

4. Dan internistične onkologije z mednarodno udeležbo

TARČNA ZDRAVILA V ONKOLOGIJI



ONKOLOŠKI
INŠTITUT
LJUBLJANA

INSTITUTE
OF ONCOLOGY
LJUBLJANA



SLOVENSKO ZDRAVNIŠKO
DRUŠTVO

Onkološki inštitut Ljubljana
Sektor za internistično onkologijo

Sekcija za internistično
onkologijo

Petek, 14.11.2008



- 14.15 – 14.45 B. Štrukelj**
Razvoj in mehanizem delovanja tarčnih zdravil
- 14.45 – 15.00 Razprava**
- 15.00 – 15.30 I. Aurer**
Tarčno zdravljenje limfomov
(Target treatment of malignant lymphomas)
- 15.30 – 15.45 Razprava**
- 15.45 – 16.15 ODMOR**
- 16.15 – 16.45 F. Ciardiello**
Tarčno zdravljenje GI tumorjev
(Target treatment of GI tumors)
- 16.45 – 17.00 Razprava**
- 17.00 – 17.30 M. Tiseo**
Tarčno zdravljenje raka pljuč
(Target treatment of lung cancer)
- 17.30 – 17.45 Razprava**

Sobota, 15.11.2008



- 8.00 – 9.00 Skupščina Sekcije za internistično onkologijo**
9.00 – 13.20 Predstavitev primerov
- 9.00 – 10.00 Predstavitev bolnika z nevroendokrinim rakom
Mentor: J. Ocvirk
Predstavitev: M. Boc, B. Gregorič
- 10.00 – 11.00 Predstavitev bolnika s hepatocelularnim rakom
Mentor: J. Ocvirk
Predstavitev: T. Mesti, M. Ebert
- 11.00 – 11.20 ODMOR
- 11.20 – 12.20 Predstavitev bolnika z rakom neznanega izvora
Mentor: B. Zakotnik
Predstavitev: C. Kuhar-Grašič, A. Rusjan
- 12.20 – 13.20 Predstavitev primera bolnice z rakom dojke
Mentor: T. Čufer
Predstavitev: K. Vojakovič, M. Humar
- 13.20 Zaključek**



TARGET TREATMENT OF MALIGNANT LYMPHOMAS

Igor Aurer, MD, PhD

Division of Hematology
Department of Internal Medicine
University Hospital Center and
Medical School
Zagreb, Croatia

LYMPHOMAS

- WHO classification of malignant neoplasms
 - Haematopoietic neoplasms
 - Lymphoid neoplasms
 - B-cell neoplasms
 - T/NK-cell neoplasms
 - Hodgkin's lymphoma

B-CELL NEOPLASMS

- IMMATURE
 - B acute lymphoblastic leukemia / lymphoblastic lymphoma
- PERIPHERAL
 - Chronic lymphocytic leukemia / small lymphocytic lymphoma
 - Lymphoplasmocytoid lymphoma / Waldenstroem's macroglobulinaemia
 - Follicular lymphoma (grade 1-3)
 - Mantle-cell lymphoma
 - Marginal zone lymphoma (nodal, extranodal, splenic)
 - Large-cell (diffuse, mediastinal, intravascular, primary effusional)
 - Burkitt
 - Grey zone
 - Hairy-cell leukemia
 - Multiple myeloma

T- AND NK-CELL NEOPLASMS

- **IMMATURE**
 - T lymphoblastic leukemia / lymphoblastic lymphoma
- **PERIPHERAL**
 - (Adult T lymphocytic leukemia, NK leukemia,...)
 - Peripheral T/NK-cell lymphoma (not otherwise specified, enteropathy associated, angioimmunoblastic, nasal type, hepatosplenic,...)
 - Anaplastic large-cell (systemic, cutaneous)
 - Cutaneous T-cell lymphomas (Mycosis fungoides, Sezary syndrome,...)

HODGKIN'S LYMPHOMA

- Nodular lymphocyte predominant
- Classical Hodgkin's lymphoma
 - Diffuse lymphocyte predominant
 - Nodular sclerosis
 - Type I and II
 - Mixed cellularity
 - Lymphocyte depletion

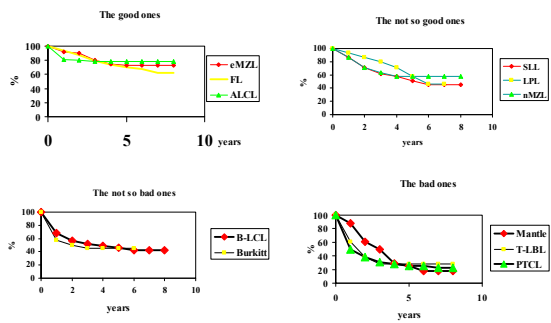
NHLs – CLINICAL CLASSIFICATION

- **INDOLENT**
 - Long survival without treatment
 - Conventional chemotherapy is not curative
 - Anthracycline-based chemotherapy does not prolong survival
 - Repetitive remissions becoming ever shorter
 - Small cells
 - Mostly B-cell derived
 - Mostly correspond to low-grade NHLs
- **AGGRESSIVE**
 - Short survival without treatment
 - Conventional anthracycline-based chemotherapy curative in a significant proportion of cases
 - Mostly large cells
 - B and T
 - Mostly correspond to intermediate and high-grade NHLs
- **VERY AGGRESSIVE**
 - Very short survival without treatment
 - Very aggressive treatment

NHLs – CLINICAL CLASSIFICATION

- **INDOLENT**
 - Chronic lymphocytic leukemia / small lymphocytic lymphoma
 - Lymphoplasmocytoid lymphoma
 - Follicular lymphoma
 - Marginal-zone lymphoma (Hairy-cell leukemia)
 - Mycosis fungoides
- **AGGRESSIVE**
 - B large-cell
 - Mantle-cell
 - Peripheral T/NK-cell
 - Anaplastic large-cell
- **VERY AGGRESSIVE**
 - Burkitt
 - B/T acute lymphoblastic leukemia / lymphoblastic lymphoma

NHLs - DISEASE COURSE (pre-rituximab era)



The non-Hodgkin's lymphoma classification project. Blood 1997.

HODGKIN'S LYMPHOMA

- Aggressive B-lymphoma with a good prognosis

TARGET TREATMENT OF LYMPHOMAS

- Lymphomas are not a single disease
- Different lymphomas – different biology, course and response to treatment

therefore

- Different lymphomas – different target treatment strategies

EVIDENCE-BASED MEDICINE

- A 1 Randomized controlled trials
(Non-randomized trials with dramatic effect)
- B 2 Cohort studies
- B 3 Case-control studies
- C 4 Case series
- D 5 Expert opinion

TARGET TREATMENT OF LYMPHOMAS Biological basis

- [Lymphomas are derived from lymphoid cells](#)
 - Number of strong antigens evolutionary designed to be recognised by immunocompetent cells
 - Excellent targets for antibodies
 - Function of B cells can be substituted with ivlg
 - AIDS epidemic has taught physicians how to deal with T-cell deficient patients
 - *B-cell differentiation has been molecularly dissected*
 - *Smart drugs affecting processes important for a specific step in B-cell differentiation*

TARGET TREATMENT OF LYMPHOMAS drugs

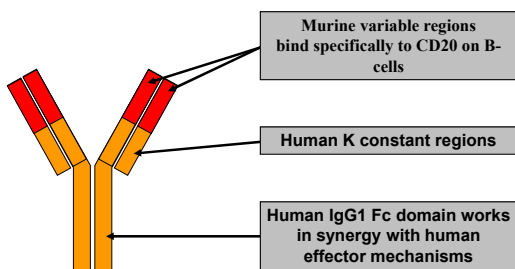
- **Monoclonal antibodies**
 - **Unconjugated, conjugated** (to radioactive isotopes or toxins)
- Proteasome inhibitors
 - Bortezomib
- Immunomodulators
 - Thalidomide, lenalidomide
- HDAC inhibitors
- *Antiangiogenic drugs*
- *M-TOR inhibitors, HSP inhibitors...*

MONOCLONAL ANTIBODIES RITUXIMAB

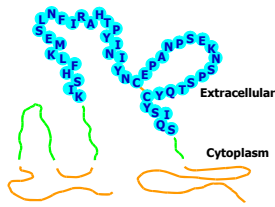
- The big **R**



Rituximab: a chimeric human/mice monoclonal antibody



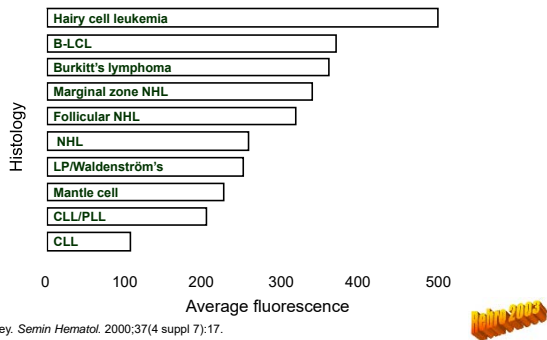
CD20 molecule



- Transmembrane phosphoprotein
- Single extracellular loop
- Natural ligand unknown
- Physiologic function uncertain
- Present on most B-cell neoplasms
- Resistant to internalization or shedding after antigen binding

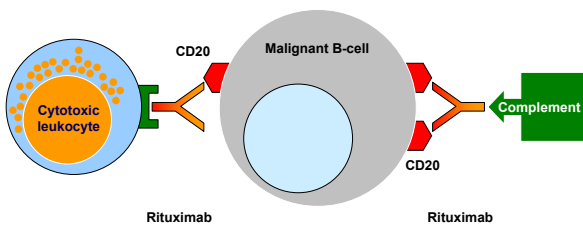
Einfield et al. EMBO J 1988;7:711-7

EXPRESSION OF CD20 IN B-CELL NEOPLASMS



Maloney. Semin Hematol. 2000;37(4 suppl 7):17.

Interaction of rituximab with immunological mechanisms of the host



Adapted from Male D, et al., *Advanced Immunology* 1996: 1.1-1.16

RITUXIMAB TOXICITY

- Rare infusion reactions
 - Allergy to murine proteins
 - Cytokine-release syndrome
- Reduced IgM levels with prolonged use
- Hematological toxicity negligible
 - Ideal for combining with chemotherapy

ALEMTUZUMAB antiCD52

- First monoclonal antibody designed for treatment of hematological neoplasia
 - clinical development hindered by toxicity and incompetence of pharmaceutical industry
- CD52
 - Present on granulocytes, lymphocytes and most NHLs

ALEMTUZUMAB TOXICITY

- Severe and frequent infusion reactions
 - Do not occur with sc administration
- Subacute skin reactions after sc administration
- Hematological toxicity unpredictable
 - Occasionally severe granulocytopenia and/or thrombocytopenia in 1st week of treatment
- Severe immunodeficiency
 - AIDS type: CMV, PCP, fungi etc.
 - Microbiological surveillance, preemptive treatment, early broad-spectrum antibiotic coverage

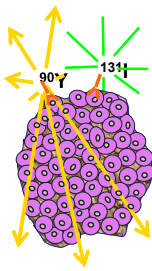
CONJUGATED ANTIBODIES
Biological basis

- Radioactive isotope or toxin bound to antibody
- Antibody targets the tumor
- Radioactivity or toxin increases tumor cell kill

Anti-CD20 abs conjugated with radioactive isotopes

- Ibritumomab with ⁹⁰Y (Zevalin) and tositumomab with ¹³¹I (Bexxar)
- Toxicity
 - Prolonged subacute hematological
- Not adequate for
 - pts. with bone marrow infiltration > 25%
 - reduced bone marrow function

Choice of isotope



Properties	⁹⁰ Yttrium	¹³¹ Iodine
Half-life	64 hours	192 hours
Energy emitter	Beta (2.3 MeV)	Gamma (0.36 MeV) Beta (0.6 MeV)
Path length	χ_{90} 5 mm	χ_{90} 0.8 mm
Urinary excretion	Minimal 7% in 7 days	Extensive/variable 46 - 90% in 2 days
Dosing	Based on weight and platelet count	Clearance based dosing using whole body dosimetry
Administration	Outpatient	Inpatient or restrictions to protect family/public

HDAC INHIBITORS

- HDAC = histone deacetylase
 - Deacetylation necessary for transcription
 - Inhibitors inhibit gene transcription
- Vorinostat
 - Toxicity
 - gastrointestinal, asthenia, hyperglycemia, hematological, respiratory

DRUGS REGISTERED FOR MM, USEFUL IN NHL

- | | |
|--|--|
| <ul style="list-style-type: none">• BORTEZOMIB• Proteasome inhibitor• Intravenous application 4x/3wks.• Toxicity<ul style="list-style-type: none">– neuropathy, thrombocytopenia, nausea & vomiting, diarrhea... | <ul style="list-style-type: none">• THALIDOMIDE, LENALIDOMIDE• Mode of action unknown<ul style="list-style-type: none">– Immunomodulator, antiangiogenic agent,...• Continuous oral application• Toxicity thalidomide<ul style="list-style-type: none">– Neuropathy, DVT, sedation, constipation• Toxicity lenalidomide<ul style="list-style-type: none">– Hematological, DVT |
|--|--|

DLBCL

- Front-line treatment
 - chemotherapy + **rituximab**
 - ↑ OS by 15%, PFS and RR by 20%
 - [recommendation grade A](#)
- Salvage, R-naive pts.
 - chemotherapy + **rituximab**
 - ↑ RR and PFS by 20%, OS not significant (later treatment?)
 - [recommendation grade A](#)
- Salvage, R-pretreated patients
 - chemotherapy + **rituximab**
 - everybody does it but no data
 - [recommendation grade D](#)
- Possible indications
 - **Zevalin or Bexxar** + BEAM for pretransplant conditioning
 - **Zevalin or Bexxar** for salvage treatment – RR 20-50%, TTP 6 mo.

- Burkitt
 - Chemotherapy + **rituximab**
 - ↑ OS by > 20%
 - [recommendation grade B](#)
- Mantle-cell lymphoma
 - Front-line and salvage in R-naive pts.
 - Chemotherapy + rituximab
 - ↑ PFS, OS not significant (later treatment?)
 - [recommendation grade A](#)
 - Rituximab maintenance
 - [recommendation grade C](#)
 - Zevalin / Bexxar not very effective
 - MRD treatment
 - [recommendation grade C](#)
 - Relapsed / refractory
 - **Bortezomib** RR 35%, some responses long-lasting
 - **Thalidomide** and **lenalidomide** RR 50%

INDOLENT NHLs

- FL
 - **Rituximab** monotherapy
 - Effective, non-toxic alternative to chemotherapy
 - **Rituximab** + chemotherapy
 - ↑ OS 2,5%/year for at least 4 years
 - [recommendation grade A](#)
 - **Zevalin / Bexxar** for remission consolidation in R-naive pts. ↑ PFS, OS too early
 - [recommendation grade A](#)
 - Effect in pts. receiving R+chemo smaller
 - Zevalin/Bexxar for R+chemo resistant pts.
 - RR 50%, some responses long-lasting
 - [recommendation grade B](#)
- Indolent non-FL
 - As FL but less evidence

MYCOSIS FUNGOIDES / SEZARY

- Vorinostat
 - HDAC inhibitor
 - RR 50%, toxicity gastrointestinal
- Denileukin diftitox
 - Recombinant protein hybrid of IL-2 and diphtheria toxin
 - RR 35%, toxicity systemic + immunosuppression
- Alemtuzumab (anti CD52)
 - RR 55%, severe cellular immunosuppression
- Bexaroten
 - Retinoid (differentiating agent)
 - RR 48% TTP 10 mo, hyperlipidemia

DRUGS IN TRIALS

- Lenalidomide
 - Maintenance and induction combinations with chemotherapy in indolent and mantle-cell NHL, possibly other B-NHLs
- Bortezomib
 - Induction treatment in MCL, possibly T-NHL
- Anti-CD80
 - Combination with rituximab or chemotherapy in B-NHL and HL
- Increased potency anti-CD20
 - Indolent NHLs failing R, CLL
- Zevalin
 - Remission consolidation in DLBCL
- Alemtuzumab
 - Combination with chemotherapy for T-NHL

DRUGS IN TRIALS

- HDAC inhibitors
 - HL and T-NHL
- M-TOR inhibitors
 - Everolimus, temsirolimus
 - In combination for induction, monotherapy for maintenance
 - Indolent NHL, MCL,...
- Bevacizumab
 - + chemotherapy for induction of DLBCL
- Enzastaurin (PKC inhibitor)
 - Maintenance in B-NHLs
- Anti-CD22 + ozogamycin
 - Indolent NHL, induction

DISAPPOINTMENTS

- Anti-CD30s
- Epratuzumab
- FTIs (farnesyl-transferase inhibitors)
- ...

**TARGET TREATMENT OF LYMPHOMAS
CONCLUSIONS**

- Rituximab
 - Revolution in the treatment of B-NHL
- Radioimmunotherapy
 - Here to stay
 - Probably better for consolidating remissions than as monotherapy
- Bortezomib, thalidomide, lenalidomide
 - Useful for relapsed/refractory MCL
- Other drugs
 - We'll see whether they'll live up to the expectations

Target treatment of lung cancer

*Dott. Marcello Tiseo
Oncologia Medica
Azienda Ospedaliero-Universitaria di Parma*

Therapeutic paradigms and background in advanced NSCLC

- Cytotoxic chemotherapy improves survival in the 1st and 2nd line setting
- In 1st line, 2 drugs (platinum + third generation agent) are better than 1
- In 2nd line, docetaxel or pemetrexed are CT registered
- Targets of chemotherapy are largely DNA, tubulin and topoisomerases; consequences of inhibiting these targets are broad
- Lung cancer is molecularly very complex
- The heterogeneity of lung cancer provides opportunity for both one drug/one target as well as one drug/multiple targets

Efficacy plateau of cytotoxic chemotherapy in NSCLC

Study	Drugs	# Pts	%, St. IV	%, ORR	MST	%, 1-YS
Kelly, 2001 SWOG 9503	Vnr/Cis	202	88	28	8	33
	Tax225/Cb	208	89	25	8	36
Schiller, 2002 ECOG 1594	Tax135/Cis	292	89	21.3	8.1	31
	Gem/Cis	288	86	21	8.1	36
	Txt/Cis	293	86	17.3	7.4	31
	Tax225/Cb	290	86	15.3	8.3	35
Scagliotti, 2002 ILCP	Vnr/Cis	201	81	30	9.5	37
	Gem/Cis	205	81	30	9.8	37
	Tax225/Cb	201	82	32	9.9	43
Belani, 2002 TAX 326	Vnr/Cis	404	67	25	10.1	41
	Txt/Cis	408	67	32	11.3	46
	TxT/Cb	402	67	24	9.4	38

How to improve results?

- **New cytotoxics**
- **Personalized chemotherapy according to the patient's genetic make-up**
- **Molecular targeted therapies**
 - **Drugs to treat biologically homogenous cancer patient population**
 - **Tumor specific molecular abnormality**
 - **Tumor specific molecular profile**
 - **Expression of a specific receptor or antigen**

Where have the successes been thus far in advanced NSCLC?

Recent advances in advanced NSCLC

- ECOG 4599 and AVAiL trials – Bevacizumab added to chemotherapy improves clinical outcomes
- FLEX trial – Cetuximab added to chemotherapy improves clinical outcomes
- BR21 trial – Erlotinib improves clinical outcomes versus placebo in refractory, advanced NSCLC
- INTEREST trial – Gefitinib is not inferior to docetaxel in refractory, advanced NSCLC

Phase III Trial of Bevacizumab in Non-Squamous NSCLC: ECOG 4599

Eligibility:

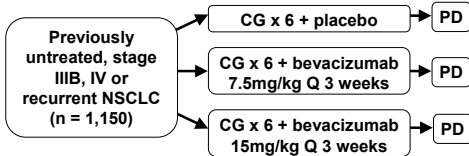
- Non-squamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

(PC)
Paclitaxel 200 mg/m²
Carboplatin AUC = 6
(q 3 weeks) x 6 cycles

(PCB)
PC x 6 cycles
+
Bevacizumab
(15mg/kg q 3 wks) to PD

Sandler et al. NEJM 2006

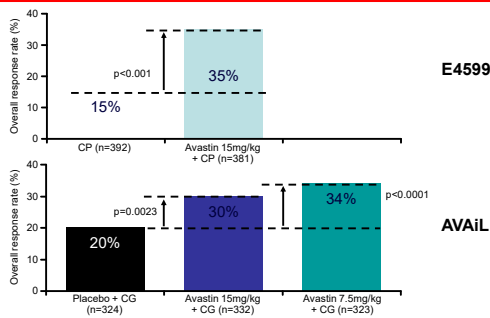
Phase III Trial of Bevacizumab in Non-Squamous NSCLC: AVAiL trial



- Cisplatin 80mg/m² i.v. every 3 weeks; gemcitabine 1,250mg/m² on days 1 and 8 of each 3-week cycle
- Primary endpoint: progression-free survival
- Secondary endpoint: overall survival and response rate

Manegold et al. ASCO 2007
Manegold et al. ESMO 2008

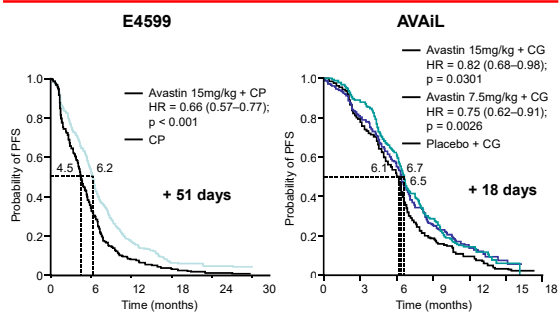
Overall response rates have increased significantly with Bevacizumab



CP = carboplatin/paclitaxel; CG = cisplatin/gemcitabine

Sandler et al. NEJM 2006
Manegold et al. ASCO 2007

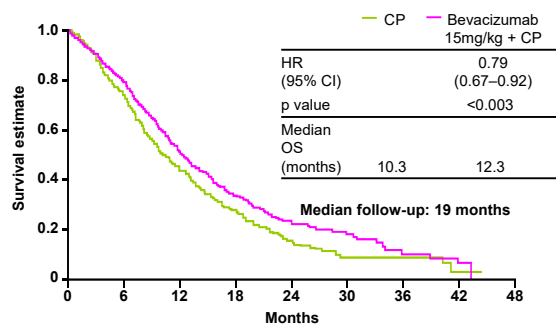
Bevacizumab-based therapy significantly improves PFS



CP = carboplatin/paclitaxel
CG = cisplatin/gemcitabine; HR = hazard ratio

Sandler et al. NEJM 2006
Manegold et al. ASCO 2007

Bevacizumab-based therapy significantly improves OS

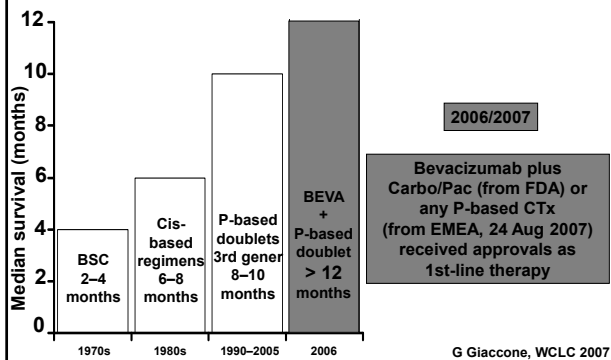


Sandler et al. NEJM 2006

Bevacizumab in advanced NSCLC

Study	Regimen	N° pts	ORR %	PFS, months	MST, months
ECOG 4599	CbT + Placebo	444	15	4.5	10.3
	CbT + Bev 15	434	35 <i>p</i> = .001	6.2 HR = .66	12.3 HR = .79 <i>p</i> = .003
AVAiL	CG + Placebo	347	20	6.1	13.1
	CG + Bev 7.5	345	34 <i>p</i> = .0001	6.7 HR = .75	13.6 HR = .93
	CG + Bev 15	351	30 <i>p</i> = .0017	6.5 HR = .82	13.4 HR = 1.03

1ST-line therapy in advanced NSCLC: significant milestones



Patient selection for bevacizumab therapy

Inclusion	Exclusion
Non-squamous NSCLC	Grade ≥ 2 haemoptysis
Chemo-naïve	Radiological evidence of tumour invasion of major blood vessels
Inoperable stage IIIB-IV or recurrent	Brain metastases or spinal cord compression
ECOG PS of 0-1	Uncontrolled hypertension
	History of thrombotic or haemorrhagic disorders
	Therapeutic anticoagulation within 10 days of first dose

Sandler et al. NEJM 2006
Manegold et al. ASCO 2007

Severe (grade ≥ 3) haematologic toxicity in ECOG and AVAiL trials

	Placebo + PC n = 440	Bevacizumab 15 mg/kg + PC n = 437	p
Neutropenia	16.8	25.5	< 0.002
Anemia	0.2	1.6	< 0.04
	0.9	0	ns

	Placebo + CG n = 327	Bevacizumab 7.5 mg/kg + CG n = 330	Bevacizumab 15 mg/kg + CG n = 329
Neutropenia	32	40	36
Anemia	23	27	23
	14	10	10

Sandler et al. NEJM 2006
Manegold et al. ASCO 2007

Elderly analysis of ECOG trial

- 224 patients aged ≥ 70 years in E4599
- No improvement in survival with PCB vs PC:
 - PFS: 5.9 m vs. 4.9 m; $p = .063$
 - OS: 12.1 m vs. 11.3 m; $p = .4$
- More Grade 3/4 toxicity in elderly patients on PCB arm:

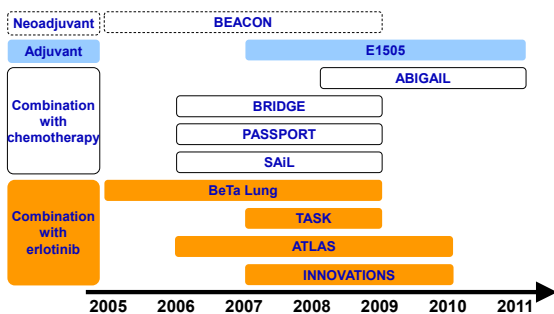
	≥ 70 y	< 70 y	p value
Neutropenia (G4)	34%	22%	.02
Melena/GI bleed	3.5%	1%	.005
Muscle weakness	8%	2%	.02
Motor neuropathy	3.5%	$< 1\%$.05
Tx-related deaths	6%	3%	.08

Ramalingam et al. J Clin Oncol 2008

in first-line treatment: conclusions

- Two large trials:
 - One ECOG 4599 with a control arm doing poor, showed and improved RR, PFS and survival
 - One with a very good control arm showed an improved RR, not clinically meaningful PFS and no benefit on survival
- Both with increased risk of toxicity and an increase in cost
- On selected patients

exploring therapeutic options now and in the future



Recent advances in advanced NSCLC

- ECOG 4599 and AVAiL trials – Bevacizumab added to chemotherapy improves clinical outcomes
- FLEX trial – Cetuximab added to chemotherapy improves clinical outcomes
- BR21 trial – Erlotinib improves clinical outcomes versus placebo in refractory, advanced NSCLC
- INTEREST trial – Gefitinib is not inferior to docetaxel in refractory, advanced NSCLC

FLEX
A randomized, multi-center, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the 1st-line treatment of patients with advanced non-small cell lung cancer (NSCLC)

R. Pirker, A. Szczesna, J. von Pawel, M. Krzakowski, R. Ramlau, K. Park, U. Gatzemeier, E. Bajetta, M. Emig, J. Pereira

On behalf of all FLEX Investigators

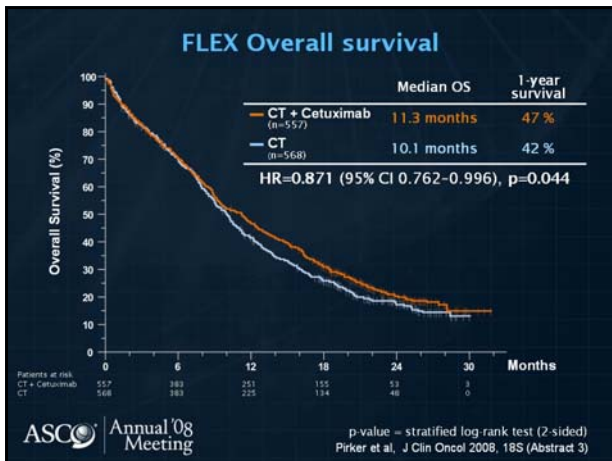
ASCO Annual '08 Meeting

Medical University of Vienna, Vienna, Austria; Mazowieckie Centrum Leczenia Chorob Płuc i Gruzi, Otwock, Poland; Asklepios Fachklinikum Muenchen-Gauting, Gauting, Germany; Centrum Onkologii - Instytut im. Marii Skłodowskiej-Curie, Warszawa, Poland; Wielkopolskie Centrum Chorob Płuc i Gruzi, Poznan, Poland; Samsung Medical Center, Seoul, Republic of Korea; Hospital Christusdorf, Hamburg, Germany; Fondazione IEO Istituto Nazionale dei Tumori, Milano, Italy; Merck Serono, Darmstadt, Germany; Instituto de Cancer - Arnaldo Vieira de Carvalho, Sao Paulo, Brazil

FLEX
Study design

Chemotherapy (CT)	Cetuximab
Cisplatin 80 mg/m ² day 1 Vinorelbine 25 (30) mg/m ² days 1, 8 Every 3 weeks, up to 6 cycles	initial dose 400 mg/m ² then 250 mg/m ² weekly

ASCO Annual '08 Meeting



- ### Flex Study: Results
- 67% of screened pts (85% EGFR+) eligible
 - RR: 29 vs 36% (p = 0.012)
 - PFS: 4.8 vs 4.8 months
 - TTF: 3.7 vs 4.2 months (p = 0.015)
 - **MS: 10.1 vs 11.3 months**
 - **1-Year survival: 42 vs 47% (HR 0.87, p = 0.044)**
 - Results unaffected by histology
 - Limited benefit in Asiatics

FLEX Safety profile

Adverse Events Grade 3/4	CT + Cetuximab (n=548)	CT (n=562)
Any event	91 % ¹	86 %
Neutropenia	53 %	51 %
Febrile neutropenia	22 % ¹	15 %
Anemia	14 %	17 %
Acne-like rash (only grade 3) ²	10 % ¹	<1 %
Diarrhea	5 % ¹	2 %
Infusion-related reactions	4 % ¹	<1 %
Treatment-related deaths	3 %	2 %

ASCO Annual '08 Meeting
¹ p<0.05
² There was no grade 4 acne-like rash

FLEX regimen: Pro and Contra

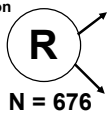
	PRO	CONTRA
Efficacy	●	
CT regimen		●
Toxicity		●
Histology	●	
Patients selection		●
Costs		●

Phase III Trial of Taxane/Cb ± Cetuximab: BMS-099 Study Design

1st line treatment for advanced NSCLC

Stratification

- Site
- PS
- Taxane



Paclitaxel 225 mg/m² d1 or
Taxotere 75 mg/m² d1 +
Carboplatin AUC = 6 d1
Q3wk for a maximum of 6 cycles +
Cetuximab
400 mg/m² d1 wk1; 250 mg/m²

Paclitaxel 225 mg/m² d1 or
Taxotere 75 mg/m² d1 +
Carboplatin AUC = 6 d1
Q3wk for a maximum of 6 cycles

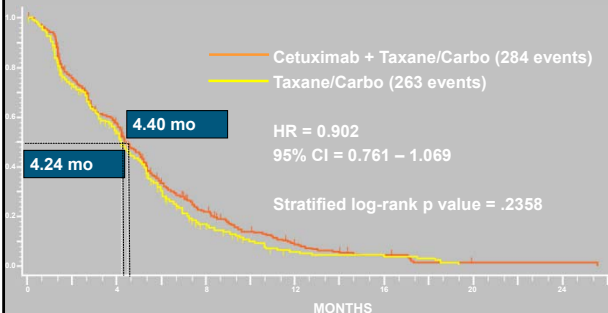
Primary endpoint: PFS (by IRRC)

Secondary endpoints: RR, OS, QOL, Safety

IRRC = Independent Review Radiologists Committee

Lynch et al. WCLC 2007

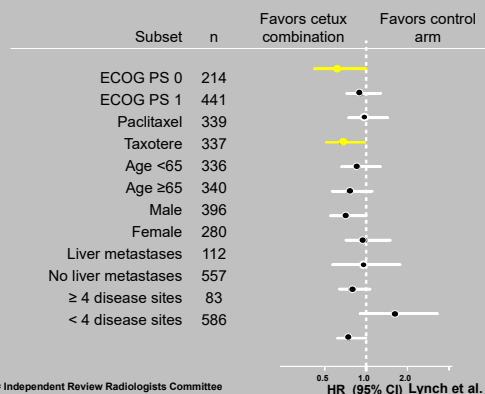
Phase III Trial of Taxane/Cb ± Cetuximab: PFS per IRRC



IRRC = Independent Review Radiologists Committee

Lynch et al. WCLC 2007

BMS-099: PFS in Pre-Planned Subsets



Contribution of cetuximab in first-line treatment: conclusions

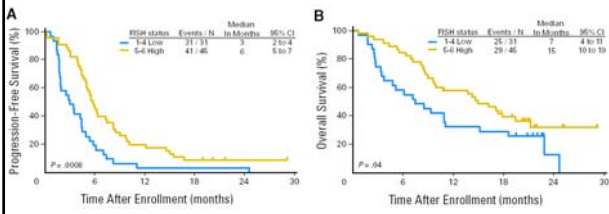
- Two large trials:
 - FLEX trial, with a not very standard CT arm, showed an improvement in RR and survival (not in PFS)
 - In BMS-099 difference in PFS and OS did not reach statistical significance (greater PFS improvements in patients on Taxotere)
- Survival benefit: same magnitude (1,2-1,3 months) in two trials (but BMS-099 lower power than FLEX trial)
- Both with increased risk of toxicity and an increase in cost
- Not histology selection, but EGFR IHC + patients (?)

Survival summary in phase III trials with bevacizumab and cetuximab

Treatment	EXPER. ARM (MS - mos)	CONTROL ARM (MS - mos)	p value
ECOG 4599 (bevacizumab) NEJM 2006	12.3	10.3	0.003
AVAiL (bevacizumab) ESMO 2008	13.6	13.1	NS
FLEX (cetuximab) ASCO 2008	11.3 12*	10.1 10.3*	0.044
BMS 099 (Taxane-Cetux) press release	9.7	8.4	NS

* Only non-squamous

Increased *EGFR* Gene Copy Number Detected by Fluorescent In Situ Hybridization Predicts Outcome in Non-Small-Cell Lung Cancer Patients Treated With Cetuximab and Chemotherapy



Treatment Arm and <i>EGFR</i> FISH Status	No. of Patients	OR (%) ^a	DCR (%)
All patients			
FISH negative	31	26	55
FISH positive	45	45	81 [‡]

Hirsch et al. J Clin Oncol 2008

Phase II study of cetuximab with cisplatin-docetaxel in the first-line treatment of biologically selected patients with advanced NSCLC: GOIRC trial

- NSCLC, stage IIIB-IV, PS 0-1
- availability of tissue specimen for EGFR FISH determination

↓

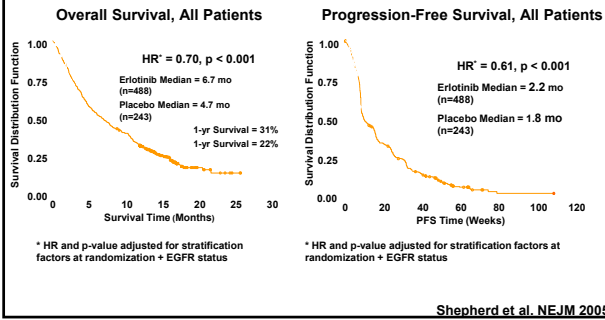
Cetuximab 400 mg/m² at the 1st infusion, subsequently 250 mg/m² weekly and Cisplatin 75 mg/m² and Docetaxel 75 mg/m² i.v. on day 1 of a 21 days cycle

The primary end-point is RR; this is non-randomized phase II study in which all patients will be accrued and treated with cetuximab-cisplatin-docetaxel and the activity in terms of response rate compared between those with positive biological features (EGFR FISH +, 40% of the overall population) versus those with negative ones (EGFR FISH -)

Recent advances in advanced NSCLC

- ECOG 4599 and AVAiL trials – Bevacizumab added to chemotherapy improves clinical outcomes
- FLEX trial – Cetuximab added to chemotherapy improves clinical outcomes
- BR21 trial – Erlotinib improves clinical outcomes versus placebo in refractory, advanced NSCLC
- INTEREST trial – Gefitinib is not inferior to docetaxel in refractory, advanced NSCLC

BR.21: Erlotinib versus placebo Overall Survival and PFS



Erlotinib and Gefitinib: BR21 and ISEL trials

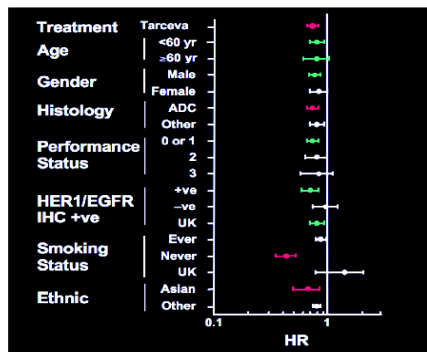
Table 3. Efficacy of erlotinib and gefitinib in the BR.21 and ISEL trials

	Erlotinib [20]	Gefitinib [21]
Overall study population		
n	427	959
Objective response (%)	8.9	8
Stable disease (%)	35	32
Progressive disease (%)	38	37
Nonevaluable (%)	17*	23
Overall survival	HR, 0.70; 95% CI, 0.58–0.85; $p < .001$	HR, 0.89; 95% CI, 0.77–1.02; $p = .087$
1-year survival rate	31%	27%
Subset analyses		
Adenocarcinoma	HR, 0.70; 95% CI, 0.6–0.9; $p = .008$ (n = 365)	HR, 0.84; 95% CI, 0.68–1.03; $p = .089$ (n = 812)
Never smokers	HR, 0.4; 95% CI, 0.3–0.6; $p < .001$ (n = 146)	HR, 0.67; 95% CI, 0.49–0.92; $p = .012$ (n = 375)
Asian ethnicity	HR, 0.6; 95% CI, 0.4–1.0; $p = .06$ (n = 91)	HR, 0.66; 95% CI, 0.48–0.91; $p = .01$ (n = 342)

*Includes patients whose disease progression could not be confirmed.
Abbreviations: CI, confidence interval; HR, hazard ratio; ISEL, Iressa Evaluation in Lung Cancer.

Shepherd et al. NEJM 2005, Thatcher et al. Lancet 2005

BR21: survival benefit with Erlotinib across all subgroups



BR21: survival benefit with Erlotinib across all biological subgroups

- Response rate to erlotinib is higher in patients with mutations, IHC+ tumours and high gene copy number
- The survival benefit from erlotinib was greater, although not significantly, in patients with exon 19 or 21 mutations, IHC+ tumours and in those with high gene copy number, but none of the interaction p values was significant

Tsao et al. NEJM 2005

Prospective trials of EGFR-TKIs in patients with EGFR mutations

Author	Agent	RR (%)	PFS	OS/1-yr
Pas-Ares	Erlotinib	31/38 (82)	13.3	NR/81
Morikawa	Gefitinib	13/20 (65)	9.7	NR
Sunaga	Gefitinib	16/21 (77)	13	NR
Sutani	Gefitinib	21/27 (77)	9.4	15.4/NR
Inoue	Gefitinib	12/16 (75)	9.7	NR
Asahina	Gefitinib	12/16 (75)	8.9	NR
Sequist	Gefitinib	17/31 (55)	11.4	20.8/73
		122/169 (72)		

IPASS: Study Design

- Patients**
- Chemo-naïve
 - Age ≥18 years
 - Adenocarcinoma histology
 - Never or light ex-smokers*
 - Life expectancy ≥12 weeks
 - PS 0-2
 - Measurable stage IIIB / IV disease

Gefitinib
(250 mg / day)

Carboplatin
(AUC 5 or 6) /
paclitaxel
(200 mg / m²)
3 weekly[#]

- Endpoints**
- Primary**
- Progression-free survival (non-inferiority)
- Secondary**
- Objective response rate
 - Overall survival
 - Quality of life
 - Disease-related symptoms
 - Safety and tolerability
- Exploratory**
- Biomarkers
 - EGFR mutation
 - EGFR-gene-copy number
 - EGFR protein expression

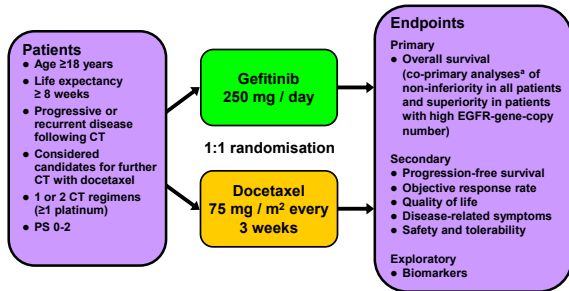
*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; [#]limited to a maximum of 6 cycles
 Carboplatin / paclitaxel was offered to gefitinib patients upon progression
 PS, performance status; EGFR, epidermal growth factor receptor

ESMO 2008

Recent advances in advanced NSCLC

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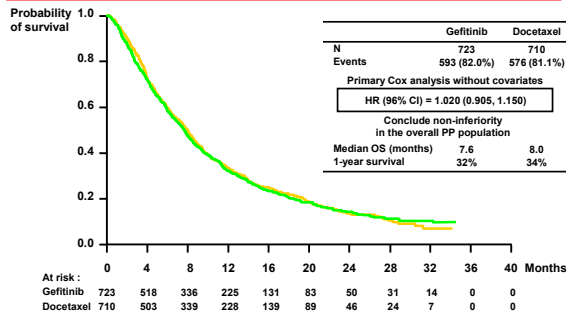
INTEREST study design



^aModified Hochberg procedure applied to control for multiple testing
CT, chemotherapy; PS, performance status

Douillard et al, WCLC 2007

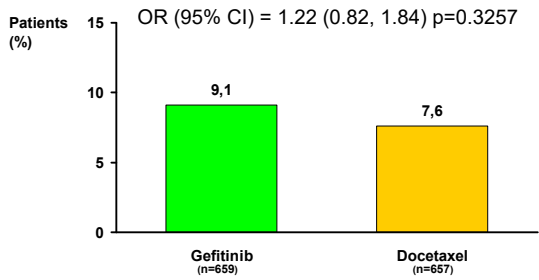
INTEREST study: Overall survival



Per-protocol (PP) population
Pre-specified NI limit in HR terms (translates to 250% effect retention [Rothmann 2003]) = 1.154
NI, non-inferiority; HR, hazard ratio; OS, overall survival

Douillard et al, WCLC 2007

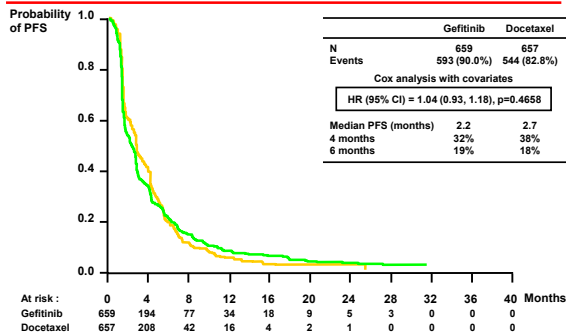
INTEREST study: objective tumour response



Evaluable for response (EFR) population
OR >1 implies a greater chance of response on gefitinib
OR and p-value from logistic regression with covariates
OR, odds ratio; CI, confidence interval

Douillard et al, WCLC 2007

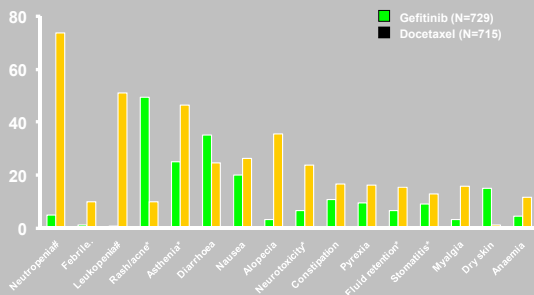
INTEREST study: Progression-free survival



Evaluable for response (EFR) population; HR <1 implies a lower risk of progression on gefitinib; PFS, progression-free survival

Douillard et al, WCLC 2007

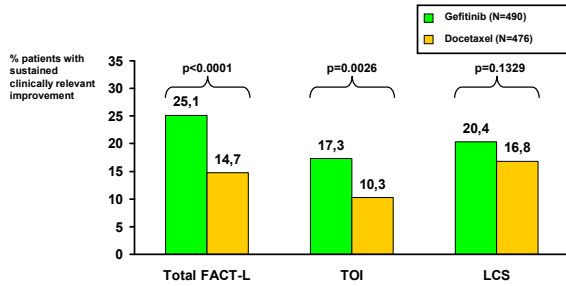
Most common AEs (≥ 10% on either treatment) with ≥ 3% difference between treatments



*Worsening in lab value from baseline
*Grouped term (sum of several preferred terms)

Douillard et al, WCLC 2007

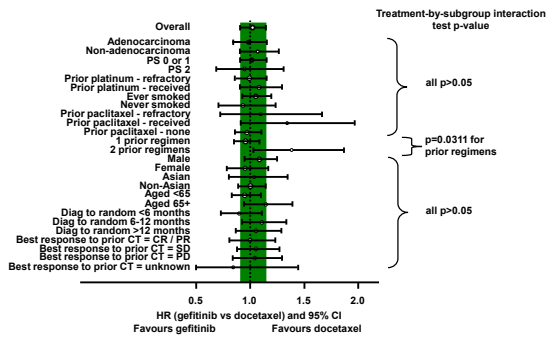
Quality of life and symptom improvement rates



Evaluate for quality of life population
 p-values from logistic regression with covariates. Clinically relevant improvement pre-defined as 6-point improvement for FACT-L and TOI; 2-point improvement for LCS, maintained for at least 21 days
 EFQ, evaluable for quality of life; FACT-L, Functional Assessment of Cancer Therapy-Lung;
 TOI, Trial Outcome Index; LCS, Lung Cancer Subscale

Douillard et al, WCLC 2007

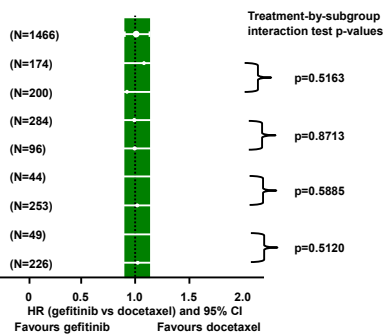
Overall survival by clinical subgroups



Overall PP population. Cox analysis without covariates

Douillard et al, WCLC 2007

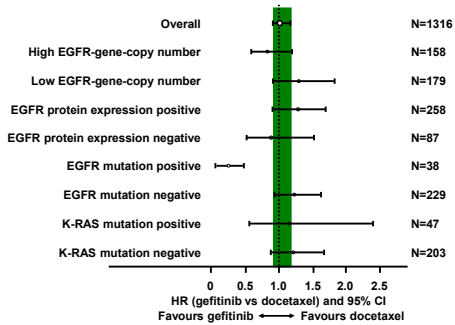
Overall survival by biomarker subgroup



ITT population; Cox analysis without covariates

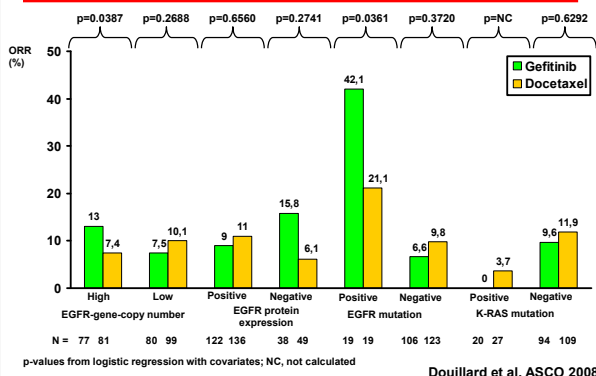
Douillard et al, ASCO 2008

Progression-free survival by biomarkers



Douillard et al, ASCO 2008

Objective response rate by treatment and biomarker status

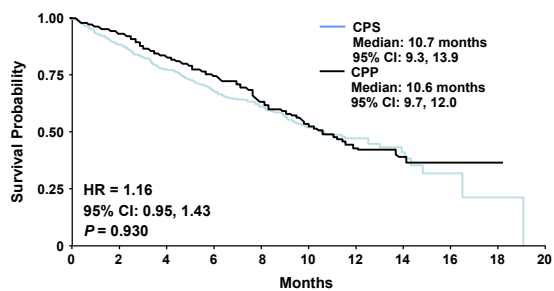


Douillard et al, ASCO 2008

Exploratory biomarkers summary

- Consistent with the overall result, OS was similar for gefitinib and docetaxel irrespective of EGFR gene-copy number, EGFR protein expression or EGFR mutation or K-RAS mutation status
 - on both treatments, patients with EGFR mutations lived longer than those without
- PFS was similar for both treatments in all biomarker subgroups apart from patients with EGFR mutations, where PFS was longer for gefitinib than docetaxel
- No differences in ORR between treatments were seen in biomarker subgroups apart from high EGFR gene-copy number and EGFR mutations, where ORR was higher for gefitinib than docetaxel
- These findings should be interpreted in the context of exploratory analyses often based on small numbers and the tests performed on archival diagnostic tumour tissue

ESCAPE: CbP + Sorafenib Overall Survival (ITT Population)



Patients at Risk

CPS	464	406	354	268	155	86	47	16	7	1
CPP	462	426	377	300	157	83	34	13	5	1

Scagliotti et al, ESMO IASLC 2008

Sunitinib and Vandetinib: A Model for One Drug/Multiple Targets

- Both are multi-targeted RTK inhibitors
- Active in a number of solid tumors
- Sunitinib: approved for use in renal cell carcinoma and imatinib-refractory GIST
- Vandetinib and Sunitinib currently in Phase III testing in NSCLC
- Both have tolerable toxicity profiles
- Inhibition of which targets account for the activity (and for that matter the toxicity) of these agents?

Conclusions

- Cytotoxic chemotherapy is targeted therapy but is non-specific relative to our thinking of new agents targeting specific receptor pathways
- The One Drug/One Target strategy is effective in combination with cytotoxic chemotherapy (ECOG 4599, AVAiL and FLEX trials)
- The One Drug/One Target strategy is also effective as a single agent (BR.21 and INTEREST trials)
- The One Drug/Multiple Target strategy may be a more effective strategy when using targeted therapies alone (ongoing clinical trials)

True or Not?

Avoid bevacizumab in patients with:

- **Cardiac disease**
- **Hypertension**
- **CNS lesions**
- **Coagulopathy (on anticoagulation)**
- **Peritoneal metastases**
- **Recent surgery**
- **“Central” or “large” chest lesions**

Safety of bevacizumab treatment in patients receiving full-dose anticoagulation (FDAC)

- Patients receiving FDAC for prophylactic purposes are eligible for bevacizumab therapy
- In the AVAiL trial, no grade ≥ 3 pulmonary haemorrhage events were reported in patients receiving FDAC

	Patients receiving FDAC (n=86)			Non-anticoagulated patients (n=900)		
	Placebo + CG (n=28)	Bev 15* + CG (n=26)	Bev 7.5* + CG (n=32)	Placebo + CG (n=299)	Bev 15* + CG (n=303)	Bev 7.5* + CG (n=298)
Pulmonary haemorrhage						
All grades (%)	10.7	19.2	6.3	4.7	8.9	7.0
Grade ≥ 3 (%)	0	0	0	0.7	1.0	1.7

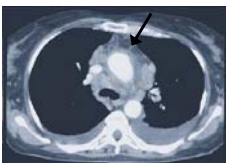
*mg/kg

Leigh et al. Eur J Cancer Suppl 2007

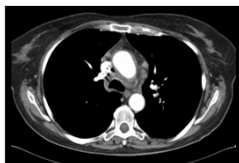
Appropriate patient selection for bevacizumab therapy: central tumour

- Patients with centrally located tumours are eligible for bevacizumab therapy
- Such patients can be successfully treated with bevacizumab

October 2007
Before bevacizumab



December 2007
During bevacizumab



Scans courtesy of Dr Martin Reck

NEVROENDOKRINI GASTROENTEROPANKREATIČNI TUMORJI (GPNET)

Predstavitev kliničnih primerov

Marko Boc, dr.med.
Brigita Gregorič, dr.med.
Mentor: dr. Janja Ocvirk, dr.med.

- groba incidenca v Evropi 3/100.000
- najpogostejše po 50. letu, razen neuroendokrini tumorji apendiksa, ki največkrat nastanejo okoli 30. leta
- bolniki z genetsko predispozicijo za GPNET pričnejo obolevati povprečno 15 let prej kot ljudje s sporadičnim GPNET
- MEN-1 (multipla endokrini neoplazija)
 - mutacija tumor supresorskega gena na 11q k.=>AD dedovanje
 - prevalenca 2/100.000
 - pogostejši predvsem PNET: 45% somatostatinomov, 25-40% gastrinomov, 15% GFRomov in 10% glukagenomov
- vHL (von Hippel-Lindau)
 - prevalenca 1/30-40.000
 - mutacija tumor supresorskega gena na 3p k.=>AD dedovanje
 - za PNET oboli 12-17 % bolnikov
- NF-1 (neurofibromatoza tip 1)
 - prevalenca 1/3-4.000
 - mutacije tumor supresorskega gena na 17q k.=>AD dedovanje
- narašča incidenca PNET in NET rektuma

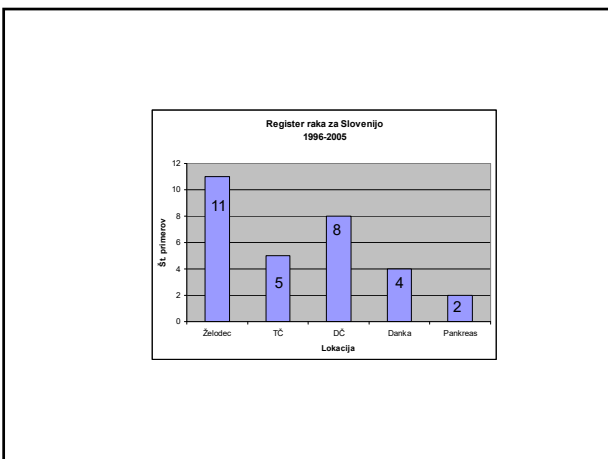
GPNET
heterogena skupina tumorjev

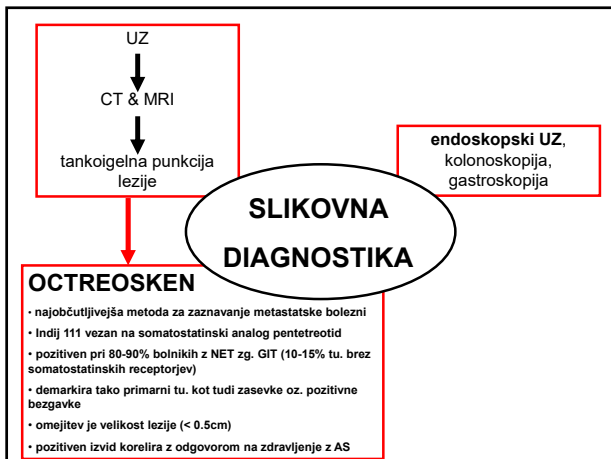
Lokalizacija primarnega tumorja:

- zgornji GIT: želodec, duodenum, **pankreas**
- srednji GIT: **jejunum, ileum (23-28%)**, apendiks, desni hemikolon
- spodnji GIT: levi hemikolon, rektum;

Maligni potencial:

- dobro diferenciran endokrini tumor (karcinoid)
- dobro diferenciran endokrini karcinom (maligni karcinoid), nizko maligni, globoko invazivni ali metastatski
- slabo diferenciran endokrini karcinom, visoko maligni
- mešani endokrini in eksokrini karcinom
- številne redke neuroendokrinsko sorodne lezije





Stadij in TNM:

Gradus	Število mitoz (10 HPF) ^a	Ki67 Index (%) ^b
G1	<2	<(=) 2
G2	2-20	3-20
G3	>20	<20

^aHPF ("high power field")=2mm², vsaj 40 pregledanih polj na mestu največje gostote mitoz
^bMIPI protiteleso

T (primarni tumor)	N (regionalne bezgavke)	M (oddaljene metastaze)
TX T0 T1 T2 T3 T4	NX N0 N1	MX M0 M1
Stadij I Stadij Ila Ila Illa Ilib Stadij IIV		T1 NO MO T2 NO MO T3 NO MO T4 NO MO kKt N1 MO kKt kKt N1 M1

• nevroendokrini markerji - PGP 9.5, sinaptofizin, kromogranin A
 • določitev GIT ali pankreatičnih hormonov z imunohistokemijo
 • vaskularna, perinevralna in limfatična invazija
 • ekscizijski robovi
 • infiltracija sosednjih tkiv (seroza, muscularis propria)
 • status bezgavk in distalne metastaze

Kirurško zdravljenje:

- preoperativno moramo preprečiti karcinoidno krizo
 - dolgotrajna rdečica kože, hipo- oz. hipertenzija, hud bronhospazem, motnje srčnega ritma
- profilaksa: kontinuirana i.v. infuzija Octreotida 50 mcg/h 12 h pred operacijo in 48 h po operaciji
- odstranitev primarnega tumorja
 - povečanje OS z 69 mesecev na 139 mesecev
- odstranitev primarnega tumorja in jetrnih metastaz
 - klinasta resekcija, delna hepatektomija
 - možno pri 20% bolnikov, perioperativna mortaliteta <3%
 - manj simptomov, izboljšanje kvalitete življenja
 - 5-letno preživetje 61%, brez OP 30% (mediano prež. 3-4 leta)^{*}

*Flöckinger U et al.Neuroendocrinology 2004; 80, 394-424

Selektivna (kemo)-embolizacija, RFA, krioblacija

Tarčna RT (na analog somatostatina vezani izotopi)

- Itrij 90 & Lutecij 177
- predvsem izboljšanje kvalitete življenja preko ↓ simptomov
 - PR 12-34%, MR 12-14%, SD 28-56%*
 - mediani TTP (Itrij 90) 30 m, mediani OS 59 m¹
 - mediani TTP in mediani OS (Lutecij 177) >30 m¹
 - indicirani pri bolnikih z pozitivnim oktreoskenom
 - !!! ledvična funkcija in penije!!!

Analogi somatostatina

- octreotid, lanreotid
 - predvsem dobra kontrola simptomov (↓ v 40-80%)¹
 - znižanje biokemičnih markerjev (kromogranin, 5-HIAA) v 40%¹

IFN z ali brez analoga somatostatina

- enake indikacije kot analogi somatostatina

KT (RR <10%)

- monoterapija adriamicin ali 5-FU => RR >20%
- DTIC manj učinkovit
- streptozotocin & klorozotocin najbolj učinkovita (!!!NEFROTOKSIČNA!!!)
- polikemoterapija 5-FU/DTIC/epidriamicin => PR 50%, SD 25%, PD 3%²
- bolj učinkovita pri hitro rastočih tumorjih (predvsem cisplatin/etoposid)

Tarčna zdravila bevacizumab, sunitinib, sorafenib, m-TOR inhibitor

- v raziskavah faze II uspešni pri inhibiciji rasti tu.

¹Plockinger U et al. Neuroendocrinology 2004; 80, 394-424

²Bajetta E et al. Ann Oncol 13 (2002) 614-621

1. KLINIČNI PRIMER

- 58-letna bolnica
- glede mlg. družinsko obremenjena
- 1957 prebolela hepatitis, drugače zdrava

- preiskave 2001:
 - UZ ugotovljena dilatacija pankreatičnega voda,
 - CT in endoskopski UZ trebuha pokažeta cc. 2 cm veliko tvorbo v glavi trebušne slinavke,
 - ERCP potrdi zaporo in razširitev pankreatičnega voda vse do repa trebušne slinavke (zapora in spremembe so kroničnega tipa)

1. KLINIČNI PRIMER

- maj 2001 – OP
 - subtotalna duodenopankreatomija z ohranjenim pilorusom
 - R0 resekcija
 - negativne bezgavke (0/29)
 - H (Inštitut za patologijo MF): endokrini karcinoid
 - 30% celic poz. na glukagon (glukagonom)
 - ponujeno zdravljenje z interferonom, ki ga bolnica odkloni
 - redna spremljava, UZ in nivo kromogranina bp

- februar 2007
 - UZ pokaže 3 spremembe v jetrih: 1x3 cm v DJR in dve manjši v LJR
 - MRI: več lezij v jetrih
 - OCTREOSKEN: potrdi 3 UZ ugotovljene lezije => poz. somatostatinski receptorji (drugje brez kopičenja)
 - močno zvišan kromogranin (749ng/L, norm <39ng/L) in zvišan 5 HIAA v urinu (5.5, norm 2-8mg/34h)
 - C 2008 (jetrna lezija-MRI): endokrini karcinoid
 - H 2001 (revizija na OI): endokrini karcinoid → **KOMBINACIJA**
 - nizka proliferacijska aktivnost
 - celice poz. na kromogranin in sinaptofizin
 - 30% celic pozitivnih na glukagon
 - 20% celic pozitivnih na VIP in PGP 9.5
 - ostale reakcije (serotonin, gastrin, insulin, somatostatin, PP) neg.

• **INTERFERON** => enake indikacije kot za somatostatinske analoge, izjema karcinoidna kriza

• glede na kontrolo simptomov primerljiv z analogi somatostatina

• 13 raziskav (1986-2003), različne doze interferona (TTP 12 mesecev, mediano preživetje 44-80 mesecev)

Št. bolnikov	Št. evaluiranih bolnikov	CR	PR	SD	PD
302	95% (287/302)	0	10% (29/287)	73% (185/253)	18% (44/243)

Pöckinger U et al. Neuroendocrinology 2004, 80, 394-424

1. KLINIČNI PRIMER

- prične zdravljenje z **Sandostatin LAR** in **KT** po shemi FDE (5-FU(5-fluorouracil), DTIC(dakarabazin), epirubicin)
- prejme 9. ciklusov (zadnjega 07/2008)
- kontrolni MRI (50% regres bolezni)
 - CR metastaz endokrinega karcinoma
 - ostajajo 3 metastaze, ki kopičijo octreotid
- avgust 2008 – resekcija 3 jeternih metastaz
 - H (OJ): metastaze neuroendokrinega tumorja
 - histološka slika skladna z prejšnjimi
 - PROFILAKSA!
- številni zapleti po OP
- zaključila zdravljenje brez bolezni

• **ANALOGI SOMATOSTATINA** izboljšajo simptome pri bolnikih z karcinoidnim sindromom (anti-sekretorni efekt)

• zmanjšanje biokemičnih markerjev pri 40% in izboljšanje simptomov pri 40-80% bolnikov

• antiproliferativni učinek neraziskan

	PR+CR	SD
	<10%	24-57%

• učinkovitost lanreotida in octreotida je primerljiva

• dozo je potrebno individualno stetrirati

• stranski učinki

blagi – abdominalne kolike, napihnjenost, steatoreja

hujši – nastanek žolčnih kamnov (50%, redko simptomatski), persistentna steatoreja in posledična malabsorbcija

Pöckinger U et al. Neuroendocrinology 2004, 80, 394-424

Adverse effect	NCI CTC grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Nausea/vomiting	16 (20)	16 (20)	3 (4)	-
Diarrhoea	7 (9)	4 (5)	-	-
Mucositis	15 (18)	12 (15)	2 (2)	-
Albopexia	2 (2)	7 (10)	29 (36)	21 (27)
Anemia	5 (6)	9 (11)	1 (1)	-
Sepsis	3 (4)	5 (6)	-	-
Anaemia	12 (15)	8 (10)	4 (5)	-
Leukopenia	4 (5)	6 (7)	2 (2)	3 (4)
Neutropenia	3 (4)	10 (12)	10 (12)	8 (11)
Thrombocytopenia	3 (4)	1 (1)	2 (2)	-

2. KLINIČNI PRIMER

- 60 letna bolnica
- družinska anamneza glede mlg. pozitivna
- od leta 1996 spremljana na OI zaradi histol. verif. MALT limfoma desne gl. arotis, v povezavi s Sjögrenovim sy, st. po tnzilektomiji, st. po TELA
- 2001 - dermoidna cista v predelu trtice
- sept. 2001 OP (drenaža in biospija) => H neg.
- preiskave:
 - UZ abdominalna & endoUZ - tu. za dist. rektumom, ki iz tega ne izrašča
 - MRI - tu. pred sakrumom, trtico velikosti 3 x 4 cm
 - octreoscan - kopičenje v sp. delu sakruma in pred trtico
 - transrektalna punkcija lezije
 - C: neuroendokrini karcinoid, ki ga imunohistokemično ne morejo potrditi
 - H: najverjetneje neuroendokrini karcinom oz. karcinoid
- dec. 2001 OP => ekspiracija tu. z delno resekcijo sakruma in trtice
 - H: neuroendokrini tu., z dezmoplazijo, nizke stopnje mlg.

2. KLINIČNI PRIMER

Zdravljenje:

- kirurško
 - tu. neradikalno odstranjen, kontrolni octreoscan pokaže ostanke oz. recidiv v medenici na dveh mestih
 - možnost zanosa celic tu. v biopsijski kanal
- sistemsko => indicirano zdravljenje z Yttrium 90-DOTEC (prejme 2. aplikaciji v Baslu)
- stranski učinki - ↓ ledvične funkcije, pancitopenija

Sledenje – UZ, MRI, 5-HIAA v urinu, kromogranin

April 2005 (3 leta) => bolečine na mestu prim. tu., ki se stopnjujejo že dalj časa

- octreoscan => kopičenje v post.delu sakruma in v jetrih => ponovitev bolezni
- UZ trebuha => potrdi številne lezije v jetrih
- indicirano zdravljenje z Lutecij 177-DOTEC (aplikacijo prejme v Baslu)
- stranski učinki - ↓ ledvične funkcije, pancitopenija

Center	Agens	N	CR n/%	PR n/%	MR n/%	SD n/%	PD n/%
Rotterdam	[111In-DTPA0]octreotide	26	0	0	5/19	11/42	10/38
New Orleans	[111In-DTPA0]octreotide	26	0	2/8	NA	21/81	3/12
Milan	[90Y-DOTA0, Tyr3]octreotide	21	0	6/29	NA	11/52	4/19
Basel	[90Y-DOTA0, Tyr3]octreotide	74	3/4	15/20	NA	48/65	8/11
Basel	[90Y-DOTA0, Tyr3]octreotide	33	2/6	9/27	NA	19/57	3/9
Rotterdam	[90Y-DOTA0, Tyr3]octreotide	54	0	4/7	7/13	33/61	10/19
Rotterdam	[177Lu-DOTA0, Tyr3]octreotide	76	1/1	22/29	9/12	29/39	14/18

Kwekkeboom DJ et al. J Nucl Med 2005; 46 Suppl 1:62

2. KLINIČNI PRIMER

- dosežena stagnacija zasevkov v jetrih
- bolnica brez znakov karcinoidnega sy.

Junij 2007 (5 let)

- MRI in octreoscan => stagnacija lokalno in progres jetrnih zasevkov
- september 2007 => Lutecij 177-DOTEC (prejme v Baslu)
- zadnja kontrola sept. 2008 (**6 let**) – stagnacija, bolnica je brez znakov karcinoidnega sy.

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HEPATOCELIČNI RAK

Dnevi internistične onkologije
November 2008

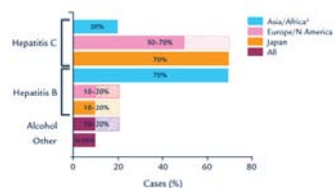
Maja Ebert Moltara, Tanja Mesti
Mentor: Janja Ocvirk

EPIDEMIOLOGIJA:

Incidenca:

❖ 8.29/100.000 v EU

❖ 1,6-3,2/100.000 v Sloveniji



Internistični dnevi onkologije, November 2008

DIAGNOZA:

Anamneza in status

(slabost, utrujenost, slab apetit, hujšanje, bolečine v zgornjem delu trebuha, zlatenica)

UZ, MRI ali CT

Zvišan AFP > 400ng/ml

Internistični dnevi onkologije, November 2008

TNM klasifikacija

T1	Solitarni tumor brez vaskularne invazije
T2	Solitarni tumor z vaskularno invazijo ali multipli tumorji ne večji od 5 cm
T3	Multipli tumorji, večji od 5 cm ali tumor, ki zajema večjo vejo portalne ali hepatične vene
T4	Tumor ali tumorji z direktno invazijo v sosednje organe razen v žolčnik, ali perforacija visceralnega peritoneja
N0	Ni zasevkov v področnih bezgavkah
N1	Zasevki v regionalnih bezgavkah
M0	Ni oddaljenih zasevkov
M1	Oddaljeni zasevki

Stadij I	T1N0M0
Stadij II	T2N0M0
Stadij IIIA	T3N0M0
Stadij IIIB	T4N0M0
Stadij IIIC	TxN1M0
Stadij IVB	TxNxM1

Internistični dnevi onkologije, November 2008

Child-Pugh klasifikacija

	1	2	3
ascites	odsoten	blag	močan
Bilirubin (nmol/l)	< 34,2	34,2-51,3	> 51,3
Albumin (g/l)	35	28-35	< 28
Protrombinski čas (%)	do 50	30-50	< 30
encefalopatija	0	1-2	3-4

Child A	5-6 točk
Child B	7-9 točk
Child C	10-15točk

Internistični dnevi onkologije, November 2008

Zdravljenje:

- ❖ stadij bolezni
- ❖ stanje jetrnega tkiva
- ❖ splošna bolnikovo stanje

Internistični dnevi onkologije, November 2008

Resektabilni tumorji (T1, T2, T3, nekateri T4; N0; M0)

Kirurška resekcija ali jeterna transplatacija (ciroza)

Kontraindikacije za kirurško zdravljenje:

- ❖ Izven jeterna bolezen
- ❖ Multipli ali bilobarni tumorji
- ❖ Napredovala jetrna bolezen
- ❖ Zajetje glavnega žolčnega voda
- ❖ Prisotnost tromboze debla vene porte ali spodnje vene cave

5 letno preživetje:

60-70% - bolniki s solitarnim tumorjem, ohranjeno jeterno funkcijo
20-50% - bolnikov s kronično bolnimi jetri

Internistični dnevi onkologije, November 2008

Transplantacija (Milanski kriteriji):

- ❖ tumor v cirotičnih jetrih manjši od 5cm, ali 2-3 tumorji manjši od 3 cm v premeru
- ❖ tumor ne sme zajemati žilnih struktur
- ❖ ne sme biti prisotne izven jeterne bolezn

5-letno preživetje: do 70%

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Neresektabilni tumorji (T2, T3 in T4, N0, M0)

- ❖ transplantacija
- ❖ operacija - resekcija
- ❖ kemoembolizacija
(pri multifokalnem HCC z zadovoljivo jeterno rezervo)
- ❖ perkutano etanolno injiciranje - PEI
(pri manj kot 3 nodulih manjših od 5 cm)
- ❖ perkutana radiofrekvenčna ablacija - RFA
(za manjše od 5 cm in manj kot 4)
- ❖ sorafenib
- ❖ vključitev v klinične raziskave
- ❖ paliativna oskrba

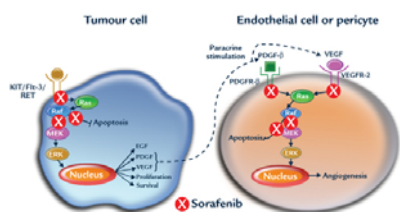
Internistični dnevi onkologije, November 2008

Napredovali tumorji (katerikoli T,N+,M1)

- ❖ sorafenib
- ❖ vključitev v klinične raziskave
- ❖ paliativna oskrba

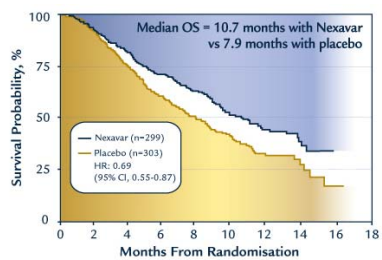
Internistični dnevi onkologije, November 2008

Sorafenib, Nexavar®



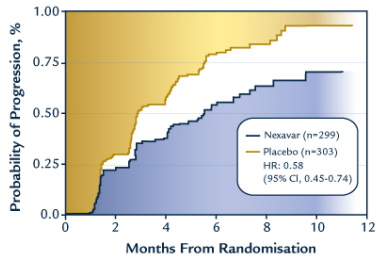
Internistični dnevi onkologije, November 2008

SHARP: Sorafenib HCC Assessment Randomized Protocol Trial



Internistični dnevi onkologije, November 2008

SHARP: Sorafenib HCC Assessment Randomized Protocol Trial



Internistični dnevi onkologije, November 2008

NEŽELENI UČINKI SORAFENIBA (SHARP študija)

	Sorafenib (N=297)		Placebo (N=302)	
	Vse stopnje (%)	G4/G3 (%)	Vse stopnje (%)	G4/G3 (%)
skupaj	80		52	
driska	39	8/0	11	2/0
utrujenost	22	3/1	16	3/<1
roka-noga sindrom*	21	8/0	3	<1/0
anoreksija	14	<1/0	3	1/0
alopecija	14	0/0	2	0/0
slabost	11	<1/0	8	1/0
izguba TT	9	2	1	0/0
srbenje	8	0/0	7	<1/0
Suha koža	8	0/0	4	0/0
Bolečine v trebuhu	8	2/0	3	1/0
krvavitve	7	1/0	4	1/<1
bruhanje	5	1/0	3	1/0
hripavost	6	0/0	1	0/0
hipertenzija	5	2/0	2	1/0

* palmo-plantarne eritodisestezije

ZAKLJUČEK:

Sorafenib

- ❖ je multikinazni inhibitor, ki deluje na poti RAF/MEK/ERK in blokira tako celično proliferacijo kot angiogenezo HCC
- ❖ signifikantno podaljša OS za 44% (46 vs. 34 tednov)⁵
- ❖ za dvakrat podaljša čas do radioliškega progosa (24 vs. 12 tednov)⁵
- ❖ podaljša čas do progosa simptomov (18 vs. 21 tednov, vendar razlika ni signifikantna)⁵
- ❖ najpogostejši stranski učinki: driska, kožne spremembe, alopecija in palmo-plantarne eritodisestezije⁵

Internistični dnevi onkologije, November 2008

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Internistični dnevi onkologije, November 2008

HEPATOCELIČNI RAK

(prikaz primera 1)

Dnevi internistične onkologije
November 2008

Tanja Mesti, Maja Ebert Moltara
Mentor: Janja Ocvirk

prikaz primera

51 letni bolnik

Razvade: etilik, kadilec

Družinska anamneza: oče umrl zaradi raka na prostati, mama zaradi srčnega infarkta

Spremljajoče bolezni:

- Etilična jetrna ciroza, Child A
- Hepatorenalni sindrom
- Ledvična insuficienca II stopnje
- Erozivna gastropatija
- Varice požiralnika I stopnje
- Trombocitopenija
- Mikrocitna anemija

Redna terapija:

Ortanol, Aldactone, Edemid, Portalak

prikaz primera

September 2001: **Hospitalizacija v SB Murska Sobota**

Dekompensacija etilične jetrne ciroze s ledvično insuficienco II stopnje, ascites, hiperamonemija, hiperurikemija

UZ trebuha:

5 cm velika hiperehogena tvorba v V. jetrnem segmentu desno - sum na HCC;

CT trebuha:

Ekspanzivni proces v jetrih - sum na HCC.

Rtg pc:

Nekoliko povečano srce na račun levega prekata. V pljučih intersticijske spremembe - najverjetneje posledica kajenja. Ni metastaz.

prikaz primera

Oktober 2001: Pregled na OI

- **Status:**
spider nevusi po koži;
palmarni eritem;
ginekomastija;
sistolni šum nad prekordijem;
jetra tipna 3cm pod DRL-jem;
vtisljivi edemi goleni in stopala
- **PS** WHO 0-1
- **TI** 93,5 kg.
- **Citopatološki izvid:**
dobro diferenciran HCC
- **Histopatološki izvid:**
dobrodiferenciran HCC,
glandularni in trabekularni tip.

Laboratorijski izvidi:	
Hb	97
MCV	87,3
Tr	125
Kreatinin	121
Urea	12,7
GFR	84
Urat	633
AF	2,18
PČ	0,60
INR	1,41
AFP	4,16

prikaz primera

51 letni bolnik z HCC, PS WHO 0-1,
etilična jetrna ciroza, Child A, hepatorenalni sindrom, renalna insuficienca II stopnje, trombocitopenija, mikrocitna anemija

Kako bi bolnika zdravili?

- a) Operacija
- b) Kemoembolizacija
- c) RFA
- d) PEI
- e) Transplantacija
- f) Sistemska terapija
- g) Paliativna oskrba

prikaz primera

November 2001 (OI):

Prva kemoembolizacija z mitomicinom in lipiodolom.

Kontrolni CT trebuha (december 2001):
Povečana, grčasta jetra, v V. segmentu desno 4 cm nejasno omejena sprememba.

Januar 2002 (OI):

Druga kemoembolizacija z mitomicinom in lipiodolom

Kontrolni CT trebuha (februar 2002):
Lezija v V. jetrnem segmentu desno nekoliko večja, predvsem na račun kolekcije lipiodola.

prikaz primera

Februar 2002 (OI):
51 letni bolnik z HCC
PS WHO 0-1
 St.po kemoembolizaciji - lezija nespremenjene velikosti.

Kako bi bolnika zdravili sedaj?

- a) Kemoembolizacija
- b) Operacija
- c) RFA
- d) PEI
- e) Transplantacija
- f) Sistemska terapija
- g) Paliativna oskrba

prikaz primera

Marec 2002:
 Opravljena RFA

Kontrolni CT trebuha (april 2002):
 v V. jetrnem segmentu desno lezija velikosti 3,1x 3cm

prikaz primera

Januar 2003:
51 letni bolnik z HCC
AFP 10,95 IU/ml
Kontrolni UZ trebuha: v V. jetrnem segmentu desno lezija velikosti 4 x 6 cm.

Kako bi bolnika zdravili sedaj?

- a) Kemoembolizacija
- b) Operacija
- c) RFA
- d) PEI
- e) Transplantacija
- f) Sistemska terapija
- g) Paliativna oskrba

prikaz primera

Februar 2003:
 Drugič RFA

Kontrolni CT trebuha (marec 2003):
 v V. jetrnem segmentu desno cirotično spremenjenih jeter lezija 4,5 x 5,5cm.
 2/3 so po RFA povsem koagulirani. Približno 2,5 x 2,6 cm velik mediokranialni del je videti še aktiven s posameznimi žilnimi signali.

prikaz primera

December 2003:
51 letni bolnik z multifokalnim HCC,
jetna ciroza Child C
AFP 201,30 IU/ml
Kontrolni UZ trebuha: multifokalne spremembe v jetrih- V., VI., VII. in VIII. jetrnem segmentu desno, sled proste tekočine.

Kako bi bolnika zdravili sedaj?

a) kemoembolizacija
 b) Operacija
 c) RFA
 d) PEI
 e) Transplantacija
 f) Sistemska terapija
 g) **Paliativna oskrba**

HEPATOCELIČNI RAK

(prikaz primera 2)

Dnevi internistične onkologije
November 2008

Maja Ebert Moltara, Tanja Mesti
Mentor: Janja Ocvirk

prikaz primera

PRVI PREGLED NA OI

moški, 53 let, PS: WHO 0

Dg: primarni jeterni tumor (HCC) v cirotičnih jetrih

Potek zdravljenja HCC pred pregledom na OI:

3x kemoemboliziran z Doxorubicinom

Spremljajoče bolezni bolezni:

- hepatitis C (od l. 1997),
- periferna angiopatija
- arterijska hipertenzija
- st. po holecistektomiji

prikaz primera

Kako bi bolnika zdravili?

- Operacija
- Kemoembolizacija
- RFA
- PEI
- Transplantacija
- Sistemska terapija
- Paliativna oskrba

prikaz primera					
datum	anamneza	Status	lab	doza	
17.12.2007	brez težav	WHO 0	AFP 13434	800mg	UZ trebuha: 3 seg: 5 cm 7-8. seg: 2,2 cm
28.1.2008	2x tiščanje v prsnem košu	PS: WHO 1	AFP 13172	800mg	CT abdomna: več ascitesa, 3 seg: 5 cm z nekrozo 7 seg: nekroza
10.3.2008	driska	PS: WHO 1-2 TT ↓ 4kg znaki ascitesa edemi gležnjevi	AFP 13206	800mg	Dopler ven: izključena GVT
21.4.2008	2x drenaža ascitesa	PS: WHO 1-2 koža: luščenje in rdečina, znaki ascitesa, edemi	AFP 6899	800mg	

prikaz primera					
datum	anamneza	status	lab	Doza	
5.6.2008	splošno dobro počutje, hujšanje, drenaža 1x na 3 tedne	PS: WHO 1 TT ↓ 11kg	AFP 1593	800mg	CT abdomna: obsežen ascites, difuzno spremenjena jetra z žariščnimi hipodeznimi lezijami (L/D), karcinoma?
17.7.2008	slabost, pogosto bruhanje, večkrat driska (5-10x odvajanje)	PS: WHO 1-2 ikteričen	AFP 928	prekinitiv za 4 tedne	Drenaža: 3l (19.6.) Koprokultura: neg.
14.8.2008	hospitaliziran zaradi bruhanja in drisk	PS: WHO 1-2		400mg	Drenaža

Rak neznanega izvora – Predstavitev primerov

Mag. Cvetka Grašič Kuhar, dr. med.
Astrid Lui Rusjan, dr.med.
Prof. dr. Branko Zakotnik, dr. med.

Definicija raka neznanega izvora

VT DeVita et al. Cancer Principles of Oncology, 8th ed., 2008

- **Heterogena** skupina tumorjev (3-5% vseh rakov):
 - **ob diagnozi** so prisotni **zasevki**, **ne** uspemo pa ugotoviti **mesta primarnega tumorja**
 - **nizko preživetje** (srednje =5 mes, 1-letno =22%, 5-letno=5%)
- **Diagnoza:**
 - iz metastatske lezije: citol. punkcija → **DIBiopsija** → ekscizijska biopsija; NE odprta biopsija!
- patološka evaluacija: svetlobni mikroskop +**
 - imunoperoksidazno barvanje:** določitev celičnih encimov in normalnih tkivnih komponent
 - elektronska mikroskopija** (nevrosekretorne granule, premelanosomi, dezmosomi)
 - molekularna genetika** (i12p, t(15,12), hematološki tumorji, sarkomi)

Imunoperoksidazna barvanja v d dg. slabo diferenciranih karcinomov

Karcinom	Epitel. m. (CK 7, CK 20), EMA+ Vimentin-, CLA-, S-100-
Kolorektalni ca.	CK 7-, CK 20+
Pljučni ca. -adenoca. -ostali NSCLC -SCLC	TTF-1+, Surf-A in Surf-B+ CK 7+, CK 20- TTF-1+, kromogranin+, NSE+
Nevroendokrini ca.	NSE, kromogranin, epitel. m.
Germinalni tumorji	β-HCG, α-FP, Oct4 transkr. f.+ PLAP+, epitel. m.+
Ca. prostate	PSA+, epitel. m.+ (CK 7-, CK 20-)
Ca. dojke	ER, PgR+, Her2+, CK 7+, CK 20-, epitel. m. +
Ca. pankreasa	CA 19-9+, CK 7+, mezotelin+, trifol f. +

Osnovne histološke skupine raka
neznane izvora (svetlobni mikroskop)

DOBRO/SREDNJE DIFERENCIRAN ADENOKARCINOM (60%)	SLABO DIFERENCIRAN (ADENO)KARCINOM (29%)	SLABO DIFERENCIRANA MALIGNA NEOPLAZMA (5%)
PLOŠČATOCELIČNI KARCINOM (5%)	KARCINOM Z NEUROENDOKRINOD IFERENCIACIJO (1%)	

**Minimalni nabor preiskav za iskanje origa
oz. zamejitev bolezni**

E. Briassoulis et al. ESMO Clinical Recommendations. Ann Oncol 2008; 19 (Suppl 2): ii106-7.

- Anamneza
- Fizikalni pregled (vrat, dojke, rektalni pregled, mala medenica)
- Hemogram, biokemične preiskave, urin, hematest blata
- rtg pc; CT toraksa, CT/UZ abdomna, CT/UZ medenice
- PET CT pri povečanih bezgavkah na vratu in solitarni metastazi
 - dg. primar. mesta:
 - pri slabo dif. ca. v 40%
 - pri ploščatocel. ca. v 75%

**Ciljane preiskave
pri raku neznane izvora**

-ženske z zasevkom v aksilarni bezgavki	mamografija
-moški z adenokarcinomom in kostnimi zasevki	PSA
-zasevki v retroperitonealnih mediastinalnih bezgavkah, pljučih:	β-HCG, α-FP, in/ali LDH
-zasevki karcinoma v bezgavkah na vratu (ploščatocelični, adenoca.)	CT glave in vratu CT prsnega koša ali PET CT
-simptomi ali znaki za prizadetost votlih organov:	endoskopske preiskave
-zasevki v jetrih:	CEA, CA 19-9, α-FP

Zdravljenje karcinoma neznanega izvora

Podtip karcinoma	Predvideno zdravljenje
Slabo diferenc. karcinom (pretežno v bezgavkah, mlajši, kemosenzitivni)	Osnova je cisplatin
Slabo diferenciran neuroendokrini karcinom	Cisplatin/karboplatin + etopozid
Karcinoma peritoneja ali serozni adenokarcinom pri ženski	Kot ovarijski karcinom: optimalna kirurška citoredukcija, nato KT na osnovi platine
Izolirane metastaze v aksilarnih bezgavkah pri ženski	Kot rak dojke za enak stadij
Ploščatocelični karcinom v: bezgavkah na vratu zg. 2/3 bezgavke spodnja 1/3 ingvinalnih bezgavkah	Kot rak glave in vratu Kot rak pljuč Vulva, cervix, anus, penis
Kostne, jetrne ali multiple metastaze adenokarcinoma	-nizko toksična KT ali -simptomatsko zdravljenje

KT in tarčna zdravila za karcinom neznanega izvora

-**prognostično ugodna skupina** je le 10% adenokarcinomov (GI-II) in 20% slabo diferenciranih karcinomov (mlajši, v bezgavkah):

- veliko kompletnih remisij
- potencialno ozdravljivi tumorji!

-zadnja leta: tudi **prognostično neugodna skupina** ima z novimi KT shemami in biološkimi zdravili izboljšano prognozo (taksani, gemcitabin, vinorelbin, irino-/topotekan; bevacizumab, erlotinib);

-izboljšano preživetje (srednje=9 mes, 1-letno=20%, 5-letno= 5%)

Klinični primer 1/1

-moški, 65 let

-FA, OA: bp.

-sedanja bolezen:

-pol leta **hude bolečine v predelu desne rame** (ojačajo se pri ležanju; olajšajo se, če sklonjen naprej): prejemal NSAR;

-09/2006: protibolečinska ambulanta: nevropatska bolečina v desnem kostovertebralnem kotu, ki izžareva v desno ramo (th: Morfij in Xylocain po epiduralnem katetru)

-CT abdomna (09/2006): **velik ekspanziven proces v ležišču d. nadledvičnice**, infiltrira zg. pol in hilus d. ledvice ter odriva jetra

-UZ vodena aspiracijska biopsija tumorja: **maligen proces, najverjetneje metastaza slabo diferenciranega karcinoma**. V kolikor gre za bezgavko, prihaja ddg. v poštev tudi germinativni tumor (embrionalni karcinom). Dodatna IHC barvanja za germ. tumor niso razrešile dileme.

Klinični primer 1/2

-KO za urologijo UKC Lj - **eksplorativna laparotomija** (13/09/2006): inoperabilni proces v področju d. nadledvične lože, vrašča proti hrbtenici, diafragmi, v precejšnji del desnih jeter, infiltrira v cavo inf., širi se proti želodcu in pankreasu

-Urološki konzilij (19/09/2006): predlaga **paliativno obsevanje**

-Obsevanje (22.09.-05.10.2006): 10x3 Gy

-Laboratorij 20.09.2006: BLR (52/29), kre 124

-**protibolečinska th.** po epiduralnem katetru

-amb. internista onkologa (23/10/2006): določitev tumorskih markerjev: α -FP **15 740**, β -HCG, LDH normalen, CA 19-9 38, NSE 57, UZ testisov: v spodnjem delu d. testisa 2-3mm kalc.

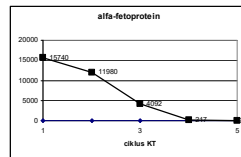
-ddg. dilema: germinalni tumor/hepatocelularni karcinom

-th. možnosti pri napredovalem germinalnem tumorju dobre, pri HCC zelo omejene poskus zdravljenja s KT po shemi BEP
(bleomicin, etopozid, cisplatin)

Klinični primer 1/3

-KT po shemi BEP x 4
(08/11/2006-10/01/2007)

-dober upad tumorskega markerja (slika)
-pancitopenija po 1. ciklusu



-ob pričetku 2. ciklusa brez kakršnekoli protiboleč. th.

-UZ trebuha po 3. ciklusu: odlična parcialna remisija
-po 4. ciklusu: tumorski marker normalen

Klinični primer 1/4

-21/02/2007: **operacija ostanka tumorja:**
'en bloc' d. nefrektomija + 6., 7. segment jeter + dorzalna muskulatura + del diafragme; (operacija trajala 10 ur, izguba krvi 18 l)

-histološki izvid: nodusi popolnoma nekrotičnega retroperitonealnega tumorja z nekrotičnimi zasevki v jetrih in hilusu ledvice. Sence nekrotičnih tumorskih celic nakazujejo možnost, da je šlo za germinalno-celični tumor

-kontrola 06/2007: bp., prišel z delom

-kontrola 09/2008: bp.

**Zaključek klinični primer 1:
Karcinom neznanega izvora –
posebna klinično-patološka entiteta**

- 'izgoreli primarni tumor' –"burned out" (germinalni tumor) (UZ testisov!)
- iz ostankov embrionalnih epiteljskih celic
- iz odraslih nediferenciranih pluripotentnih matičnih celic (so v vezivnem tkivu)
- specifične genetske spremembe v vseh celicah

Klinični primer 2/1

- Ženska, 39 let
- Napotna diagnoza: NHL, visoko maligni (citologija iz bezgavke scl levo)
- Družinska anamneza: bp
- Razvade: kadi 20 let, 10 cigaret /dan
- Sedanja bolezen: 10 dni dizurične težave, bolečine ledveno, subfebrilna, herpetični izpuščaji pod nosnico, tri meseca napetost v trebuhu, B-simptome zanika
- Status: scl levo 3 bezgavke (2-premera 0.5 cm, 1 premera 1 cm); ostali status b.p.

Klinični primer 2/2

- Punkcija bezgavke: slabo diferencirani adenokarcinom
- Biopsija bezgavke: slabo diferenciran adenokarcinom (dojka? pljuča?), ER 30%, PR 30%, HER2 neg.
- Biopsija KM: bp (Napotna dg!)
- Laboratorij: hemogramu, biokemija, ščitnični hormoni b.p.; Ca 125 77.77, Ca 15-3 145.26, CEA, Ca 19-9 bp
- Ginekološki pregled in PAP test: b.p
- Mamografija: ostanki žleznega tkiva v obeh dojkah, brez vidnih jasnih tumorskih jeder, brez vidnih polimorfnih kalcinacij
- UZ dojke: 4 mm cista v zgornjem kvadrantu desne dojke

Klinični primer 2/3

- RTG pc: b.p., CT toraksa: patološko povečane bezgavke v poteku desnega marnega žilja, v obeh kardiofreničnih kotih in v spodnjem posteriornem mediastinumu
- RTG obnosnih votlin: b.p.
- ORL pregled: b.p.
- UZ trebuha: patološko povečane bezgavke retroperitonealno, v l. Ingv. regiji ena bezg. prmera 1.1 cm
- CT abdomna: uterus v celoti nekoliko povečan, nejasno razmejen proti okolici in obema ovarijema. Maščevje v okolici uterusa strukturno nehomogeno, prisotno malo proste tekočine-izgled v smislu peritonealne karcinoze. V jetrih 3 < kot 1 cm formacije susp. za zasevke. Patološk do 1,5 cm velike bezgavke v retroperitoneju
- Sken skeleta: bp

Klinični primer 2/4

- Hematest: negativen
 - Gastroskopiija (?), kolonoskopiija (?): bp
- DDg: slabo diferencirani adenoca:
1 – dojka?
2 - ovarij?
-> KT CAP

Klinični primer 2/5

- 6x KT po shemi CAP
- 04/2006, CR (klinično CR, Ca 125 bp, Ca 15-3 pa ob 6 ciklusu iz 33 -> 38)
- ER+,PR+ -> Tamoxifen (brez mensesa, FSH, LH v menop. območju) -> normalizacija Ca 15-3

Klinični primer 2/6

- PI 1,5 let, porast Ca 15-3 .
- Ginekološki pregled in UZ male medenice: 10 mm lezija na zadnji steni uterusa.
- MR medenice: manjši miom v uteruseu, drobna cista d. ovarija.
- Mamografija, sken skeleta, Rtg pc: b.p.
- UZ trebuha: cista v jajčniku večja kot ob zadnji kontroli (4.5 cm).

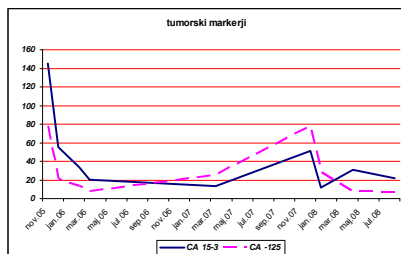
Klinični primer 2/7

- Ginekolog: vaginalna histerektomija z obojnimi adneksi ter parcialna omentektomija.
- Hisologija: slabo diferenciran endometrioidni adenokarcinom jajcevoda desno z metastazo v omentumu (z ozirom na morfološko skladnost in podoben imunofenotip, je šlo primarno najverjetneje za zasevek karcinoma jajcevoda v bezgavko na vratu)

Klinični primer 2/8

- Bolnica je prejela šest ciklov KT: Paclitaxel, Carboplatin (do 05/2008)
- 28.08.2008 zadnja kontrola: Ginekološki pregled, UZ trebuha, markerji: b.p.
- Pričela s 4-urnim delavnikom

Klinični primer 2/9



RAK DOJK

- vloga genskega podpisisa pri odločitvi o sistemskem zdravljenju

Ksenija Strojnik, Mojca Humar

Mentorica:
prof.dr. Tanja Čufer, dr.med., višja svetnica

RM, ♀ 34 let

- Družinska anamneza: brez posebnosti
- Ginekološka anamneza: menarhe 11 let, rodila 2x (prvič pri 27-ih), dojila skupno 2 leti; brez hormonske kontracepcije; konizacija dec. 2007
- Dosedanje bolezni: brez posebnosti
- Sedanja bolezen: pred 3 meseci si je zatipala 2 cm veliko zatrdlino v levi dojki retromamilarno; bezgavke v levi aksili tipno niso bile povečane

DIAGNOZA:

- mamografija: 2cm maligno jedro z okolnimi mikrokalcinacijami
- tankoigelna biopsija: karcinom dojke
- preiskave za oddaljene zasevke: negativne



MASTEKTOMIJA s takojšnjo rekonstrukcijo ter **SNB**

PATOLOGIJSKA:

- masivni DCIS solidnega, komedo in kribriformnega tipa premera 7 cm z **več žarišči invazivnega duktalnega karcinoma BDO**, največji **1.5 cm**; kirurški rob oddaljen 0.8 cm od karcinoma; **SNB 0/2**.
- **G3** (tubuli 3, jedrni polimorfizem 3, mitoze 2), brez LVI, **ER 100%**, **PR 100%**, **HER-2 neg.** (IHC 0, FISH količnik 1.0).
- Revizija: obe komponenti rasti invazivnega dela hormonsko visoko odvisni ter Her2 negativni.

SISTEMSKO ZDRAVLJENJE?



UČINKI ENDOKRINEGA ZDRAVLJENJA IN KEMOTERAPIJE PRI ZGODNJEM RAKU DOJK

- Dopolnilno hormonsko zdravljenje s tamoksifenom (pri ER+ bolnicah)
 - 40% zmanjšanje tveganja za ponovitev
 - 32% zmanjšanje smrtnosti zaradi raka dojk
- Polikemoterapija (pri vseh bolnicah)
 - 33% zmanjšanje tveganja za ponovitev
 - 17% zmanjšanje smrtnosti zaradi raka dojk

EBCTCG Lancet 2005

Adjuvant! Online
Decision making tools for health care professionals

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age: 34
Comorbidity: Major Problems
ER Status: Positive
Tumor Grade: Grade 3
Tumor Size: 1.1 - 2.0 cm
Positive Nodes: 0
Calculate For: Relapse
10 Year Risk: 44 Prognostic

Adjuvant Therapy Effectiveness

Form: Tamoxifen (Overstern 2000)
Chem: CMF-Like (Overstern 2000)
Hormonal Therapy: 40
Chemotherapy: 37
Combined Therapy: 62

Print Results PDF | Access Help and Clinical Evidence
Images for Considerations

© 2008 Adjuvant! Inc.

No additional therapy:
55.3 alive and without cancer in 10 years.
43.8 relapse.
9.9 die of other causes.

With hormonal therapy: Benefit = 14.7 without relapse.

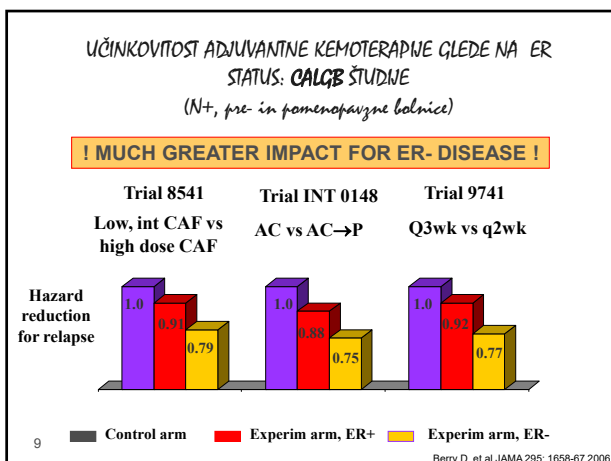
With chemotherapy: Benefit = 13.4 without relapse.

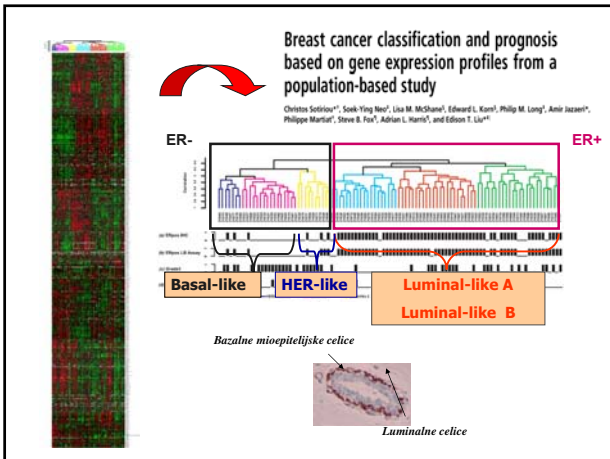
With combined therapy: Benefit = 24.1 without relapse.

PROSPEKTIVNE RANDOMIZIRANE ŠTUDIJE O DODATKU KEMOTERAPIJE K HORMONSKEMU ZDRAVLJENJU

Randomized trials	Trial Size Stage	Treatments	Outcome (DFS/OS)	Comments
Postmenopausal patients				
SWOG trial Rivkin SE, JCO 1994	892 N+, HR+	TAM 1 y +/- CMFVP	No signif. difference in DFS and OS	
IBCSG IX IBCSG, JNCI 2004	1669 N-, HR+/-	TAM 5y +/- CMF	No signif. difference in DFS and OS of adding CRT in ER+ subgroup of pts	Initial stratification according ER status
NCIC CTG Pritchard K, JCO 1997	705 N+, HR+	TAM 2y +/- CMF	No signif. difference in DFS and OS	
Premenopausal patients				
IBCSG 11-93 IBCSG, Breast Cancer Res 2008	174 N+, HR+	(OA + TAM 5y) +/- AC	No difference in DFS and OS	Premature closure of the trial due to low accrual
Premeno- and menopausal Patients				
NSABP B-20 Fisher B, Lancet 2004	788 N-, HR+	TAM 5y +/- CMF	Signif. difference in DFS and OS for premeno- but not menopausal pts	

10





GENSKI PODPISI – NAPovedniki PROGNOZE PRI ZGODNEM RAKU DOJK

- 21-genski podpis (**Oncotype DXTM**); Breast Cancer Res 2006
- 70-genski podpis (**MammaPrint[®]**); JNCI 2006
- 76-genski podpis; J Clin Oncol 2006

21-GENSKI PODPIS

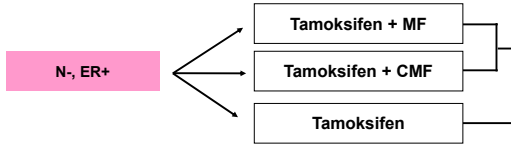
- 16 rakavih in 5 referenčnih genov iz 3 študij

Proliferacija Ki-67 STK15 Survivin Ciklin B1 MYBL2	Estrogen ER PgR Bcl2 SCUBE2	$RS = + 0.47 \times HER2 \text{ group score}$ $- 0.34 \times ER \text{ group score}$ $+ 1.04 \times Proliferation \text{ group score}$ $+ 0.10 \times Invasion \text{ group score}$ $+ 0.05 \times CD 68$ $- 0.08 \times GSTM1$ $- 0.07 \times BAG1$								
In vazija Stromolizin 3 Katepsin L2	GSTM1 BAG1 CD68									
HER2 GRB7 HER2	Referenčni β-aktin GAPDH RPLPO GUS TFRC	<table border="1"> <thead> <tr> <th>Kategorija</th> <th>RS (0-100)</th> </tr> </thead> <tbody> <tr> <td>Nizko tveganje</td> <td>RS < 18</td> </tr> <tr> <td>Srednje tveganje</td> <td>RS ≥ 18 and < 31</td> </tr> <tr> <td>Visoko tveganje</td> <td>RS ≥ 31</td> </tr> </tbody> </table>	Kategorija	RS (0-100)	Nizko tveganje	RS < 18	Srednje tveganje	RS ≥ 18 and < 31	Visoko tveganje	RS ≥ 31
Kategorija	RS (0-100)									
Nizko tveganje	RS < 18									
Srednje tveganje	RS ≥ 18 and < 31									
Visoko tveganje	RS ≥ 31									

DOBROBIT KEMOTERAPNE PRI ER+ N- RAKU DOJK GLEDE NA 21-GENSKI PODDIS

NSABP B-20 študija: dobrobit kemoterapije pri N-, ER+ bolnicah

Načrt

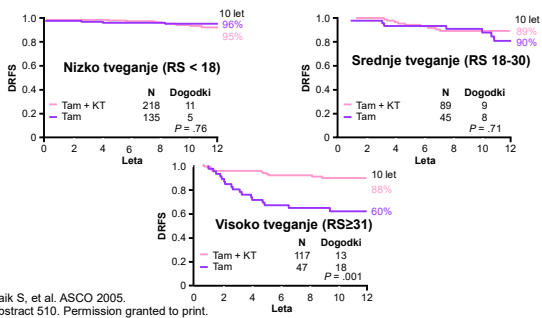


Cilj

Določitev velikosti dobrobiti kemoterapije kot funkcije 21-genskega RS (RECURRENT SCORE) podpisa

Paik S, et al. ASCO 2005. Abstract 510.

DOBROBIT KEMOTERAPNE PRI ER+ N- RAKU DOJK GLEDE NA 21-GENSKI PODDIS

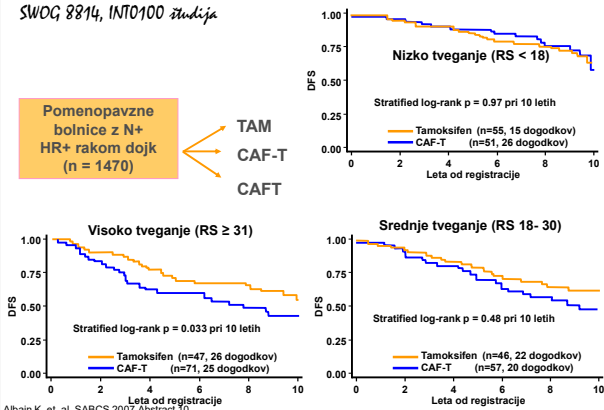


Paik S, et al. ASCO 2005. Abstract 510. Permission granted to print.

DOBROBIT KEMOTERAPNE PRI ER+ N+ DOMENOD. BOLNICAH Z RAKOM DOJK SWOG 8814, INT0100 študija

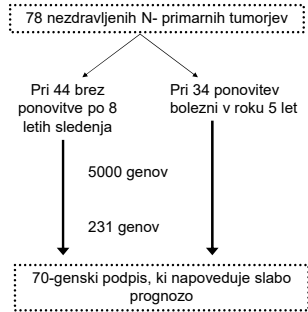
Pomenopavzne bolnice z N+ HR+ rakom dojk (n = 1470)

TAM
CAF-T
CAFT



Albain K, et al. SABCS 2007 Abstract 10

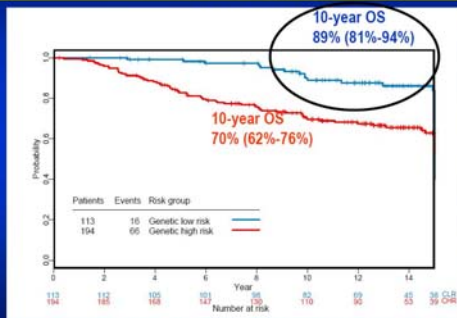
AMSTERDAMSKI 70-GENSKI PROGNOŠTIČNI PODPIS



- Nadzirana klasifikacija je odkrila 70-genski ekspresijski podpis, ki je močno napoveden za kratek interval do oddaljenih zasevkov pri N-bolnicah mlajših od 55 let.
- Slab prognostični podpis je sestavljen iz genov za regulacijo celičnega cikla, invazijo, zasevanje in angiogenezo.

Van't Veer et al. Nature 2002, 31: 530-536.

OVERALL SURVIVAL by GENE SIGNATURE RISK Validation of the Amsterdam Signature by the TRANSBIG network



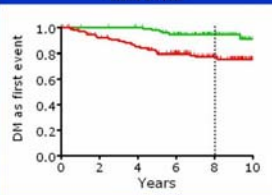
Average Survival HR \approx 2.66

Supported by EU grant 6th Framework program

TRANSBIG validation of the 70-gene signature in women with 1-3 positive nodes

n = 241 women { Good profile (n=99) Median f. up = 7,8 y
Poor profile (n=142)

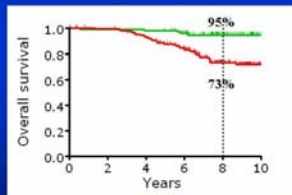
Distant metastases as first event



HR 4.1

(95%CI 1.7 - 10.0), p=0.002

Overall survival



HR 5.4

(95%CI 2.1 - 13.8), p<0.001

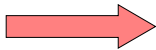
Courtesy of S. Mook; SABC 2007

M.C., ♀, 38 let

- Družinska anamneza: negativna.
- Ginekološka anamneza: menarhe pri 11-ih; rodila 2x (prvič pri 27-ih); menstruacije redne; brez hormonske kontracepcije.
- Sedanja anamneza: bolnica si je zatipala zatrdlino v desni dojki.
- Status: notranji zg. kvadrant desne dojke 3x3 cm velika okrogla zatrdlina z retrakcijo kože, lokoreg. bezgavke niso bile tipno povečane.

DIAGNOZA:

- Mamografija: na meji notranjih kvadrantov desne dojke, 3.5 cm, mestoma neostro omejen.
- Tankoigelnna biopsija: **karcinom dojke**
- Laboratorijski izvidi: bp
- Preiskave za oddaljene zasevke: negativne



KVADRANTEKTOMIJA
in **SNB**

PATOHIŠTOLOGNA:

- **Invazivni duktalni karcinom BDO**, največji premer **3 cm**; izrezan v zdravo; **SNB 0/1**;
- **G 3** (tubuli 3, jedrni polimorfizem 3, mitoze 3), **izrazita LVI**, **ER 30%**, **PR 0%**, **HER-2 negativen** (IHC 0, FISH količnik 1.3);



Adjuvant! Online
Decision making tools for health care professionals

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age: 58
Comorbidity: Minor Problems
ER Status: Positive
Tumor Grade: Grade 3
Tumor Size: 2.1 - 3.0 cm
Positive Nodes: 0
Calculate For: Relapse
10 Year Risk: 45 Prognostic

Adjuvant Therapy Effectiveness

Form: Tamoxifen (Overview 2000)
Chem: CMF-Like (Overview 2000)
Hormonal Therapy: 40
Chemotherapy: 37
Combined Therapy: 62

No additional therapy:

- 54.1 alive and without cancer in 10 years.
- 44.7 relapse.
- 1.2 die of other causes.

With hormonal therapy: Benefit = 14.8 without relapse.

With chemotherapy: Benefit = 13.6 without relapse.

With combined therapy: Benefit = 24.5 without relapse.

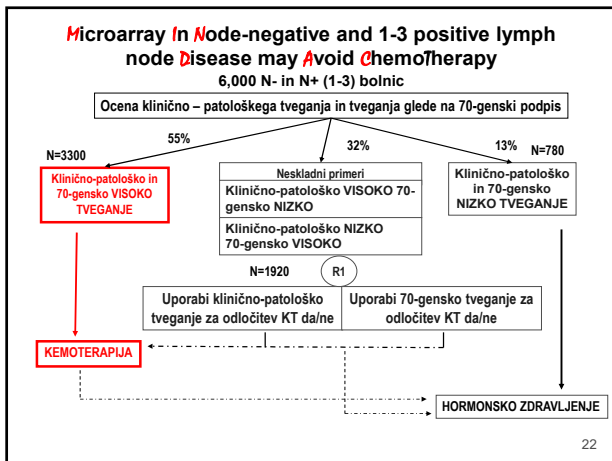
Print Results PDF | Access Help and Clinical Evidence | Images for Consultations

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St. GALLEN 2007 - priporočila

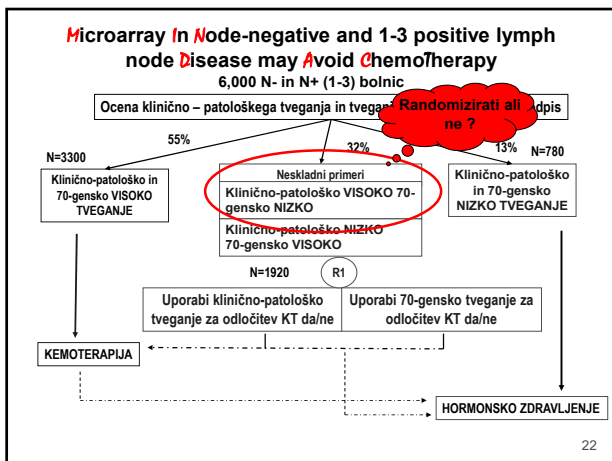
HER2/neu gene overexpression and/or amplified	HER2 negative				HER2 positive			
	highly responsive		incompletely responsive		highly responsive		incompletely responsive	
Menopausal status	pre	post	pre	post	pre	post	pre	post
Low Node negative and all of the following features: pT ≤2 cm, Grade 1, no vascular invasion, HER2(-), ER and PgR expressed, Age ≥55 years	E ^a	E ^b	E ^a	E ^b	C	C	C	C
Intermediate Node negative and at least one of the following features: pT ≤2 cm, Grade 2-3, nodular invasion, HER2(+), ER and PgR absent, Age <55 years	C → E	C → E	C → E	C → E	C	C → E	C → E	C → E
High 1-3 nodes positive AND ER and PgR expressed and HER2(-)	E	E	C → E	C → E	C	C → E	C → E	C → E
1-3 nodes positive AND ER and PgR absent OR HER2(+)	C	C	C	C	C → E	C → E	C → E	C → E
≥4 nodes positive	C → E	C → E	C → E	C → E	C	C → E	C → E	C → E

responsiveness to endocrine therapies is defined in the text.
endocrine therapy is effective for prevention and DCIS and therefore might be considered even for very low risk invasive breast cancer.
C: chemotherapy; E: endocrine therapy (selected according to menopausal status); Tr: trastuzumab (note 1: trastuzumab should not be viewed as a standard treatment in women with a primary tumor <1 cm in size and with no axillary node involvement. This is particularly true in patients with highly and perhaps also incompletely endocrine responsive disease; note 2: trastuzumab should be given concurrently and after chemotherapy or following completion of all chemotherapy according to clinical trial evidence available at present, though a majority of the Panel agreed that trastuzumab without prior or concurrent chemotherapy may become appropriate in some settings in the future.)



PRIMERJALNA TABELA ZNAČILNOSTI OBEH BOLNIC

RM, 34 let	MC, 38 let
1,5 cm tumor	3 cm tumor
G3 (mitoze 2)	G3 (mitoze 3)
Brez LVI	Izrazita LVI
ER 100% PR 100%	ER 30% PR 0%
Adjuvant! online: 44% tveganje za ponovitev	Adjuvant! online: 45% tveganje za ponovitev
Genski podpis???	MammaPrint: visoko tveganje za ponovitev



Izvedbo so finančno podprli:

Merck

Roche

GSK

Pfizer

Novartis Oncology

Shering – Plough

Jansen – Cilag

Amgen

Abbot laboratories

Pharma Swiss

MSD

LEK

Bayer

Sanofi Aventis

Astra Zeneca

Medis

Pharmadab

