ETEROGENEITÀ TUMORALE:
IL PUNTO DI VISTA DEL CLINICO

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DISCLOSURE

• I’m not a basic researcher (but just a simple clinician)

“The collaboration between clinicians and researchers is vital in an era requiring a deep understanding of the molecular biology underlying the development of cancer. ESMO 2017 will be a truly integrated congress, bringing together researchers and clinicians to help bridge the gap between innovation and clinical implementation.”

Fortunato Ciardiello, ESMO President
WHAT WE KNOW

✓ Neoplasms evolve

✓ This evolution has been recognized since 1976 and it explains the processes of both carcinogenesis and acquired therapeutic resistance

✓ The evolution of neoplasms is shaped by the selective pressures of their micro environmental ecology

✓ Between and within cancer types, tumors probably display differences in the dynamics of cancer evolution and ecology, including the rates at which new clones appear and go extinct, how different those clones are from one another and whether they appear in bursts or at a more regular pace

✓ Many of the evolutionary and ecological properties of a neoplasm are clinically relevant, though this is not always true and in most cases their clinical relevance has not yet been tested
UNANSWERED QUESTIONS

1. If some cancers are ‘born to be bad’…
   • Can a ‘genomic signature’ be incorporated with other clinical/pathological/gene expression signatures to improve our ability to identify those cancers destined to relapse?

2. In the window between primary tumor diagnosis and the clinical diagnosis of metastasis a cancer’s genome changes substantially…
   • Driver mutations at metastasis sample from a wider range of cancer genes than in primary tumors and so an even broader range of therapeutic strategies may be appropriate – how are we going to address this?
   • Which genomic alterations to target - trunk’ versus ‘branch’? How can clinical trials address this?

3. How can we improve the rate at which patients within molecular screening initiatives are fed into clinical trials?
INTER-TUMOR HETEROGENEITY

Molecular diagnosis

PRECISION MEDICINE
INTRATUMOR HETEROGENEITY
INTRATUMOR HETEROGENEITY

Genomic diversity

Johnson et al. Science 2014
INTRATUMOR HETEROGENEITY

Stromal diversity
INTRATUMOR HETEROGENEITY

Epigenomic/state of differentiation diversity
TUMOR EVOLUTION

Surgery
Radiotherapy
Chemotherapy

Relapse
INTRATUMOR HETEROGENEITY: Leading to a Sampling Bias?

- Spatial heterogeneity: genetic variation across different locations within a single tumor
- Biopsies of different areas may produce different results
SYSTEMATIC REVIEW OF DISCORDANCE RATE BETWEEN PRIMARY TUMOR AND DIFFERENT SITES OF METASTASIS

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ER CHANGES:
Frequency depends on metastatic site

TEMPORAL HETEROGENEITY: ESR1 MUTATION AS AN EXAMPLE

- Temporal heterogeneity: evolution may occur during the course of breast cancer progression.
HOW APPLICABLE ARE THESE FINDINGS TO OTHER DATA SETS?

Two recent pan-cancer analyses with high patient numbers including 1,331 patients with metastatic breast cancer allow comparison of cancer gene landscape

1. Confirm that on average, more mutations are found in metastases than primary tumors
2. Confirm that many cancer genes are more common in metastasis than primary cancer datasets
3. Consistently enriched genes include TP53, ESR1, PTEN and possibly various others

TUMOR CHARACTERIZATION
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Cell subclone specific treatment?

Treatment 1

Treatment 2

Treatment 3
TUMOR CHARACTERIZATION

- Circulating biomarkers
- Epigenomic analysis
- DNA Sequencing
- Gene expression
- IHC
FUNCTIONAL ASSAYS

Patient-derived models
Tumoroids
Characterization and Functional Analysis
Patient
Cancer Biology
DNA Sequencing
Gene expression
Epigenomics
Preclinical studies
Patient stratification
Circulating biomarkers
Tumoroids
Characterization and Functional Analysis
Preclinical studies
Cancer Biology
Patient stratification
VAN DER VELDEN et al. LBA59_PR - Expanding the use of approved drugs: The CPCT’s Drug Rediscovery Protocol (DRUP)

Study flow chart

Since Sep 2016, ~250 cases were submitted for review and about 1/3 of these patients have started study treatment.

Clinical benefit was observed in 37% (6% CR, 14% PR, 17% SD ≥ 16 weeks; all CRs and 2/3 of PRs were ongoing at the time of writing and awaiting ≥30 days confirmation)

About 2/3 of case submissions were rejected, mainly due to a general protocol ineligibility (18%)
GUPTA et al. 1628O - Development of the Manchester Cancer Research Centre Molecular Tumour Board for matching patients to clinical trials based on tumour and ctDNA genetic profiling

THE TARGET TRIAL

Tumour ChARacterisation to Guide Experimental Targeted Therapy

- Tissue sample (archival / fresh)
- DNA extraction
- Targeted panel of 24 cancer genes
  - Illumina MiSeq NGS
  - 20ng DNA input
  - Detects point mutations and indels to 5% MAF

- Blood sample (6-12ml plasma)
- ctDNA isolation
- Targeted panel of 653 cancer genes
  - NextSeq NGS
  - >5ng ctDNA input
  - Mutation and copy number evaluation

- Tissue and blood results in a realistic time frame (2-3 weeks)
Pernas Simon et al. 315TiP - AGATA molecular screening program: Implementing precision medicine in patients with advanced breast cancer in Spain
Studying the end

Surgery Radiotherapy Chemotherapy

Relapse
WALMSLEY et al. 16290 - A systematic rapid autopsy program tracks temporal and spatial heterogeneity of human tumors and identifies mechanisms of resistance to targeted therapies

Rapid Autopsy Process

Full analysis of 3 autopsy series revealed molecular alterations driving resistance to PI3K-alpha inhibitors, CDK4/6 inhibitors and FGFR inhibitors in patients with PIK3CA-altered metastatic breast cancer and FGFR2 fusion positive cholangiocarcinoma

Rapid autopsies complement serially collected tissue and liquid biopsies, providing invaluable samples for analysis of tumor heterogeneity, evolutionary dynamics and determination of resistance mechanisms to targeted therapies
TUMOR CHARACTERIZATION LEADS TO PRECISION THERAPY

Challenges:

- Samples (quality, how representative, timing)
- Bioinformatics
- More drugs and actionable targets (more research)