Preclinical strategies for precision medicine in colorectal cancer: Challenges and opportunities

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Disclosures

- Receives research grants from Merus N.V., Utrecht, The Netherlands
Only 10% of NSCLCs harbour EGFR mutations (in Caucasian patients), and only 40% of EGFR-mutant tumours respond to EGFR inhibitors:
  • overall prevalence of responders: 4%

Only 4% of NSCLCs harbour ALK translocations, and only 50% of ALK-translocated tumours respond to ALK inhibitors:
  • overall prevalence of responders: 2%
Only 10% of NSCLCs harbour EGFR mutations (in Caucasian patients), and only 40% of EGFR-mutant tumours respond to EGFR inhibitors:
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Only 4% of NSCLCs harbour ALK translocations, and only 50% of ALK-translocated tumours respond to ALK inhibitors:
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Precision cancer medicine stands on exceptions
Compensatory Pathways in Oncogenic Kinase Signaling and Resistance to Targeted Therapies: Six Degrees of Separation

Livio Trusolino and Andrea Bertotti

• Response to BRAF or MEK inhibition in BRAF mutant melanoma: 60%

• Response to BRAF or MEK inhibition in BRAF mutant CRC: 2%
Compensatory Pathways in Oncogenic Kinase Signaling and Resistance to Targeted Therapies: Six Degrees of Separation

Livio Trusolino and Andrea Bertotti

- Response to BRAF or MEK inhibition in BRAF mutant melanoma: 60%
- Response to BRAF or MEK inhibition in BRAF mutant CRC: 2%

‘Drivers’ not always are ‘targets’
From Bench to Bedside: Does Preclinical Practice in Translational Oncology Need Some Rebuilding?

Andrea Bertotti and Livio Trusolino
The littlest patient
Cutting-edge mouse models fuel hope for understanding and treating cancer

By Jennifer Couzin-Frankel, in New York City
Targeted therapies in metastatic colorectal cancer (mCRC): Limitations and open issues for precision cancer medicine

• In unselected patients, objective response rates to anti-EGFR antibodies are approximately 10%

• The only routine response biomarker is a negative predictor: KRAS mutations in codons 12 and 13 (40% of all CRCs)

• Other negative response biomarkers have been identified and are now progressively being introduced into diagnostic practice (rare KRAS mutations, NRAS and BRAF mutations, for an additional 15%)

• Novel response biomarkers need to be identified, together with ‘pertinent positives’ and ‘pertinent negatives’
Response to cetuximab in unselected xenopatients

48%  32%  12%
"Quadruple negative" CRCs: Terra incognita

35%  43%  22%
Regression: Discovery of pertinent positives
Regression: Discovery of pertinent positives

Bertotti al., Nature 2015
Regression: Discovery of pertinent positives

ISS2 amplification/mutation (8)
IRS2 silencing lessens dependency on the EGFR pathway

Barbara Lupo
Tumour stabilisation: Discovery of co-extinction targets

Zanella et al., Science Transl. Med. 2015
Comprehensive molecular characterization of human colon and rectal cancer

The Cancer Genome Atlas Network

IGF2 is overexpressed in a fraction of CRCs
IGF2 overexpression is enriched in mCRC cases that respond to cetuximab with disease stabilisation.
IGF2 overexpression is enriched in mCRC cases that respond to cetuximab with disease stabilisation.

Xenopatients

Patients


Sabine Tejpar and Eva Budinská
IGF2 targeting is synergistic with cetuximab in IGF2 overexpressors

Francesca Cottino, Eugenia Zanella, Francesco Sassi, Giorgia Migliardi
Resistance: Discovery of actionable biomarkers
Resistance: Discovery of actionable biomarkers

Quadruple WT
MET amplification
HER2 amplification

Resistance: Discovery of actionable biomarkers

IRS2 amplification/mutation (8)
HER2 amplification (5)

Bertotti et al., Cancer Discovery 2011
Resistance: Discovery of actionable biomarkers

- IRS2 amplification/mutation (8)
- HER2 amplification (5)
- MET amplification (3)

Bardelli et al., *Cancer Discovery* 2013
Resistance: Discovery of actionable biomarkers

- IRS2 amplification/mutation (8)
- HER2 amplification (5)
- MET amplification (3)
- HER2 V777L mutation (2)
- HER2 S310Y mutation (1)
- HER2 L866M mutation (1)

Kavuri et al., *Cancer Discovery* 2015
Resistance: Discovery of actionable biomarkers

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- EGFR V843I mutation (1)
- EGFR G465E mutation (1)
- EGFR G465R mutation (1)

Bertotti et al., Nature 2015
Resistance: Discovery of actionable biomarkers

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Bertotti et al., *Nature* 2015
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- FGFR1 amplification (3)
- PDGFRA mutation (3)

Bertotti et al., *Nature* 2015
Quadruple WT
MET amplification
HER2 amplification

Resistance: Discovery of actionable biomarkers

- PDGFRA mutation (3)
- FGFR1 amplification (3)
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- HER2 L866M mutation (1)
- HER2 S310Y mutation (1)
- MEK1 K57N mutation (1)

Bertotti et al., *Nature* 2015
Resistance biomarkers: From correlations to causative significance

Barbara Lupo

**Quadruple WT**
- MET amplification
- HER2 amplification

**P-EGFR**
- P-ERK
- Tubulin

**Cetuximab (μg/ml)**
- Mock
- EGFR G465E

**Relative cell number (treated/untreated)**

**Cetuximab (μg/ml)**
- Mock
- MEK K57N

**Relative cell number (treated/untreated)**

**Cetuximab (μg/ml)**
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DDK
- P-ERK
- ERK
- Tubulin

**Cetuximab (μg/ml)**
- Mock
- EGFR G465E
From a black box... (2010)
... To a rainbow of opportunities (2015)

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- MEK1 K57N mutation (1)
Therapeutic opportunities:
Targeting new EGFR epitopes in EGFR-extra mutant cases

Giorgia Migliardi, Francesca Cottino, Valentina Vurchio

Francesco Sassi
A small molecule-antibody combination of anti-EGFR/HER2 therapies induces tumour shrinkage

Leto et al., *Clin. Cancer Res.* 2015
The HERACLES trial: Targeting HER2 in KRAS WT, cetuximab-resistant mCRC

Heracles and the Hydra (Early Hellenistic Period), Musei Capitolini, Rome
The HERACLES Trial: From xenopatients to patients

Sartore-Bianchi, Trusolino et al., *Lancet Oncology* 2016
## Acknowledgments

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