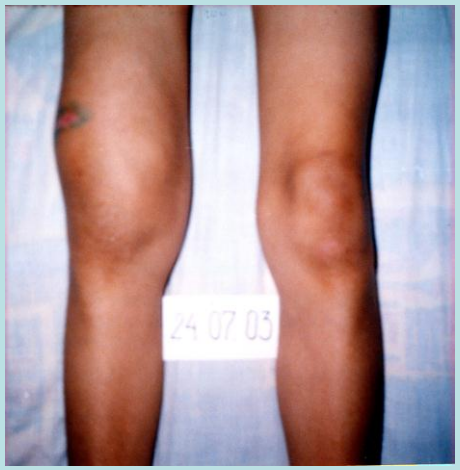
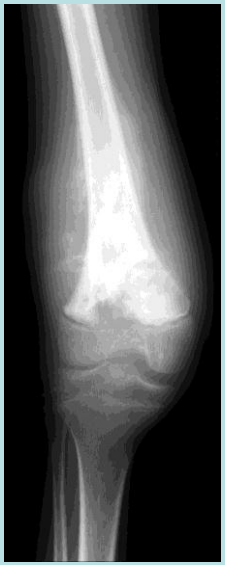
New Treatment Strategies in Osteosarcoma





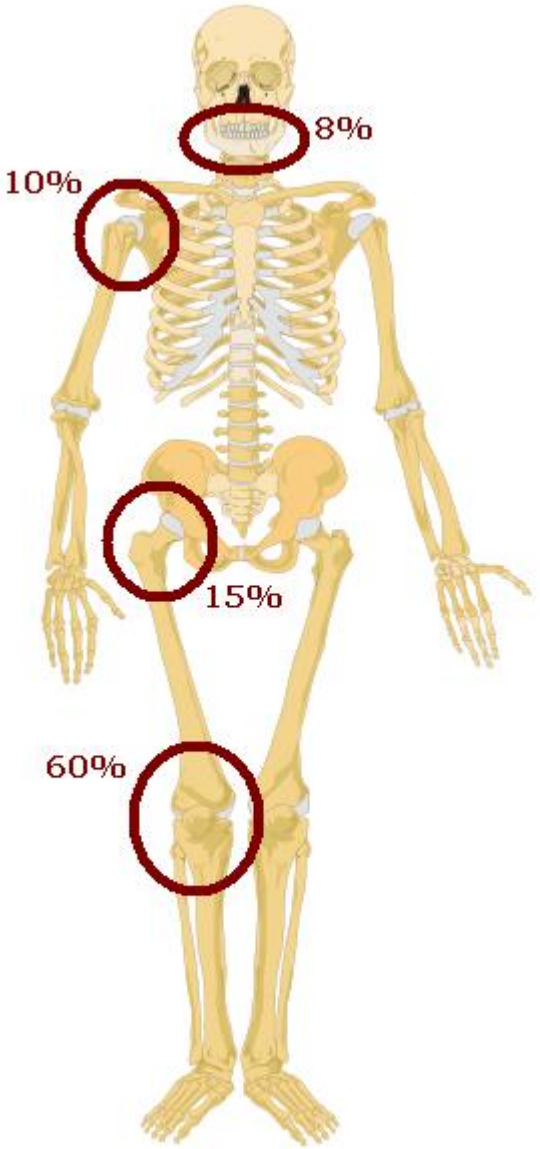
PD Dr. Claudia Blattmann, Prof. Dr. Stefan Bielack
Olgahospital
Klinikum Stuttgart
Germany

STUTTGART

Klinikum Stuttgart

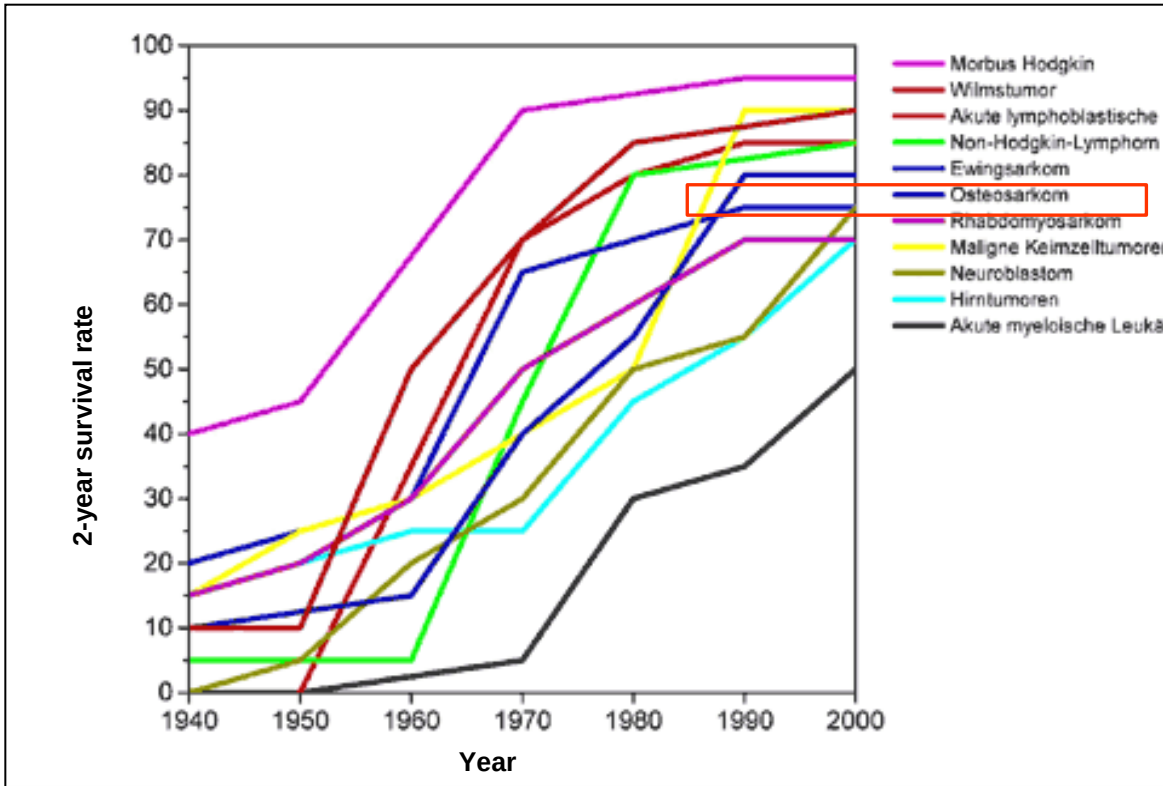
Introduction

- Most common bone tumor in children, adolescents and young adults
- Clinical manifestation: distal femur (42%), prox. Tibia (23%), humerus (10%
- 15-20% clinically detectable metastases (> 80% lung; bone)



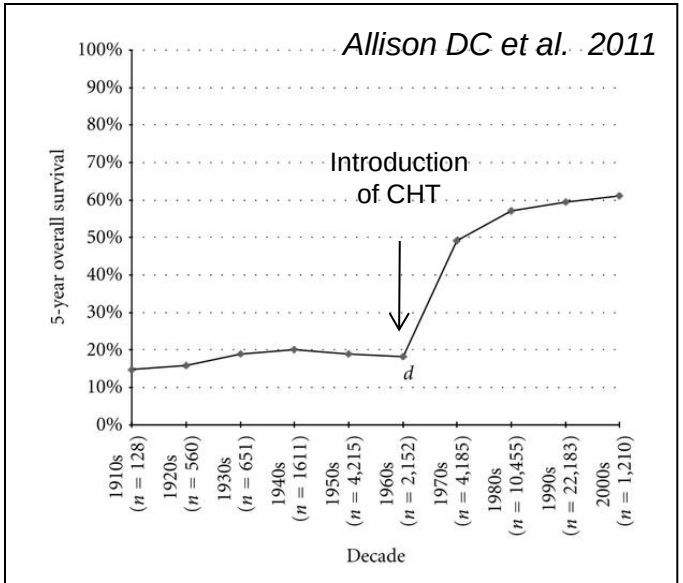
Prognostic factors

- Incomplete surgery
- Poor response to pre-operative chemotherapy
- Primary metastases
- Axial location
- Tumour size

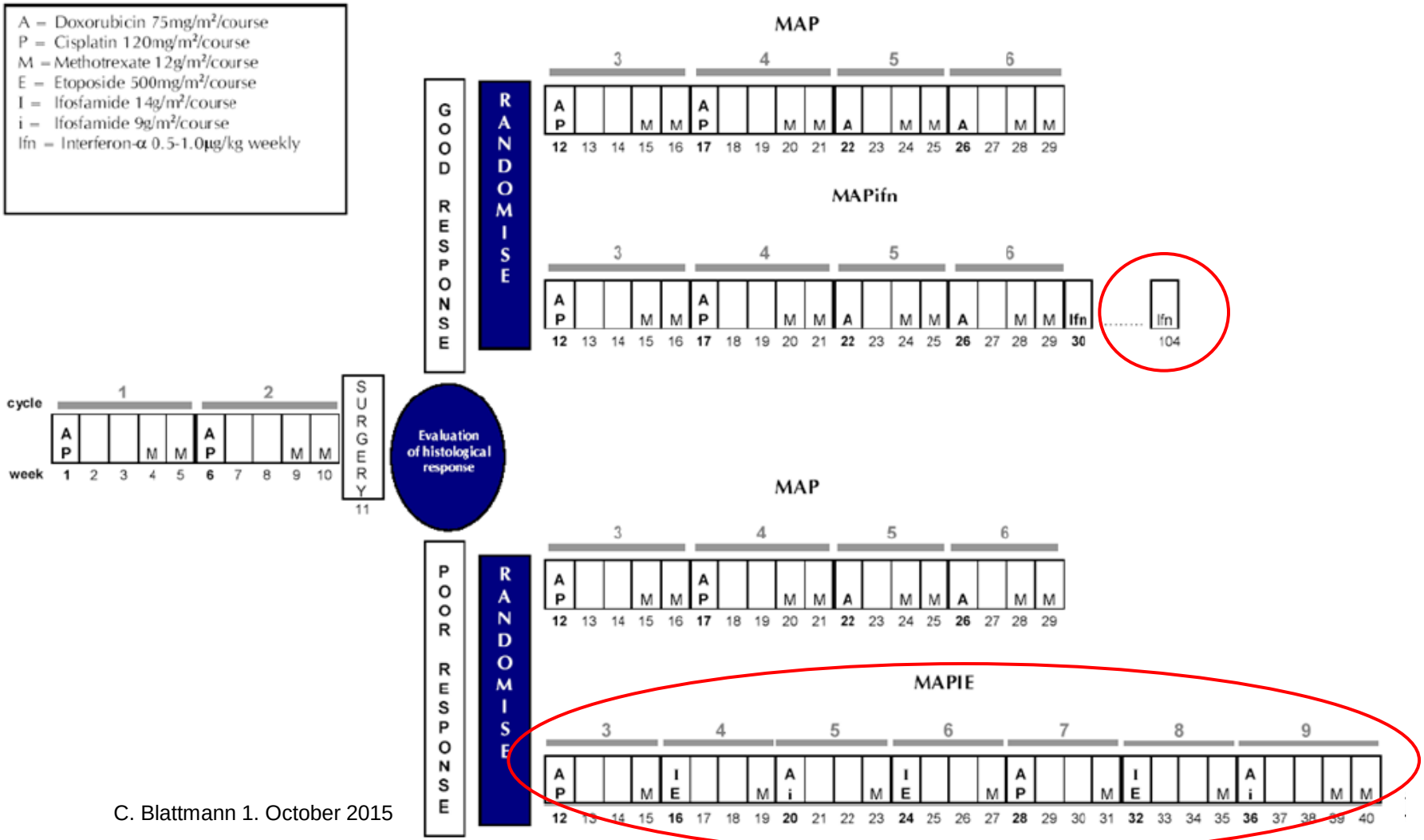


Treatment strategies in the past

- Until the 1970s: surgery (5 year overall survival 20%)
- After: introduction of **multiagent chemotherapy** (pre and post-operatively) + surgery→ 5 year overall survival 60-70%
- The most active chemotherapeutic agents for osteosarcoma are doxorubicin, cisplatin, methotrexate, ifosfamide, etoposide
- **Surgery** is still the gold standard of local treatment
- **Radiotherapy** is applied in case of non-resectable tumors or refusal of surgery



EURAMOS1 (European And American Osteosarcoma Studies)

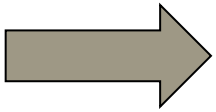


EURAMOS1

Results Poor Responder

- Poor response was reported in 1,059 patients, 618 consented to randomization (310 MAP, 308 MAPIE)
- Intensified chemotherapy (MAPIE) was associated with greater toxicity and more secondary malignancies
- There was **no advantage** in EFS and overall survival.

Bielack et al., manuscript in preparation



Recommendation: postoperativ MAP for good and poor responders

EURAMOS1
Results Good Responders

VOLUME 33 · NUMBER 20 · JULY 10 2015
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial

- Good response in 1,041 of 2,260 registered patients.
- 271 of 357 (76%) patients started IFN-α-2b, 105 (39%) **stopped earlier**
- 132/271 (49%) patients required **dose reduction or delays**
- **Median duration** of therapy was **67** weeks (intended: 104 weeks!)
- Main reasons were **toxicity** (45%), **progression** (24%), **refusial or patients choice** (17%), **clinician decisian** (7%)
- **Toxicity** reported in 268/271 patients: hematologic, flu-like symptoms, pain, left ventricular systolic dysfunction (no fatal, grade 4: 12%, grade 3: 38%, grade 1-2: 39%)
- **3-year EFS** for MAP and MAP plus IFN: **74% vs 77%** (not statistically significant)

EURAMOS1
Results Results Good Responders

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Interpretation of the data is limited!

- ¼ of patients allocated to IFN-α-2b never started it
- Only 1/3 of patients completed planned protocol treatment

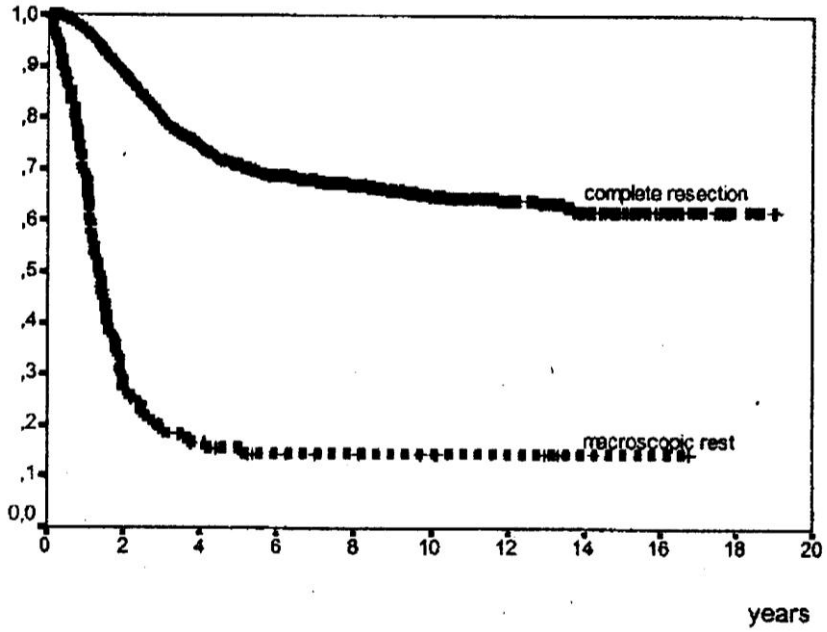
→ Why was the compliance so low?

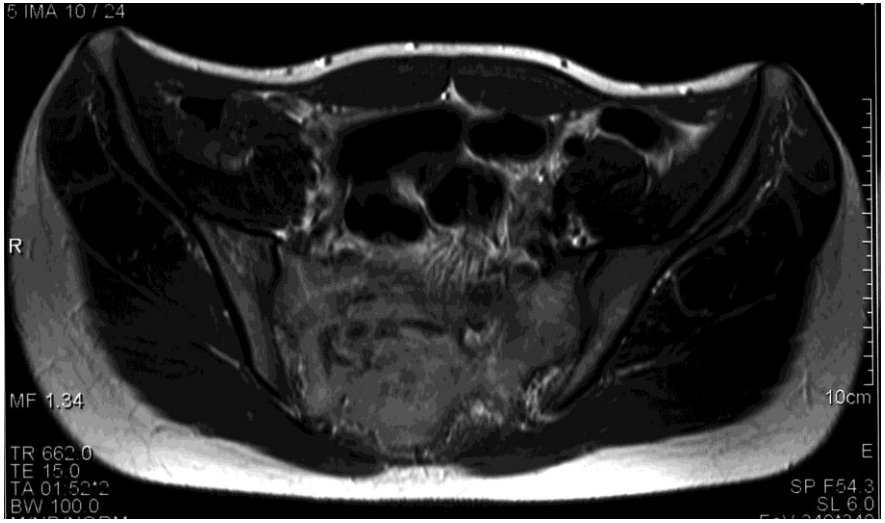
- Long previous exposure to 29 weeks of chemotherapy?
- Awareness of a favorable prognosis for good responders?

This data does not support the routine use of IFN-α-2b as maintenance treatment

What are the perspectives of treatment in osteosarcoma?

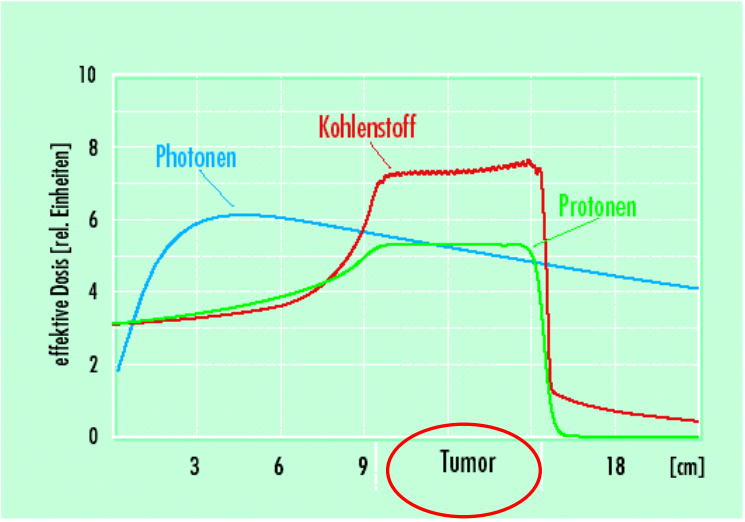
New local treatment approaches

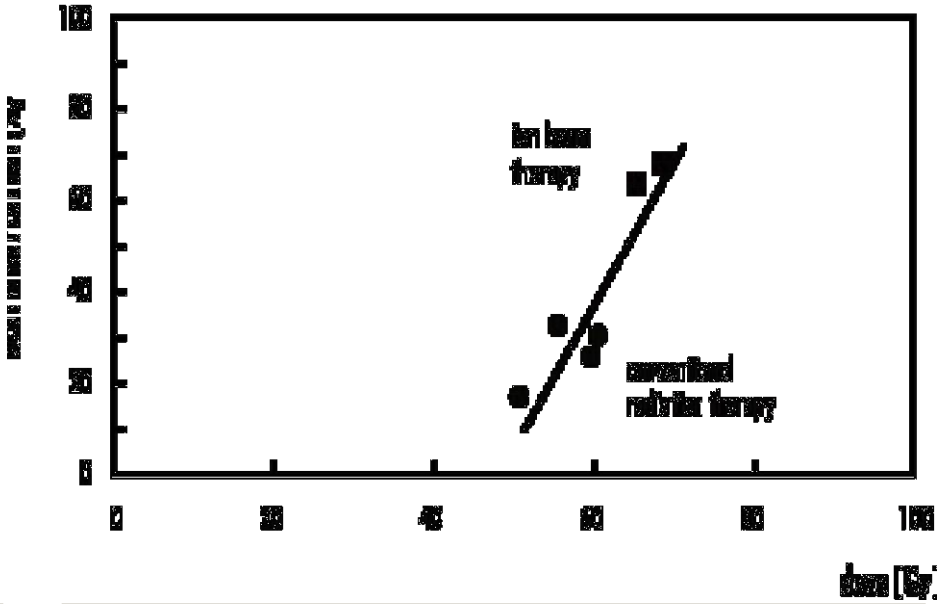




New local treatment approaches

Heavy Ion Radiotherapy (HIT)





Advantages

- Higher targeted precision
- Higher biological effectiveness
- Increase in the dosage compared to XRT (15-35%)

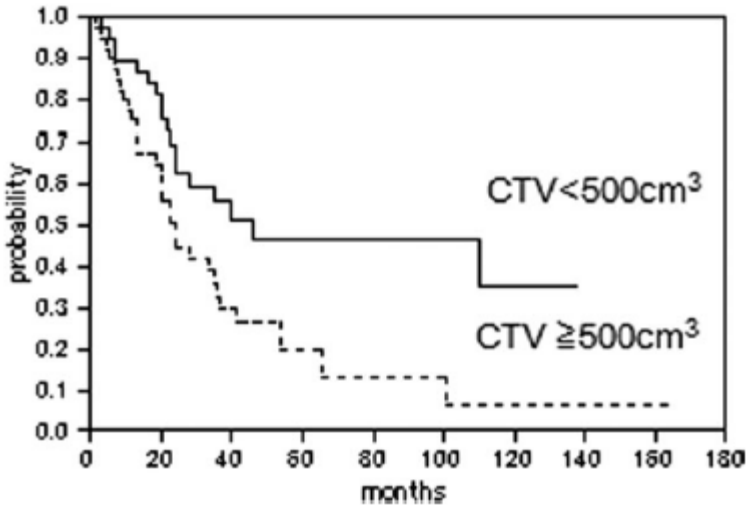
Disadvantages

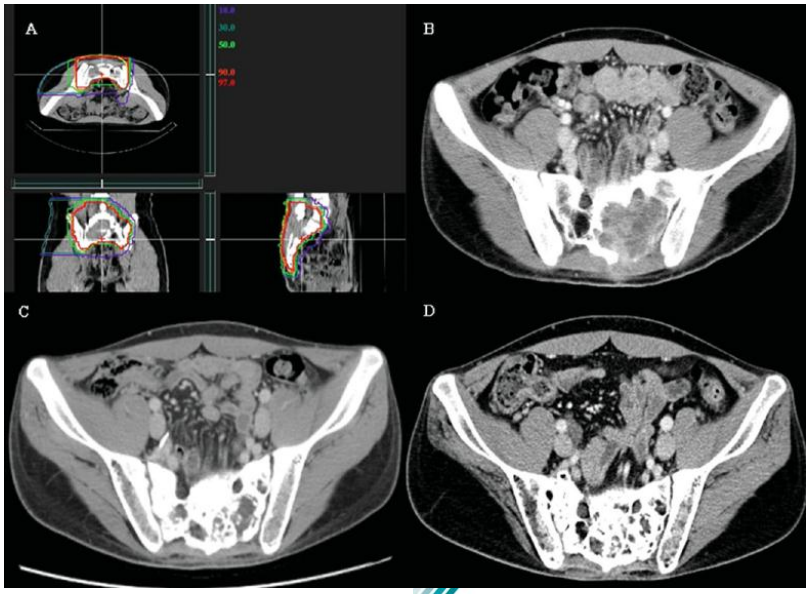
- Only a few centers worldwide (e.g. Heidelberg, Berkley, Chiba)
- Higher costs
- Long-term side effects?

Impact of Carbon Ion Radiotherapy for Unresectable Osteosarcoma of the Trunk

Akira Matsunobu, MD[1,2]; Reiko Imai, MD, PhD[1]; Tadashi Kamada, MD, PhD[1]; Takeshi Imaizumi, MD, PhD[1]; Hiroshi Tsuji, MD, PhD[1]; Hirohiko Tsujii, MD, PhD[1]; Yoshiyuki Shioyama, MD, PhD[2]; Hiroshi Honda, MD, PhD[2]; Shin-ichiro Tatezaki, MD, PhD[3]; for the Working Group for Bone and Soft Tissue Sarcomas

- 78 patients with non resectable osteosarcoma
- Heavy ion radiotherapy with 70,4 GyE
- 5J.-survival rate 33% (in case of tumorvol. < 500 cm^3 up to 46 %)
- Low toxicity: mainly skin, Grad IV only in 3 / 78 patients





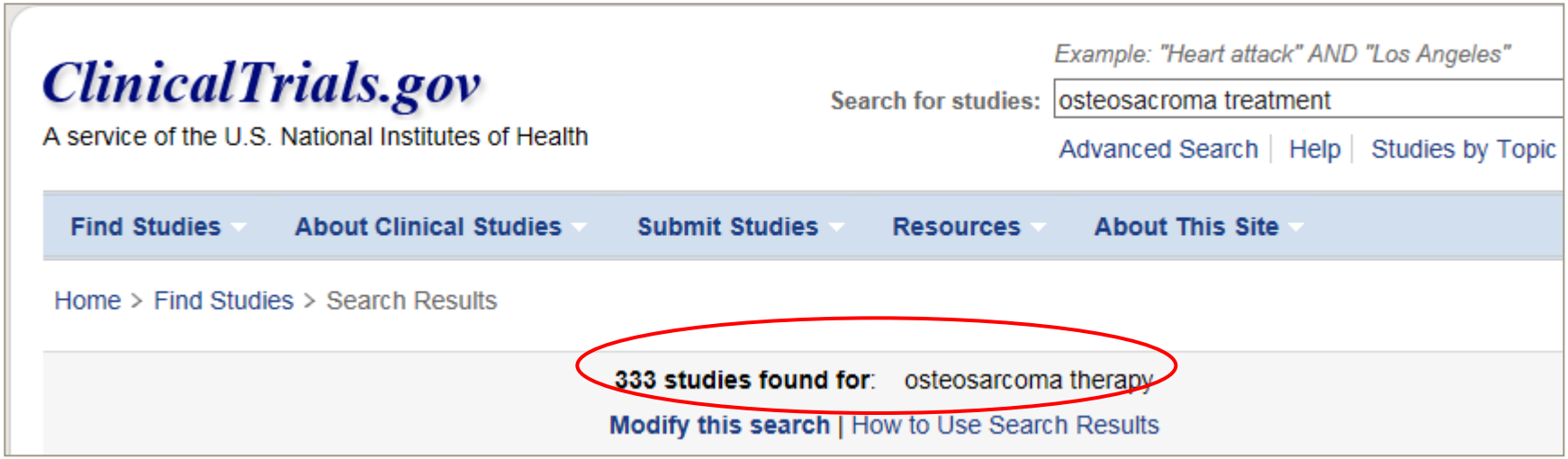
New local treatment approaches

Heavy Ion Radiotherapy (HIT)

Non-randomized therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with non-resectable osteosarcoma

Claudia Blattmann[1*†], Susanne Oertel[2†], Daniela Schulz-Ertner[3], Stefan Rieken[2], Sabine Haufe[4], Volker Ewerbeck[5], Andreas Unterberg[6], Irini Karapanagiotou-Schenkel[7], Stephanie E Combs[2], Anna Nikoghosyan[2], Marc Bischof[2], Oliver Jäkel[2], Peter Huber[2], Andreas E Kulozik[1], Jürgen Debus[2]

Neoadjuvante Standard Chemotherapy (e.g. EURAMOS1)	**Heavy Ion Radiotherapy (HIT)** (60-66 GyE= 20-22d),	Postoperatively Standard Chemotherapy (e.g. *EURAMOS1*)
Week 1 to 10	**Week 11 to 14**	**Week 15 to 32**


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Example: "Heart attack" AND "Los Angeles"
Search for studies: osteosacroma treatment
Advanced Search | Help | Studies by Topic
Find Studies
About Clinical Studies
Submit Studies
Resources
About This Site
Home > Find Studies > Search Results
333 studies found for: osteosarcoma therapy
Modify this search | How to Use Search Results

New treatment strategies (selection)

ClinicalTrials.gov

Agent (trade name)	Mode of action / Target
Mifamurtide (Mepact®)	Activation of macrophages and monocytes
Ipilimumab (Yervoy®), Nivolumab (Opdivo®)	Checkpoint blockade
Denosumab (Prolia®, XGEVA®)	Antibody (RANKL)
Trastuzumab (Herceptin®)	Antibody (HER2/neu)
Bevacizumab (Avastin®)	Antibody (VEGF)
Sorafenib (Nexavar®)	Tyrosinakinase-Inhibitor (Raf, VEGF, …)
Temsirolimus / Everolimus (Torisel®/Certican®)	mTOR inhibitor
Inhaled lipid cisplatin	Chemotherapy

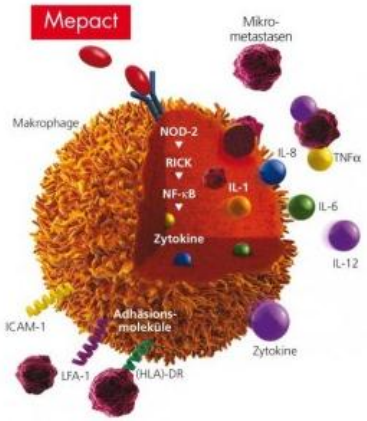
Immunotherapy

Targeted therapy

Immunotherapies

New treatment strategies

Mifamurtide (liposomal muramyl tripeptide phosphatidyl ethanolamine, L-MTP-PE, Mepact®)



- Synthetic analogue of a component of the mycobacterial cell wal
- Stimulates immune system (activation of macrophages and monocytes)
- Investigation in a large randomized phase III trial of primary osteosarcoma (CCG/POG-INT033), 662 patients
- 4 treatment arms: 1) MAP, 2) MAP + L-MTP-PE 3) MAP + Ifo 4) MAP + Ifo + L-MTP-PE
- MTP-PE 2mg/m2 2x/week i.v., 12 weeks

<u>Results are published in 2005 and 2008</u>

→ *Meyers PA et al., JCO 2005:* **„No significant impact of L-MTP-PE on EFS“**

Reanalysis with the endpoints EFS and OS, longer follow-up

→*Meyers PA et al., JCO 2008:* **„Significant improvement of L-MTP-PE on overall survival (70 vs 78%, p 0.03)“**

New treatment strategies

Mifamurtide (liposomal muramyl tripeptide phosphatidyl ethanolamine, L-MTP-PE, Mepact®)

- Statistical and interaction concerns were risen after publication in 2008

→ Result: No practice-changing conclusions!

But

MTP-PE received marketing authorization for the treatment of non-metastatic , resectable osteosarcoma in the EU in 2009

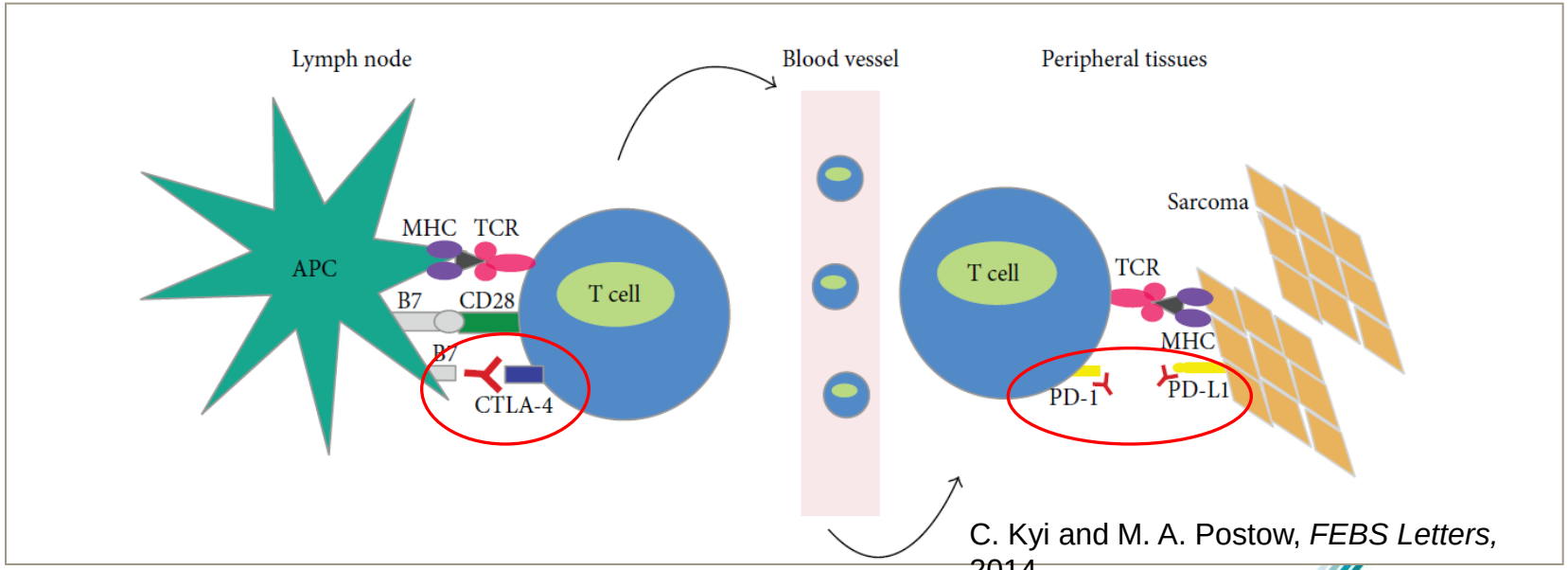
The agent warrants additional clinical data,
actually lacking because there is no industry support

New treatment strategies

Checkpoint blockade (Ipilimumab, Nivolumab)

- Monoclonal AB targeting CTLA-4 (cytotoxic T-lymphocyte associated protein-4) and PD-1 (programmed cell death protein 1) which are negative immune regulators of immune response in the tumor environment

→ Promoting of T cell activation against tumors



C. Kyi and M. A. Postow, *FEBS Letters,* 2014

New treatment strategies

Checkpoint blockade (Ipilimumab; Nivolumab)

- **Ipilimumab**: binding to CTL4, approved by the FDA for the treatment of metastatic melanoma; studies in synovial sarcoma
- **Nivolumab**: binding to PD-1-Receptor, treatment of nonsmall cell lung cancer
- **Osteosarcoma:**

Phase I Study of Ipilimumab (Anti-CTLA-4) in Children and Adolescents With Treatment-Resistant Cancer

This study has been completed.

Sponsor:
National Cancer Institute (NCI)

Information provided by:
National Institutes of Health Clinical Center (CC)

ClinicalTrials.gov Identifier:
NCT01445379

First received: September 30, 2011
Last updated: December 11, 2014
Last verified: November 2014
History of Changes

Nivolumab With or Without Ipilimumab in Treating Patients With Metastatic or Unresectable Sarcoma

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by National Cancer Institute (NCI)

Sponsor:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
National Cancer Institute (NCI)

ClinicalTrials.gov Identifier:
NCT02500797

First received: July 15, 2015
Last updated: September 18, 2015
Last verified: August 2015
History of Changes

New treatment strategies
Trastuzumab (HER2-Ab)

J Clin Oncol. 2012 Jul 10;30(20):2545-51. doi: 10.1200/JCO.2011.37.4546. Epub 2012 Jun 4.

Phase II trial of trastuzumab in combination with cytotoxic chemotherapy for treatment of metastatic osteosarcoma with human epidermal growth factor receptor 2 overexpression: a report from the children's oncology group.

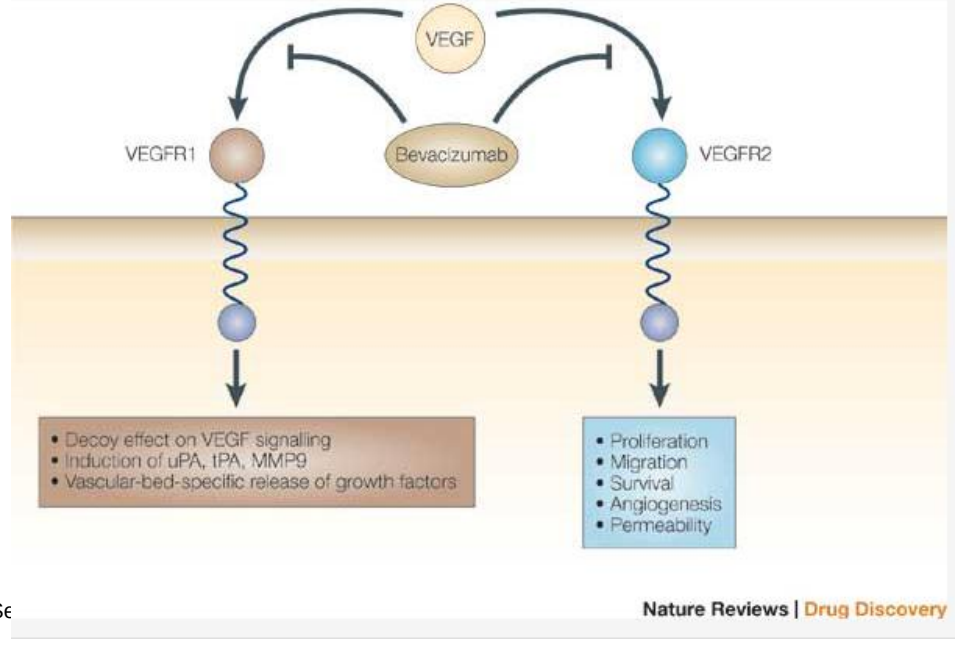
Ebb D[1], Meyers P, Grier H, Bernstein M, Gorlick R, Lipshultz SE, Krailo M, Devidas M, Barkauskas DA, Siegal GP, Ferguson WS, Letson GD, Marcus K, Goorin A, Beardsley P, Marina N.

- 96 patient with newly diagnosed metastatic osteosarcoma, 41 HER2 positive (IHC)
- Intensive chemotherapy plus trastuzumab (34 weeks) for patients with HER2-positive disease
- OS 59% (HER2-) vs 50% (HER2+), **no significant difference between the HER2+ and HER2- group, therapeutic benefit remains uncertain in osteosarcoma.**

New treatment strategies
Bevacizumab (VEGF Ab)

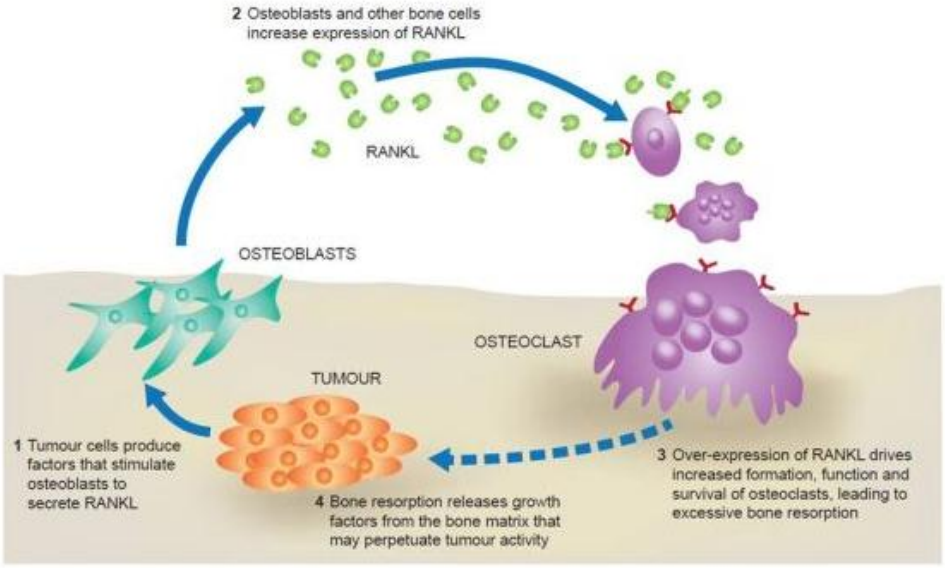
- Encouraging in vitro data
- Phase I studies in relapsed pediatric solid tumors (*Wagner L, Ped Blood Cancer 2013, Venkatramani R et al., PLoS One 2013*)

→ **Objective responses were noted in Wilms tumor, medulloblastoma and hepatocellular carcinoma but not in osteosarcoma**

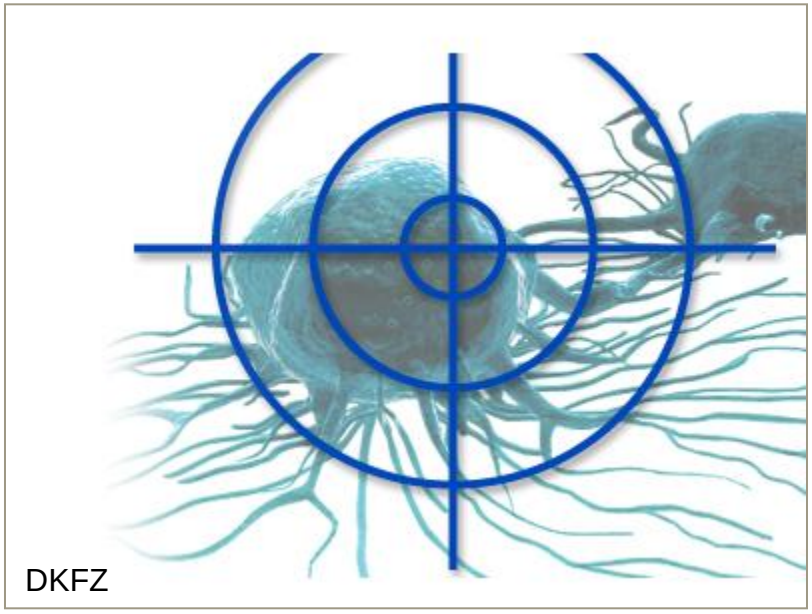


New treatment strategies
Denusomab (RANKL AB)

- Receptor activator of nuclear factor κB lig (RANKL) is expressed in metastatic bone cancer cells and has been suggested to play a key role in cell migration and metastatic behavior.
- Encouraging preclinial data and case reports.
- **A phase II clinical trail is expected to open in 2015 to assess the efficacy in patienst with refractory or relapsed osteosarcoma**



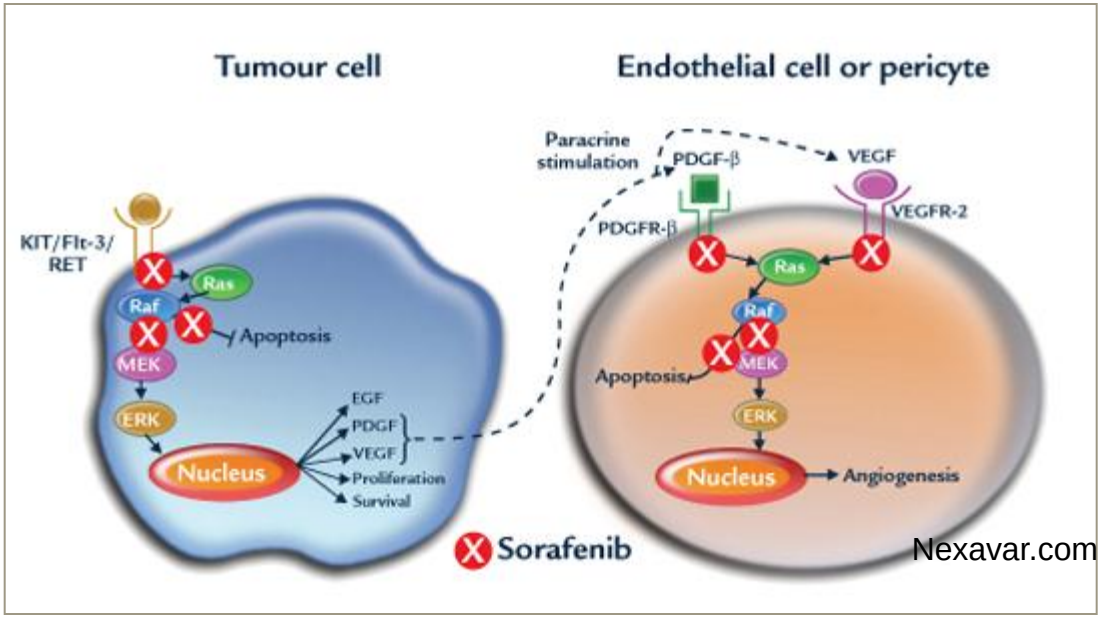
Targeted therapies



New treatment strategies

Multikinase inhibitors (Sorafenib, Nexavar®)

- Oral multikinase inhibitor of vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and Raf.
- FDA approved for liver, thyroid and kidney cancer.



New treatment strategies
Multikinase inhinitors (Sorafenib)

Lancet Oncol. 2015 Jan;16(1):98-107. doi: 10.1016/S1470-2045(14)71136-2. Epub 2014 Dec 11.

Sorafenib and everolimus for patients with unresectable high-grade osteosarcoma progressing after standard treatment: a non-randomised phase 2 clinical trial.

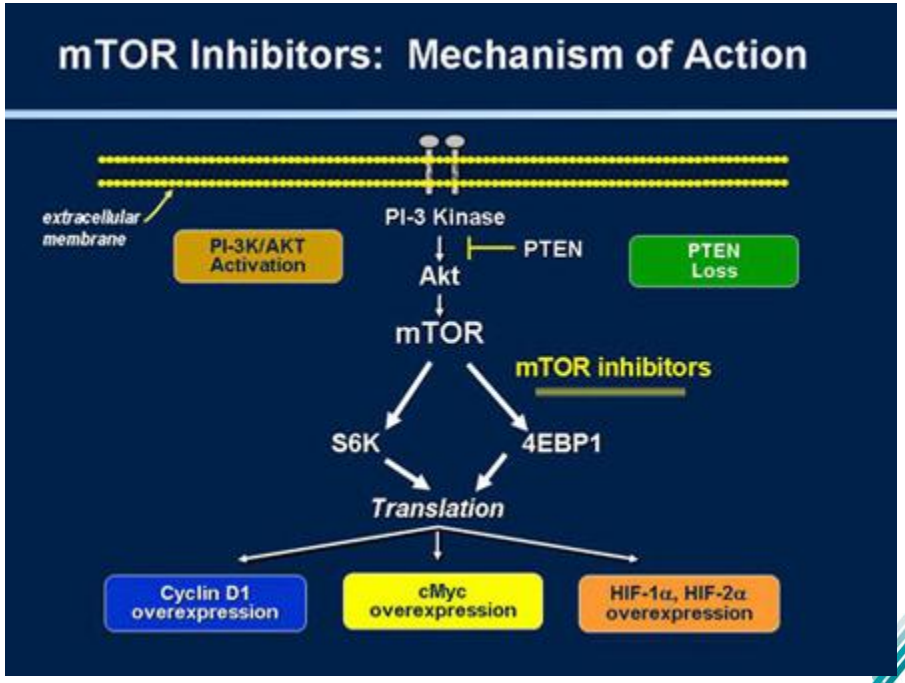
Grignani G[1], Palmerini E[2], Ferraresi V[3], D'Ambrosio L[4], Bertulli R[5], Asaftei SD[6], Tamburini A[7], Pignochino Y[4], Sangiolo D[4], Marchesi E[2], Capozzi F[4], Biagini R[8], Gambarotti M[9], Fagioli F[6], Casali PG[5], Picci P[10], Ferrari S[2], Aglietta M[4]; Italian Sarcoma Group.

- 38 patients with relapsed or unresectable osteosarcoma progressing after standard treatment (methotrexate, cisplatin, and doxorubicin, with or without ifosfamide)
- Patients received 800 mg sorafenib plus 5 mg everolimus once a day until disease progression or unacceptable toxic effects.
- The primary endpoint was 6 month progression-free survival (PFS).

The study did not attain the prespecified target of 6 month PFS of 50% or greater.

New treatment strategies
mTOR inhibitors (Everolimus, Sirolimus, Temsirolimus)

- Promising preclinical data
- ClinicalTrials.gov2015: **16 trials** investigating mTOR inhibitors +/- targeted therapy (e.g. sorafenib), chemotherapy (e.g. gemcitabine) or immunotherapy (e.g. IGF1-R antibody (cixutumumab))



New treatment strategies
mTOR inhibitors (Temsirolimus + Cixutumumab)

Pediatr Blood Cancer 2015;62:440–444

Phase II Study of Cixutumumab in Combination With Temsirolimus in Pediatric Patients and Young Adults With Recurrent or Refractory Sarcoma: A Report From the Children's Oncology Group

Lars M. Wagner, MD,[1]* Maryam Fouladi, MD,[1] Atif Ahmed, MD,[2] Mark D. Krailo, PhD,[3] Brenda Weigel, MD,[4] Steven G. DuBois, MD,[5] L. Austin Doyle, MD,[6] Helen Chen, MD,[6] and Susan M. Blaney, MD[7]

- 43 patients with recurrent or refractory sarcoma
- Cixutumumab (IGF-1R Ab) 6 mg/kg and temsirolimus 8 mg/m d1, every 4 weeks, 1-7 cycles (median 2 cycles)

No objective responses were observed, 16% of patients were progression-free at 12 weeks.

New treatment strategies
mTOR inhibitors (Ridaforolimus)

VOLUME 31 · NUMBER 19 · JULY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Results of an International Randomized Phase III Trial of the Mammalian Target of Rapamycin Inhibitor Ridaforolimus Versus Placebo to Control Metastatic Sarcomas in Patients After Benefit From Prior Chemotherapy

George D. Demetri, Sant P. Chawla, Isabelle Ray-Coquard, Axel Le Cesne, Arthur P. Staddon, Mohammed M. Milhem, Nicolas Penel, Richard F. Riedel, Binh Bui-Nguyen, Lee D. Cranmer, Peter Reichardt, Emmanuelle Bompas, Thierry Alcindor, Daniel Rushing, Yang Song, Ruey-min Lee, Scot Ebbinghaus, Joseph E. Eid, John W. Loewy, Frank G. Haluska, Pierre F. Dodion, and Jean-Yves Blay

- 702 patients received blinded study drug.
- Ridaforolimus induced a mean **1.3% decrease in target lesion** size **versus a 10.3%**
increase with placebo (P .001).
- **Median OS** with ridaforolimus 90 weeks versus 85 weeks with placebo.
- **AEs** more common with ridaforolimus (stomatitis, infections, fatigue, thrombocytopenia **(64.1% vs 25.6%** in the placebo group))

Conclusion:
Ridaforolimus treatment led to a modest, but significant effect on sarcomas.

Chemotherapy

New treatment strategies
Inhaled cisplatin

Pediatr Blood Cancer 2013;60:580–586

Inhaled Lipid Cisplatin (ILC) in the Treatment of Patients With Relapsed/Progressive Osteosarcoma Metastatic to the Lung

Alexander J. Chou, MD,[1]* Renu Gupta, MD,[2] Moshe D. Bell, MD,[3] Kathleen O'Day Riewe, MD,[3] Paul A. Meyers, MD,[1] and Richard Gorlick, MD[3]

- 19 patients, ILC via nebulizer every 2 weeks, metastasectomy in patients after 2 cycles if possible.
- No hematologic toxicity, nephrotoxicity or ototoxicity. Nausea/vomiting (≥grade 3) in n=1. Respiratory symptoms in 13/19 patients. Minimal systemic cisplatin exposure.
- 11 patients had bulky disease, and all progressed prior to cycle 7.
- N=1 PR, N=6 had SD after 2 cycles, underwent metastasectomy, and n=2 remained free from pulmonary recurrence 1 year after initiation of therapy.

Conclusion: Further studies of ILC are warranted.

How can we improve treatment / understanding of osteosarcoma?

- **Problems**
  - Tumors with high genome complexicity and low incidence

- **Aims**
  - Collaborative programs are needed!
  - Application of new technical methods (multiple compound testing), whole genome sequencing (WGS)) to perform genomic tumor analysis in large sample sets

→ National Cancer Institute´s *Therapeutically Applicable Research to Generate Effective Treatments program (TARGET)*

→ *German Consortium of Translational Cancer Reasearch (DKTK)*

German Consortium of Translational Cancer Reasearch DKTK (2012)

Thank you for your attention