Metastatik Kolorektal Kanser Tedavisinde
Yeni Biyobelirteçler Sonrası
Panitumumab

Prof. Dr. N. Faruk Aykan

Antalya – 22 Mart 2014
1952 - 1953
St. Louis, ABD
The discovery of *nerve growth factor* (NGF) in the beginning of the 1950's is a fascinating example of how a skilled observer can create a concept out of apparent chaos. Until this time, experimental neurobiologists did not understand how the development of the nervous system was regulated to result in the final complete innervation of the body. The investigation of NGF's role in the development of the nervous system, as well as later, in adult neural function, has been a lifelong dedication for Rita Levi-Montalcini. Developmental biologist *Rita Levi-Montalcini*, who in the beginning of 1950's moved from her homeland Italy, to Viktor Hamburger's laboratory in St. Louis, USA, showed in 1952 that when tumours from mice were transplanted to chick embryos they induced potent growth of the chick embryo nervous system, specifically sensory and sympathetic nerves. Since this outgrowth did not require direct contact between the tumour and the chick embryo, Rita Levi-Montalcini concluded that the tumour released a *nerve growth-promoting factor* which had a selective action on certain types of nerves. Following this discovery, Rita Levi-Montalcini turned to a more sensitive cell culture system in order to measure NGF activity in various extracts. NGF proved to be an extremely potent biological substance. A sensory or sympathetic nerve cell reacted within 30 seconds to the addition of minute quantities of NGF. One billionth part of a gram of NGF per ml of culture medium exerted a potent growth-promoting effect. A few minutes after the addition of NGF, nerve fibres began to grow out from the ganglion which after a day's exposure to NGF resembled a sun surrounded by rays (Figure 1). This biological assay to detect NGF paved the way for the next step in this pathway of discovery - identification of the active nerve growth-promoting substance.
Figure 1. The classical biological assay for the measurement of NGF which was developed by Rita Levi-Montalcini. Sensory ganglion dissected from chick embryo is cultured in the presence of extract to be measured. Nerve fibre outgrowth from the chick ganglion is determined after 24 hours. The lowest concentration of the extract which causes a halo of nerve fibre outgrowth (right hand side figure) contains 1 biological unit of NGF. This is equivalent to a concentration of approximately 10 nanograms NGF/ml culture medium (10 ng=1/100,000 of 1 milligram). The left hand side ganglion has been incubated without NGF being present in the medium and is in the process of dying. The figure has been published in Scientific American 1979, 240, p. 48.
The Characterization of NGF

In 1953, biochemist Stanley Cohen, joined the research group in St. Louis. Three years later they had purified a nerve growth-promoting extract from mouse tumour which contained both protein and nucleic acids. To determine which of these components was active, Stanley Cohen added snake venom containing a high concentration of a nucleic acid-degrading enzyme. To his surprise, the snake venom contained more nerve growth-promoting activity than the tumour itself. When added alone to the incubation medium, the snake venom induced an enormous outgrowth of sympathetic nerve fibres. The group followed up this unexpected finding by systematically searching for the presence of NGF in various tissues. In 1958, they discovered another rich source of NGF - a salivary gland in the male mouse.
The Discovery of EGF

During the course of his studies of NGF Stanley Cohen observed an unexpected acceleration of development when he injected salivary gland extract to newborn mice. The mice displayed precocious eyelid opening and tooth eruption. The explanation was that the salivary gland extract contained another growth factor apart from NGF. Cohen termed this substance *epidermal growth factor* (EGF) because it could stimulate the proliferation of epithelial cells in skin and cornea. He raised antibodies against EGF as he previously had against NGF.

In the following years Cohen purified and determined the amino acid sequence of EGF (Figure 2). For the first time scientists had a factor available which stimulated epithelial cell growth and allowed studies of the growth process. Cohen and his coworkers found that EGF enhanced a cascade of events including stimulation of glucose and amino acid transport, activation of protein synthesis and initiation of DNA synthesis and cell replication. In later studies both Cohen and others have shown that EGF stimulates the growth of a large variety of cells including fibroblasts, liver cells, and vascular cells as well as endocrine cells the thyroid, ovaries and pituitary glands.
Fig. 3. Photographs showing the extent of incisor eruption in control and treated 8-day-old mice and rats. A, Control mouse; B, mouse injected daily with 2 μg per 1.5 g of body weight of the tooth-lid factor; C, control rat; and D, rat injected daily with 1 μg per 1.5 g of body weight of the tooth-lid factor.
Figure 2. The amino acid sequence of EGF with placement of disulfide bonds. The figure has been published in J. Biol. Chem. 1973, 248, p. 7670.
Epidermal Growth Factor-Receptor-Protein Kinase Interactions

CO-PURIFICATION OF RECEPTOR AND EPIDERMAL GROWTH FACTOR-ENHANCED PHOSPHORYLATION ACTIVITY

(Received for publication, December 11, 1979)

Stanley Cohen,‡§ Graham Carpenter,‡¶ and Lloyd King, Jr.¶¶

From the Departments of ‡Biochemistry and ¶¶Medicine (Dermatology), Vanderbilt University School of Medicine, and ‡Veterans Administration Hospital, Nashville, Tennessee 37233
Kinase growth factor pathway

Tyrosine kinase receptor

Activated receptor

Ligand binding

Signal transduction

Proliferation
Survival
Migration

Tumour growth and metastases

Cell membrane

Tyrosine kinase domain
The Nobel Prize in Physiology or Medicine 1986

"for their discoveries of growth factors"

Stanley Cohen
1/2 of the prize
USA

Rita Levi-Montalcini
1/2 of the prize
Italy and USA
The Erb Family of Receptor Tyrosine Kinases

(Human Epidermal Growth Factor Receptors)
EGFR expression in CRC

 ✓ EGFR overexpression in CRC: 49 – 82 %
 ✓ EGFR testing has no predictive value for response to anti-EGFR !

a: Primary CRC, b: Metastasis

Monoclonal antibodies (cetuximab, panitumumab)

Tyrosine kinase inhibitors (gefitinib, erlotinib, CI-1033, EKB-569...)

Signal Transduction
## Anti-EGFR Monoclonal Antibodies

<table>
<thead>
<tr>
<th></th>
<th>Cetuximab</th>
<th>C225</th>
<th>Chimeric IgG1</th>
<th>ERBITUX</th>
<th>Merck Serono</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>ABX-EGF</td>
<td>Fully human IgG2</td>
<td>VECTIBIX</td>
<td>Amgen</td>
<td></td>
</tr>
</tbody>
</table>
Ligands

Homo-ou hétérodimère HER

RAS

RAF

MEK

ERK

PI3K

STAT

AKT

mTOR
Specific mutations result in a constitutively active RAS protein

**Mutant KRAS**

- Inactive RAS
- Active RAS

Hyperproliferation

**Mutant NRAS**

- Inactive RAS
- Active RAS

Suppression of apoptosis

Potential relationship between *KRAS* status and response to EGFR monoclonal antibodies, alone or in combination with irinotecan, in chemorefractory patients

Nonresponder:
- *BRAF* mutation 10%
- Loss of PTEN or PI3K mutation % unknown
- Reason unknown % unknown

Nonresponder: *KRAS* mutant 40%

Responds to standard dose 22%

Responds to increased dose*~5%

*KRAS* wildtype

*KRAS* mutant
BRAF mutasyonu
BRAF V600E

MSS Tm. lerde % 10
MSI-H Tm. lerde %13-78

Prognostik Meta-analiz (26 çalışma)
Mortalite artışı HR=2.25


FIGURE 1 | RAS-RAF pathway and immunohistochemical staining of colorectal cancer specimens with BRAF V600E mutation specific monoclonal antibody. (A) Strong immunopositivity in cancer cells with a BRAF V600E mutation. (B) No staining of cancer cells in a specimen without BRAF V600E mutation. Original magnifications are 200×. (C) Schematic RAS-RAF pathway (orange boxes) and inhibitors of components of this pathway (blue boxes). Arrows indicate an activation process, and blocked arrows an inhibition process.

Thiel and Ristimäki
Frontiers in Oncology November 2013 | Volume 3 | Article 281
Panitumumab - a Fully Human Anti-EGFR mAb Inhibits Ligand Binding and EGFR Dimerisation

- Fully human, monoclonal IgG2 antibody
- Binds with high affinity and specificity to the extracellular domain of the human EGFR
  - Dissociation constant: KD=0.05 nM
- Inhibits receptor activation of all known EGFR ligands
- Inhibits EGFR-dependent activity including cell activation and cell proliferation in various tumours

Panitumumab Inhibits EGFR Dimerisation and Subsequent Downstream Signalling

Panitumumab in 1\textsuperscript{st}-line mCRC

Analysis of \textit{KRAS}/\textit{NRAS} and \textit{BRAF} mutations in the phase III PRIME study of panitumumab plus FOLFOX versus FOLFOX as 1\textsuperscript{st}-line treatment for metastatic colorectal cancer
Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated Metastatic Colorectal Cancer: The PRIME Study

Jean-Yves Douillard, Salvatore Siena, James Cassidy, Josep Tabernero, Ronald Burkes, Mario Barugel, Yves Humblet, György Bodoky, David Cunningham, Jacek Jassem, Fernando Rivera, Ilona Kocáková, Paul Ruff, Maria Błasińska-Morawiec, Martin Šmakal, Jean-Luc Canon, Mark Rother, Kelly S. Oliner, Michael Wolf, and Jennifer Gansert
PRIME Trial
FOLFOX4 ± Panitumumab in 1st-line Treatment of Metastatic CRC

Metastatic CRC (n=1183) 1:1

FOLFOX4 (Q2W)

Disease assessment every 8 weeks

End of treatment

Long term follow up

Stratification by:
- Performance status (ECOG 0-1 vs. 2)
- Geographic region: Western Europe, Canada, and Australia vs. Rest of the World

Study endpoints: PFS (1°); OS, ORR, safety, HRQoL

HRQoL, Health-related Quality of Life

www.amgentrials.com; protocol ID: 20050203; ClinicalTrials.gov identifier: NCT00364013.
PRIME Trial
FOLFOX4 ± Panitumumab in 1\textsuperscript{st}-line Treatment of Metastatic CRC

Patient number: 1183

K-ras exon 2 evaluated: 1096 93%

- 440 40% K-ras mutant
- 656 60% K-ras wild type
**PRIME RAS/RAF Primary Analysis**

**PFS in Patients with WT KRAS Exon 2 mCRC<sup>1</sup>**

Original WT KRAS exon 2 testing

![Graph showing event-free survival in patients with WT KRAS Exon 2 mCRC.](image)

- **Panitumumab + FOLFOX4 (n=325)**: 199 (61) events, median (95% CI) 9.6 (9.2–11.1) months.
- **FOLFOX4 (n=331)**: 215 (65) events, median (95% CI) 8.0 (7.5–9.3) months.

**HR=0.80 (95% CI: 0.66–0.97)**

**p=0.02**

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PRIME RAS/RAF Primary Analysis
OS in Patients with WT KRAS Exon 2 mCRC

Original WT KRAS exon 2 testing

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events n (%)</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFOX4 (n=325)</td>
<td>165 (51)</td>
<td>23.9 (20.3–28.3)</td>
</tr>
<tr>
<td>FOLFOX4 (n=331)</td>
<td>190 (57)</td>
<td>19.7 (17.6–22.6)</td>
</tr>
</tbody>
</table>

HR=0.83 (95% CI: 0.67–1.02)
p=0.072

K-ras Mutant hastalarda

**Figure B**

- **Panitumumab + FOLFOX**
  - Events: 167 (76)
  - Median months: 7.3 (6.3 to 8.0)
- **FOLFOX4**
  - Events: 157 (72)
  - Median months: 8.8 (7.7 to 9.4)

**HR = 1.29 (95% CI, 1.04 to 1.62)**

**P = .02**

**Figure D**

- **Panitumumab + FOLFOX**
  - Events: 152 (69)
  - Median months: 15.5 (13.1 to 17.6)
- **FOLFOX**
  - Events: 142 (65)
  - Median months: 19.3 (16.5 to 21.8)

**HR = 1.24 (95% CI, 0.98 to 1.57)**

**P = .068**

**Survival Analysis**

- **No. of patients at risk**
  - Panitumumab + FOLFOX: 221
  - FOLFOX alone: 219

- **Time (months)**
  - Range: 0 to 36
Panitumumab–FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer

Jean-Yves Douillard, M.D., Ph.D., Kelly S. Oliner, Ph.D., Salvatore Siena, M.D., Josep Tabernero, M.D., Ronald Burkes, M.D., Mario Barugel, M.D., Yves Humblet, M.D., Ph.D., Gyorgy Bodoky, M.D., Ph.D., David Cunningham, M.D., Jacek Jassem, M.D., Ph.D., Fernando Rivera, M.D., Ph.D., Ilona Kocáková, M.D., Ph.D., Paul Ruff, M.D., Maria Błasińska-Morawiec, M.D., Martin Šmakal, M.D., Jean Luc Canon, M.D., Mark Rother, M.D., Richard Williams, M.B., B.S., Ph.D., Alan Rong, Ph.D., Jeffrey Wiezorek, M.D., Roger Sidhu, M.D., and Scott D. Patterson, Ph.D.
PRIME Trial
FOLFOX4 ± Panitumumab in 1\textsuperscript{st}-line Treatment of Metastatic CRC

Patient number: 1183

Pan Ras\* evaluated: 1060 90%

- 548 52% ras mutant
- 512 48% ras wild type

Pan Ras\*: K-ras exon 2, 3 ve 4 + N-ras exon 2, 3 ve 4
**PRIME study RAS analysis**

*RAS status – prevalence of RAS mutations among 1,060 evaluable patients*

**PRIME (KRAS exon 2)** (refinement of patient population by RAS mutation status)

- **MT KRAS** (exon 3, 4) \( n = 60/641 \) (9.4%)
- **MT NRAS** (exon 2, 3, 4) \( n = 48/641 \) (7.5%)

**MT KRAS exon 3 (codon 61) & exon 4 (codons 117/146); MT NRAS exon 2 (codons 12/13), exon 3 (codon 61) & exon 4 (codon 117/146)**

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PRIME RAS/RAF Analysis

RAS-RAF Mutation hot spots

**EXON 1**
- **RAS**
  - **KRAS**
  - **NRAS**

**EXON 2**
- 12 13
- Additional MT found in KRAS WT
- 3% (22/641)

**EXON 3**
- 61
- 4% (24/641)
- 8% (53/641)

**EXON 4**
- 117 146
- 6% (36/641)
- 3% (22/641)
- 0% (0/641)

**EXON 15**
- **RAF***
  - **BRAF**

- 600
- 8% (53/641)

PRIME *RAS/RAF* Analysis – Primary Analysis Set
PFS in Patients with WT *RAS* mCRC

**WT RAS**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFOX4 (n=259)</td>
<td>156 (60)</td>
</tr>
<tr>
<td>FOLFOX4 (n=253)</td>
<td>170 (67)</td>
</tr>
</tbody>
</table>

HR=0.72 (95% CI: 0.58–0.90)  
*p*=0.004

PRIME RAS/RAF Analysis – Primary Analysis Set
OS in Patients with WT RAS mCRC

WT RAS

Events
n (%) Median (95% CI) months

- Panitumumab + FOLFOX4 (n=259)
- FOLFOX4 (n=253)

HR=0.78 (95% CI: 0.62–0.99)

p=0.043

**PRIME RAS/RAF Biomarker Analysis**

Analysis of Genotype Subgroups – Prognostic impact of *BRAF* V600E mutations regardless of treatment arm

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>Favours WT</th>
<th>Favours MT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAS: FOLFOX4</td>
<td>310</td>
<td>0.92 (0.63–1.35)</td>
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<tr>
<td>RAS: Pmab + FOLFOX4</td>
<td>310</td>
<td>0.58 (0.39–0.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>BRAF</em> exon 15 (codon 600): FOLFOX4</td>
<td>309</td>
<td>0.45 (0.29–0.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>BRAF</em> exon 15 (codon 600): Pmab + FOLFOX4</td>
<td>310</td>
<td>0.38 (0.23–0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>KRAS</em> exon 3 (codon 61): FOLFOX4</td>
<td>320</td>
<td>1.15 (0.57–2.33)</td>
<td></td>
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<tr>
<td><em>KRAS</em> exon 3 (codon 61): Pmab + FOLFOX4</td>
<td>318</td>
<td>0.48 (0.24–0.99)</td>
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<tr>
<td><em>KRAS</em> exon 4 (codon 117/146): FOLFOX4</td>
<td>311</td>
<td>1.07 (0.52–2.16)</td>
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<tr>
<td><em>KRAS</em> exon 4 (codon 117/146): Pmab + FOLFOX4</td>
<td>309</td>
<td>0.73 (0.41–1.29)</td>
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<tr>
<td><em>KRAS</em> exon 3/4 combined: FOLFOX4</td>
<td>311</td>
<td>1.10 (0.66–1.84)</td>
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<tr>
<td><em>KRAS</em> exon 3/4 combined: Pmab + FOLFOX4</td>
<td>310</td>
<td>0.62 (0.39–0.98)</td>
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</tr>
<tr>
<td><em>NRAS</em> exon 2 (codon 12/13): FOLFOX4</td>
<td>321</td>
<td>1.12 (0.52–2.38)</td>
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<tr>
<td><em>NRAS</em> exon 2 (codon 12/13): Pmab + FOLFOX4</td>
<td>316</td>
<td>0.61 (0.27–1.37)</td>
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<td></td>
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<tr>
<td><em>NRAS</em> exon 3 (codon 61): FOLFOX4</td>
<td>319</td>
<td>0.57 (0.30–1.08)</td>
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<tr>
<td><em>NRAS</em> exon 3 (codon 61): Pmab + FOLFOX4</td>
<td>317</td>
<td>0.57 (0.28–1.16)</td>
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<tr>
<td><em>NRAS</em> exon 2/3/4 combined: FOLFOX4</td>
<td>312</td>
<td>0.77 (0.47–1.27)</td>
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<tr>
<td><em>NRAS</em> exon 2/3/4 combined: Pmab + FOLFOX4</td>
<td>315</td>
<td>0.57 (0.33–0.99)</td>
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</tr>
</tbody>
</table>

*BRAF* V600 mutations appeared to be prognostic conferring a poor prognosis regardless of treatment arm

**PEAK Trial**
mFOLFOX6 + Panitumumab or Bevacizumab in 1\textsuperscript{st}-line Treatment of WT KRAS exon 2 mCRC (Open Label, Phase 2)

- **Study endpoints:** PFS\textsuperscript{*} (1\textdegree); OS, ORR, resection rate, safety, exploratory biomarker analysis

\textsuperscript{*}PFS, progression-free survival; defined as time from date of randomisation to date of first radiographic disease (per modified RECIST v1.0), or death within 60 days after the last evaluable tumour assessment or randomisation (whichever is later). Patients not meeting the criteria by the cut-off date were censored at the last evaluable tumour assessment date; OS, overall survival; ORR, objective response rate; mFOLFOX6, modified FOLFOX6

PEAK Trial
Key Eligibility Criteria

- Metastatic adenocarcinoma of the colon or rectum
- WT KRAS exon 2 tumour status
- No prior chemotherapy, anti-VEGF therapy, or anti-EGFR therapy for mCRC
- Measurable disease
- ECOG performance status 0–1
- Adequate haematologic, renal and hepatic function
- Signed informed consent

ECOG, Eastern Cooperative Oncology Group
PEAK Trial Expanded RAS Analysis
Prevalence of Mutations in PEAK Tumour Samples within the WT KRAS Exon 2 Subset (80% Ascertainment*)

*Ascertainment defined as percentage of patients with a known codon sequence result at all listed positions above; N/A, not applicable

PEAK Trial Biomarker Analysis

PFS in Patients with WT KRAS exon 2 and WT RAS mCRC Treated with Panitumumab + mFOLFOX6

- **Original WT KRAS exon 2 (ITT set)**
  - Panitumumab + mFOLFOX6 (n=142): 90 (63) events, Median (95% CI) 10.9 (9.4–13.0) months
  - Bevacizumab + mFOLFOX6 (n=143): 94 (66) events, Median (95% CI) 10.1 (9.0–12.6) months

- **WT RAS (exons 2,3,4 of KRAS/NRAS)**
  - Panitumumab + mFOLFOX6 (n=88): 50 (57) events, Median (95% CI) 13.0 (10.9–15.1) months
  - Bevacizumab + mFOLFOX6 (n=82): 60 (73) events, Median (95% CI) 9.5 (9.0–12.7) months

- **HR** *=0.87 (95% CI: 0.65–1.17) **p**=0.35
- **HR** *=0.65 (95% CI: 0.44–0.96) **p**=0.03

*Data cutoff 30 May 2012; *Stratified Cox proportional hazards model

PEAK Trial Biomarker Analysis
OS in Patients with WT KRAS exon 2 and WT RAS mCRC Treated with Panitumumab + mFOLFOX6 with Longer Follow-Up Time#

WT KRAS exon 2 (ITT set)

WT KRAS exon 2 (ITT set) and WT RAS (exons 2,3,4 of KRAS/NRAS)

Panitumumab + mFOLFOX6 (n=142)

Bevacizumab + mFOLFOX6 (n=143)

Events n (%) Median (95% CI) Months

Panitumumab + mFOLFOX6 (n=88)

Bevacizumab + mFOLFOX6 (n=82)

Events n (%) Median (95% CI) months

HR* = 0.62 (95% CI: 0.44–0.89) p=0.009

HR* = 0.63 (95% CI: 0.39–1.02) p=0.058

#Data cutoff 3 Jan 2013; *Stratified Cox proportional hazards model; NR, not reached

The Marriage of Growth Factor Inhibitors and Chemotherapy: Bliss or Bust?

Stephen Staal, Division of Hematology Oncology, Department of Medicine, University of Florida, Gainesville, FL
Michael J. O’Connell, National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA
Carmen J. Allegra, Division of Hematology Oncology, Department of Medicine, University of Florida, Gainesville, FL
Phase III PACCE Trial:
First Line Bevacizumab + CT ± Panitumumab

MCRC

Oxaliplatin based CT n = 800

RANDOMISE

Panitumumab
Bevacizumab

Bevacizumab

Irinotecan based CT n = 200

Panitumumab
Bevacizumab

Bevacizumab

Hecht et al. World GI Barcelona 2007
## PFS & OS

<table>
<thead>
<tr>
<th></th>
<th>Ox-CT + BEV (n=410)</th>
<th>Ox-CT + BEV + Pmab (n=413)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (m)</td>
<td>11.1 ay</td>
<td>9.6 ay</td>
<td>1.27 (1.05-1.53)</td>
</tr>
<tr>
<td>OS (m)</td>
<td>&gt;24 ay</td>
<td>19.4 ay</td>
<td>1.43 (1.11-1.83)</td>
</tr>
<tr>
<td>ORR</td>
<td>46%</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Iri-CT + BEV (n=115)</th>
<th>Iri-CT + BEV + Pmab (n=115)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (m)</td>
<td>11.7</td>
<td>10.1</td>
<td>1.21 (0.80-1.82)</td>
</tr>
<tr>
<td>OS (m)</td>
<td>20.5</td>
<td>20.7</td>
<td>NR</td>
</tr>
<tr>
<td>ORR</td>
<td>39%</td>
<td>43%</td>
<td>1.15 (OR)</td>
</tr>
</tbody>
</table>

Hecht, ASCO GI 2008, abstracts 273 and 279
PACCE study

Adding panitumumab to oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab in 1st-line

- results in a decreased median PFS in patients with KRAS wildtype

- results in a decreased median OS in oxaliplatin-treated patients with KRAS wildtype

✔ Addition of panitumumab increased toxicity
✔ Cohort of irinotecan-treated patients was relatively small, with safety as primary endpoint
First-line panitumumab plus irinotecan/5-fluorouracil/leucovorin treatment in patients with metastatic colorectal cancer

Claus-Henning Köhne · Ralf Hofheinz · Laurent Mineur · Henry LeTOCHA · Richard Greil · Josef Thaler · Eva Fernebro · Erick Gamelin · Lucy DeCosta · Meinolf Karthaus

Received: 28 March 2011 / Accepted: 1 September 2011
Abstract

Purpose Panitumumab monotherapy is approved for KRAS wild-type (WT) metastatic colorectal cancer (mCRC) progressing after standard chemotherapy. This study evaluated first-line panitumumab plus FOLFIRI in patients with mCRC.

Methods In this phase II, single-arm study, panitumumab (6 mg/kg) and FOLFIRI [irinotecan (180 mg/m²) and leucovorin (400 mg/m²) followed by a 5-fluorouracil 400 mg/m² bolus and a 2,400–3,000 mg/m² continuous infusion] were administered every 14 days until progression. Data were analysed descriptively overall and by tumour KRAS status.

Results KRAS data were available for 145/154 (94%) patients: 59% KRAS WT and 41% mutant (MT); mean follow-up was 39.5 versus 35.8 weeks, respectively. Objective responses occurred in 49% of patients: 56% versus 38% in the KRAS WT versus MT groups [(18% difference (95% CI 1–35%); odds ratio 2.1 (95% CI 1.0–4.4)]; median duration of response was 13.0 versus 7.4 months. More patients in the WT group underwent R0 resection (8% vs. 5%); median progression-free survival also favoured this group (8.9 vs. 7.2 months). The most common adverse events (any grade) were integument toxicities (98%), diarrhoea (79%) and stomatitis/oral mucositis (51%).

Fig. 2 Progression-free survival
Panitumumab in 2\textsuperscript{nd}-line mCRC

The 20050181 study: Panitumumab + FOLFIRI treatment in WT $RAS$ mCRC
Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer

20050181 study

FOLFIRI ± panitumumab in 2nd-line treatment of metastatic CRC

Metastatic CRC \( (n = 1186) \)

1:1

FOLFIRI (Q2W) + panitumumab 6 mg/kg (Q2W)

Disease assessment every 8 weeks

End of treatment

Long term follow up

- Study endpoints: **PFS** and **OS** (1°), **ORR**, safety


ORR, objective response rate
20050181 study
Key eligibility criteria

- ≥18 years of age
- Adenocarcinoma of the colon / rectum
- Radiographically confirmed disease progression ≤6 months after prior 1st-line fluoropyrimidine-based chemotherapy
- No prior EGFR inhibitor therapy or irinotecan
- Measurable disease
- Paraffin-embedded tumour tissue from primary tumour or metastasis available for central biomarker testing
- ECOG performance status of 0, 1, or 2
### 20050181 study KRAS exon 2 analysis
#### Demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>WT KRAS (n = 597)</th>
<th>MT KRAS (n = 486)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Panitumumab + FOLFIRI (n = 303)</td>
<td>FOLFIRI (n = 294)</td>
</tr>
<tr>
<td><strong>Sex – men, n (%)</strong></td>
<td>188 (62)</td>
<td>191 (65)</td>
</tr>
<tr>
<td><strong>Age – years, median (min, max)</strong></td>
<td>60 (28, 84)</td>
<td>61 (29, 86)</td>
</tr>
<tr>
<td><strong>Race – white, n (%)</strong></td>
<td>294 (97)</td>
<td>278 (95)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>288 (95)</td>
<td>273 (93)</td>
</tr>
<tr>
<td>2</td>
<td>15 (5)</td>
<td>21* (7)</td>
</tr>
<tr>
<td><strong>Primary tumour type, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>187 (62)</td>
<td>189 (64)</td>
</tr>
<tr>
<td>Rectal</td>
<td>116 (38)</td>
<td>105 (36)</td>
</tr>
<tr>
<td><strong>Sites of metastatic disease, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>51 (17)</td>
<td>59 (20)</td>
</tr>
<tr>
<td>Liver + other</td>
<td>205 (68)</td>
<td>189 (64)</td>
</tr>
<tr>
<td>Other only</td>
<td>47 (16)</td>
<td>44 (15)</td>
</tr>
<tr>
<td>Missing or unknown</td>
<td>0 (0)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td><strong>Prior oxaliplatin therapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior oxaliplatin therapy, n (%)</td>
<td>204 (67)</td>
<td>191 (65)</td>
</tr>
<tr>
<td><strong>Prior bevacizumab therapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior bevacizumab therapy, n (%)</td>
<td>55 (18)</td>
<td>60 (20)</td>
</tr>
</tbody>
</table>


*Included 1 patient with ECOG 3
### 20050181 study *KRAS* exon 2 analysis

**Efficacy in patients with WT *KRAS* tumours**

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + FOLFIRI (n = 303)</th>
<th>FOLFIRI (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months</strong></td>
<td>5.9</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Hazard ratio (P-value)</strong></td>
<td>0.73 (P = 0.004)</td>
<td></td>
</tr>
<tr>
<td><strong>Median OS, months</strong></td>
<td>14.5</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Hazard ratio (P-value)</strong></td>
<td>0.85 (P = 0.12)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR, n (%) (95% CI)</strong></td>
<td>(35) (30–41) (n = 297)</td>
<td>(10) (7–14) (n = 285)</td>
</tr>
</tbody>
</table>

By central review; *P < 0.001 (descriptive); exact test of odds ratio stratified by randomisation factors*

20050181 study RAS analysis
Mutation hotspots

**KRAS**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Position</th>
<th>Mutation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2#</td>
<td>12, 13</td>
<td>44.9%</td>
</tr>
<tr>
<td>3</td>
<td>59, 61</td>
<td>4.4%</td>
</tr>
<tr>
<td>4</td>
<td>117, 146</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

**NRAS**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Position</th>
<th>Mutation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12, 13</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>59, 61</td>
<td>5.6%</td>
</tr>
<tr>
<td>4</td>
<td>117, 146</td>
<td>0%</td>
</tr>
</tbody>
</table>

Overall RAS ascertainment rate: 85%

18% (107/597) of WT KRAS exon 2 tumours have RAS mutations

Prevalence is defined as mutations detected in a population of WT KRAS exon 2 patients whose tissues were deemed evaluable for RAS testing; #The KRAS exon 2 data is from the overall population; WT RAS, KRAS & NRAS exons 2/3/4


RAS ascertainment rate: 85%; WT RAS, WT KRAS & NRAS exons 2/3/4
20050181 study RAS analysis
OS (primary analysis)

**WT RAS**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (95% CI) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + FOLFIRI (n = 204)</td>
<td>127 (62)</td>
</tr>
<tr>
<td>FOLFIRI (n = 211)</td>
<td>141 (67)</td>
</tr>
</tbody>
</table>

HR = 0.803 (95% CI, 0.629–1.024)
Log-rank p-value = 0.08


RAS ascertainment rate: 85%; WT RAS, WT KRAS & NRAS exons 2/3/4
### 20050181 study RAS analysis

#### Refinement of patient population by WT RAS status (primary analysis)

<table>
<thead>
<tr>
<th></th>
<th>WT KRAS exon 2(^1)</th>
<th>WT RAS(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Panitumumab + FOLFIRI (n = 303)</td>
<td>FOLFIRI (n = 294)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Hazard ratio (P-value)</td>
<td>0.73 (P = 0.004)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>14.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Hazard ratio (P-value)</td>
<td>0.85 (P = 0.12)</td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>35 (30–41) (n = 297)</td>
<td>10 (7–14) (n = 285)</td>
</tr>
</tbody>
</table>

## 20050181 study RAS analysis

### Refinement of patient population by MT RAS status (primary analysis)

<table>
<thead>
<tr>
<th></th>
<th>MT KRAS exon 2&lt;sup&gt;1&lt;/sup&gt;</th>
<th>MT RAS&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Panitumumab + FOLFIRI (n = 238)</td>
<td>FOLFIRI (n = 248)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>Hazard ratio (P-value)</td>
<td>0.85 (P = 0.14)</td>
<td></td>
</tr>
<tr>
<td>Median OS, months</td>
<td>11.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Hazard ratio (P-value)</td>
<td>0.94 (P = *ND)</td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>13 (9–18) (n = 232)</td>
<td>14 (10–19) (n = 237)</td>
</tr>
</tbody>
</table>


*ND, not done; WT RAS, WT KRAS & NRAS exons 2/3/4
20050181 study RAS analysis

Conclusions

- 18% WT KRAS exon 2 patients harboured additional RAS mutations
- Improvements were seen in the treatment effect by PFS and OS in WT RAS patients compared to WT KRAS exon 2 patients
- MT RAS patients are unlikely to benefit by the addition of panitumumab to FOLFIRI
- Adverse events similar to those reported in the panitumumab + FOLFIRI arm of WT KRAS exon 2 patients
  - No new safety signals were identified
- These results support RAS testing to determine potentially appropriate mCRC patients for panitumumab treatment
Panitumumab in 3rd-line mCRC

Randomised Phase 3 Study of Panitumumab with Best Supportive Care vs. Best Supportive Care Alone as 3rd-line Treatment in Patients with Metastatic Colorectal Cancer: the 20020408 Trial RAS Analysis
Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer

Eric Van Cutsem, Marc Peeters, Salvatore Siena, Yves Humblet, Alain Hendlitz, Bart Neyns, Jean-Luc Canon, Jean-Luc Van Laethem, Joan Maurel, Gary Richardson, Michael Wolf, and Rafael G. Amado
Panitumumab in mCRC Patients who have Failed Chemotherapy – Schema for Pivotal Phase 3 (20020408) and Optional Crossover Study (20030194)

231 patients
- 147 with multi-marker info
- 82 KRAS WT mCRC

Best Supportive Care (BSC) (n=232)
- 232 patients
- 141 with multi-marker info
- 71 KRAS WT mCRC

Panitumumab 6.0 mg/kg Q2W + BSC (n=231)

Optional Panitumumab Crossover Study (20030194; n=176)
- 176 patients
- 110 with multi-marker info
- 56 KRAS WT mCRC

- 76% of BSC alone patients entered crossover study

Study endpoints:
- PFS (1°)
- ORR (per mRECIST version 1.0)
- OS

Randomisation stratification:
- ECOG score: 0-1 vs. 2
- Geographic region

- 20020408 compared efficacy and safety of pmab + BSC vs. BSC in previously treated KRAS exon 2 mCRC patients
- Local and central reviews were conducted for all assessments
- Archival CRC samples were analyzed for KRAS mutations (codons 12-13) using allele-specific PCR (DxS/Qiagen)

Fig 1. Consolidated Standards of Reporting Trials diagram. BSC, best supportive care.
Fig 2. Progression-free survival (all randomly assigned analysis set). BSC, best supportive care.
### Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>WT KRAS exon 2</th>
<th>MT KRAS exon 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Panitumumab + BSC (n = 124)</td>
<td>BSC (n = 119)</td>
</tr>
<tr>
<td>Sex – male, %</td>
<td>83 (67)</td>
<td>76 (64)</td>
</tr>
<tr>
<td>Age – years, median (min, max)</td>
<td>62.5 (29–82)</td>
<td>63.0 (32–81)</td>
</tr>
<tr>
<td>Race – white, %</td>
<td>122 (98)</td>
<td>118 (99)</td>
</tr>
<tr>
<td>ECOG performance status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>53 (43)</td>
<td>40 (34)</td>
</tr>
<tr>
<td>≥2*</td>
<td>56 (45)</td>
<td>62 (52)</td>
</tr>
<tr>
<td></td>
<td>15 (12)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Primary tumour site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>86 (69)</td>
<td>82 (69)</td>
</tr>
<tr>
<td>Rectum</td>
<td>38 (31)</td>
<td>37 (31)</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy – yes, n (%)</td>
<td>50 (40)</td>
<td>32 (27)</td>
</tr>
<tr>
<td>Prior lines of chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>79 (64)</td>
<td>63 (53)</td>
</tr>
<tr>
<td>3</td>
<td>41 (33)</td>
<td>49 (41)</td>
</tr>
</tbody>
</table>

*Of patients treated with BSC, one patient with WT KRAS status and one patient with MT KRAS status had an ECOG PS of 3.
# 20020408 study KRAS exon 2 analysis

Summary of efficacy data

## WT KRAS exon 2

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + BSC (n = 124)</th>
<th>BSC (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n</td>
<td>115</td>
<td>114</td>
</tr>
<tr>
<td>Median OS, weeks</td>
<td>8.1</td>
<td>7.6</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.99 (0.75–1.29)</td>
<td></td>
</tr>
<tr>
<td>Median PFS, weeks</td>
<td>12.3 (8.3–16.1)</td>
<td>7.3 (7.0–7.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.45 (0.34–0.59)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>16.9 (10.8–24.7)</td>
<td>0 (0.0–0.31)</td>
</tr>
</tbody>
</table>

Patterson SD, et al. J Clin Oncol 2013; 31 (suppl):abstract 3617 (and poster);
## 20020408 study KRAS exon 2 analysis
### Summary of efficacy data

### MT KRAS exon 2

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + BSC (n = 84)</th>
<th>BSC (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n</td>
<td>79</td>
<td>95</td>
</tr>
<tr>
<td>Median OS, weeks</td>
<td>4.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td>1.02 (0.75–1.39)</td>
</tr>
<tr>
<td>Median PFS, weeks</td>
<td>7.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td></td>
<td>0.99 (0.73–1.36)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**20020408 study RAS analysis**

**KRAS and NRAS mutation hotspots in the 20020408 study**

---

**KRAS**

- **EXON 2***: 12% (5% in WT KRAS exon 2 subset)
- **EXON 3**: 5%
- **EXON 4**: 5%

- **EXON 2**: 43%

**NRAS**

- **EXON 2**: 12% (3% in WT NRAS exon 2 subset)
- **EXON 3**: 61%
- **EXON 4**: 117%

- **EXON 1**: 4%

---

Percentages have been rounded; *KRAS exon 2 data from overall population; remaining data within WT KRAS exon 2 subset and based on samples that yielded a result.

# 20020408 study RAS analysis

## PFS (quantitative interaction test for treatment and KRAS status)

<table>
<thead>
<tr>
<th>WT RAS, n</th>
<th>136</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n</td>
<td>131</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.36 (0.25–0.52)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WT KRAS exon 2 / MT other RAS, n</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PFS events</td>
<td>27</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.71 (0.31–1.65)</td>
</tr>
<tr>
<td>P-value for Quantitative Interaction Test</td>
<td>0.080</td>
</tr>
</tbody>
</table>

WT KRAS exon 2

- HR = 0.45 (95% CI, 0.34–0.59)
- P < 0.001

WT RAS

- HR = 0.36 (95% CI, 0.25–0.52)
- P < 0.001

**Events**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (%)</th>
<th>Median, weeks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab + BSC</td>
<td>115 (93)</td>
<td>12.3 (8.3–16.1)</td>
</tr>
<tr>
<td>BSC</td>
<td>114 (96)</td>
<td>7.3 (7.0–7.7)</td>
</tr>
<tr>
<td>Panitumumab + BSC</td>
<td>70 (96)</td>
<td>14.1 (10.3–23.3)</td>
</tr>
<tr>
<td>BSC</td>
<td>61 (97)</td>
<td>7.0 (6.0–7.4)</td>
</tr>
</tbody>
</table>

Patterson SD, et al. J Clin Oncol 2013; 31 (suppl):abstract 3617 (and poster);
Panitumumab in 3rd-line mCRC

The ASPECCT study: Panitumumab or cetuximab treatment in WT KRAS exon 2 mCRC (open-label, phase 3 study)
ASPECT study

Panitumumab vs. cetuximab in 3rd-line treatment of WT KRAS exon 2 mCRC (open-label, phase 3)

- Study endpoints: OS (1°); PFS, ORR, safety
- Crossover between arms during study treatment was not allowed

Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation); Protocol ID: 20080763; ClinicalTrials.gov identifier: NCT01001377.
ASPECTT study
Key eligibility criteria

• ≥18 years
• Metastatic adenocarcinoma of the colon or rectum
• WT KRAS exon 2 tumour status
• No prior anti-EGFR therapy
• Disease progression or intolerability on irinotecan-, oxaliplatin- and fluorouracil-based therapy for mCRC
• Measurable or non-measurable disease
• Adequate hematologic, renal, hepatic, metabolic function
• No symptomatic brain metastases
• Signed informed consent

Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation);
Protocol ID: 20080763; ClinicalTrials.gov identifier: NCT01001377.
ASPECTT study
Statistical considerations I

• Non-inferiority design
  – Compare the effect of panitumumab vs. cetuximab on OS

• Treatment effect of cetuximab compared to BSC was derived from the CO.17 trial¹
  – 9.5 vs. 4.8 months, HR = 0.55

• Retention rate
  – What fraction of the treatment effect of cetuximab over BSC is preserved by panitumumab (point estimate and CI)?

Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation);

CI, confidence interval
ASPECCT study
OS (primary analysis)

HR = 0.97 (95% CI, 0.84–1.11)
P = 0.0007
Z-score = -3.19
Retention score = 1.06 (95% CI, 0.82–1.29)

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab (n = 499)</th>
<th>Cetuximab (n = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events n (%)</td>
<td>383 (76.8)</td>
<td>392 (78.4)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>10.4 (9.4–11.6)</td>
<td>10.0 (9.3–11.0)</td>
</tr>
</tbody>
</table>

**ASPECTCT study**

**Objective response rates (primary analysis)**

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab (n = 486)</th>
<th>Cetuximab (n = 485)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best tumour response over the study, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response</td>
<td>105 (21.6)</td>
<td>96 (19.8)</td>
</tr>
<tr>
<td>Stable disease or non-CR / non-PD</td>
<td>226 (46.5)</td>
<td>236 (48.7)</td>
</tr>
<tr>
<td><em><em>Patients with objective response</em>, n (%)</em>*</td>
<td>107 (22.0)</td>
<td>96 (19.8)</td>
</tr>
<tr>
<td>Rate (95% CI), %</td>
<td>22.02</td>
<td>19.79</td>
</tr>
<tr>
<td></td>
<td>(18.41–25.97)</td>
<td>(16.34–23.62)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>1.15</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>(0.83–1.58)</td>
<td></td>
</tr>
</tbody>
</table>

*CR, complete response; PD, progressive disease*
## ASPECT study

### Incidence of ≥ grade 3 AEs of interest (primary analysis)

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>Panitumumab (n = 496)</th>
<th>Cetuximab (n = 503)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>20 (4.0)</td>
<td>34 (6.8)</td>
</tr>
<tr>
<td>Others</td>
<td>9 (1.8)</td>
<td>16 (3.2)</td>
</tr>
<tr>
<td><strong>Treatment-related fatal AEs</strong></td>
<td>0 (0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>430 (86.7)</td>
<td>440 (87.5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>60 (12.1)</td>
<td>48 (9.5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serious</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Hypomagnesaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>143 (28.8)</td>
<td>95 (18.9)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>27 (5.4)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>9 (1.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td><strong>Infusion reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>14 (2.8)</td>
<td>63 (12.5)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (0.2)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0 (0)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>91 (18.3)</td>
<td>89 (17.7)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7 (1.4)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (0.6)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

## NCCN Guidelines Version 3.2014
Colon Cancer

### CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 9)

<table>
<thead>
<tr>
<th>Patient appropriate for intensive therapy²</th>
<th>Initial Therapy</th>
<th>Therapy After First Progression</th>
<th>Therapy After Second Progression</th>
<th>Therapy After Third Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX³ ± bevacizumab or CapeOX⁴ ± bevacizumab⁵,⁶</td>
<td>FOLFIR⁵,¹⁰ ± bevacizumab or FOLFIRI ± ziv-aflibercept¹¹ or Irinotecan¹⁰ ± bevacizumab or Irinotecan¹⁰ ± ziv-aflibercept¹¹ or FOLFIRI + (cetuximab or panitumumab)⁶,¹²-¹⁵ (KRAS/NRAS WT gene only)⁸ or (Cetuximab or panitumumab)⁶,¹²-¹⁵ (KRAS/NRAS WT gene only)⁸</td>
<td>(Cetuximab or panitumumab)⁶,¹²-¹⁵ (KRAS/NRAS WT gene only)⁸ + irinotecan;¹⁰ for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)⁶,¹²-¹⁵ (KRAS/NRAS WT gene only)⁸ or Regorafenib¹⁶</td>
<td>Regorafenib (if not given previously) or Clinical trial or Best supportive care¹⁷</td>
</tr>
<tr>
<td></td>
<td>or FOLFOX³ ± panitumumab⁶,⁷ (KRAS/NRAS WT gene only)⁸,⁹</td>
<td></td>
<td>Regorafenib or Clinical trial or Best supportive care¹⁷</td>
<td></td>
</tr>
</tbody>
</table>
### CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:

<table>
<thead>
<tr>
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<th>Therapy After First Progression</th>
<th>Therapy After Second Progression</th>
<th>Therapy After Third Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI&lt;sup&gt;10&lt;/sup&gt; ± bevacizumab&lt;sup&gt;5,6&lt;/sup&gt; or FOLFIRI&lt;sup&gt;10&lt;/sup&gt; ± cetuximab or panitumumab&lt;sup&gt;6,7&lt;/sup&gt; (KRAS/NRAS WT gene only)&lt;sup&gt;8,9&lt;/sup&gt;</td>
<td>FOLFOX&lt;sup&gt;3,5&lt;/sup&gt; ± bevacizumab or CapeOX&lt;sup&gt;4,5&lt;/sup&gt; ± bevacizumab</td>
<td>(Cetuximab or panitumumab)&lt;sup&gt;6,12-15&lt;/sup&gt; (KRAS/NRAS WT gene only)&lt;sup&gt;8&lt;/sup&gt; + irinotecan;&lt;sup&gt;10&lt;/sup&gt; for patients not able to tolerate combination, consider single agent (cetuximab or panitumumab)&lt;sup&gt;6,12-15&lt;/sup&gt; (KRAS/NRAS WT gene only)&lt;sup&gt;8&lt;/sup&gt; or Regorafenib&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Regorafenib (if not given previously) or Clinical trial or Best supportive care&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- Patient appropriate for intensive therapy<sup>2</sup>
Terapötik endikasyon (Türkiye)

• VECTİBİX,
  – daha önce panitumumab veya diğer anti-EGFR tedavileri kullanmamış,
  – ECOG performans skoru: 0-1 olan, KRAS wild tip metastatik kolorektal kanserde
  – birinci veya ikinci seri tedavide,
  – FOLFOX veya FOLFİRİ kombinasyon kemoterapi rejimlerinin sadece birisi ile
  – progresyona kadar kullanımında endikedir.
  – Progresyon durumunda veya beraberindeki kemoterapi rejiminin değiştirilmesi durumunda panitumumab veya başka bir anti-EGFR tedavisi kullanılamaz.

• Önerilen panitumumab dozu iki haftada bir verilmek üzere 6 mg/kg vücut ağırlığı şeklindedir.
I tell young people: Do not think of yourself, think of others. Think of the future that awaits you, think about what you can do and do not fear anything.

Rita Levi-Montalcini
April 23, 1909 - December 30, 2017