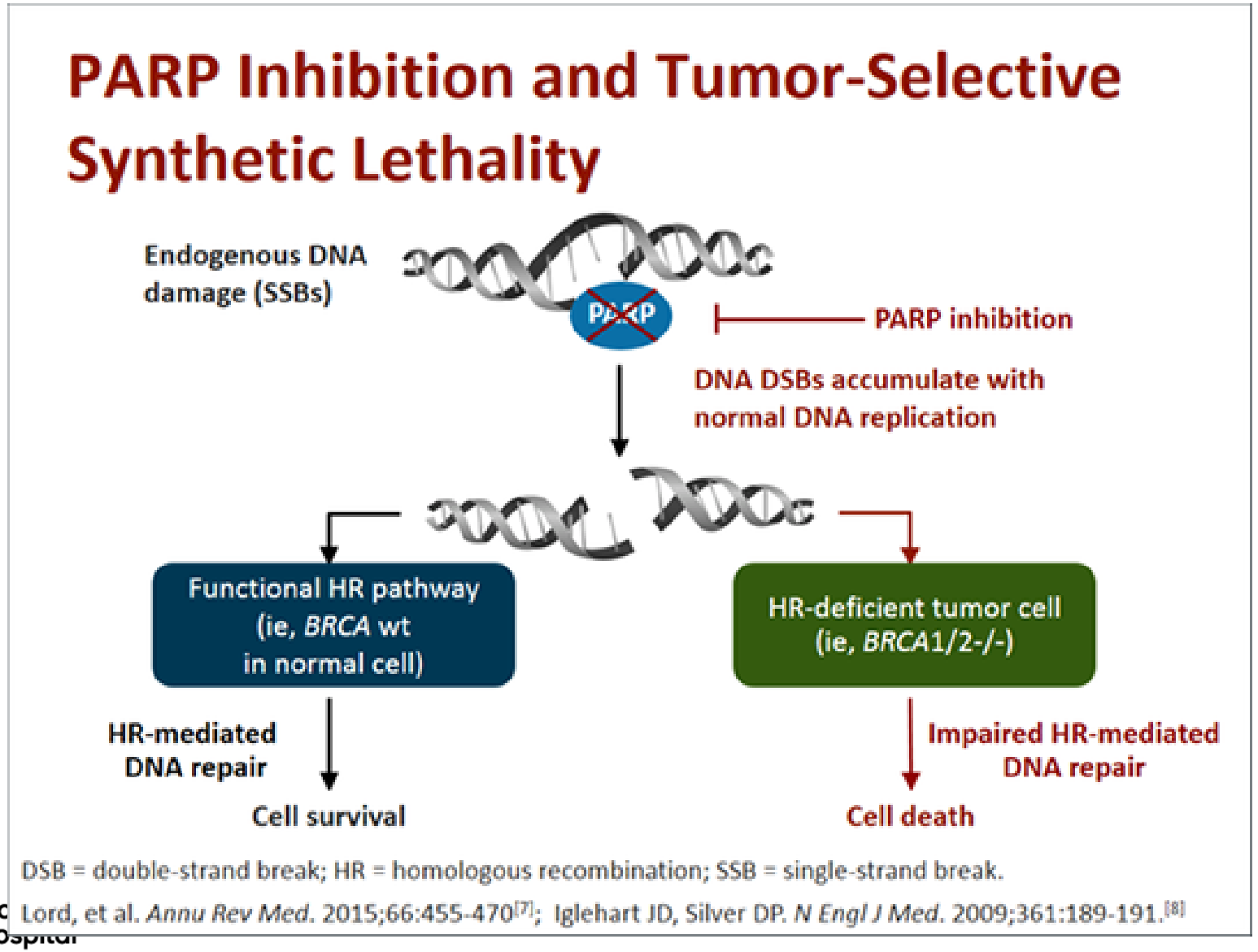
**Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial**

*Amit M Oza, David Cibula, Ana Oaknin Benzaquen, Christopher Poole, Ron H J Mathijssen, Gabe S Sonke, Nicoletta Colombo, Jiří Špaček, Peter Vuylsteke, Holger Hirte, Sven Mahner, Marie Plante, Barbara Schmalfeldt, Helen Mackay, Jacqui Rowbottom, Elizabeth S Lowe, Brian Dougherty, J Carl Barrett, Michael Friedlander*

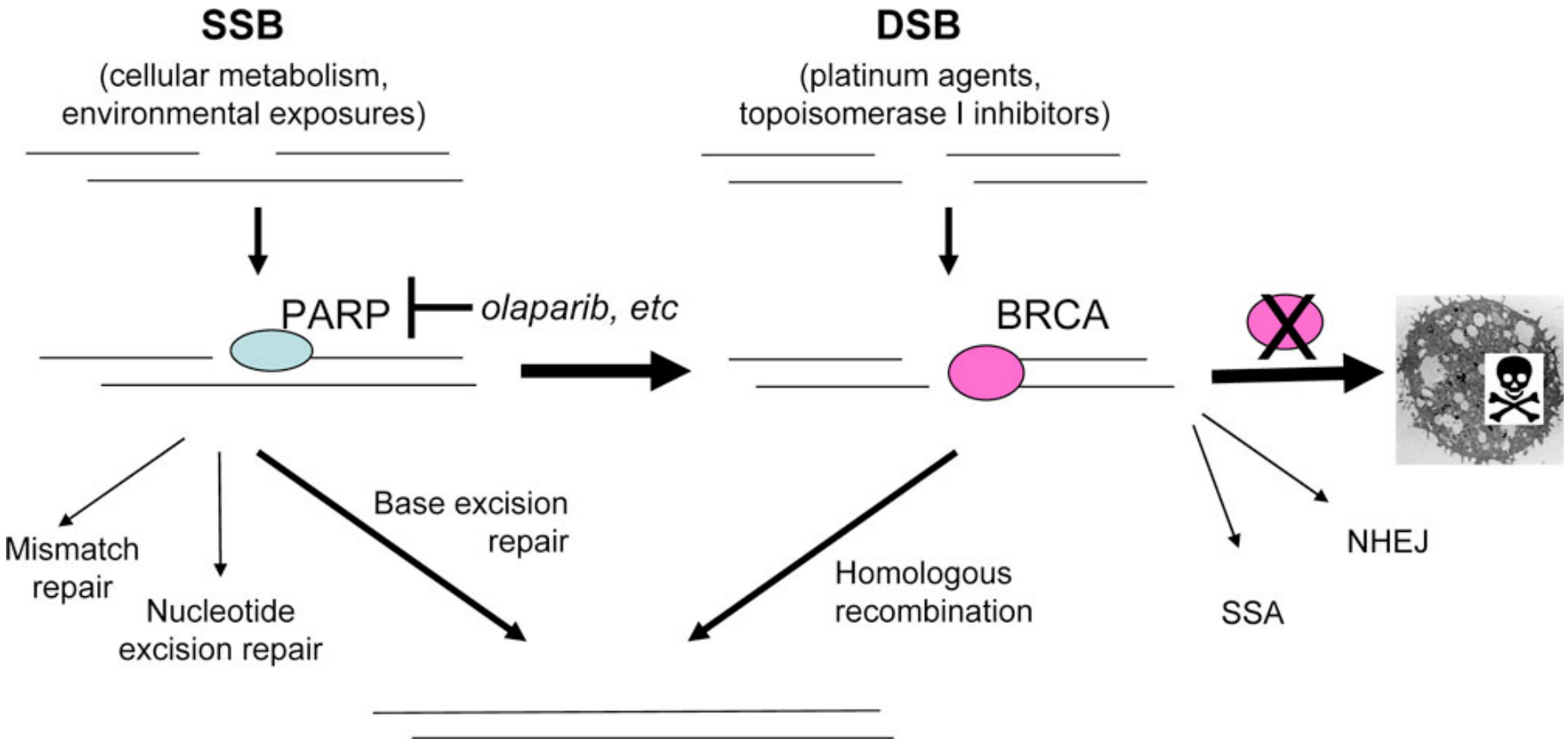
Lancet Oncology 2015;16:87-97
(see also Ledermann et al, Lancet Oncology 2016;17:1579-89)

- Questions for Discussion:
  a) What is the biologic rationale for olaparib in “recurrent platinum-sensitive” ovarian cancer?
  b) What is definition of “recurrent platinum-sensitive”?
  c) What is the diagnostic for “recurrent platinum-sensitive”? (Trick question.)
  d) What is the role for BRCA-mutation testing to select patients for this treatment strategy? (Not a trick question.)

# Olaparib and BRCA



# Olaparib and Platinum

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# Case Study 2: A Diagnostic for Ovarian Cancer Targeted Therapy

## Part 2

- Questions for Discussion:
  a) What is the biologic rationale for olaparib in “recurrent platinum-sensitive” ovarian cancer?
  b) What is definition of “recurrent platinum-sensitive”?
  c) What is the diagnostic for “recurrent platinum-sensitive”? (Trick question.)
  d) What is the role for BRCA-mutation testing to select patients for this treatment strategy? (Not a trick question.)

Preclinical data suggest that olaparib might potentiate the efficacy of DNA-damaging chemotherapies, including platinum-containing drugs such as carboplatin.[13,14] The combination of carboplatin with paclitaxel, a mitotic inhibitor, is widely used to treat patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer.[4]

Patients had received a maximum of three previous courses of platinum-based chemotherapy and, in the investigator's opinion, were progression free for at least 6 months before randomisation. Other key eligibility

There is none.

BRCA-testing is still needed for the on-label use of olaparib.
This study supports expanding the use of olaparib to non-BRCA patients.

# Case Study 3: Multiple Mutation Analysis for Lung Cancer Targeted Therapy

*J Thorac Oncol*. 2015 May ; 10(5): 768–777. doi:10.1097/JTO.0000000000000516.

## Multi-institutional oncogenic driver mutation analysis in lung adenocarcinoma: The Lung Cancer Mutation Consortium experience

Lynette M. Sholl, MD[#1], Dara L. Aisner, MD PhD[#2], Marileila Varella-Garcia, PhD[#2,3], Lynne D. Berry, PhD[#4], Dora Dias-Santagata, PhD[5], Ignacio I. Wistuba, MD[6], Heidi Chen, PhD[4], Junya Fujimoto, MD PhD[6], Kelly Kugler, BA[3], Wilbur A. Franklin, MD[2], A. John Iafrate, MD PhD[5], Marc Ladanyi, MD[7], Mark G. Kris, MD[7], Bruce E. Johnson, MD[9], Paul A. Bunn, MD[3,8], John D. Minna, MD[10], David J. Kwiatkowski, MD PhD[9], and on behalf of the LCMC Investigators

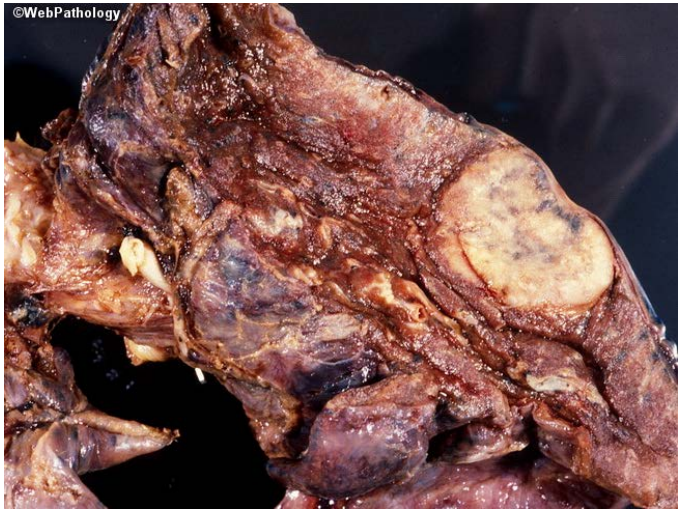
- Questions for Discussion:
  a) Why is tissue from a surgical resection specimen preferable for multiple mutation testing?
  b) What type(s) of error does inter-institutional validation reduce?
  c) What type(s) of error does proficiency testing reduce?
  d) Why is this type of study essential in developing novel diagnostics?

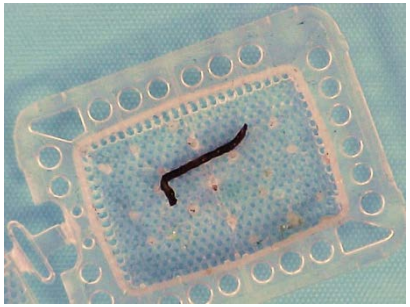
# Case Study 3: Multiple Mutation Analysis for Lung Cancer Targeted Therapy

- Questions for Discussion:

  a) Why is tissue from a surgical resection specimen preferable for multiple mutation testing?

**Results—**1007 specimens had mutation analysis performed, and 733 specimens had all 10 genes analyzed. Mutation identification rates did not vary by analytic method. Biopsy and cytology specimens were inadequate for testing in 26% and 35% of cases compared to 5% of surgical specimens. Among the 1007 cases with mutation analysis performed, *EGFR, KRAS, ALK*, and



Above:
core biopsy

Below:
cytology specimen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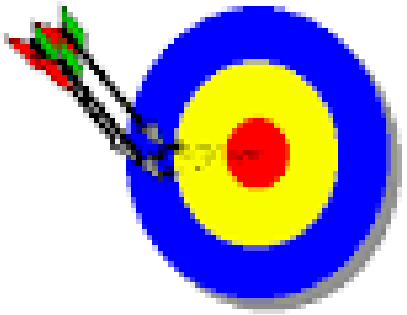
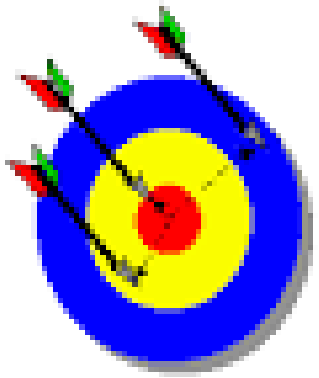
# Analytical validity requires low systematic and low random error.

## Two Types of Error

| systematic error | random error |
| --- | --- |
| poor accuracy | poor precision |
| definite causes | nonspecific causes |
| reproducible | not reproducible |

- "DRIFT"





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# Analytical validity requires low systematic and low random error.

| The ACCE framework | |
|---|---|
| **A**nalytical performance and validation | technical performance - sensitivity, specificity, limit of detection, sample processing |
| **C**linical validation | operational standards from sample collection through DNA processing to clinical performance (sensitivity, specificity etc) compared to the 'gold standard' test |
| **C**linical utility | value of the test for the individual – does the test & subsequent intervention(s) lead to an improved health outcome ? |
| **E**thical, legal & social implications of the test | risks, benefits & cost implications |

Fig. 1. When is a DNA test ready for the clinic? (Adapted from Haddow JE PG. ACCE: a model process for evaluating data on emerging genetic tests. In: Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease. New York: Oxford University Press; 2003. p. 217–33) [13].

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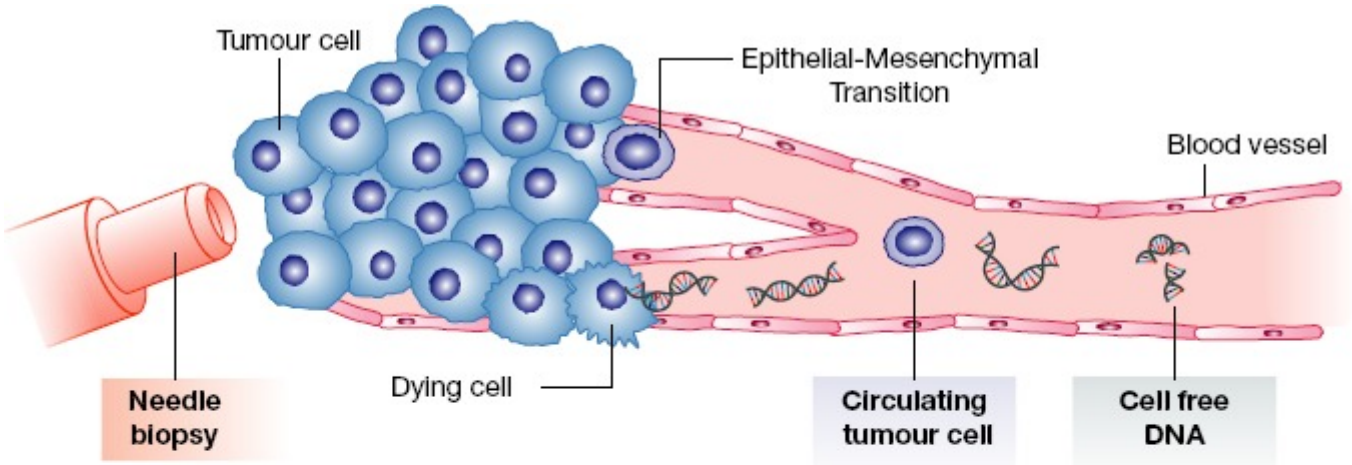
# Case Study 3: Multiple Mutation Analysis for Lung Cancer Targeted Therapy

- Questions for Discussion:
  a) Why is this type of study essential in developing novel diagnostics?




| | Biopsy | CTC | cfDNA |
|---|---|---|---|
| Invasive | + | – | – |
| All patients eligible | – | + | + |
| Instrumentation required | + | + | – |
| WGA required | – | + | +/– |
| RNA profiling | + | + | – |
| Research applicability | +++ | ++ | + |
| Biomarker applicability | – | ++ | +++ |

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# Case Study 3: Multiple Mutation Analysis for Lung Cancer Targeted Therapy

- Questions for Discussion:
  a) Why is this type of study essential in developing novel diagnostics?

What do we need to make circulating tumour DNA (ctDNA) a routine diagnostic test in lung cancer?

Reyes Bernabé [a,b], Nicholas Hickson [c], Andrew Wallace [c], Fiona Helen Blackhall [a,d,*]

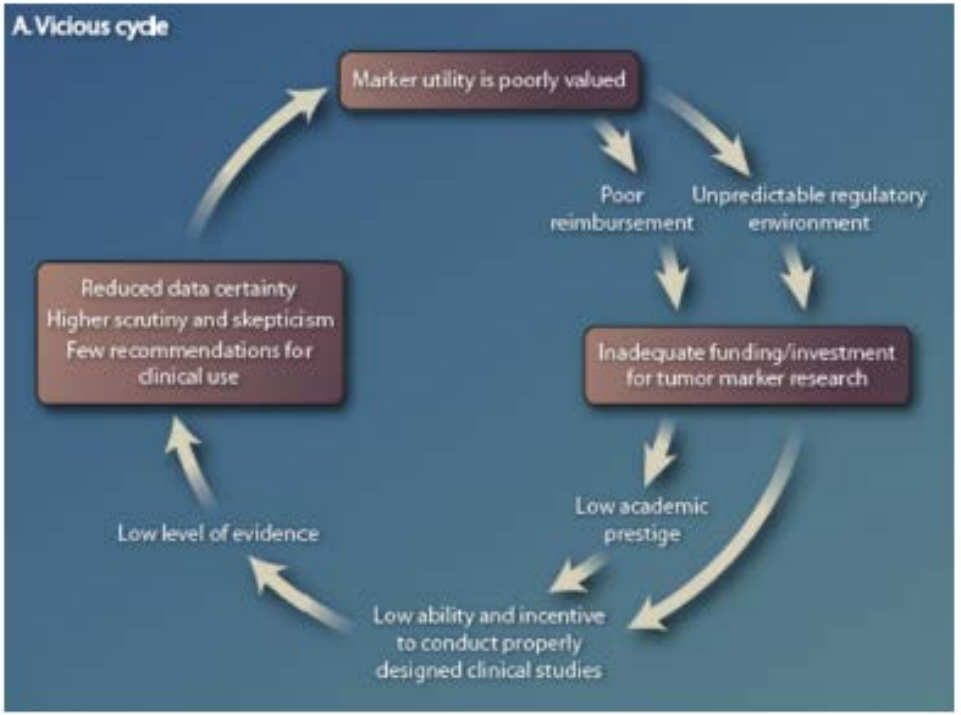
Table 2
Results for clinical outcomes of patients according to plasma EGFR mutation status in randomised trials of EGFR-TKIs versus chemotherapy and the IFUM phase IV study.

| Study [ref] (TKI) | Method (see Table 1 for abbreviations) | ctDNA test performance (tissue as reference) | | | Clinical outcome for TKI versus chemotherapy (CT) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Tissue + | | Plasma + | |
| | | Specificity (PPV) | Sensitivity (NPV) | Concordance | RR % | PFS (Hazard ratio) | RR % | FS (Hazard ratio) |
| **Studies evaluating first-line EGFR-TKIs** | | | | | | | | |
| IPASS [29] (G) | DxS ARMS | 100% | 43.1% | 66.3% | 69 versus 48.5% | 0.70 | 75 versus 64% | 0.29* |
| IFUM [41] (G) | Therascreen RGQ | 99.8% (98.6%) | 65.7% (93.8%) | 94.3% | 60 | NA | 77 | NA |
| EURTAC [43] (E) | Taqman | 100% | 78% | 72.7% | 65.1 versus 16.1% | 0.34 | No difference | 0.36** |
| FASTACT-2 [44] (E) (note CT ± E) | Cobas blood | 96% (94%) | 75% (85%) | 88% | – | 0.25 | 66.vs24.2%*** | 0.22 |
| LUX-LUNG 3 [16] (A) | Therascreen 29 | – | – | 60.5% | – | – | – | 0.35 |
| LUX-LUNG 6 [16] (A) | | | | | | | | 0.25 |
| ENSURE [12,34] (E) | Cobas v2 | (96.8%) | (81.4%) | 77% | 62.7 versus 33.6% | 0.34 | NA | NA |
| AURA3 [5,12] (O) | Cobas v2 | – | – | – | 71% versus 31% | 0.3 | 77% versus 39% | 0.42 |

Abbreviations: TKI: tyrosine kinase inhibitor, PPV: positive predictive value, NPV: negative predictive value, G: gefitinib, E: erlotinib, A: afatinib, O: osimertinib, RR: response rate, PFS: progression free survival (median months) HR: Hazard Ratio, NA: not assessed (single arm study), NS: not stated, *significant interaction test for biomarker p value < 0.05, **E independent predictor in multivariate analysis, ***based on cycle 3 ctDNA EGFR mutation status.

# Wrap-up

- Diagnostics is a relatively neglected area in clinical trials design.
- A good diagnostic must have analytical validity, clinical validity, and clinical utility.
- We are now beginning to learn from our past mistakes—the resulting biomarkers will be that much better for it!




Dan Hayes, 2013

**Table 2 – Important definitions for tumor biomarker semantics.**

Analytical validity
- Does the tumor biomarker test accurately and reliably measure the analyte of interest in the appropriate patient specimen?

Clinical validity
- Does the tumor biomarker test accurately and reliably identify a clinically or biologically defined disorder, or separate one population into two or more groups with distinct clinical or biological outcomes or differences?

Clinical utility
- Are there high levels of evidence that use of the tumor biomarker test to guide clinical decisions result in improved measurable clinical outcomes compared with those if the biomarker test results were not applied?

Modified from (Teutsch et al., 2009).

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# References


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  Bernabé et al, Eur J Cancer 2017;81:66-73