

Answer 1:

### Bibliographic Information

**Fluorescently labeled cetuximab to evaluate head and neck cancer response to treatment.** Gleysteen, John P.; Duncan, Ryan D.; Magnuson, J. Scott; Skipper, Joni B.; Zinn, Kurt; Rosenthal, Eben L. Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, University of Alabama at Birmingham, Birmingham, AL, USA. *Cancer Biology & Therapy* (2007), 6(8), 1181-1185. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 148:417398 AN 2008:48210 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Objective:** Combining the therapeutic and diagnostic properties of targeted antibodies may improve clin. assessment of disease with limited added toxicity during treatment. **Methods:** Mice (n = 10) were xenografted with SCC-1 tumor cells and then treated with radiation, cisplatin and cetuximab. Brightfield and fluorescent imaging was performed after systemically injecting fluorescently labeled cetuximab prior to treatment and at six or ten weeks after initiation of treatment. The relative fluorescence intensity was detd. for each image. **Results:** The tumor luminosity measured before (week 0), during (week 6) and after treatment (week 10) did not significantly change. Actual tumor measurement corresponded to fluorescent measurements of tumors both before treatment and after treatment. Complete response to therapy occurred in one animal, where resoln. of the tumor correlated with loss of fluorescent activity. **Conclusions:** This preclin. data suggests combining the diagnostic and therapeutic properties of cetuximab may be clin. useful.

Answer 2:

### Bibliographic Information

**Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer.** Tabertero, Josep; Van Cutsem, Eric; Diaz-Rubio, Eduardo; Cervantes, Andres; Humblet, Yves; Andre, Thierry; Van Laethem, Jean-Luc; Soulie, Patrick; Casado, Esther; Verslype, Chris; Valera, Javier Sastre; Tortora, Giampaolo; Ciardiello, Fortunato; Kisker, Oliver; de Gramont, Aimery. Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain. *Journal of Clinical Oncology* (2007), 25(33), 5225-5232. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal written in English. CAN 148:253533 AN 2007:1464324 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Purpose:** This phase II study investigated the efficacy and safety of cetuximab combined with std. oxaliplatin-based chemotherapy (infusional fluorouracil, leucovorin, and oxaliplatin [FOLFOX-4]) in the first-line treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer (mCRC). **Patients and Methods:** The activity of cetuximab plus oxaliplatin was investigated in colon cancer cell lines and xenograft models. In the clin. study, patients with mCRC received on day 1 of a 14 day cycle, cetuximab (initial dose 400 mg/m<sup>2</sup> during week 1, then 250 mg/m<sup>2</sup> weekly) followed by FOLFOX-4 (oxaliplatin 85 mg/m<sup>2</sup> on day 1; leucovorin 200 mg/m<sup>2</sup> on days 1 and 2, followed by fluorouracil 400 mg/m<sup>2</sup> bolus then 600 mg/m<sup>2</sup> i.v. infusion during 22 h on days 1 and 2). **Results:** The preclin. studies confirmed the supra-additive activity of cetuximab to oxaliplatin. In the clin. study, 43 patients were included, with a median age of 65 years (range, 43 to 78 years). Response rates (RRs) were 79% (unconfirmed) and 72% (confirmed), with 95% disease control. Median progression-free survival (mPFS) and median duration of response were 12.3 and 10.8 mo, resp. Ten patients (23%) underwent resection with curative intent of previously unresectable metastases. After a median follow-up of 30.5 mo, median overall survival (mOS) was 30.0 mo. Cetuximab did not increase the characteristic toxicity of FOLFOX-4 and was generally well tolerated. **Conclusion:** Cetuximab in combination with FOLFOX-4 is a highly active first-line treatment for mCRC, showing encouraging RR, mPFS, and mOS values. The treatment resulted in a high resectability rate, which could potentially result in an improved cure rate. This combination is under phase III development.

Answer 3:

**Bibliographic Information**

**Supra-additive antitumor effect of sunitinib malate (SU11248, Sutent) combined with docetaxel. A new therapeutic perspective in hormone refractory prostate cancer.** Guerin, O.; Formento, P.; Lo Nigro, C.; Hofman, P.; Fischel, J. L.; Etienne-Grimaldi, M. C.; Merlano, M.; Ferrero, J. M.; Milano, G. Nice General Hospital, Nice, Fr. *Journal of Cancer Research and Clinical Oncology* (2008), 134(1), 51-57. Publisher: Springer, CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 148:440375 AN 2007:1268849 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Purpose: Physiol. and mol. findings indicate over-expression of HER proteins and dysregulation of neo-angiogenesis during progression of advanced prostate cancer. The aim of this study was to test a novel rational therapeutic approach by combining docetaxel with an EGFR-targeting agent (cetuximab) and with an anti-angiogenic agent (sunitinib, SUTENT). Methods: Mice bearing well-established PC3 prostate tumors (mean tumor vol./treatment group .apprx.250 mm<sup>3</sup>) were treated every week with vehicle alone (controls), sunitinib (40 mg/kg/day, 5 days/wk for 3 wk, 0.2 mL p.o.), cetuximab (0.2 mg/kg/day, 5 days/wk for 3 wk, 0.2 mL i.p.) and docetaxel (10 mg/kg, 1 day/wk for 3 wk, 0.2 mL i.p.). Results: Each drug, administered as a single-agent, demonstrated comparable and moderate effects on tumor growth with approx. 50 % inhibition at the end of the 3-wk dosing schedule. Computed combination ratio (CR) values for tumor growth detd. on days 61, 68 and 75 after cell implantation indicated supra-additive effects for the sunitinib-docetaxel (1.53, 1.15 and 1.47, resp.) and sunitinib-cetuximab combinations (1.2, 1.32 and 1.14, resp.), and suggested additive effects only for the sunitinib-cetuximab-docetaxel combination (CR = 1). The effects on tumor growth were accompanied by a parallel diminution in tumor cell proliferation (Ki 67) and tumor vascularization (von Willebrandt factor). There were significantly higher pro-apoptotic effects (caspase-3 cleavage) obsd. for the sunitinib-docetaxel and sunitinib-docetaxel-cetuximab as compared to the other conditions. Conclusion: The supra-additive anti-tumor effect obsd. with the sunitinib-docetaxel combination might support innovative strategies in the management of advanced prostate cancer.

Answer 4:

**Bibliographic Information**

**The Activation of Natural Killer Cell Effector Functions by Cetuximab-Coated, Epidermal Growth Factor Receptor-Positive Tumor Cells is Enhanced By Cytokines.** Roda, Julie M.; Joshi, Trupti; Butchar, Jonathan P.; McAlees, Jaclyn W.; Lehman, Amy; Tridandapani, Susheela; Carson, William E., III. Integrated Biomedical Sciences Graduate Program, Arthur G. James Comprehensive Cancer Center and Solove Research Institute, Ohio State University, Columbus, OH, USA. *Clinical Cancer Research* (2007), 13(21), 6419-6428. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:424600 AN 2007:1243724 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Purpose: Natural killer (NK) cells express an activating Fc receptor (FcγRIIIa) that mediates antibody-dependent cellular cytotoxicity (ADCC) and prodn. of immune modulatory cytokines in response to antibody-coated targets. Cetuximab is a therapeutic monoclonal antibody directed against the HER1 antigen. We hypothesized that the NK cell response to cetuximab-coated tumor cells could be enhanced by the administration of NK cell-stimulatory cytokines. Exptl. Design: Human NK cells stimulated with cetuximab-coated tumor cells and interleukin-2 (IL-2), IL-12, or IL-21 were assessed for ADCC and secretion of IFN-γ and T cell-recruiting chemokines. IL-21 and cetuximab were given to nude mice bearing HER1-pos. xenografts. Results: Stimulation of human NK cells with cetuximab-coated tumor cells and IL-2, IL-12, or IL-21 resulted in 3-fold to 10-fold higher IFN-γ prodn. than was obsd. with either agent alone. NK cell-derived IFN-γ significantly enhanced monocyte ADCC against cetuximab-coated tumor cells. Costimulated NK cells also secreted elevated levels of chemokines (IL-8, macrophage inflammatory protein-1α, and RANTES) that could direct the migration of naive and activated T cells. IL-2, IL-12, and IL-21 enhanced NK cell ADCC against tumor cells treated with cetuximab. The combination of cetuximab, trastuzumab (an anti-HER2 monoclonal antibody), and IL-21 mediated greater NK cell cytokine secretion and ADCC than any agent alone. Furthermore, administration of IL-21 enhanced the effects of cetuximab in a murine tumor model. Conclusions: These results show that cetuximab-mediated NK cell activity can be significantly enhanced in the presence of NK cell-stimulatory cytokines. These factors, therefore, may be effective adjuvants to administer, in combination with cetuximab, to

patients with HER1-pos. malignancies.

Answer 5:

### Bibliographic Information

**Insulin-like Growth Factor Receptor as a Therapeutic Target in Head and Neck Cancer.** Barnes, Christopher J.; Ohshiro, Kazufumi; Rayala, Suresh K.; El-Naggar, Adel K.; Kumar, Rakesh. Departments of Molecular and Cellular Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2007), 13(14), 4291-4299. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:439642 AN 2007:784248 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**PURPOSE:** Insulin-like growth factor type I receptor (IGF-IR) plays crit. roles in epithelial cancer cell development, proliferation, motility, and survival, and new therapeutic agents targeting IGF-IR are in development. Another receptor tyrosine kinase, the epidermal growth factor receptor (EGFR), is an established therapeutic target in head and neck cancer and IGF-IR/EGFR heterodimerization has been reported in other epithelial cancers. The present study was undertaken to det. the effects of anti-IGF-IR therapeutic targeting on cell signaling and cancer cell phenotypes in squamous cell carcinomas of the head and neck (SCCHN). **Exptl. Design:** The therapeutic efficacy of the human anti-IGF-IR antibody IMC-A12 alone and in combination with the EGFR blocking antibody cetuximab (C225) was tested in SCCHN cell lines and in tumor xenografts. **RESULTS:** IGF-IR was overexpressed in human head and neck cancer cell lines and tumors. Pretreatment of serum-starved 183A or TU159 SCCHN cell lines with A12 (10 µg/mL) blocked IGF-stimulated activation of IGF-IR, insulin receptor substrate (IRS)-1 and IRS-2, mitogen-activated protein kinase, and phosphatidylinositol 3-kinase. A12 induced G0-G1 cell cycle arrest and blocked cell growth, motility, and anchorage-independent growth. Stimulation of head and neck cancer cells with either IGF or EGF resulted in IGF-IR and EGFR heterodimerization, but only IGF caused activating phosphorylation of both receptors. Combined treatment with A12 and the EGFR blocking antibody C225 was more effective at reducing cell proliferation and migration than either agent alone. Finally, TU159 tongue cancer cell xenografts grown in athymic nude mice were treated thrice weekly for 4 wk with vehicle, A12 (40 mg/kg i.p.), C225 (40 mg/kg i.p.), or both agents (n = 8 mice per group; 2 tumors per mouse). Linear regression slope anal. showed significant differences in median tumor vol. over time between all three treatment groups and the control group.

Complete regression was seen in 31% (A12), 31% (C225), and 44% (A12 + C225) of tumors. **CONCLUSION:** Here we found the overexpression of IGF-IR, the functional heterodimerization of IGF-IR and EGFR, and effective therapeutic targeting of these receptors in human head and neck cancer xenografts.

Answer 6:

### Bibliographic Information

**Quantitative PET of EGFR expression in xenograft-bearing mice using 64Cu-labeled cetuximab, a chimeric anti-EGFR monoclonal antibody.** Cai, Weibo; Chen, Kai; He, Lina; Cao, Qizhen; Koong, Albert; Chen, Xiaoyuan. Molecular Imaging Program at Stanford (MIPS), Department of Radiology and Bio-X Program, Stanford University School of Medicine, Stanford, CA, USA. *European Journal of Nuclear Medicine and Molecular Imaging* (2007), 34(6), 850-858. Publisher: Springer, CODEN: EJNMA6 ISSN: 1619-7070. Journal written in English. CAN 147:268586 AN 2007:539264 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Purpose:** Cetuximab, a chimeric monoclonal antibody targeting epidermal growth factor receptor (EGFR) on the surface of cancer cells, was approved by the FDA to treat patients with metastatic colorectal cancer. It is currently also in advanced-stage development for the treatment of several other solid tumors. Here we report for the first time the quant. positron emission tomog. (PET) imaging of EGFR expression in xenograft-bearing mice using 64Cu-labeled cetuximab. **Methods:** We conjugated cetuximab with macrocyclic chelating agent 1,4,7,10-tetraazadodecane-N,N',N'',N'''-tetraacetic acid (DOTA), labeled with 64Cu, and tested the resulting

<sup>64</sup>Cu-DOTA-cetuximab in seven xenograft tumor models. The tracer uptake measured by PET was correlated with the EGFR expression quantified by western blotting. The estd. human dosimetry based on the PET data in Sprague-Dawley rats was also calcd. Results: MicroPET imaging showed that <sup>64</sup>Cu-DOTA-cetuximab had increasing tumor activity accumulation over time in EGFR-pos. tumors but relatively low uptake in EGFR-neg. tumors at all times examd. (<5%ID/g). There was a good correlation ( $R^2 = 0.80$ ) between the tracer uptake (measured by PET) and the EGFR expression level (measured by western blotting). Human dosimetry estn. indicated that the tracer may be safely administered to human patients for tumor diagnosis, with the dose-limiting organ being the liver. Conclusion: The success of EGFR-pos. tumor imaging using <sup>64</sup>Cu-DOTA-cetuximab can be translated into the clinic to characterize the pharmacokinetics, to select the right population of patients for EGFR-targeted therapy, to monitor the therapeutic efficacy of anti-EGFR treatment, and to optimize the dosage of either cetuximab alone or cetuximab in combination with other therapeutic agents.

Answer 7:

### Bibliographic Information

**Effect of Epidermal Growth Factor Receptor Inhibitor Class in the Treatment of Head and Neck Cancer with Concurrent Radiochemotherapy In vivo.** Feng, Felix Y.; Lopez, Carlos A.; Normolle, Daniel P.; Varambally, Sooryanarayana; Li, Xiaoxin; Chun, Patrick Y.; Davis, Mary A.; Lawrence, Theodore S.; Nyati, Mukesh K. Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor, MI, USA. *Clinical Cancer Research* (2007), 13(8), 2512-2518. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:180771 AN 2007:423505 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Purpose: To optimally integrate epidermal growth factor receptor (EGFR) inhibitors into the clin. treatment of head and neck cancer, two important questions must be answered: (a) does EGFR inhibition add to the effects of radiochemotherapy, and (b) if so, which method of inhibiting EGFR is superior (an EGFR antibody vs. a small mol. tyrosine kinase inhibitor) We designed an in vivo study to address these questions. Exptl. Design: Nude mice with UMSCC-1 head and neck cancer xenografts received either single, double, or triple agent therapy with an EGFR inhibitor (either cetuximab or gefitinib), gemcitabine, and/or radiation for 3 wk. Tumor vols. and animal wts. were measured for up to 15 wk. Immunoblotting and immunofluorescent staining were done on tumors treated with either cetuximab or gefitinib alone. Results: The addn. of an EGFR inhibitor significantly delayed the tumor vol. doubling time, from a median of 40 days with radiochemotherapy (gemcitabine and radiation) alone, to 106 days with cetuximab and 66 days with gefitinib (both  $P < 0.005$ ). Cetuximab resulted in significantly less wt. loss than gefitinib. Immunoblot anal. and immunofluorescent staining of tumors show that although levels of phosphorylated AKT and extracellular signal-regulated kinase were decreased similarly in response to cetuximab or gefitinib, cetuximab caused prolonged suppression of pEGFR, pSTAT3, and BclXL compared with gefitinib. Conclusions: EGFR inhibition, particularly with cetuximab, improves the effectiveness of radiochemotherapy in this model of head and neck cancer. The correlation of response with prolonged suppression of EGFR, STAT3, and BclXL offers the possibility that these may be candidate biomarkers for response.

Answer 8:

### Bibliographic Information

**Use of fluorescent labeled anti-epidermal growth factor receptor antibody to image head and neck squamous cell carcinoma xenografts.** Rosenthal, Eben L.; Kulbersh, Brian D.; King, Teresa; Chaudhuri, Tandra R.; Zinn, Kurt R. Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA. *Molecular Cancer Therapeutics* (2007), 6(4), 1230-1238. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:26061 AN 2007:412501 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Physicians and surgeons rely on subtle tissue changes to detect the extent of tumors and the presence of residual disease in the clin.

setting. The development of a cancer-specific fluorescent contrast agent has the potential to provide real-time tumor imaging in the clinic or operating room. Because epidermal growth factor receptor (EGFR) is highly overexpressed on the surface of head and neck squamous cell carcinoma (HNSCC), we sought to det. if fluorescently labeled anti-EGFR antibody could be used to image HNSCC xenografts in vivo. Cetuximab or control isotype-matched IgG1 was conjugated with the Cy5.5 fluorochrome and systemically injected into mice bearing human split thickness skin grafts, tumor cell line xenografts, transplanted human tumor xenografts, or mouse mesothelioma tumors. Xenografts were imaged by time-domain fluorescence imaging or fluorescence stereomicroscopy. Both imaging modalities detected specific uptake of cetuximab-Cy5.5 in HNSCC xenografts with significantly higher fluorescence levels relative to control IgG1-Cy5.5. Tumor xenograft fluorescence was higher compared with background (before injection), human split thickness skin grafts, or mouse mesothelioma tumors at 24, 48, and 72 h. Fluorescence was detected in multiple HNSCC tumor cell lines with variable EGFR expression levels. Mock resections of flank tumors using fluorescence stereomicroscopy showed that small (2 mm) specimens could be detected in the surgical wound bed. These results show the feasibility of using fluorescently labeled anti-EGFR antibody to detect human tumors in the surgical setting.

Answer 9:

### Bibliographic Information

**Tumor growth inhibition with cetuximab and chemotherapy in non-small cell lung cancer xenografts expressing wild-type and mutated epidermal growth factor receptor.** Steiner, Philipp; Joynes, Christopher; Bassi, Rajiv; Wang, Su; Tonra, James R.; Hadari, Yaron R.; Hicklin, Daniel J. ImClone Systems Incorporated, New York, NY, USA. *Clinical Cancer Research* (2007), 13(5), 1540-1551. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:22955 AN 2007:230062 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Targeting the epidermal growth factor receptor (EGFR) is a validated approach to treat cancer. In non-small cell lung cancer (NSCLC), EGFR contains somatic mutations in 10% of patients, which correlates with increased response rates to small mol. inhibitors of EGFR. We analyzed the effects of the monoclonal IgG1 antibody Erbitux (cetuximab) in NSCLC xenografts with wild-type (wt) or mutated EGFR. NSCLC cell lines were grown s.c. in nude mice. Dose-dependent efficacy was established for cetuximab. To det. whether combination therapy produces tumor regressions, cetuximab was dosed at half-maximal efficacy with chemotherapy used at max. tolerated dose. Cetuximab showed antitumor activity in wt (A549, NCI-H358, NCI-H292) and mutated [HCC-827 (delE746-A750), NCI-H1975 (L858R, T790M)] EGFR-expressing xenografts. In the H292 model, cetuximab and docetaxel combination therapy was more potent to inhibit tumor growth than cetuximab or docetaxel alone. Cisplatin augmented efficacy of cetuximab to produce 6 of 10 regressions, whereas 1 of 10 regressions was found with cetuximab and no regression was found with cisplatin. Using H1975 xenografts, gemcitabine increased efficacy of cetuximab resulting in 12 of 12 regressions. Docetaxel with cetuximab was more efficacious with seven of nine regressions compared with single treatments. Cetuximab inhibited autophosphorylation of EGFR in both H292 and H1975 tumor lysates. Exploring the underlying mechanism for combination effects in the H1975 xenograft model, docetaxel in combination with cetuximab added to the antiproliferative effects of cetuximab but was the main component in this drug combination to induce apoptosis. Cetuximab showed antitumor activity in NSCLC models expressing wt and mutated EGFR. Combination treatments increased the efficacy of cetuximab, which may be important for the management of patients with chemorefractory NSCLC.

Answer 10:

### Bibliographic Information

**Antitumor activity of the combination of cetuximab, an anti-EGFR blocking monoclonal antibody and ZD6474, an inhibitor of VEGFR and EGFR tyrosine kinases.** Morelli, Maria Pia; Cascone, Tina; Troiani, Teresa; Tuccillo, Concetta; Bianco, Roberto; Normanno, Nicola; Romano, Marco; Veneziani, Bianca Maria; Fontanini, Gabriella; Eckhardt, S. Gail; De Pacido, Sabino; Tortora, Giampaolo; Ciardiello, Fortunato. Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale "F. Magrassi e A. Lanzara", Seconda Università degli Studi di Napoli, Naples, Italy. *Journal of Cellular Physiology* (2006), 208(2), 344-353. Publisher: Wiley-Liss, Inc., CODEN: JCELLX ISSN: 0021-9541. Journal written in English. CAN 145:327878 AN 2006:686139 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The epidermal growth factor receptor (EGFR) autocrine pathway plays an important role in cancer cell growth. Vascular endothelial growth factor A (VEGF-A) is a key regulator of tumor-induced endothelial cell proliferation and vascular permeability. ZD6474 is an orally available, small mol. inhibitor of VEGF receptor-2 (VEGFR-2), EGFR and RET tyrosine kinase activity. We investigated the activity of ZD6474 in combination with cetuximab, an anti-EGFR blocking monoclonal antibody, to det. the antitumor activity of EGFR blockade through the combined use of two agents targeting the receptor at different mol. sites in cancer cells and of VEGFR-2 blockade in endothelial cells. The antitumor activity in vitro and in vivo of ZD6474 and/or cetuximab was tested in human cancer cell lines with a functional EGFR autocrine pathway. The combination of ZD6474 and cetuximab detd. synergistic growth inhibition in all cancer cell lines tested as assessed by the Chou and Talalay method. In nude mice bearing established human colon carcinoma (GEO) or lung adenocarcinoma (A549) xenografts and treated with ZD6474 and/or cetuximab for 4 wk, a reversible tumor growth inhibition was caused by each drug. In contrast, a more significant tumor growth delay resulted from the combination of the two agents with an approx. 100-110 days increase in mice median overall survival as compared to single agent treatment. This study provides a rationale for evaluating in a clin. setting the double blockade of EGFR in combination with inhibition of VEGFR-2 signaling as cancer therapy.

Answer 11:

**Bibliographic Information**

**Synergistic Antitumor Effects of Combined Epidermal Growth Factor Receptor and Vascular Endothelial Growth Factor Receptor-2 Targeted Therapy.** Tonra, James R.; Deevi, Dhanvanthri S.; Corcoran, Erik; Li, Huiling; Wang, Su; Carrick, Francine E.; Hicklin, Daniel J. ImClone Systems Inc., New York, NY, USA. *Clinical Cancer Research* (2006), 12(7, Pt. 1), 2197-2207. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:312606 AN 2006:334217 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Purpose: Combination therapies that target the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) pathways, are being actively tested for the treatment of cancer. In evaluating combination strategies, the ideal combination would be one in which the treatments interact in a way that is synergistic with regard to antitumor effects. Here, we have evaluated the interaction between anti-EGFR antibody Erbitux (cetuximab) and anti-VEGFR2 antibody, DC101, in preclin. models of pancreatic (BxPC-3) and colon (GEO) cancer. Exptl. Design: Anal. of the interaction between cetuximab and DC101 in vivo used a novel method for establishing the upper 95% confidence limits for the combination index (CI) of isobologram analyses, where  $CI < 1$  indicates synergy. Assessment of tumor cell proliferation, apoptosis, VEGF prodn., and hypoxia, as well as tumor vascularization, was performed to gain insights into the mechanistic basis for synergy between agents targeting different tumor compartments. Results: Monotherapy ED50 values for tumor growth inhibition ranged from 1.8 to 2.3 mg/kg and 10.5 to 16.6 mg/kg for cetuximab and DC101, resp. From the dose response of the combination treatment, it was detd. that cetuximab and DC101 are synergistic in the BxPC-3 ( $CI = 0.1$ ,  $P < 0.01$ ) and GEO ( $CI = 0.1$ ,  $P < 0.01$ ) models. Overlapping effects on the tumor cell and vascular compartments form a basis for the interaction, with VEGF prodn. and hypoxia-inducible factor  $1\alpha$  potentially acting as mol. links between EGFR and VEGFR2 inhibition. Conclusions: Results show antitumor synergy for combined EGFR and VEGFR2 targeted therapy, supporting the significant therapeutic potential of this combination strategy.

Answer 12:

**Bibliographic Information**

**In vivo and in vitro antitumor activity of oxaliplatin in combination with cetuximab in human colorectal tumor cell lines expressing different level of EGFR.** Balin-Gauthier, Diane; Delord, Jean-Pierre; Rochaix, Philippe; Mallard, Valerie; Thomas, Fabienne; Hennebelle, Isabelle; Bugat, Roland; Canal, Pierre; Allal, Cuider. EA 3035 Laboratoire de Pharmacologie Clinique et Experimentale des Medicaments Anticancereux, Universite Paul Sabatier, Toulouse, Fr. *Cancer Chemotherapy and Pharmacology* (2006), 57(6), 709-718. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 145:305843 AN 2006:331412 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

This study aimed to assess the effect of cetuximab (C225, Erbitux, a chimeric anti-epidermal growth factor receptor (EGFR) monoclonal antibody) in combination with oxaliplatin in vitro and in vivo on four colon cancer cell lines (HCT-8; HT-29, SW620, HCT-116) expressing different levels of EGFR. In vitro, cetuximab combined with oxaliplatin significantly decreased the IC50 values of oxaliplatin in HCT-8 (EGF-R moderate) and HT-29 (EGF-R weak) cell lines, while SW620 (EGF-R neg.) and HCT-116 (EGFR strong) cell lines remained unresponsive. This combination was synergistic in HCT-8 and HT-29 cell lines while cetuximab induced no major modification of the IC50 of oxaliplatin in HCT-116 or SW620 cell lines. We then detd. the effect of cetuximab on the EGF-induced EGFR phosphorylation and we highlight a correlation between the basal level of phospho-EGFR and the response to the combination. In vivo, the combination of cetuximab plus oxaliplatin significantly inhibited tumor growth of HCT-8 and HT-29 (tumor delay or Td = 21.6±2.9 and 18.0±2.9 days resp., synergistic effect) compared to either oxaliplatin (Td=12.6±2.3 and 14.4±3.2 days resp.) or cetuximab (Td=13.4±2.9 and 14.5±2.4 days, resp.) alone in xenograft models. The combination had no effect on HCT-116 and SW-620 cell lines. The obsd. responses are strictly dependent on the cell type, and are not correlated with the level of EGFR expression but related to the basal level of phospho-EGFR. This study provides promising preclin. results for a possible clin. investigation of the combination of oxaliplatin plus cetuximab in chemorefractory colorectal tumors.

Answer 13:

**Bibliographic Information**

**Cetuximab and Irinotecan Interact Synergistically to Inhibit the Growth of Orthotopic Anaplastic Thyroid Carcinoma Xenografts in Nude Mice.** Kim, Seungwon; Prichard, Christopher N.; Younes, Maher N.; Yazici, Yasemin D.; Jasser, Samar A.; Bekele, B. Nebiyou; Myers, Jeffrey N. Departments of Head and Neck Surgery, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA. *Clinical Cancer Research* (2006), 12(2), 600-607. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 145:55478 AN 2006:63632 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Purpose: Anaplastic thyroid carcinoma (ATC) remains one of the most lethal known human cancers. Targeted mol. therapy with cetuximab, a monoclonal antibody against epidermal growth factor receptor, offers new treatment potentials for patient with ATC. Cetuximab has also been reported to have synergistic effects when combined with irinotecan, a topoisomerase inhibitor. Therefore, we hypothesized that cetuximab and irinotecan would be effective in inhibiting the growth and progression of ATC in a murine orthotopic model. Exptl. Design: The in vitro antiproliferative effects of cetuximab and irinotecan on ATC cell line ARO were examd. We also studied the in vivo effects of cetuximab and irinotecan on the growth, invasion, and metastasis of orthotopic ATC tumors in nude mice. The in vivo antitumor efficacy of cetuximab/irinotecan combination was also compared with that of doxorubicin. Results: Cetuximab alone did not show any antiproliferative or proapoptotic effect on this cell line. However, when combined with irinotecan, cetuximab potentiated the in vitro antiproliferative and proapoptotic effect of irinotecan. Cetuximab, irinotecan, and cetuximab/irinotecan combination resulted in 77%, 79%, and 93% in vivo inhibition of tumor growth, resp. Incidences of lymph node metastasis, laryngeal invasion, and tumor microvessel d. were also significantly decreased in these treatment groups. Furthermore, the cetuximab/irinotecan combination was significantly more effective than doxorubicin in inhibiting the growth of orthotopic ATC xenografts. Conclusions: Combination therapy with cetuximab/irinotecan inhibits the growth and progression of orthotopic ATC xenografts in nude mice. Given the lack of curative options for patients with ATC, combination therapy with cetuximab and irinotecan treatment warrants further study.

Answer 14:

**Bibliographic Information**

**Novel Toll-Like Receptor 9 Agonist Induces Epidermal Growth Factor Receptor (EGFR) Inhibition and Synergistic Antitumor Activity with EGFR Inhibitors.** Damiano, Vincenzo; Caputo, Rosa; Bianco, Roberto; D'Armiento, Francesco P.; Leonardi, Antonio; De Placido, Sabino; Bianco, A. Raffaele; Agrawal, Sudhir; Ciardiello, Fortunato; Tortora, Giampaolo. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Universita di Napoli Federico II, Naples, Italy. *Clinical Cancer Research* (2006), 12(2), 577-583.

Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:55475 AN 2006:63629 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Purpose:** Immunostimulating Toll-like receptor 9 (TLR9) agonists cause antitumor activity interfering also with cancer proliferation and angiogenesis by mechanisms still incompletely understood. We hypothesized that modified TLR9 agonists could impair epidermal growth factor receptor (EGFR) signaling and, by this means, greatly enhance EGFR inhibitors effect, acting on both the receptor targeting and the immunol. arm. **Exptl. Design:** We used a novel second-generation, modified, immunomodulatory TLR9 agonist (IMO), alone and in combination with the anti-EGFR monoclonal antibody cetuximab or tyrosine kinase inhibitor gefitinib, on the growth of GEO and cetuximab-resistant derivs. GEO-CR colon cancer xenografts. We have also evaluated the expression of several proteins crit. for cell proliferation, apoptosis, and angiogenesis, including EGFR, mitogen-activated protein kinase, Akt, bcl-2, cyclooxygenase-2, vascular endothelial growth factor, and nuclear factor- $\kappa$ B. **Results:** IMO inhibited GEO growth and signaling by EGFR and the other proteins crit. for cell proliferation and angiogenesis. IMO plus the anti-EGFR antibody cetuximab synergistically inhibited tumor growth, signaling proteins, and microvessel formation. EGFR signaling inhibition by IMO is relevant because IMO cooperated also with EGFR tyrosine kinase inhibitor gefitinib in GEO tumors, while it was inactive against GEO-CR xenografts. On the other hand, IMO boosted the non-EGFR-dependent cetuximab activity, causing a cooperative antitumor effect in GEO-CR cells. Finally, combination of IMO, cetuximab and chemotherapeutic irinotecan eradicated the tumors in 90% of mice. **Conclusion:** IMO interferes with EGFR-related signaling and angiogenesis and has a synergistic antitumor effect with EGFR inhibitors, esp. with cetuximab, boosting both the EGFR dependent and independent activity of this agent. Moreover, this therapeutic strategy could be translated in patients affected by colorectal cancer.

Answer 15:

### Bibliographic Information

**Correlation of pharmacokinetics with the antitumor activity of Cetuximab in nude mice bearing the GEO human colon carcinoma xenograft.** Luo, F. R.; Yang, Z.; Dong, H.; Camuso, A.; McGlinchey, K.; Fager, K.; Flefleh, C.; Kan, D.; Inigo, I.; Castaneda, S.; Rose, W. C.; Kramer, R. A.; Wild, R.; Lee, F. Y. Pharmaceutical Research Institute, Oncology Drug Discovery, Bristol-Myers Squibb Company, Princeton, NJ, USA. *Cancer Chemotherapy and Pharmacology* (2005), 56(5), 455-464. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 144:183961 AN 2005:1156569 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

**Purpose:** The epidermal growth factor receptor (EGFR), a protein tyrosine kinase expressed in many types of human cancers including colon and breast, has been strongly assocd. with tumor progression. Cetuximab, an IgG1 anti-EGFR chimeric mouse/human monoclonal antibody, has been proven to be effective in the treatment of advanced colon cancer. To date, there has not been a study to systematically evaluate the pharmacokinetics (PK) of Cetuximab in a preclin. model and to further explore any correlation of drug exposure between animal models and cancer patients. In the present study, we characterized the PK of Cetuximab in nude mice at efficacious dose levels and further compared the preclin. optimal dose and active plasma drug concn. with those detd. in clin. studies. **Exptl. design:** The antitumor activity of Cetuximab was evaluated using the GEO human colon carcinoma xenografts implanted s.c. in nude mice. The drug was administered i.p. every 3 days for five total injections (inj) (q3dx5) at dose levels ranging from 1 mg/inj to 0.04 mg/inj. The plasma PK of Cetuximab was detd. at dose levels of 1.0, 0.25, and 0.04 mg/inj with a single bolus iv or i.p. administration in nude mice. The tumoral PK of Cetuximab was detd. at dose levels of 0.25, and 0.04 mg/inj with a single bolus i.p. administration in nude mice bearing GEO tumor xenografts. The plasma and tumoral levels of Cetuximab were quantitated by an ELISA assay. **Results:** Cetuximab demonstrated a dose-dependent antitumor activity at dose levels of 0.25, 0.1, and 0.04 mg/inj, with a statistically significant tumor growth delay (in reaching a tumor target size of 1 gm) of 18 days ( $P < 0.001$ ), 12.3 days ( $P < 0.01$ ), and 10 days ( $P < 0.01$ ) for 0.25, 0.1, and 0.04 mg/inj, resp. A sep. study employing the same treatment schedule showed that Cetuximab was equally active at dose levels ranging from 0.25 mg/inj to 1 mg/inj.

Therefore, dose levels of Cetuximab from 1 mg/inj to 0.04 mg/inj can be considered to be within the efficacious range, while dose levels of 0.25 mg/inj or higher appeared to be optimal for the antitumor activity of Cetuximab in the GEO tumor model. When Cetuximab was given iv to mice, the elimination half life ( $t_{1/2}$ ) was 39.6, 37.8, and 42.2 h for doses of 1.0, 0.25, and 0.04 mg/inj,

resp., suggesting a similar disposition kinetics of Cetuximab within this dose range. The vol. of distribution (Vd) ranged from 0.062 l/kg to 0.070 l/kg, suggesting that Cetuximab is primarily confined to the plasma compartment with limited peripheral tissue distribution. Clearance (CL) was similar and no apparent PK satn. was obsd. across the dose ranging from 0.04 mg/inj to 1.0 mg/inj. When mice were administered with a single bolus i.p. administration at doses of 1, 0.25, and 0.04 mg/inj, the max. plasma concn. (Cmax) was 407.6, 66.4, and 16.5 µg/mL. The area under the curve of plasma drug concn. (AUC) was 19212.4, 3182.4, and 534.5 µg/mL h, for 1.0, 0.25, and 0.04 mg/inj, resp. The av. steady state plasma concn. (Css avg) for the multiple dosing schedule was estd. to be 73.1 µg/mL at 0.25 mg/inj and was considered as an active plasma drug concn. The max. tumoral concn. of Cetuximab was 2.6 and 0.53 ng/mg-tumor while the tumoral drug exposure was 112.6 and 18.3 ng/mg h for 0.25 and 0.04 mg/inj, resp. The EGFR was estd. to be nearly completely occupied by Cetuximab at the optimal dose of 0.25 mg/inj. Conclusion: In the present study, we compared the preclin. optimal dose and the corresponding active plasma concn. detd. in mice with those being obsd. in cancer patients, i.e. 65-100 µg/mL. The preclin. optimal dose of 0.25 mg/inj was significantly lower than the current clin. dose. However, the active plasma concn. at 0.25 mg/inj is within the range of the active drug concns. in cancer patients treated with Cetuximab under the current optimal dosing regimen. It appears that the active plasma drug concn. detd.

in preclin. model predicts better than the optimal preclin. dose for the clin. development of antibody drugs.

Answer 16:

### Bibliographic Information

**Treatment of Human Tumor Xenografts with Monoclonal Antibody 806 in Combination with a Prototypical Epidermal Growth Factor Receptor-Specific Antibody Generates Enhanced Antitumor Activity.** Perera, Rushika M.; Narita, Yoshitaka; Furnari, Frank B.; Gan, Hui K.; Murone, Carmel; Ahlqvist, Marika; Luwor, Rodney B.; Burgess, Antony W.; Stockert, Elisabeth; Jungbluth, Achim A.; Old, Lloyd J.; Cavenee, Webster K.; Scott, Andrew M.; Johns, Terrance G. Ludwig Institute for Cancer Research, Melbourne Branch, Tumor Targeting Program, Austin Hospital, Heidelberg, Australia. *Clinical Cancer Research* (2005), 11(17), 6390-6399. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:329467 AN 2005:972438 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

Monoclonal antibody (mAb) 806 is a novel epidermal growth factor receptor (EGFR) antibody with significant antitumor activity that recognizes a mutant EGFR commonly expressed in glioma known as delta2-7 EGFR (de2-7 EGFR or EGFRvIII) and a subset of the wild-type (wt) EGFR found in cells that overexpress the receptor. We have used two human xenograft mouse models to examine the efficacy of mAb 806 in combination with mAb 528, a prototypical anti-EGFR antibody with similar specificity to cetuximab. Treatment of nude mice, bearing s.c. or i.c. tumor human xenografts expressing the wt or de2-7 EGFR, with mAbs 806 and 528 in combination resulted in additive and in some cases synergistic, antitumor activity. Interestingly, mAb 528 was also effective against xenografts expressing the ligand independent de2-7 EGFR when used as a single agent, showing that its antitumor activity is not merely mediated through inhibition of ligand binding. When used as single agents, neither mAbs 806 or 528 induced down-regulation of the de2-7 EGFR either in vitro or in vivo. In contrast, the combination of antibodies produced a rapid and dramatic decrease in the total cell surface de2-7 EGFR both in vitro and in xenografts. Consistent with this decrease in total cell surface de2-7 EGFR, we obsd. up-regulation of the cell cycle inhibitor p27KIP1 and a decrease in tumor cell proliferation as measured by Ki-67 immunostaining when the antibodies were used in combination in vivo. Thus, mAb 806 can synergize with other EGFR-specific antibodies thereby providing a rationale for its translation into the clinic.

Answer 17:

### Bibliographic Information

**Prediction of active drug plasma concentrations achieved in cancer patients by pharmacodynamic biomarkers identified from the geo human colon carcinoma xenograft model.** Luo, Feng R.; Yang, Zheng; Dong, Huijin; Camuso, Amy; McGlinchey, Kelly; Fager, Krista; Flefleh, Christine; Kan, David; Inigo, Ivan; Castaneda, Stephen; Wong, Tai W.; Kramer, Robert A.; Wild, Robert; Lee, Francis Y. *Oncology Drug Discovery*, Pharmaceutical Research Institute, Princeton, NJ, USA. *Clinical Cancer Research* (2005), 11(15), 5558-5565. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 143:458236 AN 2005:690588 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Epidermal growth factor receptor (EGFR), a protein tyrosine kinase expressed in many types of human cancers, has been strongly associated with tumor progression. Cetuximab is an IgG1 anti-EGFR chimeric mouse/human monoclonal antibody that has been approved for the treatment of advanced colon cancer. Using human tumor xenografts grown in nude mice, we have determined the in vivo pharmacodynamic response of cetuximab at efficacious doses. Three pharmacodynamic end points were evaluated: tumoral phospho-EGFR, tumoral mitogen-activated protein kinase (MAPK) phosphorylation, and Ki67 expression. The pharmacodynamic study was conducted in nude mice bearing Ge0 tumors following a single i.p. administration of 0.25 and 0.04 mg. The tumors were analyzed by immunohistochemistry. The levels of phospho-EGFR were quantitated by an ELISA assay. At 0.25 mg, phospho-EGFR was maximally inhibited by 91% at 24 h, whereas the level of inhibition decreased to 72% by 72 h. At 0.04 mg, the maximum inhibition of phospho-EGFR was 53% at 24 h, whereas the level of inhibition decreased to 37% by 72 h. The time course of phospho-EGFR inhibition and recovery seemed to correlate with the pharmacokinetics of cetuximab. Immunohistochemical analysis showed that phospho-MAPK and Ki67 expression were inhibited between 24 and 72 h at 0.25 and 0.04 mg. A pharmacokinetic/pharmacodynamic model was established and predicted that the plasma concentration of cetuximab required to inhibit 90% of phospho-EGFR was 67.5 µg/mL. Phospho-EGFR/phospho-MAPK could be useful clinical biomarkers to assess EGFR inhibition by cetuximab.

Answer 18:

**Bibliographic Information**

**Inhibition of Glioblastoma Angiogenesis and Invasion by Combined Treatments Directed Against Vascular Endothelial Growth Factor Receptor-2, Epidermal Growth Factor Receptor, and Vascular Endothelial-Cadherin.** Lamszus, Katrin; Brockmann, Marc A.; Eckerich, Carmen; Bohlen, Peter; May, Chad; Mangold, Ulrich; Fillbrandt, Regina; Westphal, Manfred. Department of Neurosurgery, Institute for Anatomy II, University Hospital Hamburg-Eppendorf, Hamburg, Germany. *Clinical Cancer Research* (2005), 11(13), 4934-4940. Publisher: American Association for Cancer Research, CODEN: CCRE4 ISSN: 1078-0432. Journal written in English. CAN 143:404193 AN 2005:585335 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

**Purpose:** Inhibition of angiogenesis can influence tumor cell invasion and metastasis. We previously showed that blockade of vascular endothelial growth factor receptor-2 (VEGFR-2) with the monoclonal antibody DC101 inhibited intracerebral glioblastoma growth but caused increased tumor cell invasion along the preexistent vasculature. In the present study, we attempted to inhibit glioma cell invasion using a monoclonal antibody against the epidermal growth factor receptor (EGFR), which in the context of human glioblastomas, has been implicated in tumor cell invasion. In addition, we analyzed whether blockade of vascular endothelial (VE)-cadherin as a different antiangiogenic target could also inhibit glioblastoma angiogenesis and growth. **Exptl. Designs:** Nude mice who received intracerebral glioblastoma xenografts were treated using monoclonal antibodies against VEGFR-2 (DC101), EGFR (C225), and VE-cadherin (E4G10) either alone or in different combinations. **RESULTS:** Increased tumor cell invasion provoked by DC101 monotherapy was inhibited by 50% to 66% by combined treatment with C225 and DC101. C225 inhibited glioblastoma cell migration in vitro, but had no effect on the volume of the main tumor mass or on tumor cell proliferation or apoptosis in vivo, either alone or in combination with DC101. The anti-VE-cadherin monoclonal antibody E4G10 was a weaker inhibitor of tumor angiogenesis and growth than DC101, and also caused a weaker increase in tumor cell invasion. **Conclusions:** Inhibition of angiogenesis achieved by blocking either VEGFR-2 or VE-cadherin can cause increased glioma cell invasion in an orthotopic model. Increased tumor cell invasion induced by potent inhibition of angiogenesis with DC101 could be inhibited by simultaneous blockade of EGFR.

Answer 19:

**Bibliographic Information**

**Cetuximab: an epidermal growth factor receptor chimeric human-murine monoclonal antibody.** Harding, Joanne; Burtness, Barbara. Prous Science, Barcelona, Spain. *Drugs of Today* (2005), 41(2), 107-127. Publisher: Prous Science, CODEN: MDACAP ISSN: 0025-7656. Journal; General Review written in English. CAN 143:58106 AN 2005:332175 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

A review. The epidermal growth factor receptor (EGFR) is a member of the ErbB family of receptors. It is composed of extracellular domains, including a ligand-binding domain, a hydrophobic transmembrane region and a tyrosine kinase-contg. cytoplasmic region. Stimulation of the EGFR by endogenous ligands, EGF or transforming growth factor- $\alpha$  (TGF- $\alpha$ ), results in a conformational change in the receptor, permitting it to enter into dimers and other oligomers. Dimerization results in activation of intracellular tyrosine kinase, protein phosphorylation and stimulation of various cell signaling pathways that mediate gene transcription and cell cycle progression. The EGFR is expressed on normal human cells but higher levels of expression of the receptor have also been shown to be correlated with malignancy in a variety of cancers. In addn., expression of the EGFR by malignant cells is assocd. with poor prognosis and resistance to therapy. Cetuximab is a chimeric human-murine monoclonal antibody that binds competitively and with high affinity to the EGFR. Binding of the antibody to the EGFR prevents stimulation of the receptor by endogenous ligands and results in inhibition of cell proliferation, enhanced apoptosis, and reduced angiogenesis, invasiveness and metastasis. Binding of cetuximab to the receptor also results in internalization of the antibody-receptor complex which leads to an overall downregulation of EGFR expression. The EGFR is a prime target for new anticancer therapy, and other agents in development include small mol. tyrosine kinase inhibitors and antisense therapies. Preclin. studies have demonstrated that cetuximab reduces chemotherapy and radiotherapy resistance in human tumor cell lines in vitro and in nude mice bearing xenografts of human tumors. In clin. and preclin. studies cetuximab has been shown to induce response to treatment when used in combination with chemotherapy in patients previously refractory to chemotherapy.

Based on these studies, cetuximab can be added to regimens using docetaxel, cisplatin, carboplatin, irinotecan, paclitaxel and fluorouracil and may add to treatment efficacy. Phase I dose-finding studies showed that satn. of cetuximab clearance occurred after administration of 400 mg/m<sup>2</sup> as a loading dose followed by weekly infusions of 250 mg/m<sup>2</sup>. The most commonly reported adverse event assocd. with cetuximab treatment is an acneiform rash that occurs in 70-80% of patients treated with cetuximab. The rash is rarely dose- or treatment-limiting, and may diminish in intensity with continued exposure to cetuximab. Improvement may be seen after treatment with topical antibiotic prepns., topical steroids or topical retinoids. The rash resolves fully after discontinuation of cetuximab treatment. EGFR is widely expressed in skin and skin biopsies in areas involved with the characteristic cetuximab eruption demonstrate neutrophilic folliculitis. In fact, anal. of four phase II clin. trials of cetuximab in combination with chemotherapy in patients with colorectal cancer, squamous cell carcinoma of the head and neck, or pancreatic cancer showed that development of the acneiform rash was significantly correlated with response to treatment; grade 3 rash may be esp. predictive of response. It is possible that development of acneiform rash may become an important clin. prognostic marker. Serious cetuximab-related toxicities include hypersensitivity, infusion reactions and interstitial lung disease. Results of a large phase II study have shown response when used in combination with irinotecan in 22.9% of patients with EGFR-expressing, irinotecan-refractory, colorectal cancer. Cetuximab has recently been approved for this indication in the United States, Switzerland, Iceland, Norway and the 25 member states of the European Union.

Other phase II and III studies show significant response to treatment in variable proportions of patients with squamous cell carcinoma of the head and neck, non-small cell lung cancer and pancreatic cancer when cetuximab is used first or second line in combination with chemotherapy. Thus, cetuximab is emerging as a very promising new therapy to be used in conjunction with existing therapies for the treatment of a spectrum of solid tumors.

Answer 20:

**Bibliographic Information**

**Epidermal Growth Factor Receptor Dynamics Influences Response to Epidermal Growth Factor Receptor Targeted Agents.** Jimeno, Antonio; Rubio-Viqueira, Belen; Amador, Maria L.; Oppenheimer, Darin; Bouraoud, Nadia; Kulesza, Peter; Sebastiani, Valeria; Maitra, Anirban; Hidalgo, Manuel. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA. *Cancer Research* (2005), 65(8), 3003-3010. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 142:456475 AN 2005:328700 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Anal. of gene expression of cancer cell lines exposed to erlotinib, a small mol. inhibitor of the epidermal growth factor receptor (EGFR), showed a marked increase in EGFR mRNA in resistant cell lines but not in susceptible ones. Because cetuximab induces EGFR

down-regulation, we explored the hypothesis that treatment with cetuximab would interfere with erlotinib-induced EGFR up-regulation and result in antitumor effects. Exposure of the resistant biliary tract cancer cell line HuCCT1 but not the susceptible A431 epidermoid cell line to erlotinib induced EGFR mRNA and protein expression. Combined treatment with cetuximab blunted the erlotinib-induced EGFR up-regulation and resulted in inhibition of cell proliferation and apoptosis in the HuCCT1 cells. Blockage of erlotinib-induced EGFR synthesis in HuCCT1 cells by small interfering RNA resulted in identical antitumor effects as cetuximab, providing mechanistic specificity. In mice xenografted with A431, HuCCT1, and the pancreatic cancer cell line Panc430, maximal growth arrest and decrease in Ki67 proliferation index were documented with combined therapy, and EGFR down-regulation was obsd. in cetuximab-treated tumors. These results may indicate that resistance to EGFR kinase inhibition may be, at least in part, mediated by a highly dynamic feedback loop consisting of up-regulation of the EGFR upon exposure to EGFR kinase inhibitors. Abrogation of this response by small interfering RNA-mediated EGFR mRNA down-regulation and/or by cetuximab-mediated protein clearance induced tumor arrest across several cancer models with different EGFR expression levels, suggesting that resistance and sensitivity are dynamic events where proportional decrease in the target rather than abs. content dictates outcome.

Answer 21:

### Bibliographic Information

**The effects of cetuximab alone and in combination With radiation and/or chemotherapy in lung cancer.** Raben, David; Helfrich, Barb; Chan, Daniel C.; Ciardiello, Fortunato; Zhao, Li Min; Franklin, Wilbur; Baron, Anna E.; Zeng, Chan; Johnson, Tim K.; Bunn, Paul A., Jr. Tobacco Related Malignancy Program, University of Colorado Cancer Center, Departments of Radiation Oncology, Medicine, Pathology, and Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, CO, USA. *Clinical Cancer Research* (2005), 11(2, Pt. 1), 795-805. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:390651 AN 2005:271390 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The epidermal growth factor receptor (EGFR) overexpressed in approx. 80% of non-small cell lung cancers (NSCLC) is a target for novel therapeutics. Concurrent chemoradiation is the current std. of care for treatment of patients with locally advanced NSCLC. However, < 20% of patients remain disease-free at 5 years despite this aggressive treatment. Cetuximab is a humanized monoclonal antibody that recognizes the human EGFR, and in previous studies, inhibited the growth of EGFR-expressing human cancer cell lines. In this report, we investigated the cellular and mol. effects of cetuximab alone and in combination with radiation and/or chemotherapy in human NSCLC cell lines with varying levels of EGFR overexpression in vitro and in vivo. We evaluated the EGFR status of a panel of human NSCLC cancer cell lines by immunohistochem. and flow cytometry. We then evaluated cetuximab effects on growth, cell cycle distribution, and downstream intracellular signaling mol. in this panel of NSCLC cancer cell lines. NSCLC cell lines were treated with cetuximab alone or in combination with radiation, chemotherapy, or chemoradiation to det. the cooperative effects of cetuximab both in vitro and in vivo in athymic nude mice bearing NSCLC xenografts. Cetuximab alone inhibited the in vitro growth of some but not all EGFR-expressing NSCLC cell lines in a dose-dependent manner. Flow cytometric anal. of cell cycle distribution after 24 h of cetuximab treatment revealed a shift into the G0/G1 phase of the cell cycle in cetuximab-sensitive EGFR-expressing cell lines and at concns. that were growth-inhibitory. There were no cell cycle changes in the EGFR-neg. cell lines. After 4 h of exposure, cetuximab reduced epidermal growth factor (EGF)-induced phosphorylation of EGFR (pEGFR) and HER-2 (pHER2) in cetuximab-sensitive cell lines but not in cetuximab-resistant cell lines. Cetuximab reduced EGF-induced phosphorylation of extracellular signal-regulated kinase-1/2 (pERK) in all EGFR-expressing cell lines.

In the absence of EGF, cetuximab alone increased the level of pEGFR and pHER2 above that seen in untreated control cells in both sensitive and resistant cell lines that were EGFR- and HER2-pos., but not in EGFR- or HER2-neg. lines. Despite the cetuximab-induced increase in phosphorylation of EGFR and HER2, peak EGF-induced levels of pEGFR and pHER2 were reduced by cetuximab in the cetuximab-sensitive lines but not in the resistant lines. Cooperative (combination index values < 1.0) growth inhibitory effects were obsd. in vitro combination assays with cetuximab and radiation only in cetuximab-sensitive NSCLC cell lines. A lack of cooperation was seen in cetuximab-insensitive NSCLC cell lines. Similar findings were obsd. with in vitro combination studies of cetuximab plus cisplatin or paclitaxel. In nude mice bearing EGFR-expressing, cetuximab-sensitive, NSCLC cell line xenografts, cetuximab plus radiation induced a marked improvement in tumor growth inhibition over either agent alone. The growth inhibitory effects of cetuximab-radiation were similar to the growth inhibitory effects of concurrent chemoradiation. Triple combination therapy of cetuximab and chemoradiation yielded a nonsignificant advantage in tumor growth control over doublet combinations

(cetuximab and radiation or chemoradiation) in vivo. Similar results in tumor growth inhibition obsd. in mice treated with cetuximab-radiation and cisplatin-radiation provide a rationale for the clin. investigation of cetuximab with concurrent radiation in selected patients with locally advanced NSCLC. Local tumor control and treatment toxicity should be evaluated between cetuximab-radiation and chemoradiation regimens. Proper patient selection will be crit. to the success of such trials and further studies are needed to identify optimal patient selection criteria.

Answer 22:

#### **Bibliographic Information**

**Therapeutic synergy of oral taxane BMS-275183 and cetuximab versus human tumor xenografts.** Rose, William C.; Wild, Robert. Pharmaceutical Research Institute, Bristol-Myers Squibb Co., Inc., Princeton, NJ, USA. *Clinical Cancer Research* (2004), 10(21), 7413-7417. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:211633 AN 2004:946698 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

Combination therapy consisting of an oral taxane, BMS-275183, and the anti-epidermal growth factor receptor monoclonal antibody, cetuximab, was assessed for enhanced therapeutic benefit in preclin. tumor models. Mice bearing human tumor xenografts, either L2987 lung or GEO colon carcinoma, were administered the aforementioned treatments singly or in combination regimens. Delays in tumor growth and tumor-free status were evaluated and combination treatments were assessed relative to optimal solo treatments. Combination therapies with the oral taxane plus cetuximab were tolerated and therapeutic synergistic outcomes obtained. The therapeutic enhancements were >1 log cell kill greater than the antitumor effect caused by either solo agent applied optimally. For example, at the max.-tolerated dose of BMS-275183, 60 mg/kg/administration, given p.o. once every 3 days for a total of six administrations (q3dx6), 1.0 gross log cell kill was achieved in mice bearing well established (100 to 200 mg) s.c. implanted L2987 tumors. Cetuximab, at an optimal dose of 1 mg/mouse, given i.p. q3dx6, produced 1.3 log cell kill. When cetuximab, 1 mg/mouse, i.p., plus BMS-275183, 25 mg/kg/administration, p.o., were both given q3dx6, the result was 2.6 log cell kill with three of eight mice cured ( $P < 0.01$ ). Similar efficacy benefits were obtained in the GEO tumor model. The combination of oral taxane BMS-275183 plus cetuximab provided therapeutically synergistic antitumor activity in two different human tumor xenograft models. Clin. evaluation of this combination is recommended.

Answer 23:

#### **Bibliographic Information**

**Combined epidermal growth factor receptor targeting with the tyrosine kinase inhibitor gefitinib (ZD1839) and the monoclonal antibody cetuximab (IMC-C225): superiority over single-agent receptor targeting.** Matar, Pablo; Rojo, Federico; Cassia, Raul; Moreno-Bueno, Gema; Di Cosimo, Serena; Tabernero, Jose; Guzman, Marta; Rodriguez, Sonia; Arribas, Joaquin; Palacios, Jose; Baselga, Jose. Laboratory of Oncology Research, Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain. *Clinical Cancer Research* (2004), 10(19), 6487-6501. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:190379 AN 2004:827178 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

#### **Abstract**

The epidermal growth factor receptor (EGFR) is abnormally activated in cancer and two classes of anti-EGFR agents, monoclonal antibodies and low-mol.-wt. tyrosine kinase inhibitors, have shown antitumor activity in patients. Because these two classes of antireceptor agents target the EGFR at different sites, we decided to explore whether the combined administration of gefitinib, a tyrosine kinase inhibitor, and cetuximab, a monoclonal antibody, had superior antitumor activity than either agent given alone. We studied the effects of the combination of gefitinib and cetuximab in a panel of human cancer cell lines and in an EGFR-dependent human tumor xenograft model (A431). The effects of these two agents on EGFR signaling, proliferation, apoptosis, and vascularization were evaluated. In addn., we analyzed, with cDNA arrays, changes in gene expression profiles induced by both

agents. The combined treatment with gefitinib and cetuximab resulted in a synergistic effect on cell proliferation and in superior inhibition of EGFR-dependent signaling and induction of apoptosis. In a series of in vivo expts., single-agent gefitinib or cetuximab resulted in transient complete tumor remission only at the highest doses. In contrast, suboptimal doses of gefitinib and cetuximab given together resulted in a complete and permanent regression of large tumors. In the combination-treated tumors, there was a superior inhibition of EGFR, mitogen-activated protein kinase, and Akt phosphorylation, as well as greater inhibition of cell proliferation and vascularization and enhanced apoptosis. Using cDNA arrays, we found 59 genes that were coregulated and 45 genes differentially regulated, including genes related to cell proliferation and differentiation, transcription, DNA synthesis and repair, angiogenesis, signaling mol., cytoskeleton organization, and tumor invasion and metastasis.

Our findings suggest both shared and complementary mechanisms of action with gefitinib and cetuximab and support combined EGFR targeting as a clin. exploitable strategy.

Answer 24:

### Bibliographic Information

**Antitumor activity of ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to anti-epidermal growth factor receptor therapy.** Ciardiello, Fortunato; Bianco, Roberto; Caputo, Roberta; Caputo, Rosa; Damiano, Vincenzo; Troiani, Teresa; Melisi, Davide; De Vita, Ferdinando; De Placido, Sabino; Bianco, A. Raffaele; Tortora, Giampaolo. Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale "F Magrassi e A Lanzara", Cattedra di Oncologia Medica, Naples, Italy. *Clinical Cancer Research* (2004), 10(2), 784-793. Publisher: American Association for Cancer Research, CODEN: CCREFA ISSN: 1078-0432. Journal written in English. CAN 141:199594 AN 2004:88615 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

### Abstract

The epidermal growth factor receptor (EGFR) autocrine signaling pathway is involved in cancer development and progression. EGFR inhibitors such as C225 (cetuximab), a chimeric human-mouse anti-EGFR monoclonal antibody, and ZD1839 (gefitinib), a small mol. EGFR-selective tyrosine kinase inhibitor, are in advanced clin. development. The potential emergence of cancer cell resistance in EGFR-expressing cancers treated with EGFR inhibitors could det. lack of activity of these drugs in some cancer patients. Vascular endothelial growth factor (VEGF) is secreted by cancer cells and plays a key role in the regulation of tumor-induced endothelial cell proliferation and permeability. ZD6474 is a small mol. VEGF flk-1/KDR (VEGFR-2) tyrosine kinase inhibitor that also demonstrates inhibitory activity against EGFR tyrosine kinase. The antitumor activity of ZD1839, C225, and ZD6474 was tested in athymic mice bearing human GEO colon cancer xenografts. GEO cell lines resistant to EGFR inhibitors were established from GEO xenografts growing in mice treated chronically with ZD1839 or C225. Expression of EGFR was evaluated by flow cytometry. Expression of various proteins involved in intracellular cell signaling was assessed by Western blotting. Tumor growth data were evaluated for statistical significance using the Student's t test. All Ps were two-sided. Although chronic administration of optimal doses of C225 or ZD1839 efficiently blocked GEO tumor growth in the majority of mice, tumors slowly started to grow within 80-90 days, despite continuous treatment. In contrast, continuous treatment of mice bearing established GEO xenografts with ZD6474 resulted in efficient tumor growth inhibition for the entire duration of dosing (up to 150 days). ZD6474 activity was also detd. in mice pretreated with ZD1839 or C225. When GEO growth was apparent after 4 wk of treatment with EGFR inhibitors, mice were either re-treated with EGFR inhibitors or treated with ZD6474.

GEO tumor growth was blocked only in mice treated with ZD6474, whereas tumor progression was obsd. in mice re-treated with C225 or ZD1839. GEO tumors growing during treatment with C225 or with ZD1839 were established as cell lines (GEO-C225-RES and GEO-ZD1839-RES, resp.). Cell membrane-assocd. EGFR expression was only slightly reduced in these cell lines compared with parental GEO cells. Western blotting revealed no major change in the expression of the EGFR ligand transforming growth factor  $\alpha$  of bcl-2, bcl-xL, p53, p27, MDM-2, akt, activated phospho-akt, or mitogen-activated protein kinase. However, both GEO-C225-RES and GEO-ZD1839-RES cells exhibited a 5-10-fold increase in activated phospho-mitogen-activated protein kinase and in the expression of cyclooxygenase-2 and of VEGF compared with GEO cells. GEO-C225-RES and GEO-ZD1839-RES growth as xenografts in nude mice was not significantly affected by treatment with either C225 or ZD1839 but was efficiently inhibited by ZD6474. Long-term treatment of GEO xenografts with selective EGFR inhibitors results in the development of EGFR inhibitor-resistant cancer cells. Growth of EGFR inhibitor-resistant tumors can be inhibited by ZD6474. These data indicate that inhibition of VEGF signaling has potential as an anticancer strategy, even in tumors that are resistant to EGF inhibitors.

Answer 25:

**Bibliographic Information****VEGF-D expression correlates with colorectal cancer aggressiveness and is downregulated by cetuximab.**

Moehler Markus; Frings Christian; Mueller Annett; Gockel Ines; Schimanski Carl-C; Biesterfeld Stefan; Galle Peter-R; Holtmann Martin-H 1st Department of Medicine, Johannes Gutenberg University, Langenbeckstrasse 1, Mainz 55101, Germany. moehler@mail.uni-mainz.de World journal of gastroenterology : WJG (2008), 14(26), 4156-67. Journal code: 100883448. ISSN:1007-9327. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 18636661 AN 2008459606 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

**AIM:** To gain mechanistic insights into the role played by epidermal growth factor receptor (EGFR) in the regulation of vascular endothelial growth factors (VEGFs) in colorectal cancer (CRC). **METHODS:** The impact of high-level expression of the growth factor receptors EGFR and VEGF receptor (VEGFR)3 and the VEGFR3 ligands VEGF-C and VEGF-D on disease progression and prognosis in human CRC was investigated in 108 patients using immunohistochemistry. Furthermore, the expression of the lymphangiogenic factors in response to the modulation of EGFR signalling by the EGFR-targeted monoclonal antibody cetuximab was investigated at the mRNA and protein level in human SW480 and SW620 CRC cell lines and a mouse xenograft model. **RESULTS:** Human CRC specimens and cell lines displayed EGFR, VEGF-C and VEGF-D expression with varying intensities. VEGF-C expression was associated with histological grade. Strong expression of VEGF-D was significantly associated with lymph node metastases and linked to a trend for decreased survival in lymph node-positive patients. EGFR blockade with cetuximab resulted in a significant decrease of VEGF-D expression in vitro and in vivo. **CONCLUSION:** In conclusion, the expression of VEGF-D in colorectal tumours is significantly associated with lymphatic involvement in CRC patients and such expression might be blocked effectively by cetuximab.

Answer 26:

**Bibliographic Information****Assessment of indocyanine green-labeled cetuximab to detect xenografted head and neck cancer cell lines.**

Withrow Kirk P; Gleysteen John P; Safavy Ahmad; Skipper Joni; Desmond Renee A; Zinn Kurt; Rosenthal Eben L Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, University of Alabama at Birmingham, Birmingham, AL 35294-0012, USA Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery (2007), 137(5), 729-34. Journal code: 8508176. ISSN:0194-5998. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17967636 AN 2007643481 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

**OBJECTIVE:** The aim of this study is to determine the efficacy of indocyanine green (ICG) conjugated to antiepidermal growth factor receptor antibody (cetuximab) to image head and neck cancer. **STUDY DESIGN:** Mice (n = 3) were injected with unconjugated ICG and imaged at 100-second intervals for a total of 1000 seconds to assess imaging characteristics. Mice (n = 10) xenografted with SCC-1 cells were then systemically injected with cetuximab conjugated to indocyanine green and imaged over a 72-hour period. To assess the sensitivity and specificity, xenografted tumors underwent subtotal resections and then were assessed for residual disease by fluorescence stereomicroscopy and confirmed by histology. **RESULTS:** Tumors demonstrated excellent fluorescence 24 hours after injection of cetuximab-ICG. There was a direct relationship between fluorescence and the given dose of cetuximab-ICG. Following subtotal resection, we found fluorescence correlated with a sensitivity of 78.4% and specificity of 96%. **CONCLUSIONS:** This study provides evidence that supports further preclinical investigation of cetuximab in the evaluation of surgical margins, but linkage to ICG lacks the sensitivity for use in a clinical setting.

Answer 27:

### **Bibliographic Information**

**In vivo detection of head and neck cancer orthotopic xenografts by immunofluorescence.** Rosenthal Eben L; Kulbersh Brian D; Duncan Ryan D; Zhang Wenyue; Magnuson J Scott; Carroll William R; Zinn Kurt Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, University of Alabama at Birmingham, Birmingham, Alabama, USA The Laryngoscope (2006), 116(9), 1636-41. Journal code: 8607378. ISSN:0023-852X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16954995 AN 2006530607 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

### **Abstract**

**PURPOSE:** To determine whether Cy5.5-labeled antiepidermal growth factor (EGFR) antibody could be used to detect head and neck squamous cell carcinoma (HNSCC) xenografts in vivo. **METHODS:** AntiEGFR antibody (cetuximab) was labeled with Cy5.5, a fluorophore with emission in the near infrared range. The cetuximab-Cy5.5 conjugate was systemically administered in subtherapeutic doses (50 microg) to mice bearing orthotopically xenografted HNSCC cell lines (SCC1, CAL27, and FaDu). As a control, isotype-matched human immunoglobulin (Ig)G1k antibody labeled with Cy5.5 was systemically injected in parallel experiments. All tumor regions (n = 6) were imaged by fluorescent stereomicroscopy at 0, 6, 24, 48, or 72 hours. Tumor size was measured by high-frequency ultrasonography at 72 hours. Transcervical partial and near-total resections were then performed with stereomicroscopic imaging after each resection. The mandible and associated structures were then resected, paraffin embedded, and then serial sectioned for analysis. **RESULTS:** Tumors could be clearly visualized by near infrared fluorescent stereomicroscopy at 48 and 72 hours after systemic administration of cetuximab-Cy5.5 but not after administration with the labeled isotype control antibody, IgG1k-Cy5.5. Ultrasound measurement of tumors (n = 5) correlated with fluorescent measurements of tumor (Spearman's coefficient, 0.92,  $P \leq .01$ ). When fluorescent stereomicroscopic findings were correlated with histologic findings in near-total resections, this technique could accurately identify residual tumor less than 1 mm in size. **CONCLUSION:** Fluorescent immunoguided neoplasm detection may be used as a diagnostic tool and to guide surgical therapy by providing real-time imaging information about the extent of disease or the presence of residual disease.