4. Dan internistične onkologije z mednarodno udeležbo

TARČNA ZDRAVILA V ONKOLOGIJI

ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

Onkološki inštitut Ljubljana
Sektor za internistično onkologijo

SLOVENSKO ZDRAVNIŠKO DRUŠTVO

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. Ciardielllo**
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

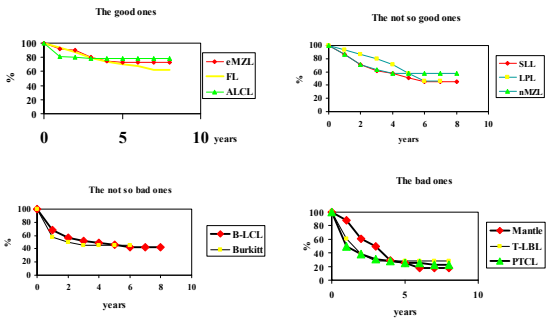
- INDOLENT
  - Long survival without treatment
  - Conventional chemotherapy is not curative
  - Anthracycline-based chemotherapy does not prolong survival
  - Repetitive remissions becoming ever shorter
  - Small cells
  - Mostly B-cell derived
  - Mostly correspond to low-grade NHLs
- AGGRESSIVE
  - 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 ivIg
  - 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*

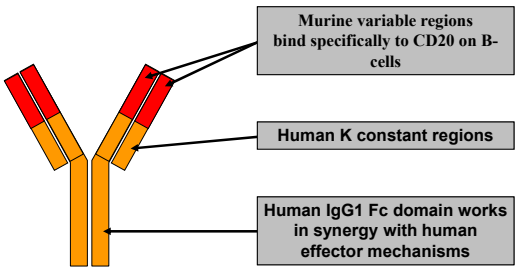
TARGET TREATMENT OF LYMPHOMAS
drugs

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

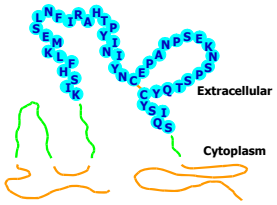
MONOCLONAL ANTIBODIES
RITUXIMAB

- The big **R**

Rituximab: a chimeric human/mice monoclonal antibody



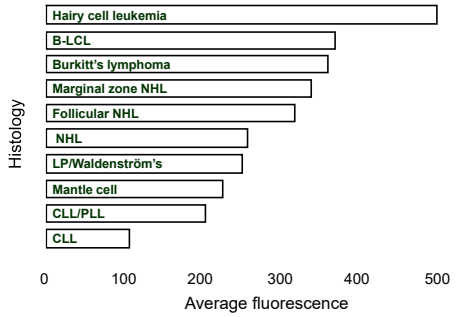
CD20 molecule



- 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

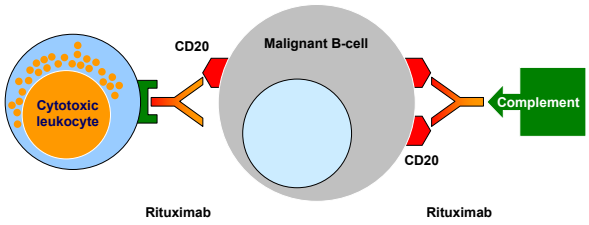
Einfield et al. EMBO J 1988;7:711–7

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-relase 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

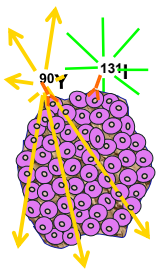
CONJUGATED ANTIBODIES
Biological basis

- 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 ^{90}Y (Zevalin) and tositumomab with ^{131}I (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

- **BORTEZOMIB**
- Proteasome inhibitor
- Intravenous application 4x/3wks.
- Toxicity
  - neuropathy, trombocytopenia, nausea & vomiting, diarrhea…
- **THALIDOMIDE, LENALIDOMIDE**
- Mode of action unknown
  - Immunomodulator, antiangiogenic agent,…
- Continuous oral application
- Toxicity thalidomide
  - Neuropathy, DVT, sedation, constipation
- Toxicity lenalidomide
  - 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 diphteria 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, tensirolimus
  - In combination for induction, monotherapy for maintentenance
  - 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 Tax225/Cb	202 208	88 89	28 25	8 8	33 36
Schiller, 2002 ECOG 1594	Tax135/Cis Gem/Cis Txt/Cis Tax225/Cb	292 288 293 290	89 86 86 86	21.3 21 17.3 15.3	8.1 8.1 7.4 8.3	31 36 31 35
Scagliotti, 2002 ILCP	Vnr/Cis Gem/Cis Tax225/Cb	201 205 201	81 81 82	30 30 32	9.5 9.8 9.9	37 37 43
Belani, 2002 TAX 326	Vnr/Cis Txt/Cis TxT/Cb	404 408 402	67 67 67	25 32 24	10.1 11.3 9.4	41 46 38

How to improve results?

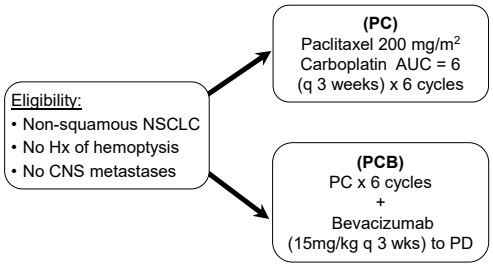
- **New cytotoxics**
- **Personalized chemotherapy according to the patient's genetic make-up**
- **Molecular targeted therapies**
  - **Drugs to treat biologically homogenous cancer patient population**
    - **Tumor specific molecular abnormality**
    - **Tumor specific molecular profile**
    - **Expression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

Where have the successes been thus far in advanced NSCLC?

Recent advances in advanced NSCLC

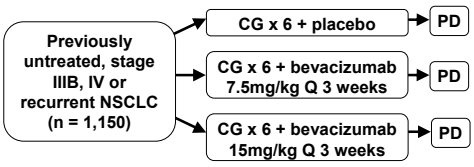
- ECOG 4599 and AVAiL trials – Bevacizumab added to chemotherapy improves clinical outcomes
- FLEX trial – Cetuximab added to chemotherapy improves clinical outcomes
- BR21 trial – Erlotinib improves clinical outcomes versus placebo in refractory, advanced NSCLC
- INTEREST trial – Gefitinib is not inferior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

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



Sandler et al. NEJM 2006

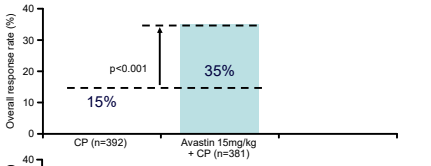
Phase III Trial of Bevacizumab in Non-Squamous NSCLC: AVAiL trial



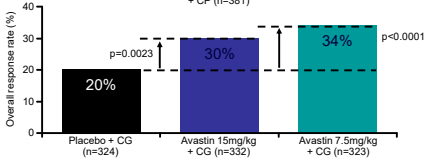
- **Cisplatin 80mg/m² i.v. every 3 weeks; gemcitabine 1,250mg/m² on days 1 and 8 of each 3-week cycle**
- **Primary endpoint: progression-free survival**
- **Secondary endpoint: overall survival and response rate**

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

Overall response rates have increased significantly with Bevacizumab



E4599

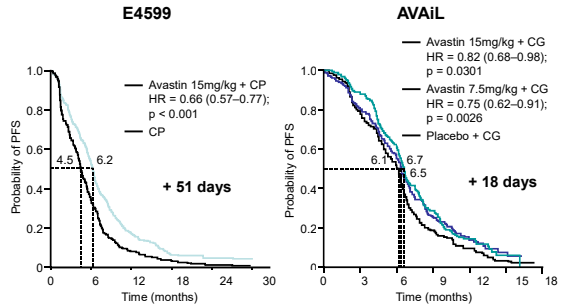


AVAiL

CP = carboplatin/paclitaxel; CG = cisplatin/gemcitabine

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

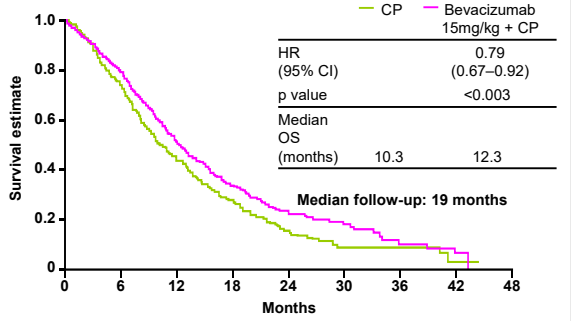
Bevacizumab-based therapy significantly improves PFS



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

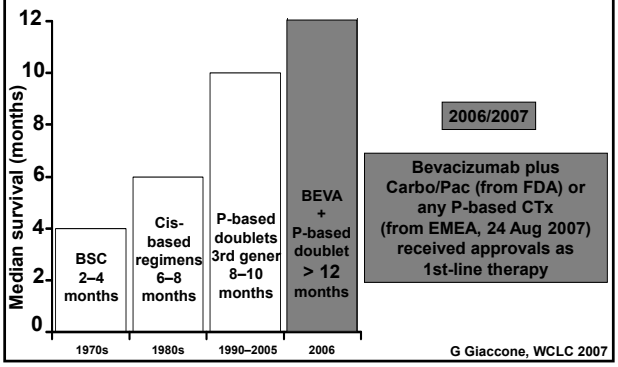


Sandler et al. NEJM 2006

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	6.2	12.3
			p =.001	HR =.66	HR =.79
					p =.003
AVAiL	CG + Placebo	347	20	6.1	13.1
	CG + Bev 7.5	345	34	6.7	13.6
			p =.0001	HR =.75	HR =.93
	CG + Bev 15	351	30	6.5	13.4
			p =.0017	HR =.82	HR =1.03

1ST-line therapy in advanced NSCLC: significant milestones



G Giaccone, WCLC 2007

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
	0.2	1.6	< 0.04
Anemia	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
	23	27	23
Anemia	14	10	10

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

ECOG 4599: severe (grade ≥ 3) non-haematological toxicity

Toxicity (grade 3-4)	PC (%) # 440	PCB (%) # 437	p value
Bleeding events	3 (0.7)	19 (4.4)	<.001
Hemoptysis	1 (0.2)	8 (1.9)*	
CNS	0	3 (0.7)	
GI	2 (0.4)^	6 (1.4)°	
Other	1 (0.2)	5 (1.1)	
Hypertension	3 (0.7)	30 (7.0)	<.001
Proteinuria	0	13 (3.1)	<.001
Headache	2 (0.5)	13 (3.0)	<.003

including * 5 deaths, ^1 death, °2 deaths

Sandler et al. NEJM 2006

AVAiL trial: severe (grade ≥ 3) non-haematological toxicity

	Placebo + CG n = 327	Bevacizumab 7.5mg/kg + CG n = 330	Bevacizumab 15mg/kg + CG n = 329
Bleeding	2%	4%	4%
Hypertension	2%	6%	9%
Proteinuria	–	0.3%	1%
Ischaemic events	5%	2%	3%
Venous thromb. events	6%	7%	7%

Manegold et al. ASCO 2007

AVAiL trial: Pulmonary haemorrhage events

	Placebo + CG n = 327	Bevacizumab 7.5mg/kg + CG n = 330	Bevacizumab 15mg/kg + CG n = 329
Pulmonary haemorrhage (all grades)	17 (4.9%)	23 (7.0%)	32 (9.7%)
Pulmonary haemorrhage (Gr ≥ 3)	2 (0.6%)	5 (1.5%)	3 (0.9%)
Fatal pulmonary haemorrhage	1 (0.3%)	4 (1.2%)	3 (0.9%)

- 38% of patients had central lesions, 4/10 patients with severe pulmonary haemorrhage had central lesions
- 9% of patients had therapeutic anticoagulation, but none of them had a severe pulmonary haemorrhage

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:

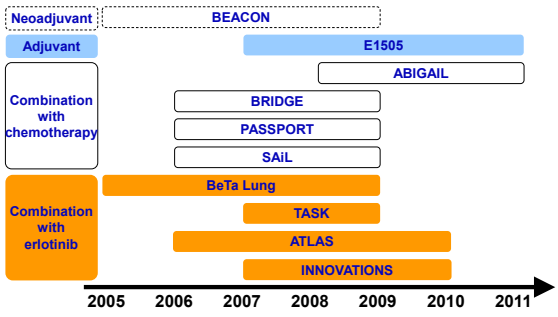
	≥ 70 y	< 70 y	*p* value
Neutropenia (G4)	34%	22%	.02
Melena/GI bleed	3.5%	1%	.005
Muscle weakness	8%	2%	.02
Motor neuropathy	3.5%	< 1%	.05
Tx-related deaths	6%	3%	.08

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
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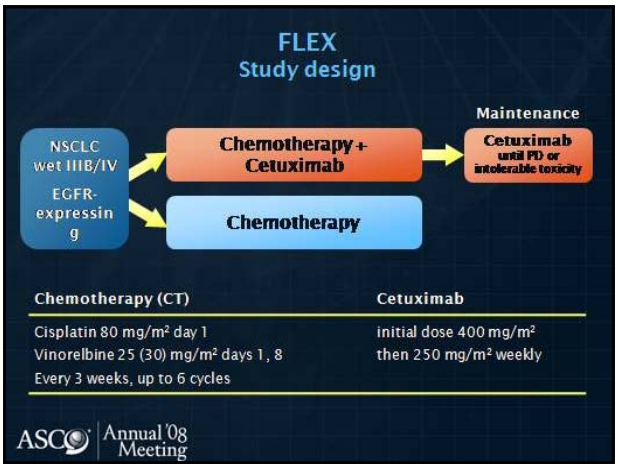
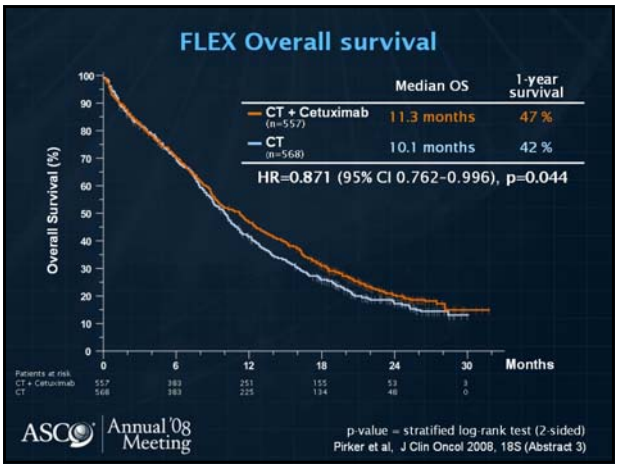




Flex Study: Results

- 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

R

N = 676

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

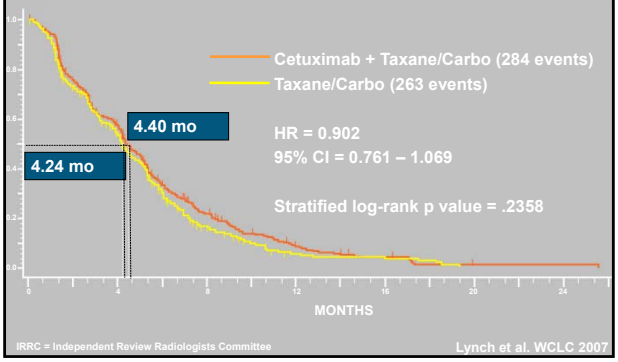
Primary endpoint: PFS (by IRRC)

Secondary endpoints: RR, OS, QOL, Safety

IRRC = Independent Review Radiologists Committee

Lynch et al. WCLC 2007

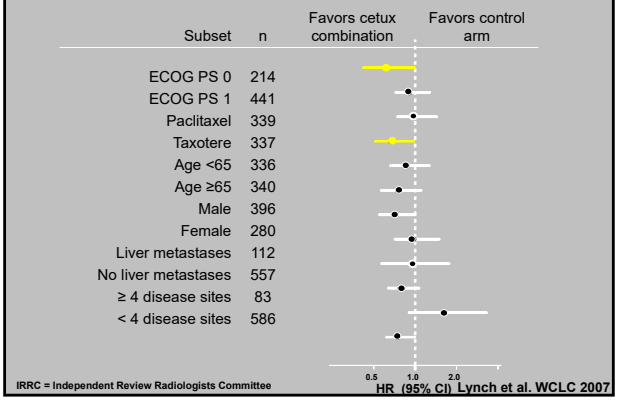
Phase III Trial of Taxane/Cb ± Cetuximab: PFS per IRRC



IRRC = Independent Review Radiologists Committee

Lynch et al. WCLC 2007

BMS-099: PFS in Pre-Planned Subsets



IRRC = Independent Review Radiologists Committee

Lynch et al. WCLC 2007

Contribution of cetuximab in first-line treatment: conclusions

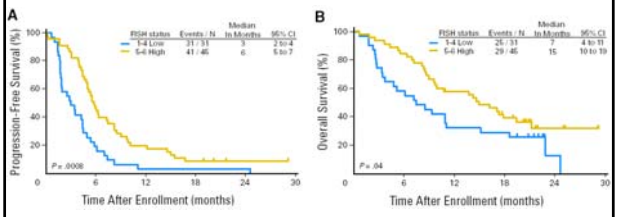
- Two large trials:
  - FLEX trial, with a not very standard CT arm, showed an improvement in RR and survival (not in PFS)
  - In BMS-099 difference in PFS and OS did not reach statistical significance (greater PFS improvements in patients on Taxotere)
- Survival benefit: same magnitude (1,2-1,3 months) in two trials (but BMS-099 lower power then 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 *EGFR* FISH Status	No. of Patients	OR (%)*	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

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- BR21 trial – Erlotinib improves clinical outcomes versus placebo in refractory, advanced NSCLC
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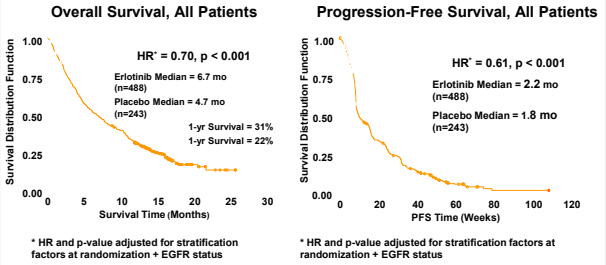
BR.21: Erlotinib versus placebo Overall Survival and PFS



Shepherd et al. NEJM 2005

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[a]	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; $p = .01$ ($n = 342$)

[a]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

Shepherd et al. NEJM 2005

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
- Chemonaïve
- 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

IPASS: Results

	Gefitinib	Carboplatin / paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)

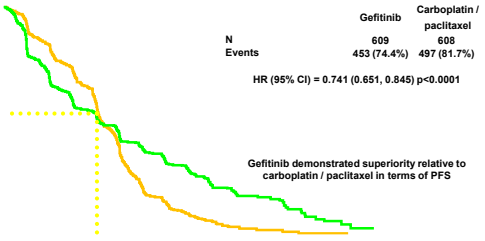
HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

Gefitinib had a more favourable tolerability profile than carboplatin / paclitaxel
QoL improvement rate was significantly greater with gefitinib than carboplatin / paclitaxel

ESMO 2008

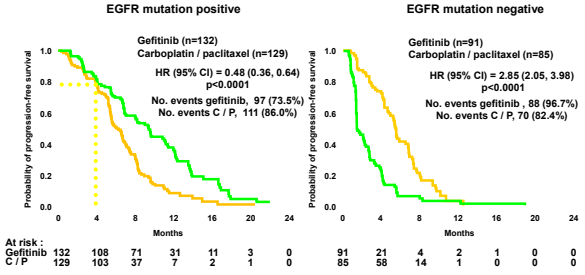
Progression-free Survival in ITT Population



Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib

ESMO 2008

Progression-free Survival in EGFR Mutation Positive and Negative Patients



At risk :

Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

91	21	4	2	1	0	0
85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

ESMO 2008

Recent advances in advanced NSCLC

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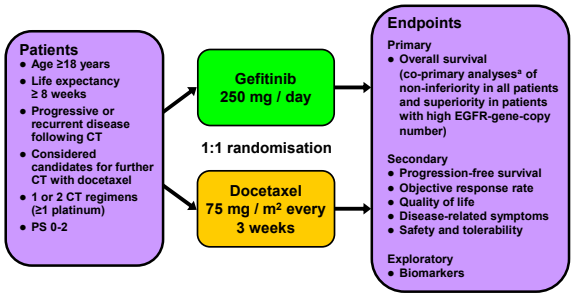
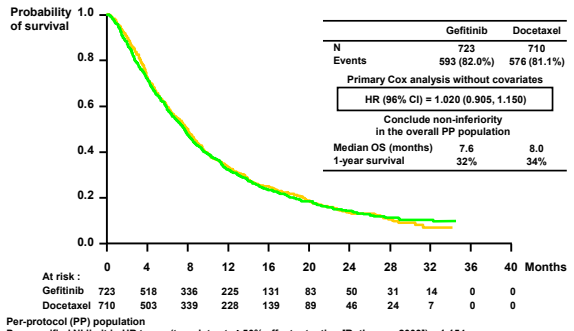
INTEREST study design



[a]Modified Hochberg procedure applied to control for multiple testing
CT, chemotherapy; PS, performance status

Douillard et al, WCLC 2007

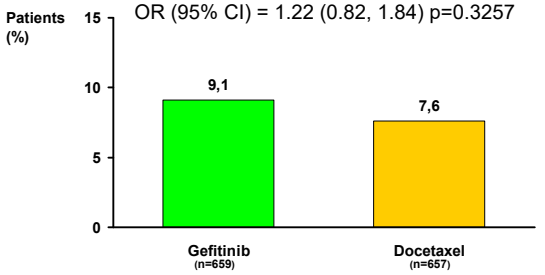
INTEREST study: Overall survival



Per-protocol (PP) population
Pre-specified NI limit in HR terms (translates to ≥50% effect retention [Rothmann 2003]) = 1.154
NI, non-inferiority; HR, hazard ratio; OS, overall survival

Douillard et al, WCLC 2007

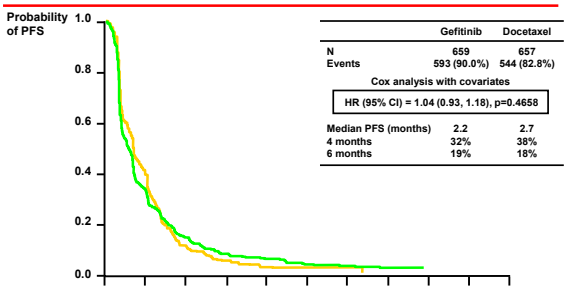
INTEREST study: objective tumour response



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



	Gefitinib	Docetaxel
N	659	657
Events	593 (90.0%)	544 (82.8%)

Cox analysis with covariates

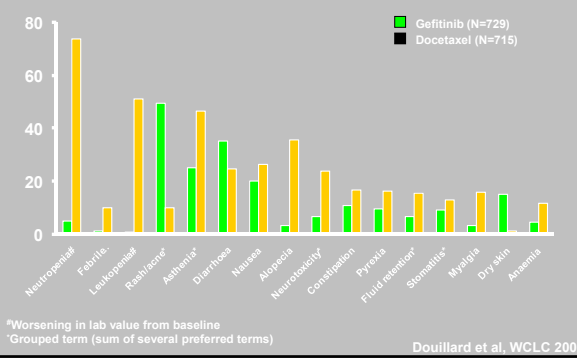
HR (95% CI) = 1.04 (0.93, 1.18), p=0.4658

Median PFS (months)	2.2	2.7
4 months	32%	38%
6 months	19%	18%

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

Douillard et al, WCLC 2007

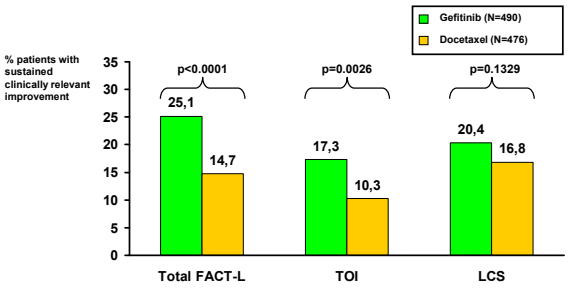
Most common AEs (≥ 10% on either treatment) with ≥ 3% difference between treatments



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

Douillard et al, WCLC 2007

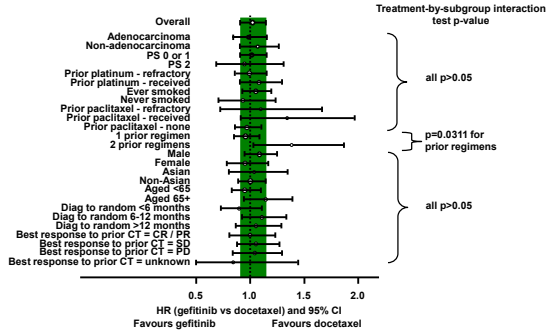
Quality of life and symptom improvement rates



Evaluable 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

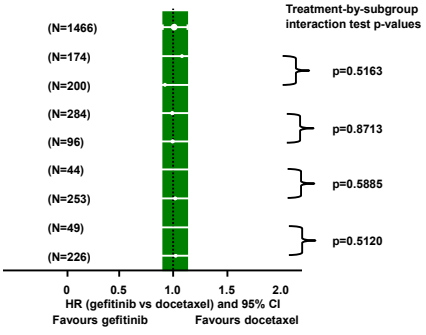
Overall survival by clinical subgroups



Overall PP population. Cox analysis without covariates

Douillard et al, WCLC 2007

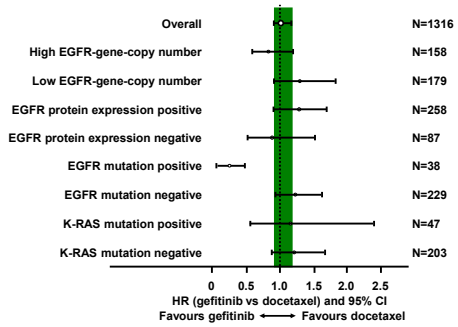
Overall survival by biomarker subgroup



ITT population; Cox analysis without covariates

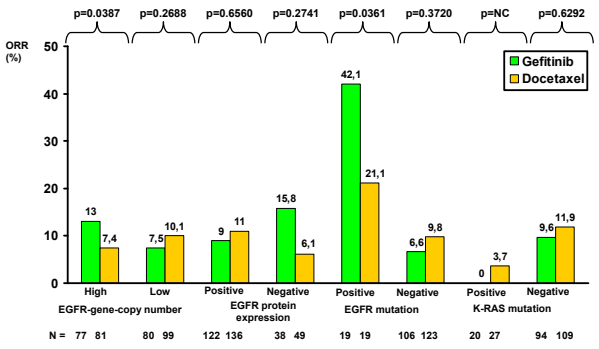
Douillard et al, ASCO 2008

Progression-free survival by biomarkers



Douillard et al, ASCO 2008

Objective response rate by treatment and biomarker status



p-values from logistic regression with covariates; NC, not calculated

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

Gefitinib versus chemotherapy

Table 4. Trials comparing gefitinib with chemotherapy

Trial	Phase (*n*)	Treatments	Response (%)	Median PFS (mos)	Median OS (mos)
SIGN [40]	II (141)	Gefitinib, 250 mg daily	13.2	3.0	7.5
		Docetaxel, 75 mg/m^2 every 3 weeks	13.7	3.4	7.1
V-15–32 [41]	III (489)[a]	Gefitinib, 250 mg daily	22.5[b]	2.0[b]	11.5[b]
		Docetaxel, 60 mg/m^2 every 3 weeks	12.8	2.0	14.0
INTEREST [42]	III (1,466)[a]	Gefitinib, 250 mg daily	9.1[c]	2.2[c]	7.6[c]
		Docetaxel, 75 mg/m^2 every 3 weeks	7.6	2.7	8.0
INVITE [44]	II (196)	Gefitinib, 250 mg daily	3.1	NR[d]	NR[d]
		Vinorelbine, 30 mg/m^2 days 1 and 8 every 3 weeks	5.1	NR	NR

Stinchcombe and Socinski, The Oncologist 2008

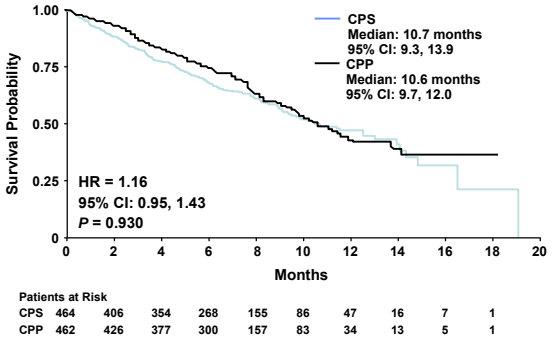
One Drug/One Target

- Paradigm validated with ECOG 4599, AVAiL, FLEX and BR.21
- If target is dominant, this strategy can be successful with or without cytotoxic chemotherapy
- Likely to be less toxic
- The biologic phenomenon of EGFR activating mutations creates a model for success for the one drug/one target approach

Randomized Trials with CT+/- Targeted Therapies in treatment-naïve NSCLC: recent failures

TARGET	AGENT	CT	OUTCOME
EGFR	gefitinib	PC/CisG	No benefit
	erlotinib	PC/CisG	No benefit
MMP's	AG3340	PC	No benefit
	BMS275291	PC	No benefit
FT (ras)	lonafarnib	PC	No benefit
PKCα	ISIS 3521	PC	No benefit
RXR	Bexarotene	PC/CisN	No benefit

ESCAPE: CbP ± Sorafenib Overall Survival (ITT Population)



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)		
Pulmonary haemorrhage	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)
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

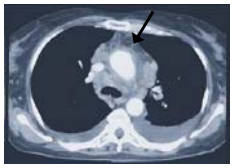
*mg/kg

Leighl et al. Eur J Cancer Suppl 2007

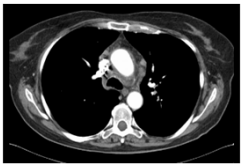
Appropriate patient selection for bevacizumab therapy: central tumour

- 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

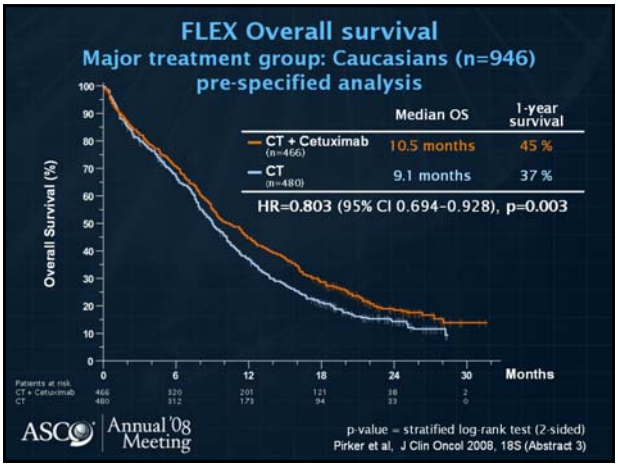
Bevacizumab in advanced NSCLC: Efficacy by Gender in ECOG trial

Parameter	Males		Females	
	PC (n=230)	PCB (n=191)	PC (n=162)	PCB (n=190)
OS, mo	8.7	11.7*	13.1	13.3
PFS, mo	4.3	6.3*	5.3	6.2*
RR, %	16	29*	14	41*

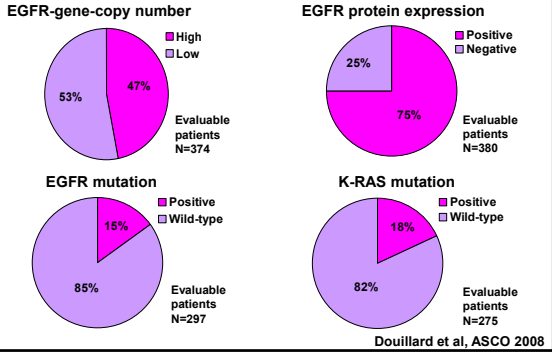
*Statistically significant

- **No survival benefit for females despite 4-fold increase in RR and statistically significant difference for PFS**
- **A number of potential explanations (statistical chance, imbalance of unmeasured prognostic factors or a true difference)**

Brahmer et al. J Clin Oncol 2006



Biomarker status in patients with evaluable samples



Douillard et al, ASCO 2008

NEVROENDOKRINI GASTROENTEROPANKREATIČNI TUMORJI (GPNET)
Predstavitev kliničnih primerov

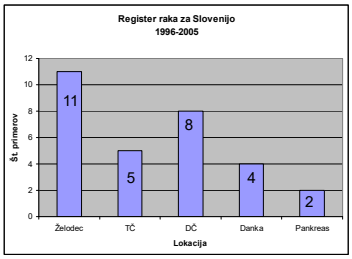
Marko Boc, dr.med.
Brigita Gregorič, dr.med.
Mentor: dr. Janja Ocvirk, dr.med.

- groba incidenca v Evropi 3/100.000
- najpogosteje po 50. letu, razen nevroendokrini 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 endokrina 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 (nevrofibromatoza 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 nevroendokrinsko sorodne lezije



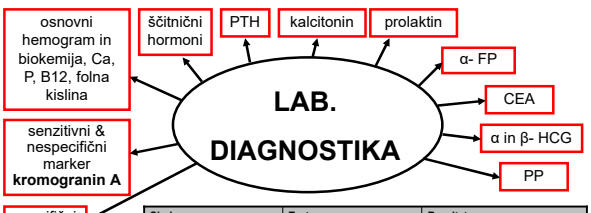
Tumor	Klinični znaki	Mesto vznika	%mlg
Insulinom	hipoglikemija, ↑ tel. teža	>95 % pankreas	> 10
Gastrinom	abd.bolečina, diareja, ulkusi, želodčna hipersekrecija	duodenum 70%, pankreas 25%	60-90
VIPom	diareja, ↓ K, ↓ Cl, metabolna acidoza, rdečica, ↓ tel.teža	90% pankreas	> 50
Glukagonom	DM, GVT, nekrolitični migratorni eritem, depresija	pankreas	> 50
Somatostatinom	DM, žolčni kamni, ↓ telesna teža, steatoreja	pankreas 6%, zg.GIT 44%	70-80
ACTHom	AH, DM, oslabelost	pankreas 30%, pljuča 50%	> 99
PTHrPom	hiperkalcemija, nefrolitiaza	pankreas	> 99
Neurotensinom	DM, diareja, rdečica, AH, ↓ tel.teža, edemi	pankreas	-
Calcitoninom		pankreas,pljuča	> 80%
GFRom	akromegalija	pankreas,pljuča	30

Karcinoidni sindrom:

- 8% od 8876 bolnikov z karcinoidnim tumorjem, incidenca 1.7%-18.4% v 6 različnih serijah, 92% bolnikov je imelo ↑ aktivnost serotonina (5-HT)*

	Ob ugotovitvi		Med potekom bolezni			
	Davis 1973	Norheim 1987	Thorson 1958	Feldman 1987	Norheim 1987	Soga 1999
Število bolnikov	91	91	79	111	91	748
SIMPTOM/ZNAK (%)						
Driska	73	32	68	73	84	67
Rdečica	65	23	74	63	75	78
Bolečina	-	10	-	-	-	34
Obstrukcija (pljuča)	8	4	18	3	15	10
Pellagra (↓ B_3)	2	-	5	-	-	-
Brez	12	-	-	22	-	-
Karcinoidno srce	11	-	41	14	33	33
DEMOGRAFIJA						
Moški (%)	59	46	64	-	46	52
Srednja starost (leta)	57	59	52	-	-	54.5
Razpon starosti (leta)	25-79	-	18-80	-	-	9-91
LOKACIJA TU. (%)						
zgornji GIT	5	9	2	-	9	33
srednji GIT	78	87	75	-	87	60
spodnji GIT	5	1	8	-	1	1
neznano	11	2	15	-	2	6

*Soga J et al. J Exp Clin Cancer Res 1999;18(2):133



Sindrom	Test	Rezultat
Karcinoid zg. GIT	24-h 5 HIAA v urinu	včasih ↑
Karcinoid sr. GIT	24-h 5 HIAA v urinu, neurokinin A in B	↑ v 70% primerov
Karcinoid sp. GIT	24-h 5 HIAA v urinu	ni ↑
Gastrinom	bazalni gastrin, test z sekretinom	↑ gastrin bazalno in po testu
Insulinom	bazalni inzulin, C peptid, stradalni test	↑ razmerje inzulin/glukagon, ↑ proinzulin, ↑ C peptid
Glukagonom	bazalni GIT hormoni, biopsija kože	↑ serumska vrednost glukagona in enteroglukagona
VIP-om	bazalni GIT hormoni	↑ bazalni VIP
PP-om	bazalni GIT hormoni	↑ bazalni PP
Somatostatinom	bazalni GIT hormoni	↑ bazalni somatostatin

UZ

↓

CT & MRI

↓

tankoigelna punkcija lezije

endoskopski UZ, kolonoskopija, gastroskopija

SLIKOVNA DIAGNOSTIKA

OCTREOSKEN

- **najobčutljivejša metoda za zaznavanje metastatske bolezni**
- **Indij 111 vezan na somatostatinski analog pentetreotid**
- **pozitiven pri 80-90% bolnikih z NET zg. GIT (10-15% tu. brez somatostatinskih receptorjev)**
- **demarkira tako primarni tu. kot tudi zasevke oz. pozitivne bezgavke**
- **omejitev je velikost lezije (< 0.5cm)**
- **pozitiven izvid korelira z odgovorom na zdravljenje z AS**

Stadij in TNM:

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

[a]HPF ("high power field")=2mm², vsaj 40 pregledanih polj na mestu največje gostote mitoz
[b]MIBI protitelo

T (primarni tumor)	
TX	neznan
T0	brez
T1	omejen na pankreas <2 cm
T2	omejen na pankreas 2-4 cm
T3	na pankreas >4 cm ali invadira v dvanajstnik, žolčni sis.
T4	vključuje bližnje organe ali velike žile
N (regionalne bezgavke)	
NX	neznano
N0	brez zasevkov v reg. bezg.
N1	z zasevki v reg. bezg.
M (oddaljene metastaze)	
MX	neznano
M0	brez zasevkov
M1	z zasevki
Stadij	
Stadij I	T1 N0 M0
Stadij IIa	T2 N0 M0
IIb	T3 N0 M0
Stadij IIIa	T4 N0 M0
IIIb	kkT N1 M0
Stadij IV	kkT kkN 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)*

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

Selektivna (kemo)-embolizacija, RFA, krioablacija

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 m[1]
  - mediani TTP in mediani OS (Lutecij 177) >30 m[1]
  - 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 indiakcije 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/epiadriamicin => 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.

[1]Plöckinger U et al. Neuroendocrinology 2004; 80; 394-424
[2]Bajetta 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 carcinoid
    - 30% celic poz. na glukagon (glukagunom)
  - 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 karcinom → **KOMBINACIJA**
  - 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), različe 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)

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

1. KLINIČNI PRIMER

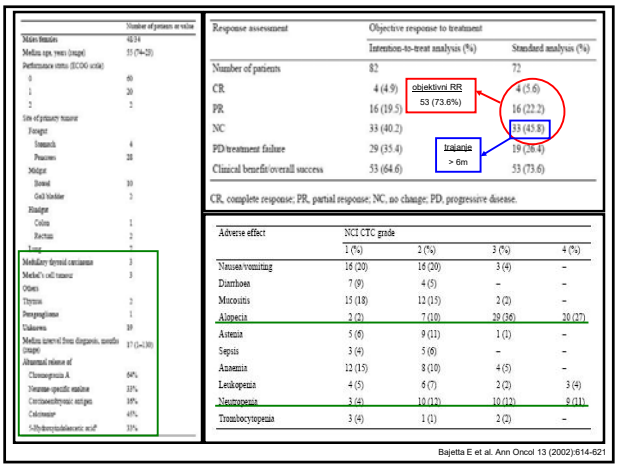
- prične zdravljenje z Sandostatin LAR in KT po shemi FDE (5-FU(5-fluorouracil), DTIC(dakarabazin), epirubicin)
- prejme 9. ciklusov (zadnjega 07/2008)
- kontrolni MRI (50% regres bolezni)
  - CR metastaz endokrinega karcinoma
  - ostajajo 3 metastaze, ki kopičijo octreotid
- avgust 2008 – resekcija 3 jeternih metastaz
  - H (OI): metastaze nevroendokrinega 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

Plöckinger U et al. Neuroendocrinology 2004; 80; 394-424



Response assessment	Objective response to treatment	
	Intention-to-treat analysis (%)	Standard analysis (%)
Number of patients	82	72
CR	4 (4.9)	4 (5.6)
PR	16 (19.5)	16 (22.2)
NC	33 (40.2)	33 (45.8)
PD/treatment failure	29 (35.4)	19 (26.4)
Clinical benefit/overall success	53 (64.6)	53 (73.6)

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

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)	–
Alopecia	2 (2)	7 (10)	29 (36)	20 (27)
Astenia	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)	–

objektivni RR 53 (73.6%)

trajanje > 6m

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

2. KLINIČNI PRIMER

- 60 letna bolnica
- družinska anamneza glede mlg. pozitivna
- od leta 1996 spremljana na OI zaradi histol. verific. 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 abdomna & 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: nevroendokrini karcinoid, ki ga imunohistokemično ne morejo potrditi
    - H: najverjetneje nevroendokrini karcinom oz. karcinoid

- dec. 2001 OP => ekstirpacija tu. z delno resekcijo sakruma in trtice
  - H: nevroendokrini 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.

REFERENCE:

1. Plöckinger U et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal timours. Neuroendocrinology 2004; 80; 394-424
2. Bajetta E et al. Efficacy of a chemotherapy combination for the treatment of metastatic neuroendocrine tumours. Ann Oncol 13 (2002):614-621
3. Baxter Oncology. Selected schedules. 12th update; 254-260
4. Rihard R et al. Enteroendocrine tumors other then carcinoid: A review oc clinically significant advances. Gastroenterology 2005; 128: 1668-1684
5. Soga J et al. Carcinoid syndrome: a statistical evaluation of 748 reported cases. J Exp Clin Cancer Res 1999; 18(2): 133
6. Garland J et al. Sandostatin LAR (long-acting ocreotide acetate) for malignant carcinoid syndrome: a 3-year expirience. Aliment Pharmacol Ther 2003; 17: 437-444
7. Hematology/Oncology clinics of north America. Neuroendocrine tumors. Junij 2007; volume 21: number 3
8. Siegbert F et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interfeon alfa and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumours - the international lanreotide and interferon alfa study group. J Clin Oncol 2003; vol 21: No 14: 2689-2696

9. UpToDate (www.uptodate.com)
10. NCCN - Cancer Guidelines for Patients and Physicians by Cancer Experts
11. (www.nccn.org)
12. Devita et al. Cancer – principles & practice of oncology; 8th edition: vol 2: 1702-1735
13. Kwekkeboom DJ et al. Overwiew of results of peptide receptor radionucleotide therapy with 3 radiolabeled somatostatin analog. J.Nucl.Med. 2005; 46 Suppl 1:62
14. Kwekkeboom DJ et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3] octreotate: toxcicity, efficiency, and survival. J. Clin. Oncol. 2008; 26:2124
15. Valkema R et al. Survival and response after peptide receptor radionucleotide therapy with [90Y-DOTAO,Tyr3] octreotide in patients with advanced GPNET tumors. Semin. Nucl. Med. 2006; 36: 147
16. De Jong M et al. Somatostatin receptor- targeted radionucleotide therapy of tumors: preclinical and clinical findings. Semin. Nucl. Med. 2002; 32: 133
17. Waldherr C et al. Tumor response and clinical benefit in NET after 7,4 GBq (90)Y-DOTATOC. J. Nucl. Med. 2002; 43: 610

HEPATOCELIČNI RAK

Dnevi internistične onkologije

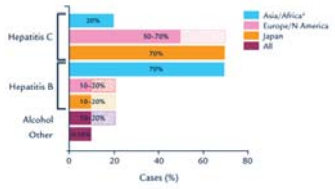
November 2008

Maja Ebert Moltara, Tanja Mesti
Mentor: Janja Ocvirk

EPIDEMIOLOGIJA:

Incidenca:

- 8.29/100.000 v EU
- 1,6-3,2/100.000 v Sloveniji



DIAGNOZA:

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

UZ, MRI ali CT

Zvišan AFP>400ng/ml

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

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

Zdravljenje:

- stadij bolezni
- stanje jetrnega tkiva
- splošna bolnikovo stanje

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 biolezen
- 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% - bolnikih s kronično bolnimi jetrni

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 bolezni

5-letno preživetje: do 70%

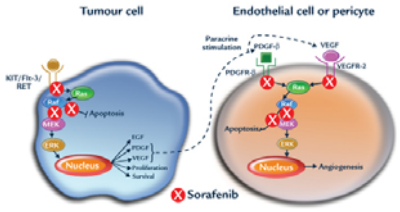
Neresektabilni tumorji (T2, T3 in T4, N0, M0)

- 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

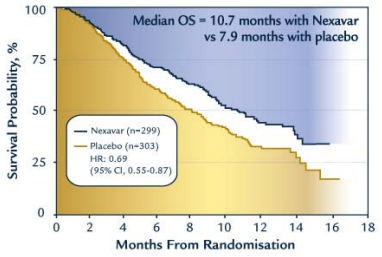
Napredovali tumorji (katerikoli T,N+,M1)

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

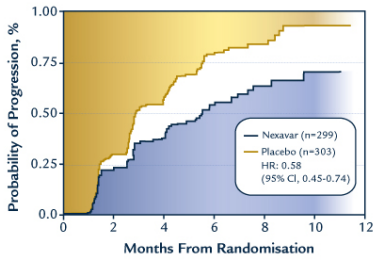
Sorafenib, Nexavar®



SHARP: **S**orafenib **H**CC **A**ssessment **R**andomized **P**rotocol Trial



SHARP: **S**orafenib **H**CC **A**ssessment **R**andomized **P**rotocol Trial



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 radiolškega progesa (24 vs. 12 tednov)[5]
- ❖ podaljša čas do progresa simptomov (18 vs. 21 tednov, vendar razlika ni signifikantna)[5]
- ❖ najpogostejši stranski učinki: driska, kožne spremembe, alopecija in palmo-plantarne eritodisestezije[5]

REFERENCEs:

1. **Hepatocellular carcinoma: ESMO Clinical Recommendation for diagnosis, treatment and follow-up**. P. Parikh, H.Malhotra, S. Jelic and on behalf of the ESMO Guidelines Working Group; Ann. Onc. 19:27-28, 2008

2. **NCCN Clinical Practice Guidelines in Oncology**

3. **Incidenca raka v Sloveniji 2004**. Ljubljana: Onkološki inštitut, Register raka za Slovenijo, 2007

4. **Prognosis of advanced hepatocellular carcinoma: comparison of three staging systems in two French clinical trials,** S. Collete, F. Bonnetain, X. Paoletti, M. Doffoel, O. Bouche, J.L. Raoul, P. Rougier, F. Masskouri, L. Bedenne & J.C. Barbare; Ann. Onc. 19: 1117-1126, 2008

5. **Sorafenib in advanced Hepatocellular Carcinoma**, J.M. Lovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, JF. Blanc, A.C. Olivera, A. Santoro and others; N Engl J Med. 2008 Jul 24;***359***(***4***):***378-90***.

HEPATOCELIČNI RAK

(prikaz primera 1)

Dnevi internistične onkologije

November 2008

Tanja Mesti, Maja Ebert Moltara
Mentor: Janja Ocvirk

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

September 2001:
Hospitalizacija v SB Murska Sobota

Dekompenzacija 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.

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
- **TT** 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**

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

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 spremenjih 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, jetrna 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

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

Kako bi bolnika zdravili?

a) Operacija
b) Kemoembolizacija
c) RFA
d) PEI
e) Transplantacija
f) Sistemska terapija
g) 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 gležnjev	AFP 13206	800mg	Dopller 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), karcinoza?
17.7. 2008	slabost, pogosto bruhal, večkrat driska (5-10x odvajanje)	PS: WHO 1-2 ikteričen	AFP 928	prekinitev 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 ddg. 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+, trifoil f. +

Osnovne histološke skupine raka neznanega izvora (svetlobni mikroskop)

DOBRO/SREDNJE DIFERENCIRAN **ADENO**KARCINOM (60%)

SLABO DIFERENCIRAN (ADENO)**KARCINOM** (29%)

SLABO DIFERENCIRANA MALIGNA NEOPLAZMA (5%)

PLOŠČATOCELIČNI KARCINOM (5%)

KARCINOM Z **NEVROENDOKRINO**D IFERENCIACIJO (1%)

Minimalni nabor preiskav za iskanje origa oz. zamejitev bolezni

E. Briasoulis 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 neznanega 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 **nevroendokrini karcinom**	**Cisplatin/karboplatin + etopozid**
Karcinoza 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 aspiracijcka 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.

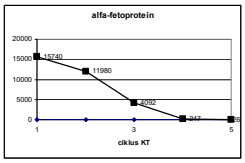
-ddg. dilema: germinalni tumor/hepatocelularni karcinom

-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., pričel 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 epitelijskih 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 izpuščaj 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 diferecirani 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 železnega 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 mamarnega 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
- Gastroskopija (?), kolonoskopija (?): 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).

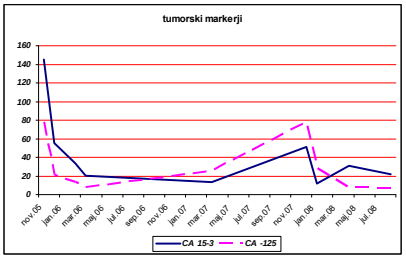
Klinični primer 2/7

- 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 ciklusov KT: Paclitaxel, Carboplatin (do 05/2008)
- 28.08.2008 zadnja kontrola: Ginekološki pregled, UZ trbuha, markerji: b.p.
- Pričela s 4-urnim delavnikom

Klinični primer 2/9



RAK DOJK

– vloga ženskega podpisa 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**

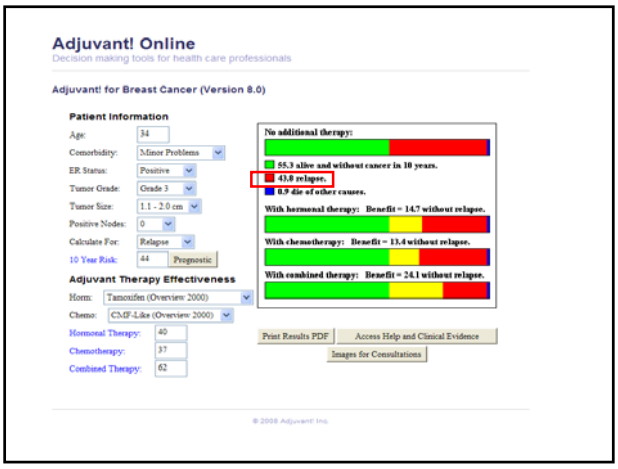
PATOHISTOLOGIJA:

- 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.

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



PROSPEKTIVNE RANDOMIZIRANE ŠTUDIJE O DODATKU KEMOTERAPIJE K HORMONSKEMU ZDRAVLJENJU

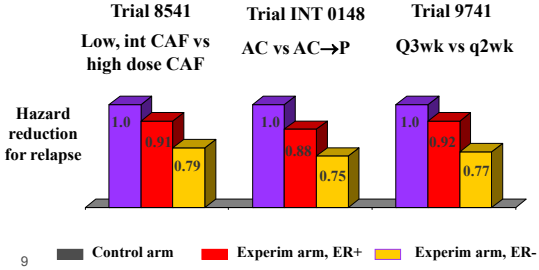
Randomized trials	Trial Size Stage	Treatments	Outcome (DFS/OS)	Comments
Pomenopausal patients				
SWOG trial Rivkin SE, JCO 1994	892 N+,HR+	TAM 1 y +/- CMFVP	No signif. difference in DFS and OS	
IBCSG IX IBCSG, JNCI 2004	1669 N- HR+/-	TAM 5y +/- CMF	No signif. difference in DFS and OS of adding ChT in 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 5 y) +/- AC	No difference in DFS and OS	Premature closure of the trial due to low accrual
Premeno-	and pomenopausal	Patients		
NSABP B-20 Fisher B, Lancet 2004	788 N-, HR+	TAM 5y +/- CMF	Signif. difference in DFS and OS for premeno- but not pomenopausal pts	

10

UČINKOVITOST ADJUVANTNE KEMOTERAPIJE GLEDE NA ER STATUS: CALGB ŠTUDIJE

(N+, pre- in pomenopavzne bolnice)

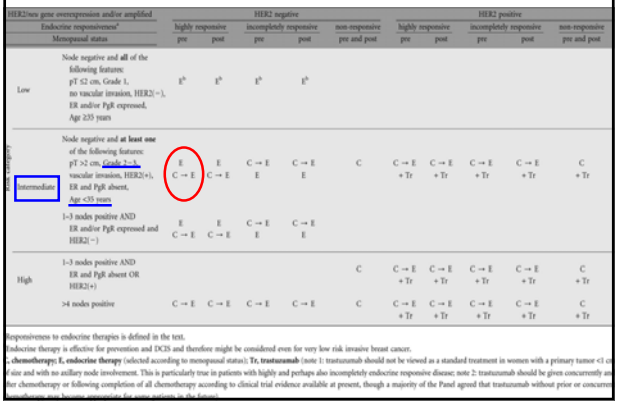
! MUCH GREATER IMPACT FOR ER- DISEASE !



9

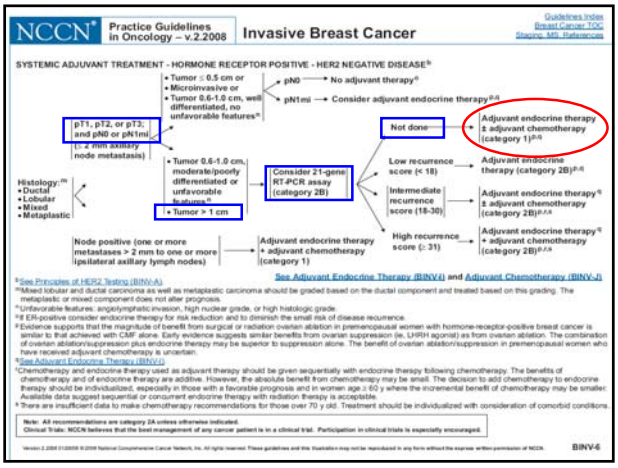
Berry D, et al.JAMA 295: 1658-67 2006

ST. GALLEN 2007 - priporočila



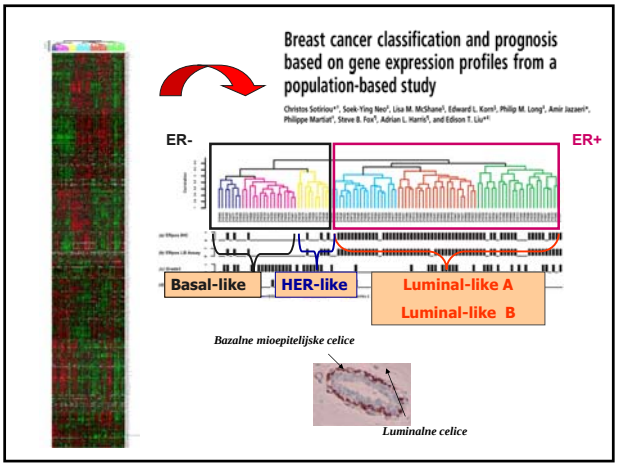
HER2/neu gene overexpression and/or amplified		HER2 negative					HER2 positive				
Endocrine responsiveness[a]		highly responsive		incompletely responsive		non-responsive	highly responsive		incompletely responsive		non-responsive
Menopausal status		pre	post	pre	post	pre and post	pre	post	pre	post	pre and post
Low	Node negative and **all** of the following features: pT ≤2 cm, Grade 1, no vascular invasion, HER2(−), ER and/or PgR expressed, Age ≥35 years	E[b]	E[b]	E[b]	E[b]						
Intermediate	Node negative and **at least one** of the following features: pT >2 cm, Grade 2–3, vascular invasion, HER2(+), ER and PgR absent, Age <35 years	E C → E	E C → E	C → E E	C → E E	C	C → E + Tr	C → E + Tr	C → E + Tr	C → E + Tr	C + Tr
	1–3 nodes positive AND ER and/or PgR expressed and HER2(−)	E C → E	E C → E	C → E E	C → E E						
High	1–3 nodes positive AND ER and PgR absent OR HER2(+)					C	C → E + Tr	C → E + Tr	C → E + Tr	C → E + Tr	C + Tr
	>4 nodes positive	C → E	C → E	C → E	C → E	C	C → E + Tr	C → E + Tr	C → E + Tr	C → E + Tr	C + Tr

Responsiveness to endocrine therapies is defined in the test.
Endocrine therapy is effective for prevention and DCIS and therefore might be considered even for very low risk invasive breast cancer.
, 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
f 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 an
ter 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 concurre



ASCO 2007 PRIPOROČILA ZA UPORABO TUMORSKIH MARKERJEV PRI RAKU DOJK

DIAGNOZA	PRIPOROČENI		BREZ PRIPOROČILA
	IME TESTA	NAMEN	TEST
Novoodkrit invazivni rak dojk	ER/PR test	Napoved odgovora na dopolnilno hormonsko zdravljenje	/
	HER-2 test	Napoved odgovora na trastuzumab in napoved odgovora na dopolnilno kemoterapijo z antraciklini	
Novoodkrit invazivni rak dojk, negativne bezgavke in ER in/ali PR pozitiven	Oncotype DX	Določanje prognoze pri ženskah, ki bodo prejela dopolnilni tamoksifen	Drugi multiparameterski testi genske ekspresije
	uPA/PAI-1 test	Določanje prognoze in vodenje uporabe dopolnilne kemoterapije s CMF	



GENSKI PODPISI – NAPOVEDNIKI PROGNOZE PRI ZGODNJEM RAKU DOJK

- 21-genski podpis (Oncotype DX™); 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

Invazija
Stromolizin 3
Katepsin L2

GSTM1
BAG1
CD68

HER2
GRB7
HER2

Referenčni
β-aktin
GAPDH
RPLPO
GUS
TFRC

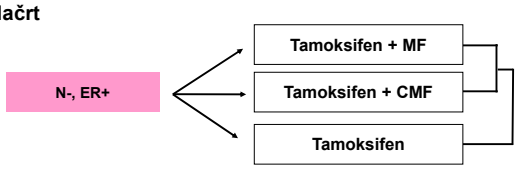
RS =
+ 0.47 X HER2 group score
- 0.34 X ER group score
+ 1.04 X Proliferation group score
+ 0.10 X Invasion group score
+ 0.05 X CD 68
- 0.08 X GSTM1
- 0.07 X BAG1

Kategorija	RS (0-100)
Nizko tveganje	RS < 18
Srednje tveganje	RS ≥ 18 and < 31
Visoko tveganje	RS ≥ 31

DOBROBIT KEMOTERAPIJE PRI ER+ N- RAKU DOJK GLEDE NA 21-GENSKI PODPIS

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

Načrt

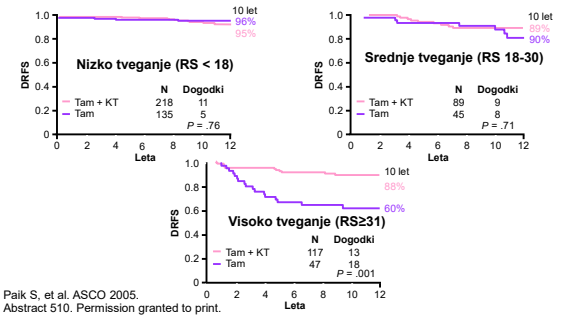


Cilj

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

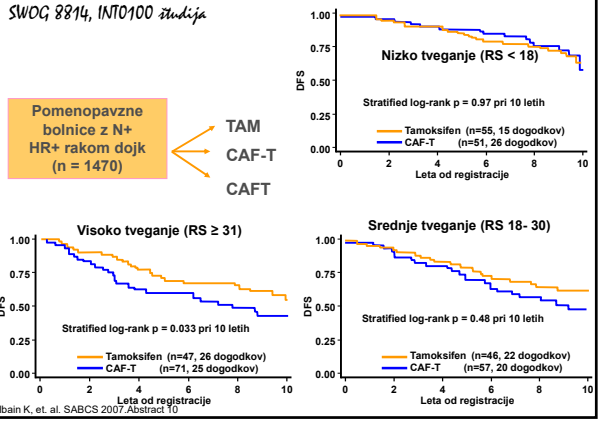
Paik S, et al. ASCO 2005. Abstract 510.

DOBROBIT KEMOTERAPIJE PRI ER+ N- RAKU DOJK GLEDE NA 21-GENSKI PODPIS



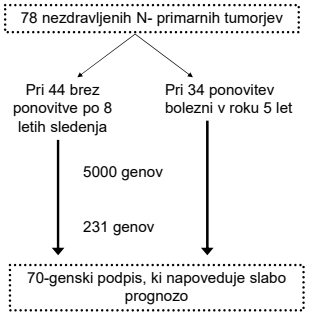
Paik S, et al. ASCO 2005. Abstract 510. Permission granted to print.

DOBROBIT KEMOTERAPIJE PRI ER+ N+ POMENOP. BOLNICAH Z RAKOM DOJK SWOG 8814, INT0100 študija



Albain K, et. al. SABCS 2007.Abstract 10

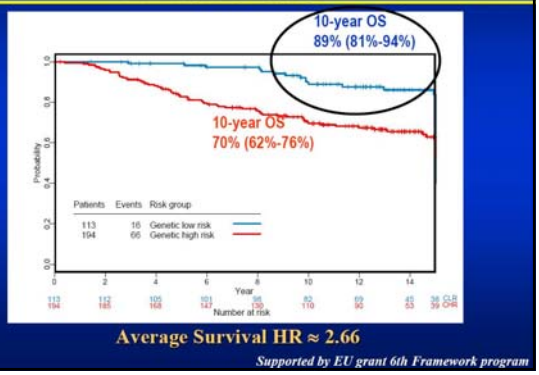
AMSTERDAMSKI 70-GENSKI PROGNOSTIČNI PODPIS



- 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

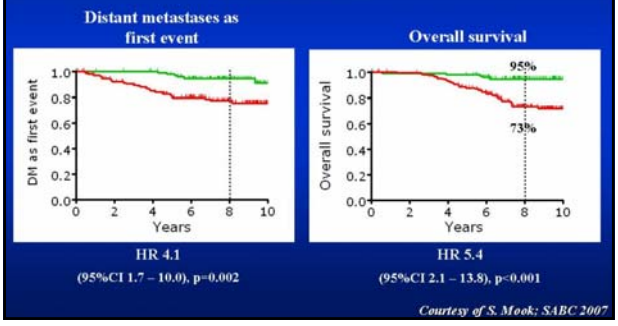


Average Survival HR ≈ 2.66

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) / Poor profile (n=142) } **Median f. up = 7.8 y**



Courtesy of S. Mook; SABC 2007

70-GENSKI PODPIS IN KT

1-3 N+, Vse bolnice (N = 241)	8-let OS, %	Events, n
Dober podpis (n = 99)	95	5
Slab podpis (n = 142)	73	34

Kemoterapija (n = 128)	8-let OS, %	Events, n
Dober podpis (n = 39)	95	2
Slab podpis (n = 89)	69	24

Brez kemoterapije (n = 101)	8-let OS, %	Events, n
Dober podpis (n = 57)	94	3
Slab podpis (n = 44)	77	10

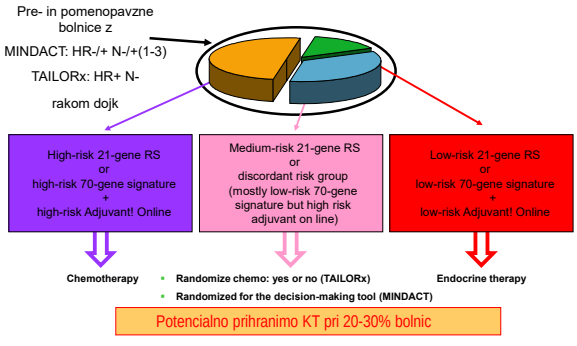
- 70-genski podpis izboljša oceno tveganja v primerjavi z Adjuvant! Online in identificira nizko rizične skupine z odlično prognozo brez KT.

Mook S, et al. 2007 SABCS. Abstract 50.

ONCOTYPE vs. MAMMAPRINT

Oncotype DX™	MammaPrint®
RT-PCR test	Genski čip
na tkivu, fiksiranem s formalinom ter vklopljenem v parafin	na sveže zamrznjenem, nefiksiranem tkivu
prognostičen test za bolnice z ER+ N- rakom dojk, zdravljene s tamoksifenom	prognostičen test za bolnice z ER+/- z N- in N+ rakom dojk
ASCO in NCCN priporočilo za klinično uporabo	Nizozemska priporočila za klinično uporabo

TAILORx (N = 10,500) IN MINDACT (N = 6000) PROSPEKTIVNI RANDOMIZIRANI ŠTUDIJI



Potencialno prihranimo KT pri 20-30% bolnic

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:

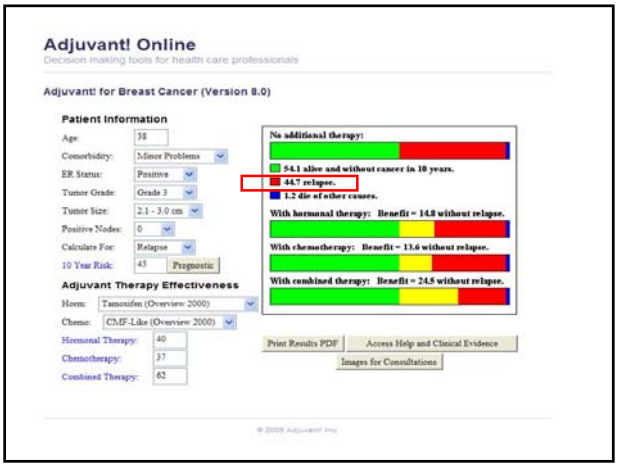
- *Mamografija*: na meji notranjih kvadrantov desne dojke, 3.5 cm, mestoma neostro omejen.
- Tankoigelna biopsija: **karcinom dojke**
- *Laboratorijski izvidi:* bp
- *Preiskave za oddaljene zasevke:* negativne

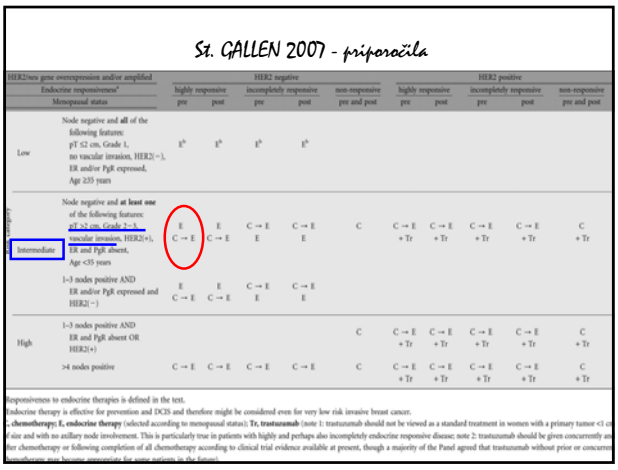
→ **KVADRANTEKTOMIJA** in **SNB**

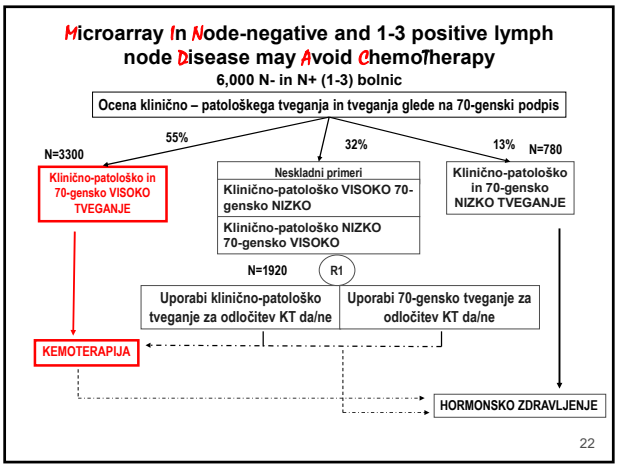
PATOHISTOLOGIJA:

- **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);


SISTEMSKO ZDRAVLJENJE?
ZNAČILNOSTI BOLNIKA
Z DOKAZI PODPRTI PODATKI
ZNAČILNOSTI TUMORJA
RAZPOLOŽLJIVA TERAPIJA

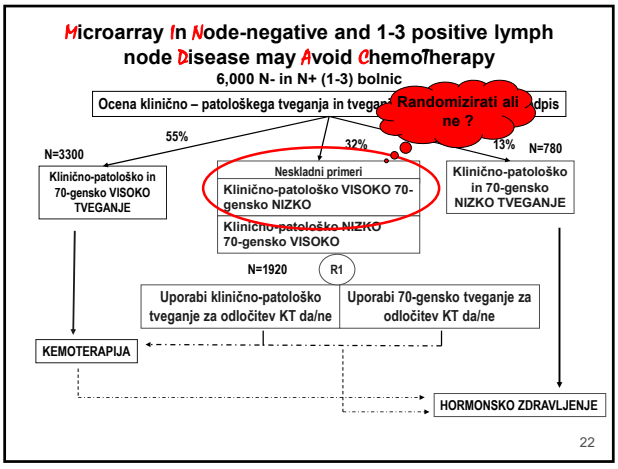

Adjuvant! Online
Decision making tools for health care professionals
Adjuvant! for Breast Cancer (Version 8.0)
Patient Information
Age: 38
Comorbidity: Minor Problems
ER Status: Positive
Tumor Grade: Grade 3
Tumor Size: 2.1 - 3.0 cm
Positive Nodes: 0
Calculate For: Relapse
10 Year Risk: 45 Prognostic
Adjuvant Therapy Effectiveness
Horm: Tamoxifen (Overview 2000)
Chemo: 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


St. GALLEN 2007 - priporočila
HER2/neu gene overexpression and/or amplified
HER2 negative
HER2 positive
Endocrine responsiveness*
highly responsive
incompletely responsive
non-responsive
Menopausal status
pre
post
pre and post
Low
Node negative and all of the following features: pT ≤2 cm, Grade 1, no vascular invasion, HER2(−), ER and/or PgR expressed, Age ≥35 years
E
Intermediate
Node negative and at least one of the following features: pT >2 cm, Grade 2–3, vascular invasion, HER2(+), ER and PgR absent, Age <35 years
E
C → E
C
C + Tr
1–3 nodes positive AND ER and/or PgR expressed and HER2(−)
High
1–3 nodes positive AND ER and PgR absent OR HER2(+)
>4 nodes positive
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.
, 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
f 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 an
fter 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



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