B INTRODUCTION TO COURSE PROJECT

13.15-14.00 Introduction to palliative care research. *Staffan Lundström*

14.00-14.25 What is meant by 'course project'? *Staffan Lundström*

14.45-15.30 Groups

15.30-16.30 Plenary discussion with experiences from previous projects. *Facilitators from the course Steering Group*

B PARTS B AND C, CONTINUED

08.30-08.45 Reflections from yesterday

08.45-10.15 Study design. *Morten Thronæs*

13.00-16.00 Literature searches. *Katrine Aronsen*

16.15-17.00 How to read an article. *Pål Klepstad*

Thursday 26 September

B INTRODUCTION TO COURSE PROJECT

08.30-08.45 Reflections from yesterday

08.45-09.10 How to plan your project and write a project description. *Morten Thronæs*

09.15-10.15 Research ethics. *Lars Ursin*

10.30-12.30 Qualitative research methods. *Aslak Steinsbekk*

C

Introduction to oncological treatment modalities

Morten Thronæs MD, PhD
St. Olavs Hospital

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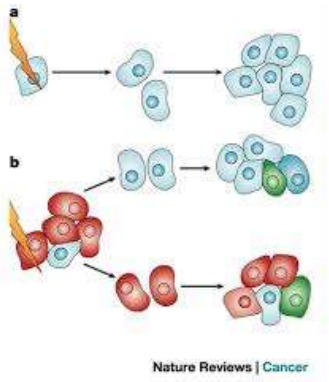
Cancer

- What is cancer?
- An umbrella of different illnesses
- Multistep process
- Most tumores are hetrogenous



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Cancer- an example

Non-Hodgkins Lymphoma

- 2002 «one disease»
- Now 40-50 entities
- Different treatment options might be possible

- What about other types of cancer?

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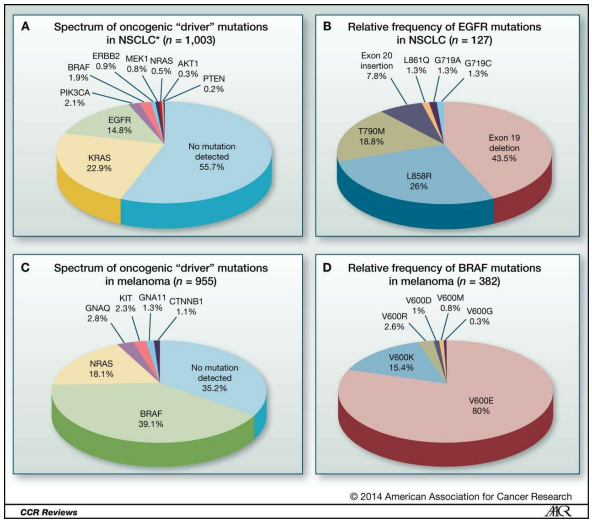
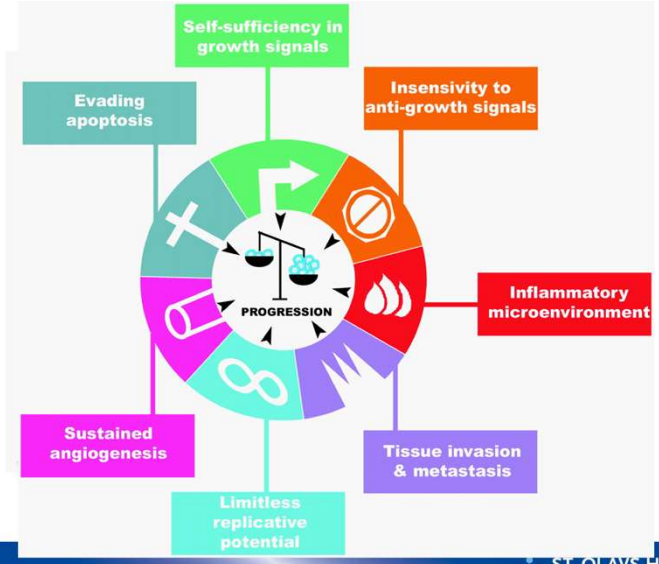
Common Cancers Now Collections of Rare Cancers

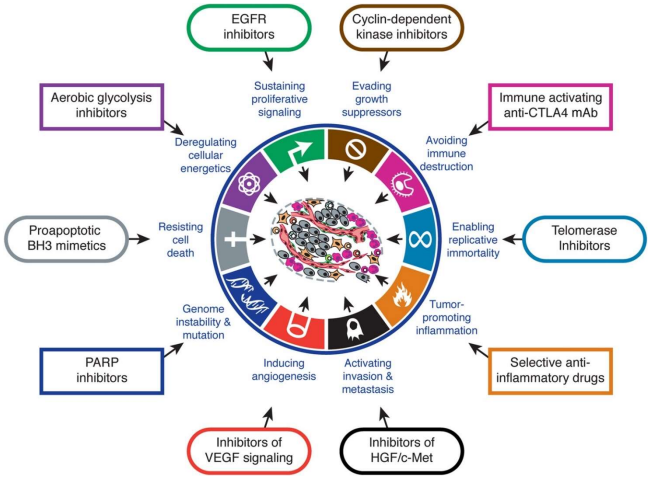


Catherine B. Meador et al. Clin Cancer Res 2014;20:2264-2275

Hallmarks of cancer (Hanahan and Weinberg)

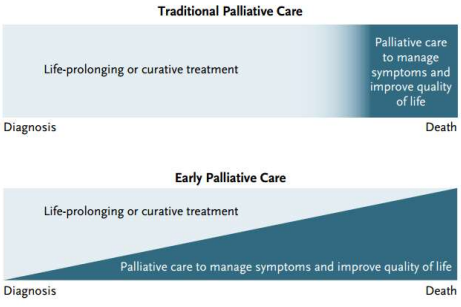


Hallmarks of Cancer: Therapeutic Implications



Cell PRESS Cell 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013)

Why should we know about this?
Palliative care is applicable early in the course of illness



Parikh NEJM 2013

Integrasjon of palliative care into oncology

- Early integration (WHO def)
- Studies demonstrating increased qol and survival (Bakital, Zimmermann, Temel)
- ASCO 2017: Online tool for reporting symptoms extends survival
  - Could be on cancer treatment for a longer period
- ASCO 2019
  - ESAS leads to survival

Cancer treatment in palliative care?

- Palliative care vs end of life care
- What kind of patients do we meet?
  - An hetrogenous population in palliative care
- Integration into oncology
- Conclusion; we have to know about cancer treatment!

Cancer treatment

- Surgery
- Radiotherapy
- Chemotherapy
- Hormon therapy
- Targeted Therapy
- Immunotherapy

- Cancer therapy- the ultimate symptom treatment?

Multimodal treatment

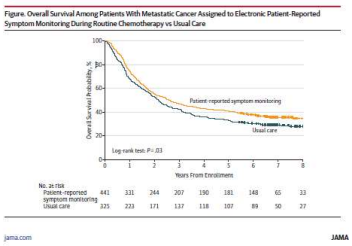
- Multidisiplinary teams
- Surgeon, Oncologists, Pathologists and Radiologists
- What about the palliative care physician?

The palliative care physician and oncological treatment
What should be our role?

VOLUME 34 · NUMBER 6 · FEBRUARY 20, 2016
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial

Ethan Basch, Allison M. Deal, Mark G. Kris, Howard I. Scher, Clifford A. Hudis, Paul Sabbatini, Lauren Rogak, Antonia V. Bennett, Amylou C. Dueck, Thomas M. Atkinson, Joanne F. Chou, Dorothy Dulko, Laura Sit, Allison Barz, Paul Novotny, Michael Fruscione, Jeff A. Sloan, and Deborah Schrag

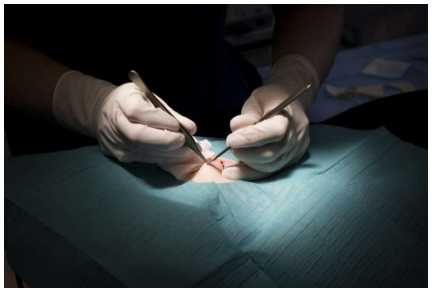


- HRQL improved more (34% v 18%) and worsened among fewer (38% v 53%)
- Less frequently admitted to the ER (34% v 41%)
- Remained on chemotherapy longer (8.2 v 6.3 m)

O.S 31.2 months (95% CI, 24.5-39.6)
vs 26.0 months (95% CI, 22.1-30.9)

Surgery

- Surgery in curative treatment- «Surgery cure the patients»
- Surgery as a part of different treatment modalities
- How is surgery used where you work?



Surgery- an example in palliative care

- Male 36 years old
- Ca testis, recurrence, metastasis in abdomen, MBS
- Ileus pump, nausea, vomiting
- PEG – percutanous endoscopic gastrostomia
  - relieving symptoms
- NRS nausea from NRS 10 to NRS 0

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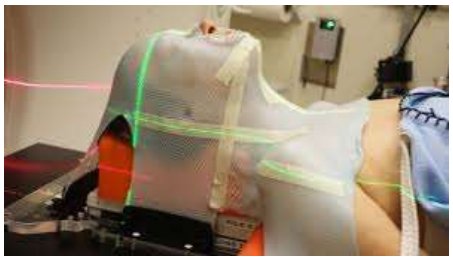
Radiotherapy

- Curative treatment
- Adjuvant treatment
- Neoadjuvant treatment
- Palliative treatment

Radiotherapy

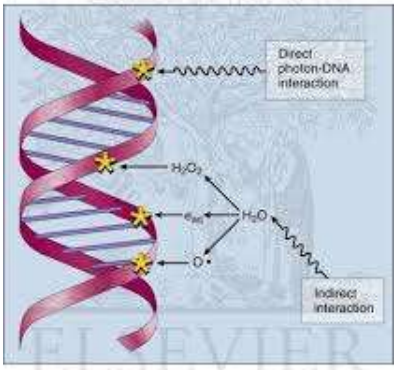
Palliative radiotherapy

- Brain metastases
- Bone metastases
  - Medulla compression
- Mediastinal tumores
- Others
  - Soft tissue
  - Intestinal
  - Pancreas



Radiotherapy

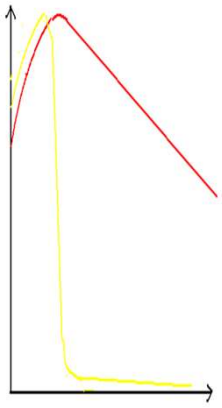
- Single or double damages in DNA
  - Direct action
  - Indirect action (free radicals)



Types of radiotherapy

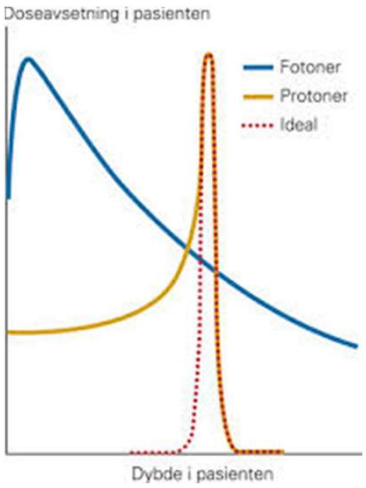
- Elektromagnetic radiation photons
- Particle radiation electrones/ protons

Photons- red, electrons- yellow



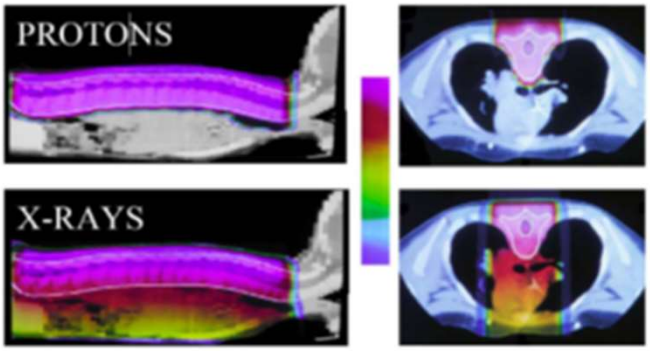
Photon and proton radiation

- Proton treatment gives lower dose to normal tissue. This might give reduction in late effects.
- Important in palliative care?



Protonterapi

Medulloblastoma



Radiotherapy

Curative treatment:

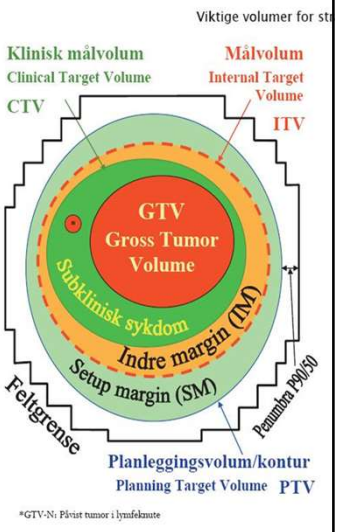
- High total dose
- Fractionated treatment (2 Gy)

Palliative treatment:

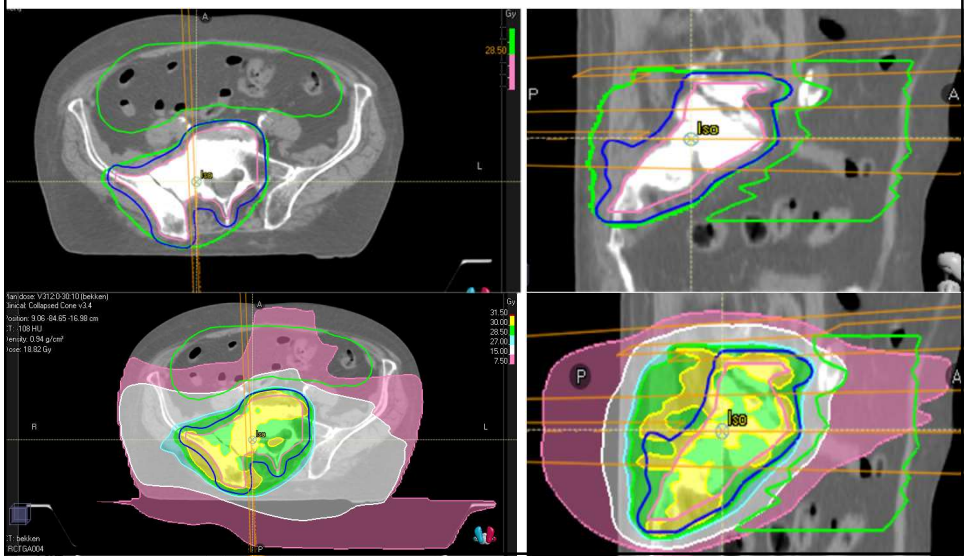
- 3 Gy x 10
- 4 Gy x 5
- 8 Gy x 1
- Lower total dose

Radiotherapy

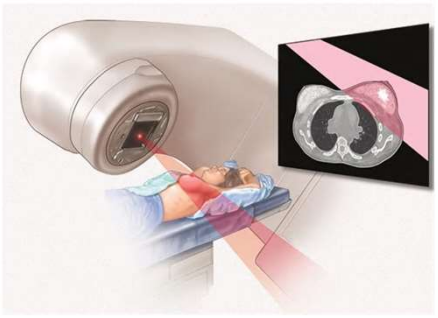
- Responce of radiotherapy larger in tumor compared to normal tissue
- Optimize radiation to tumor compared to normal tissue
- Tumor-cells undifferentiated
  - Reduced capability to repair DNA damage

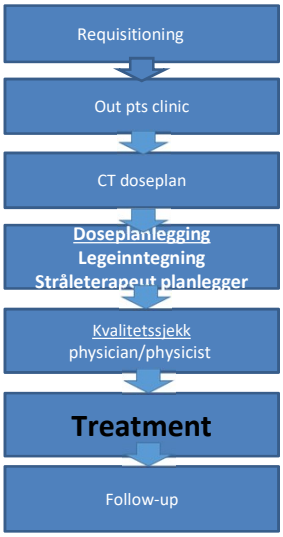


Planning radiotherapy



«The radiotherapy-trajectory»





Tissue tolerability

- Heart
  - 5% risk for death of heart disease after 15 years when doses above 30 Gy is delivered
  - 18 GY lead to ca 5 % risk for renal failure, 26 GY 50% risk.
- Spinal cord
  - 50 Gy: 0,2 % risk for myelopati
  - 60 Gy: 6 % risk for myelopati
  - 69 Gy: 50% risk for myelopati

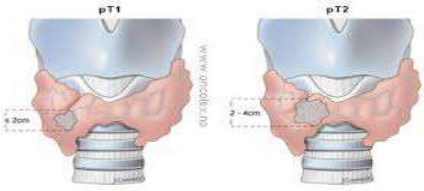
Emami et al, 1991
Lawrence, Quantec Review, 2010

Adverse effects of radiotherapy

Skin	schaemia, Ulceration, erythema
Bone	Necrosis, fracture, sarcoma
Mouth	Ulceration, xerostomia, sialitis
Bowel	Stenosis, fistula, diarrhoea Bladder Cystitis
CNS	Myelopathy
Lung	Fibrosis, Dyspnea, radiation pneumonitis
Heart	Pericardial fibrosis, cardiomyopathy
Gonads	Infertility

Isotopes

- A radioactive isotope with unstable atomic nucleus
- Short radius/ range
- Ex: strontium, samarium
- Ex: radio iod treatment-ca thyreoidea



Chemotherapy

- Low specificity
  - Side effects in normal tissue
  - Toxicity
  - Response rates?

What is Chemotherapy.

- Chemotherapy is the use of antineoplastic drugs to promote tumor cell destruction by interfering with cellular function and reproduction.
- It includes the use of various chemotherapeutic agents and hormones.

- Chemotherapy is a term used to describe any treatments that utilizes the introduction of chemical agents to an organism to help control, stop and or terminate the rapid growth of cells.
- There are 60 types of chemotherapy currently available and new ones being developed all the time.

HOW DO THE DRUGS WORK

- The drugs enter the bloodstream and reach all parts of the body
- Cytotoxic drugs destroy cancer cells by damaging them so that they can't divide and grow.
- The drugs can also affect normal cells.

- Neuropathic symptoms
- Nausea

TOXICITY

- Toxicity associated with chemotherapy can be acute or chronic.
- Cells with rapid growth rates (eg, **epithelium, bone marrow, hair follicles, sperm**) are very susceptible to damage, and various body systems may be affected as well.

Chemotherapy- how does it work?

1. Damage at DNA:

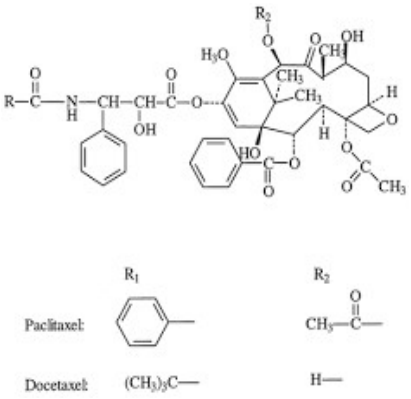
- *Akylerende* Eks. cyclofosfamid, ifosfamid. (Breast, sarcoma mm.)

2. Metabolic blocade:

- *Antimetabolitter*. Eks. folsyreanaloger(metotrexat) og pyrimidinanaloger (fluouracil). (lymphoma, . GI cancer, Breast)

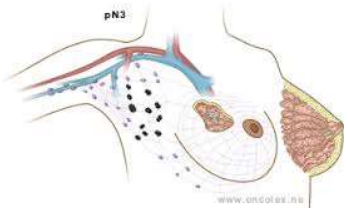
BM supression, mucosa damage

3. Inhibition of mitosis :
Vinkaalkaloider Eks Navelbine, Taxotere, Taxol. (Breast, Prostata, Lung)
BM, Mucosa, Hypersensitivity



Cytotoxic antibiotics

- ***Antracycliner*** Inhibit topoisomerase II and damage DNA. Ex. Epirubicin og doxorubicin. (Breast, lymphoma) BM, Mucosa, heart, toxic in tissue
- ***Bleomycin:*** induce chain breaks in DNA



Other anti neoplastic drugs

Carboplatin, cisplatin og oxaliplatin. (Ca testis, Ca Pulm)

- Binds to DNA
- Nausea, nevrophaty kidneys, BM

What is important to think about when palliative care patients are recieving chemotherapy?

WHO status 2 or below; could we use chemotherapy in our population?

Discuss

Combination therapy or single drug therapy?

Discuss

Hormon treatment

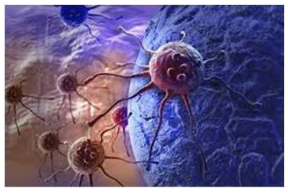
- Prostatic cancer
- Breast cancer

- Few side effects
- Possible treatment in palliative care?

Hormon treatment

Side effects:

- Tamoxifen: Venous tromboembolism endometric cancer
- Aromatase inhibitors: osteoporosis



Targeted Therapi

- A hetrogenous group of new treatment modalities
- Used as curative and palliative treatment
- The drug binds to the cancer cell in different ways (markers)
- More specific than the «old» chemotherapies
- Normal cells also affected

- A new era in the treatment of cancer
- Several drugs the last 20 years
- Effect vs costs

Targeted therapy: Palliative treatment

A lot of new drugs

Increasing every year:

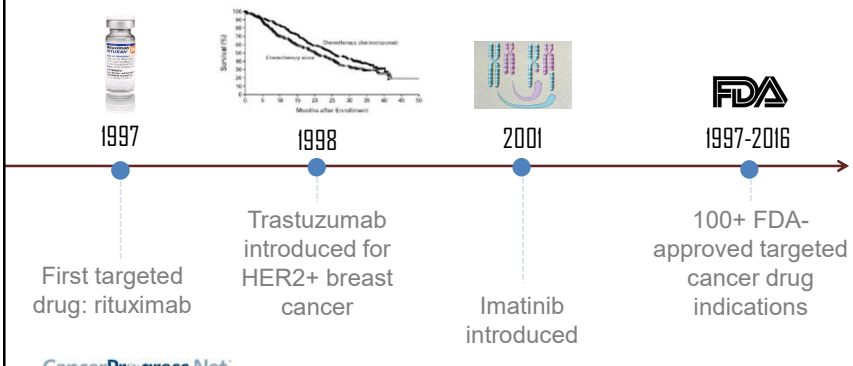
- GI cancer: Cetuximab/ bevacitumab
- Mammae: Trastuzumab, Everolimus
- Ca Prostatae: Enzalutamide
- Melanom:Ipilimumab, Vemurafenib

- Several leads to increased time to progression, some increased survival
- Cost- benefit
- Challenge: drugs that lead to long survival/ curation

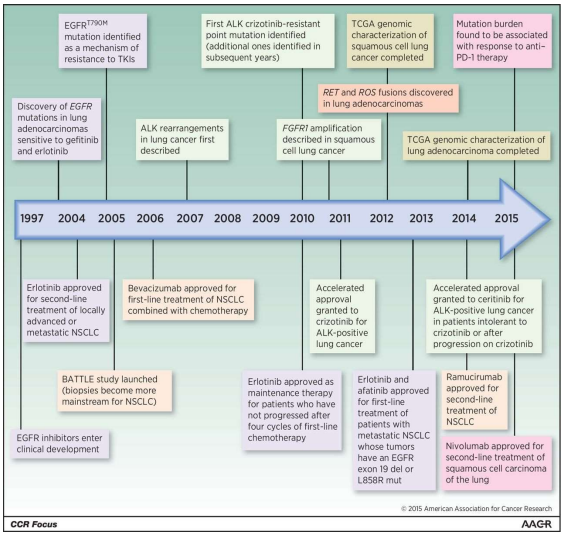
- Will palliative care in cancer change?

Precision Medicine

- Cancers classified by molecular abnormalities and site of origin
- Exceptional success when treatment is matched to a driver mutation



Timeline of Selected Major Discoveries in Lung Cancer Treatment



Source: Katerina Politi, and Roy S. Herbst Clin Cancer Res 2015;21:2213-2220

Precision Medicine

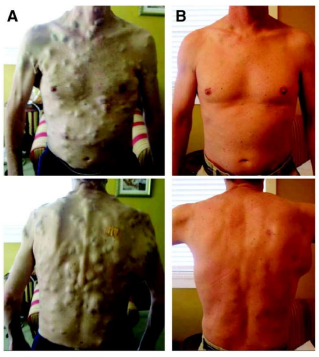
Pall care 10 yrs ago

Pall care today

Photographs were taken:

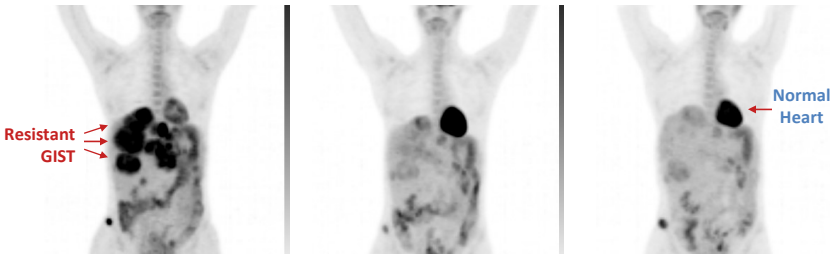
A. Before initiation of vemurafenib

B. After 15 weeks of therapy with vemurafenib



Source: Wagle, N et al. Dissecting Therapeutic Resistance to RAF Inhibition in Melanoma by Tumor Genomic Profiling. JCO August 1, 2011 vol. 29 no. 22 3085-3096

Raid Response Assessment

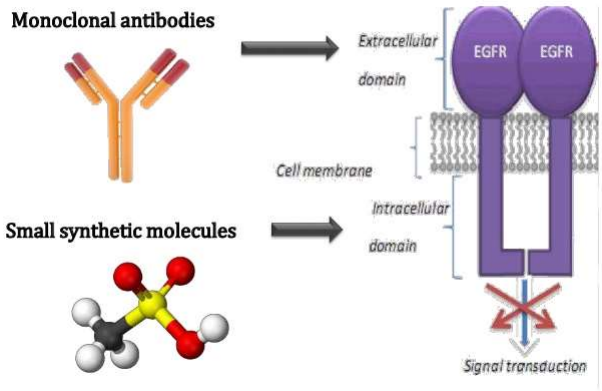


Baseline:
GIST resistant
to Imatinib

After 1 week
of Sunitinib
Therapy

After 2 months
of Sunitinib
Therapy

- **Types of targeted therapy**
- Each type of targeted therapy drug works on a specific molecular target.
- The two main groups of drugs are monoclonal antibodies and small molecule inhibitors.

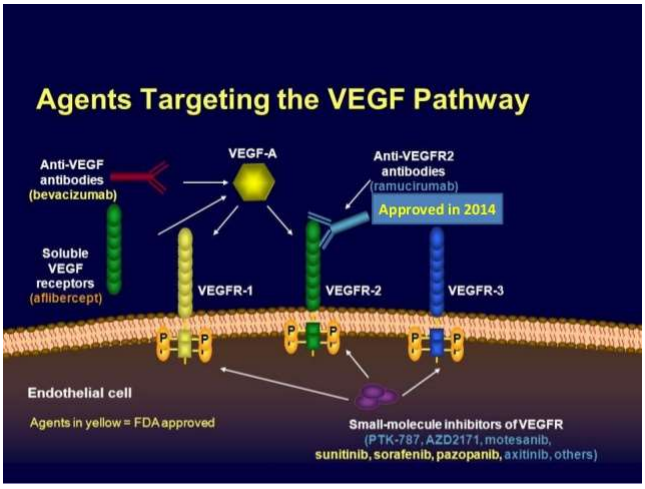


Monoclonal antibodies

- These medicines are manufactured (synthetic) versions of immune system proteins - antibodies
- The synthetic antibodies lock onto proteins on the surface of cells or surrounding tissues to interfere with the growth or survival of cancer cells in some way.
- Monoclonal antibodies can be classified as either a targeted therapy or immunotherapy, depending on the type of monoclonal antibody.

Examples of targeted therapy monoclonal antibodies

Angiogenesis inhibitors	These drugs are designed to reduce the blood supply to a tumour to slow or stop it growing. They target various receptors or proteins linked with the growth of cancer cells and stop them from working. For example, bevacizumab targets vascular endothelial growth factor (VEGF), a protein that helps new blood vessels form.
Monoclonal antibodies in the EGFR-family Ex HER2-targeted agents	Cetuximab (Erbitux) in colo-rectal cancer Inhibit proliferation and induces apoptosis HER2 is a protein that causes cancer cells to grow uncontrollably. Some targeted therapy drugs destroy the HER2 positive cancer cells, or reduce their ability to divide and grow. Examples include trastuzumab and pertuzumab, which are used to treat HER2 positive breast cancer.
Anti-CD20 monoclonal antibodies	These drugs target a protein called CD20 found on some B-cell leukaemias and non-Hodgkin lymphomas. Examples include rituximab and obinutuzumab.



Small molecule inhibitors (protein-kinase-inhibitors)

- These drugs can get inside cancer cells and block certain enzymes and proteins that tell cancer cells to grow.

Small molecule inhibitors (protein-kinase-inhibitors)

- These drugs can get inside cancer cells and block certain enzymes and proteins that tell cancer cells to grow.

Protein Kinase

- Group of enzymes that possess a catalytic subunit that transfers the gamma phosphate from nucleotide triphosphates (often ATP) to one or more amino acid residues in a protein substrate side chain
- Resulting in a conformational change affecting protein function
- Play role in signal transduction pathway – regulate cell growth & adaption to extracellular environment

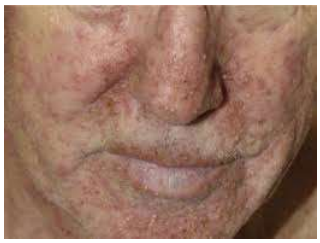
Examples of small drug inhibitors (protein-kinase-inhibitors)

Tyrosine kinase inhibitors (TKIs)	These drugs block a group of enzymes called tyrosine kinases from sending signals that tell cancer cells to grow, multiply and spread. Without this signal, the cancer cells die. Examples of TKIs include erlotinib, sunitinib, lapatinib and ibrutinib.
Mammalian target of rapamycin (mTOR) inhibitors	These drugs block mTOR, an enzyme that tells cancer cells to grow and spread. Everolimus is an mTOR inhibitor approved for use for some types of kidney cancer.
PARP inhibitors	These drugs stop the protein known as PARP from repairing damaged DNA in cancer cells. Olaparib is a PARP inhibitor approved for use in some ovarian, fallopian tube and peritoneal cancers.

Targeted Therapy

Several of these drugs lead to side effects in other organs

- Heart toxicity: Trastuzumab
- Mucosa and skin: Cetuximab
- Allergic rx: Rituximab



Curative treatment

Breast cancer:

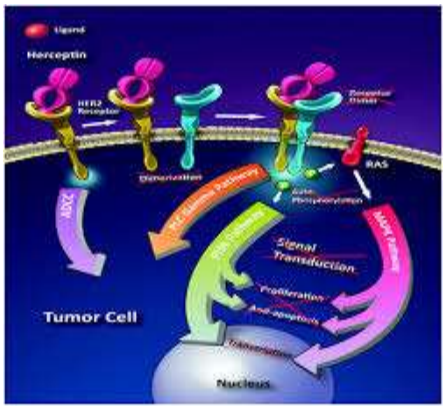
- Trastuzumab(15% of pts HER-2 positive)

Lymphoma:

- Rituximab(binds to antigen at CD 20 positive B-lymphocytes)

GIST og KML:

- Imatinib (Glivec) (inhibit Bcr-Abl-tyrosinkinase)



Radio-immunotherapy (RAIT)

RAIT	Target	Indication	Status
• ^{90}Yttrium – ibritumomab tiuxetin • ^{131}Iodine – tositumomab	Anti – CD20	NHL	Approved
• ^{90}Yttrium – epratuzumab	Anti – CD22	NHL B - cell lymphoma	Phase II
• ^{213}Bismuth – HuM195	Anti – CD33	AML	Phase II
• 90 Yttrium – daclizumab	Anti-Tac / CD25	T - cell leukemia	Phase II

Immunotherapy

- Activates our own cells so these attack cancer cells
- Metastatic Malignant melanoma and lung cancer

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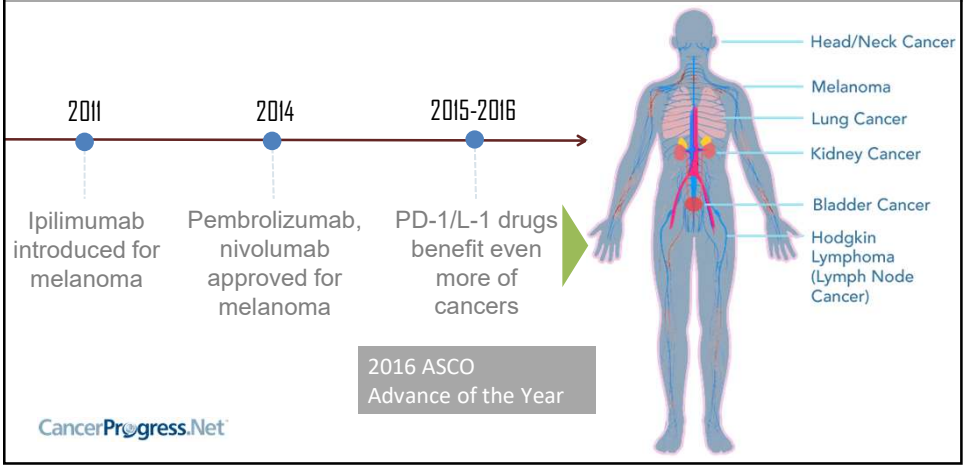
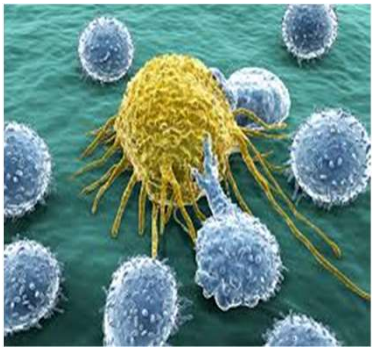
Rise of Immunotherapy

- Long-term disease control against recalcitrant cancers
- Game-changing discoveries – more coming



Immunotherapy

- Immune checkpoint-inhibitors CTLA4- inhibitors(Ipilimumab)
- Removes the breaks on the T-cells. Avoid immune down regulation
- PD-1 inhibitors (Nivolumab og Pembrolizumab)
- Activates T-cells, the inhibitor system turns off in these cells
- Result: increase proliferation and increased cytotoxic effect of the T-cells



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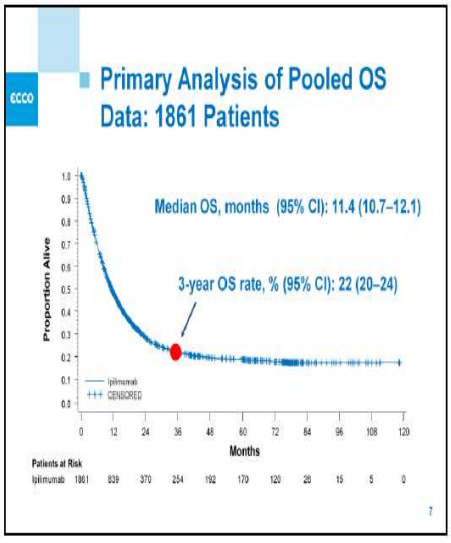
Immunterapi

- Ipilimumab (Yervoy)
- 4 treatment cycles before evaluation, three weeks between the treatment cycles; 12 weeks of treatment
- 3 months in palliative care might be a long time
- When should we stop treatment
- Who will respond?



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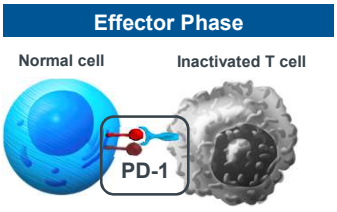
PD-1 inhibitors

- Monoclonal antibody inhibiting PD -1 (PD=Programmed Death)
- PD-1 at the surface of the T-cells. When PD-1 binds to PD-Ligand at the cancer cells, the T-cells are inhibited.
- PD-1 antibody Pembrolizumab prevent the PD-1 binding to the ligand, and the cytotoxic ability of the T-cells are activated, leading to death of cancer cells



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Side effects of immunotherapy

- Diarrhea
- Colitis
- Hepatitis
- Dermatitis
- Uveitis
- Pneumonitis
- Fatigue
- Neuromuskular symptoms

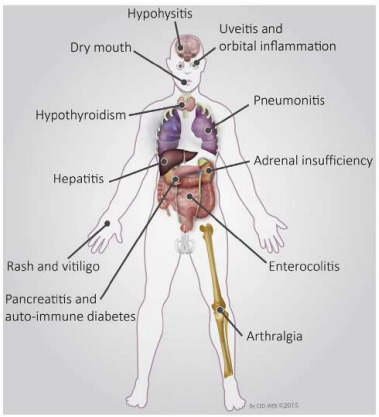

Fig. 3. The clinical spectrum of IRAEs. IRAEs: immune-related adverse events.

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obs

- Often late response
- Other challenges: Costs
- New studies ongoing
  - Combination therapy

Immunotherapy, an example

- Female, born 1964
- Bladder cancer, carcinomatosis,
- Gemcitabine/ carboplatin, 5 cycles, tox
- Side-effects, low QOL
- WHO-PS 3-4

- Atezolizumab (Tecentric)

- Fc-modifisert, humanisert immunglobulin G_1 (IgG_1) monoklonalt antistoff som bindes til PD-L1 (programmert celledødligand-1). Produseres i ovarieceller fra kinesisk hamster ved rekombinant DNA-teknologi.
- Virkningsmekanisme: Binder seg direkte til PD-L1 på tumorceller og/eller tumorinfiltrerende immunceller, blokkerer både PD-1- og B7.1-reseptorer på T-celler og antigenpresenterende celler. Stopper PD-L1/PD-1-mediert hemming av immunresponsen, inkl. reaktivering av antitumor immunrespons, uten å indusere antistoffavhengig cellulær cytotoksisitet

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Immunotherapy, an example

- 1. cycle January 16th 2019
- Ca 125: 17-168 from Dec to medio January,
- 30.01: 140
- 06.02: 79
- 19.03: 10
- 17.07:6

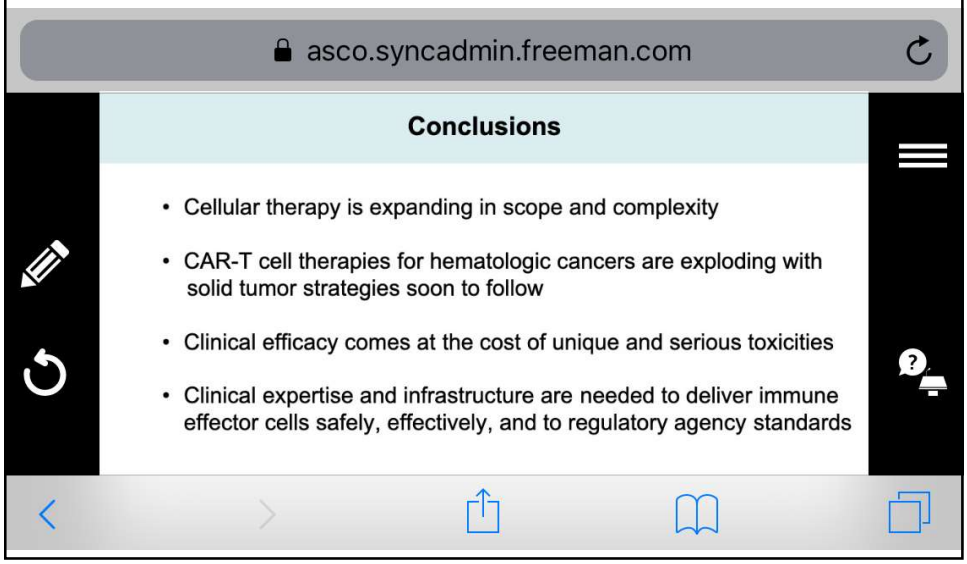
- 12 cycles
- Normal activity, WHO PS: 1, minor side-effects

CAR-T-treatment

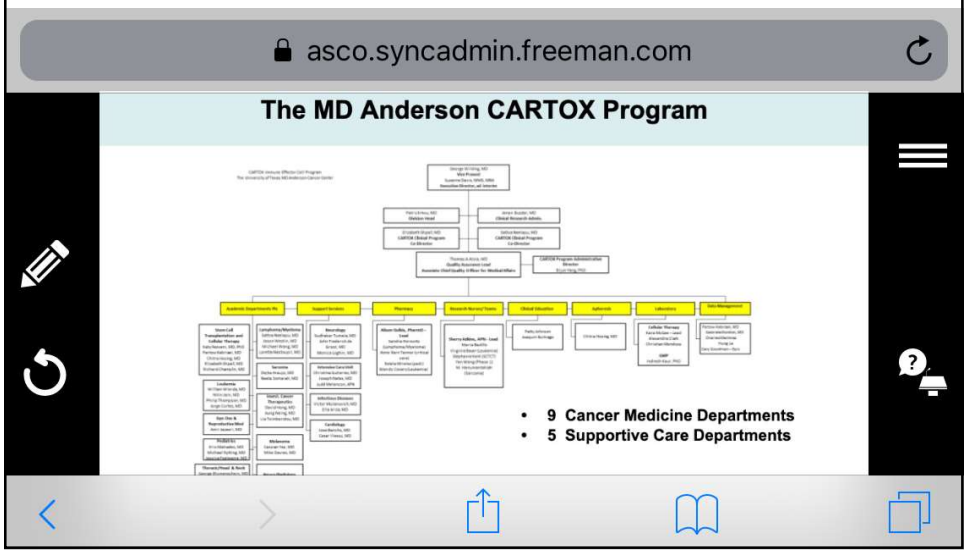
CAR-T-treatment

- CAR-T cells: Chimeric antigen receptor **T** cells
- A type of treatment in which a patient's T cells are changed (genetically engineered) in the laboratory so they will attack cancer cells.
- T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added in the laboratory.
- The special receptor is called a chimeric antigen receptor (CAR)
- Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion.

CAR-T-treatment



CAR-T-treatment



CAR-T-treatment

Cured or long time survivors

OR

Sudden death of side effects

CAR-T-treatment

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Common Toxicities of CD19 CAR T cells

Cytokine Release Syndrome (CRS)	Neurotoxicity
Fever	Global encephalopathy
Hypotension	Aphasia
Capillary leak	Seizure, seizure-like activity
Respiratory insufficiency	Obtundation
Hyperferritinemia/MAS	Tremor/myoclonus
Coagulopathy/DIC	Hallucinations
Multi-organ failure	(Rapid Onset Cerebral Edema)
(+Neurotoxicity)	

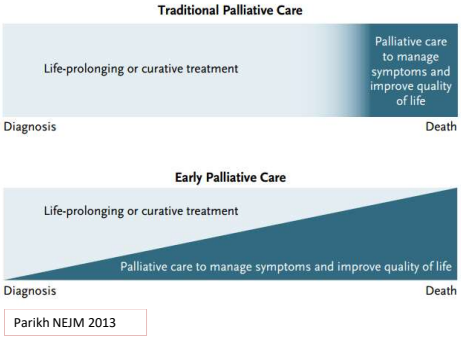
"Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)*"

*Lee et al. BBMT 2018

Symptoms rapidly resolve with

Severe symptoms do not resolve with

Palliative care is applicable early in the course of illness



Parikh NEJM 2013

Conclusion

- Oncological treatment is important in palliative care
- Different treatment options for our patients
- Might in some fases be the best symptom treatment
- The new drugs challenge old knowledge of treatment of cancer patients
- The new drugs challenge old knowledge of symptom treatment because of new sideeffects

Immunotherapy

- https://www.youtube.com/watch?v=UbFjiWOBErA
- Use 8 minutes and 41 seconds after dinner tonight and watch this video
  - Treatment of today and treatment of tomorrow

Trondheim University Hospital