

Chemotherapy, Targeted therapy, Immunotherapy

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Onkológiai Központ

Semmelweis Egyetem, Klinikai Központ

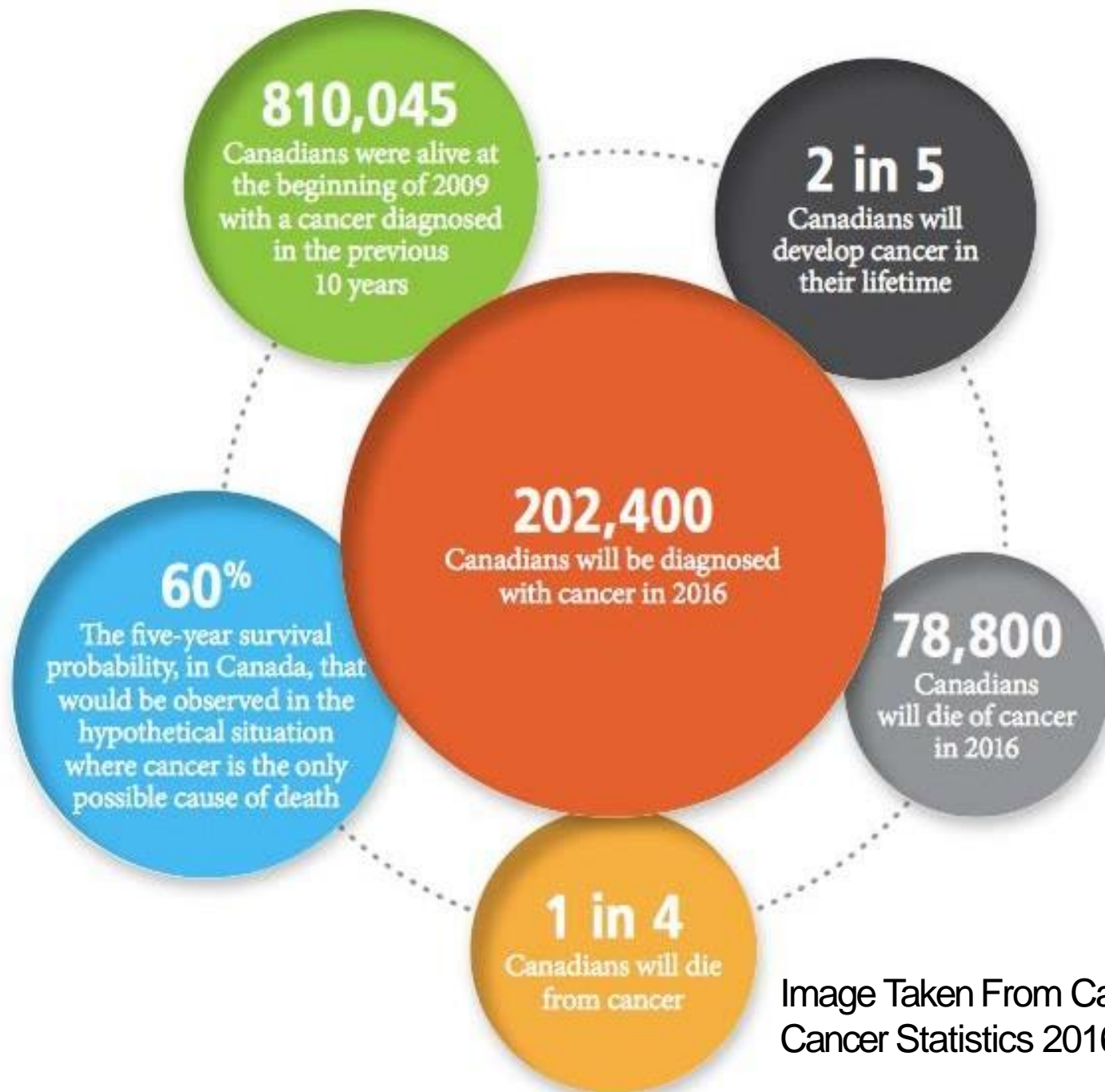
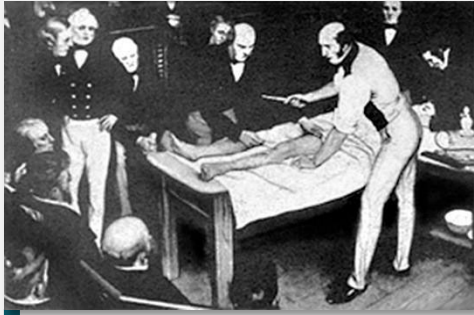


Image Taken From Canadian Cancer Statistics 2016

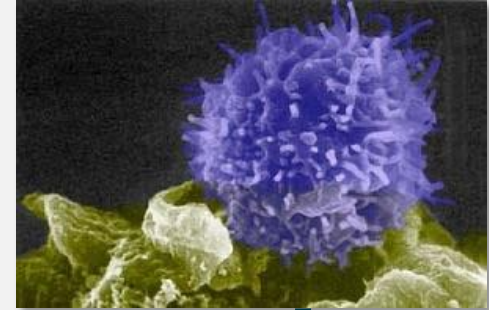
Evolution of Cancer Therapy: Treatment Modalities



Surgery
1846



Chemotherapy
1946

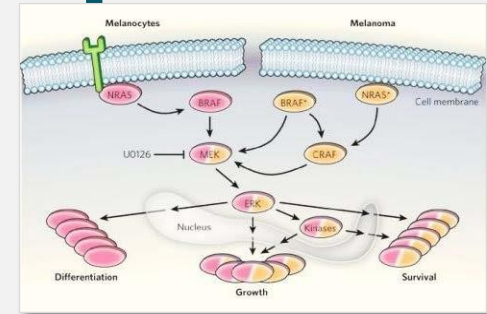
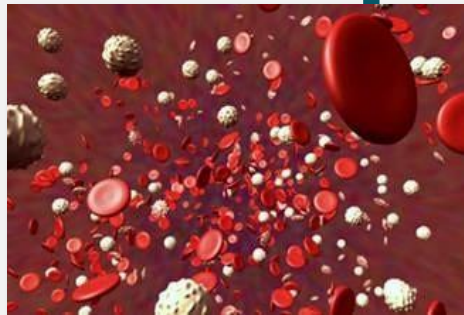


Immuno-oncology
Sipuleucel-T 2010
Ipilimumab 2011

Radiation Therapy
1901

Immunotherapy
Interferon-α 1995
Interleukin-2 1998

Targeted Therapy
1997



Systemic Oncology Therapies

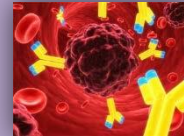
CHEMOTHERAPY

Target: rapidly dividing tumour and normal cells
Adverse events: diverse due to non-specific nature of therapy



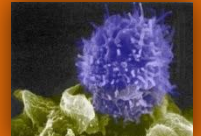
TARGETED THERAPIES

Target: specific molecules involved in tumour growth and progression
Adverse events: reflect targeted nature



I-O THERAPIES

Target: immune system
Adverse events: unique events can occur as a result of immune-system activity



Different spectrum of adverse events with each type of therapy

Require different management strategies

Chemotherapy:

Definition

- The treatment of cancer using specific chemical agents or drugs that are destructive to malignant cells and tissues. The term comes from two words that mean "chemical" and "treatment."

Cytotoxic

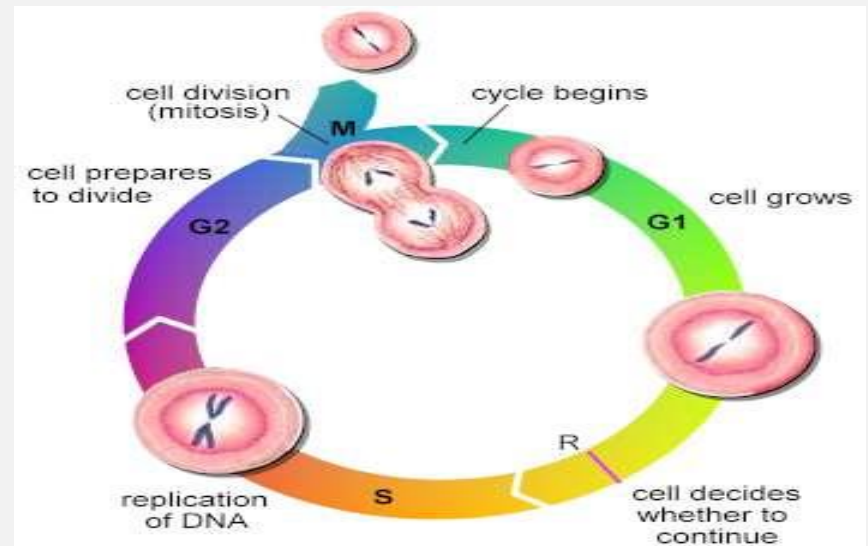
- literally translated means 'toxic to cells'.



Chemotherapy and Cancer Cells

Cell Cycle specific :

Most active against cells in a Specific phase therefore need Prolonged exposure or repeated doses.



Cell Cycle Non-specific:

Most effective against actively dividing cells but also effective in G0.

Chemotherapy

Chemotherapy may be used conventionally to:

- Cure patients
- Prolong survival
- Palliative care symptom control



Chemotherapy

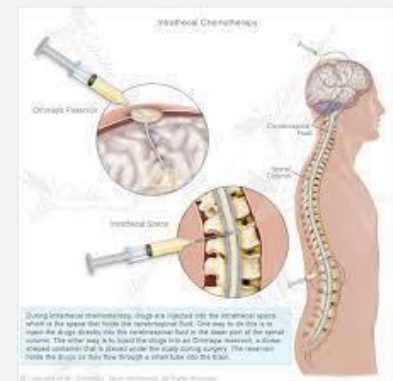
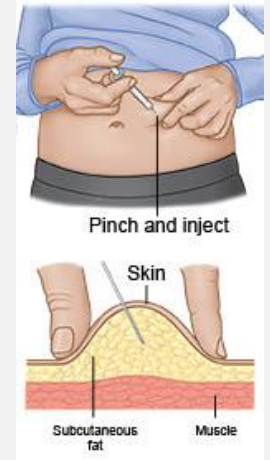
Over 50 different chemotherapy drugs

Administered as an outpatient or inpatient depending on toxicity

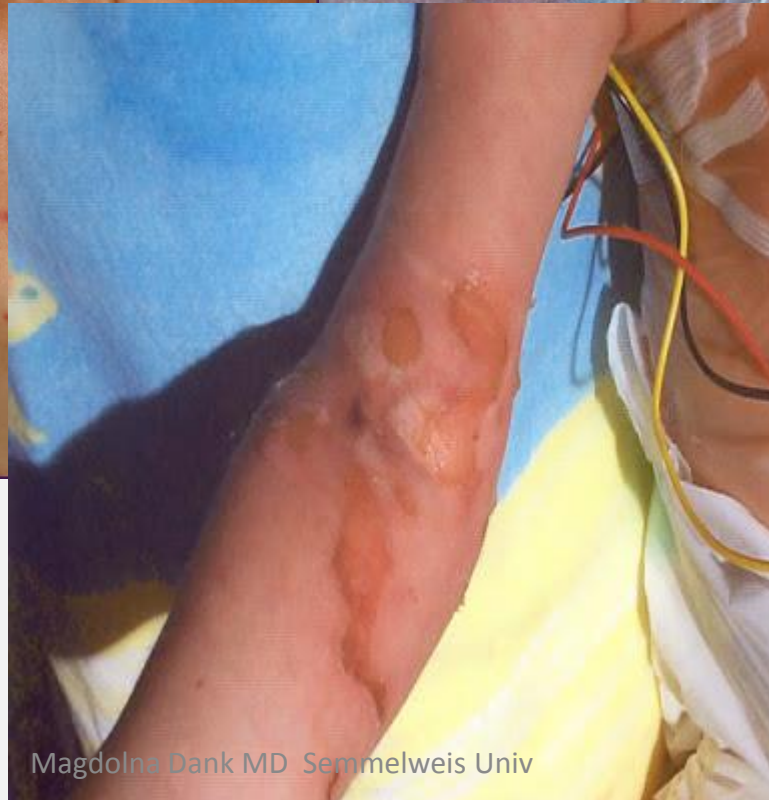
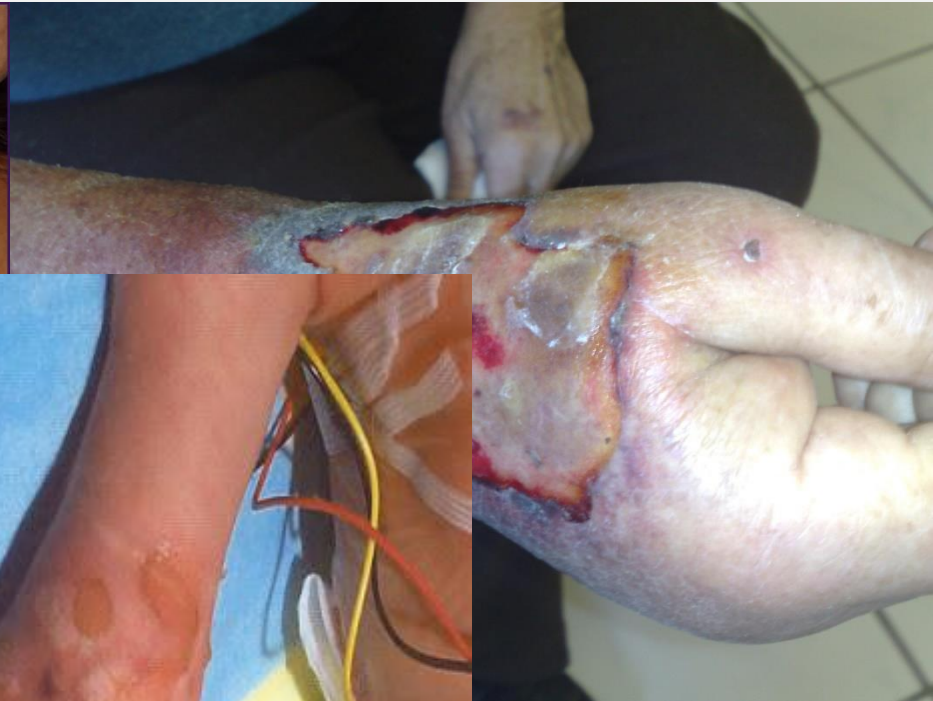
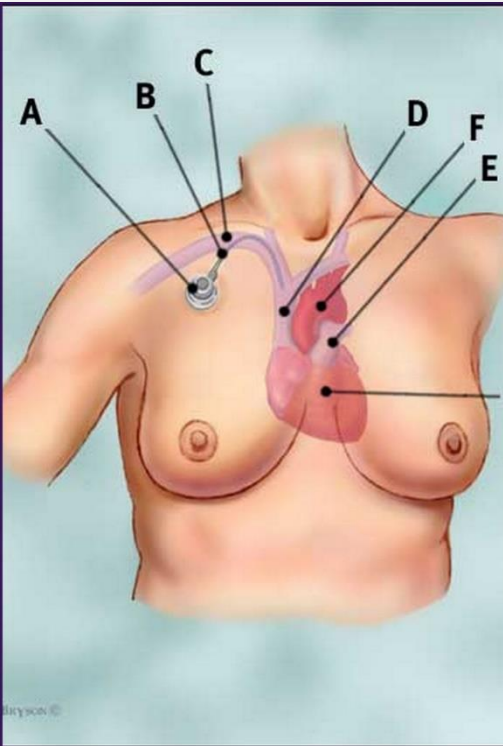
Modes of administration include:

- *Oral* e.g. capecitabine, idarubicin
- *IV*: Canula/Indwelling Central Venous Catheter
- *Sub cut* e.g. trastuzumab
- *Intracavity* e.g. pelvic cavity, bladder
- *Intrathecal* Can be fatal if wrong drug administered!

Subcutaneous Injection

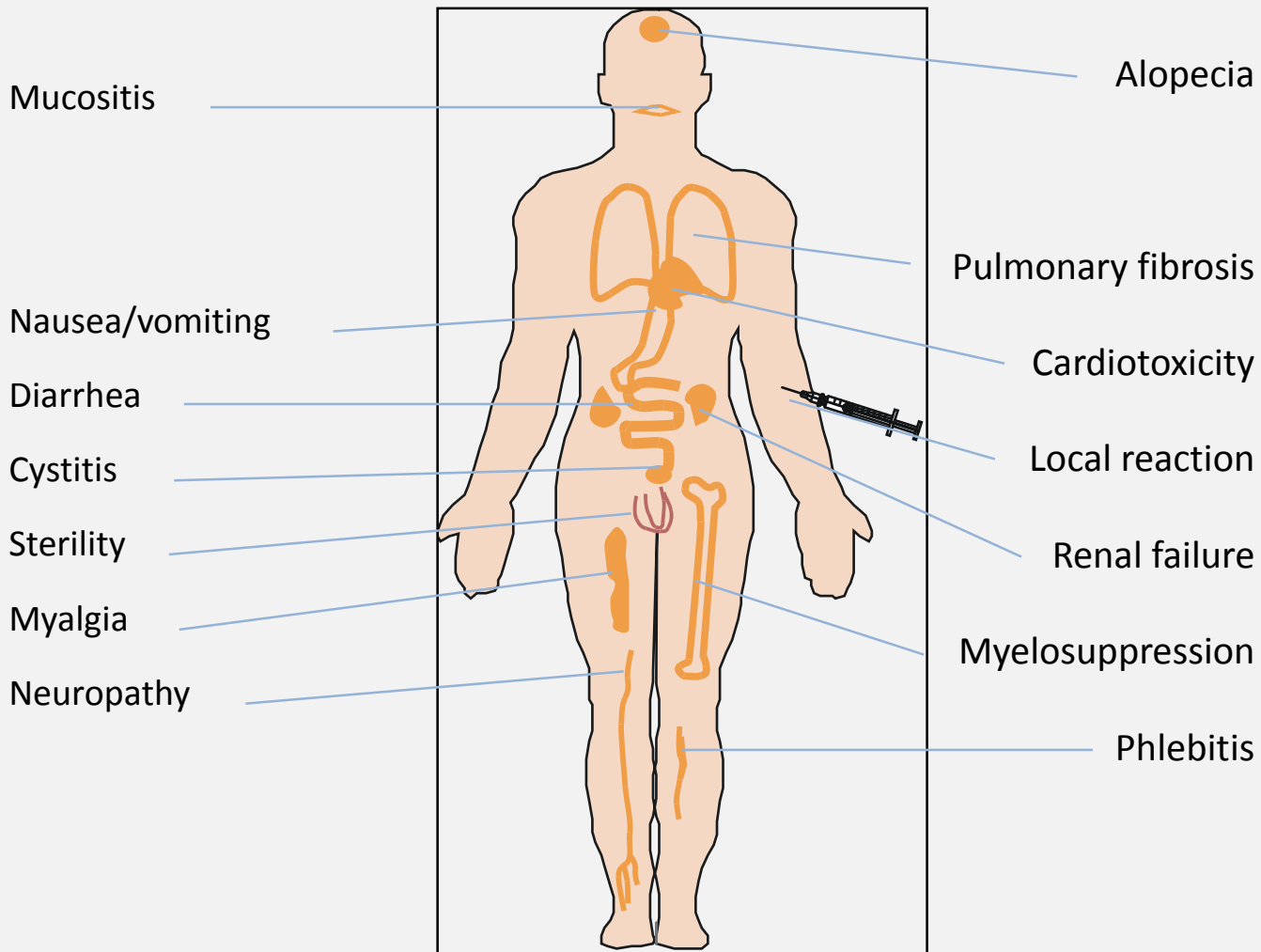


How to use chemotherapy?



Principles of chemotherapy

Side effects of chemotherapy



Chemotherapy Side Effects

- Chemotherapy targets cells which are ***dividing rapidly***.
- Chemotherapy ***cannot distinguish*** between normal cells and cancer cells
- Healthy Cells which have a high rate of growth and multiplication include cells of the **bone marrow, hair, GI mucosa and skin**.
- Side effects may be drug specific e.g. anthracyclines and cardiotoxicity, taxanes, oxaliplatin and neuropathy/constipation, bleomycin and pulmonary fibrosis
- Severity of side effects varies between drugs.
- Side effects ***often occur 7-14 days post treatment***.

Side Effects: Bone Marrow

Neutropenia:

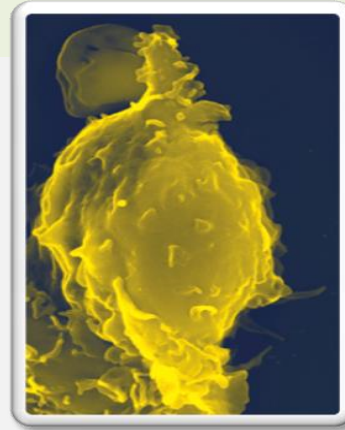
Increased risk of infection.

Anaemia:

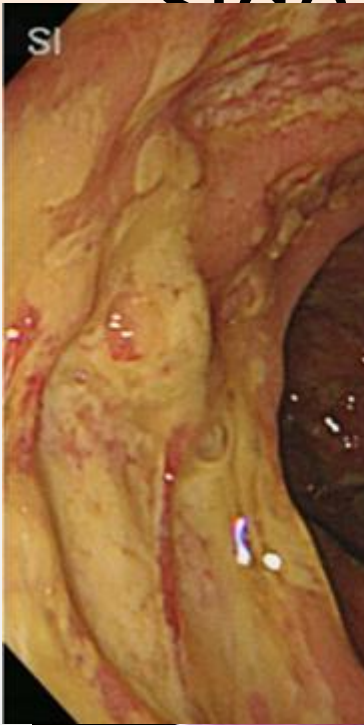
Tiredness, lethargy & breathlessness

Thrombocytopenia:

Increased risk of bleeding



Sigmoidoscopy



Side Effects

- Example of Grade 4 Mucositis



Side Effects: Body Image

- H
- V
- L
- S
- S



Side Effects: Other

- ***Fatigue***: Often multi-factorial
- ***Peripheral neuropathy***
- ***Altered Kidney Function***
- ***Changes in hearing*** (high dose Cisplatin)
- ***Cardiac Toxicity*** (Doxorubicin/ Idarubicin)
- ***Late Effects***: Infertility, secondary malignancy, growth retardation.

Clinical Case

- *Nov 2008*: 45 year old woman presents with pain because of an ovarian serous tumor and poorly differentiated



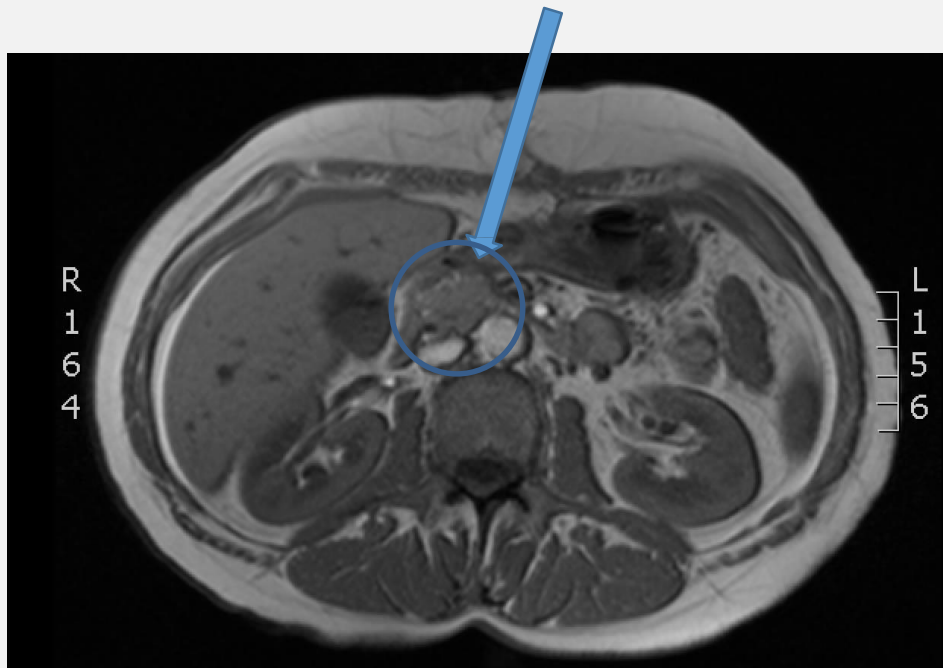
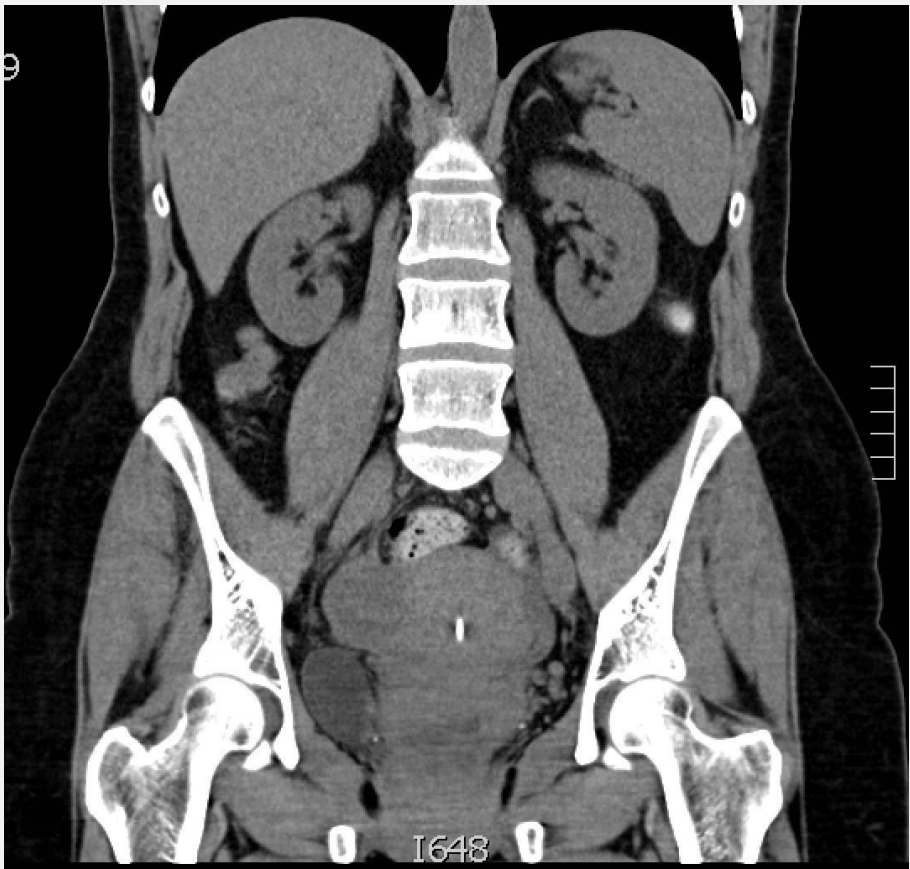
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy



- Bilateral salpingo-oophorectomy (removal of ovaries and fallopian tubes due to disease)
- CA-125= 100 U/ml

- Histology: poorly differentiated serous carcinoma with disease in omentum, peritoneum and lymphnodes. Washings:**positive**

Presentation with Ovarian Mass 2009. Residual Para-aortic LN



Diagnosis

2008.11. surgery
Peritoneal involvement

Treatment plan

- **Treatment plan:** Carboplatin and paclitaxel x6 cycles
- **Allergic reaction** to paclitaxel after 2nd cycle, so continued with single agent carboplatin completing in Jan 2009
- MRI- Mass about 1 cm ? Fibrotic. Normal CA125



6xCBP-(TXT)

Diagnosis

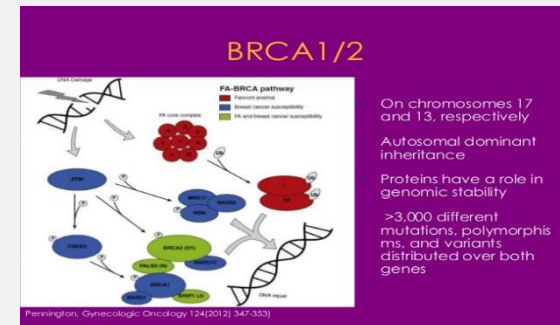
Normal CA125

2008.11. surgery
Peritoeal involvement

Recurrent ovarian cancer

November 2010

- CT: 2.3 cm mass at porta hepatis and 1.3 cm aorto-caval nodes.
Normal CA125
- **Biopsy:** high grade carcinoma
- Family history of breast and other cancers of unknown types.
- Found to have a deleterious BRCA1 germ line mutation



Diagnosis



2008.11. surgery
Peritoenal involvement

Management of recurrent ovarian cancer postsurgery

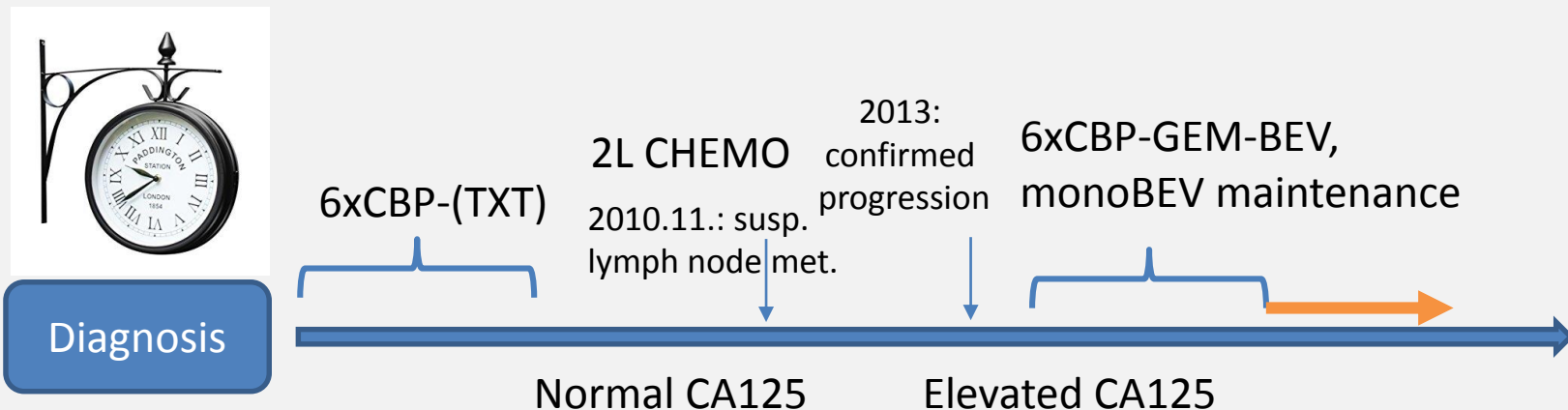
1. Further course of chemotherapy ?
2. Observation?

Again chemotherapy, with paclitaxel
and carboplatin: 2nd line chemo

Follow up

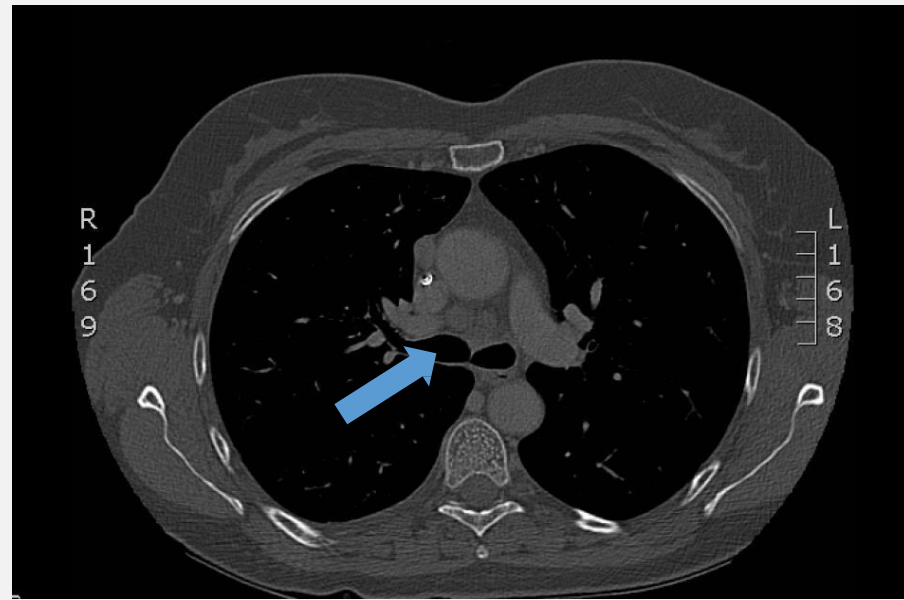
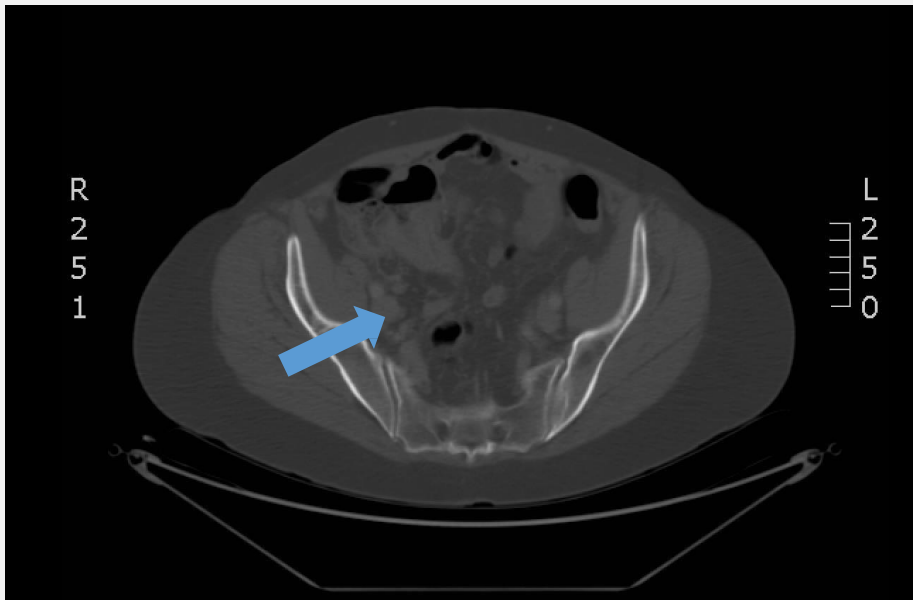
- Aug 2012: CT/PET no evidence of disease.
- *January 2013*: CA125 started to rise, reaching 930 iu/l in March 2013
- CT/PET: nodal disease; perihepatic and perisplenic deposits and nodule at pleural base

March 2013: Third line chemotherapy **Carboplatin AUC4; Gemcitabine 800 mg/m²; Bevacizumab 15 mg/kg**. 6 cycles followed by maintenance bevacizumab

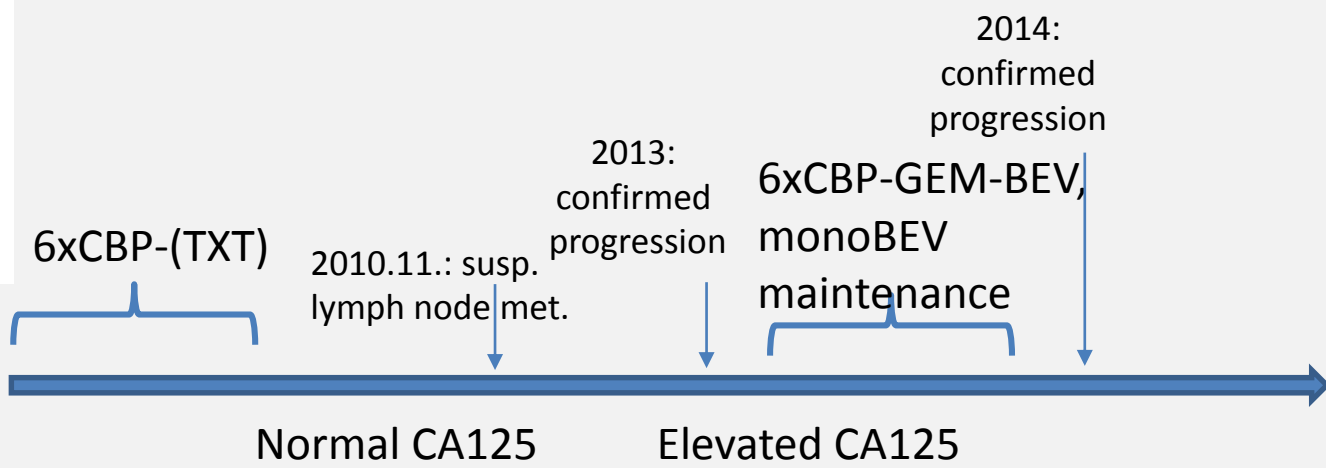


2008.11. surgery
Peritoeal involvement

Recurrent disease- 2014



Diagnosis



2008.11. surgery
Peritoeal involvement

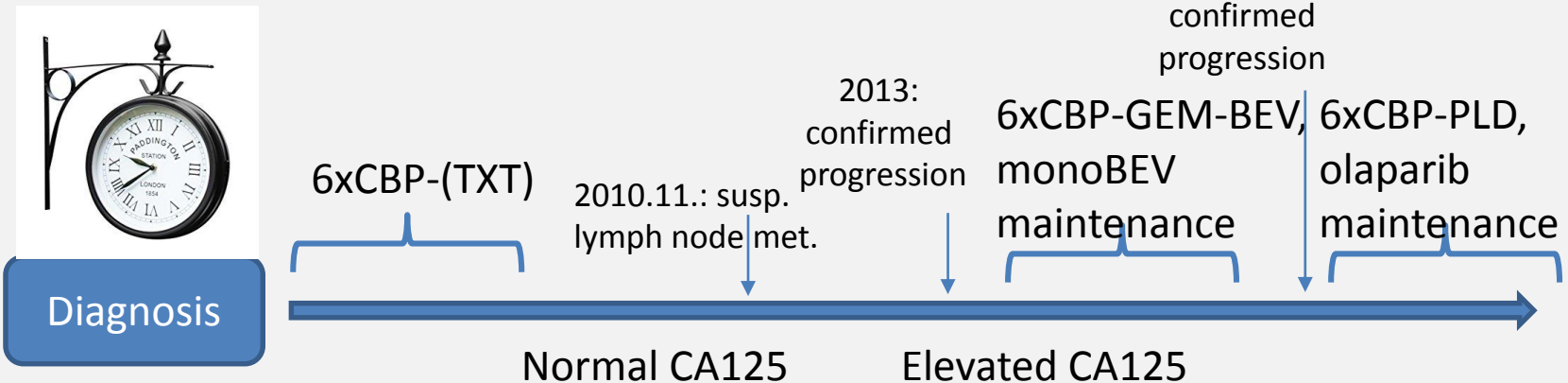
Fourth-line chemotherapy

November 2014

- Carboplatin AUC 5 and PLD 30mg/m²
- CA125 normalised after 1 cycle (24 iu/l)
- 6 cycles completed March 2015
- March 2015: *CT: Excellent response. All remaining lesions < 1 cm*

April 2015-Nov 2016 (19m long PFS)

- Olaparib 400mg (capsules) BD
- October 2015: Well. Normal CA125. Continues on treatment without toxicity



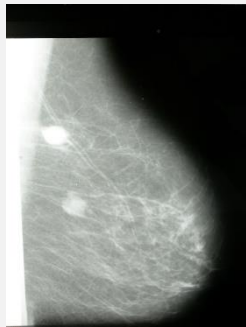
Neoadjuvant therapy in locally advanced breast cancer

Diagnosis

Primary systemic (neoadjuvant) therapy

Surgery

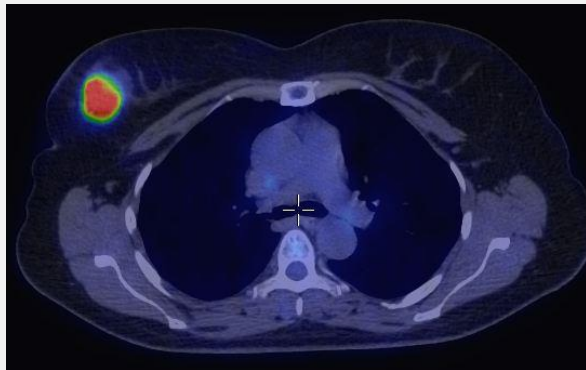
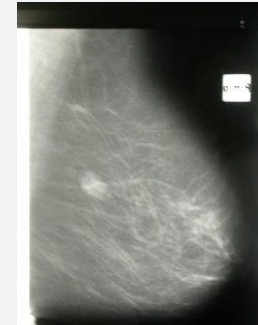
Baseline



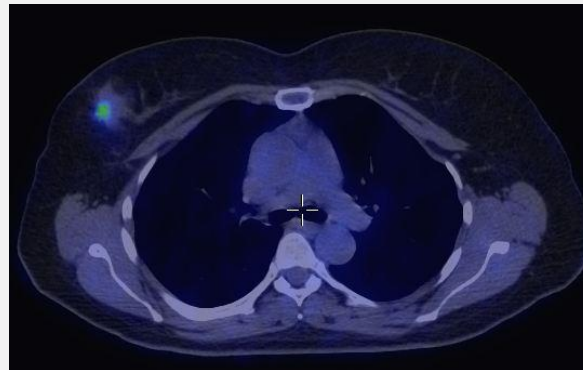
After C03



End of PST



Baseline



After C01



End of PST

Local breast cancer remission 5 years after surgery



1st line chemotherapy



2018. june



2018. august



2018. september

77y pt. 2008: breast cancer – surgery was performed: quadrantectomy + axillary block dissection

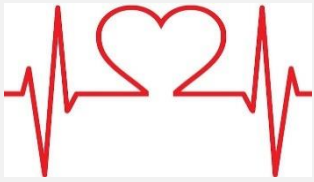
Histology: Invasive ductal carcinoma pT1b, pN2 Grade:2. ER:100%, PR:70%, Ki-67:10%, HER-2 negative

Adjuvant therapy: irradiation + endocrin therapy

8 years later:



Vass Judit dr engedélyével



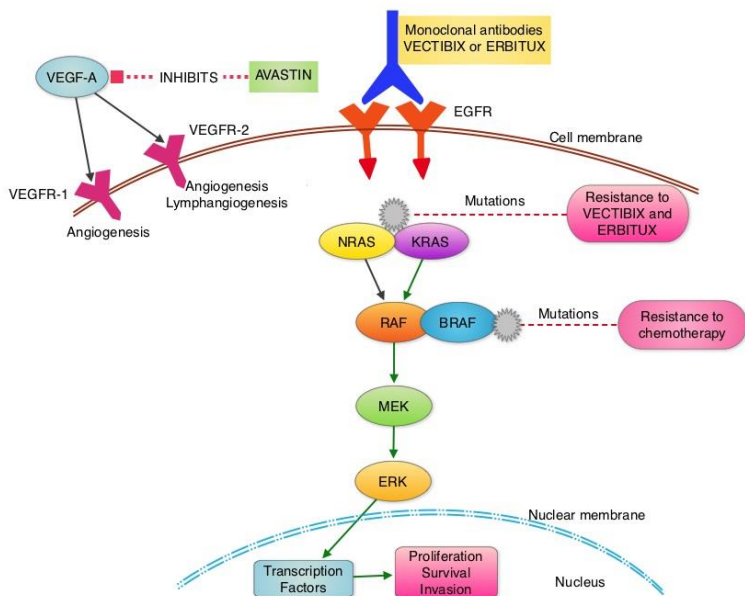
Oncocardiology – case presentation

70yo male pt., ex athlete.

- **Familiar anamnesis:** CV risk – AMI, NIDDM – and HCC, leukaemia
- **Anamnesis:**
 - **Obesity, primary hypertension, Chronic alcohol abuse and smoking**
 - Hip joint replacement, cataracta , umbilical hernia surgery
- **CV anamnesis:**
 - 2010: **RCA BMS stent implantation**, dual platelet agg. inhibition therapy, chronic ischaemic heart failure
 - 2015. Effort angina, dyspnea ECG:wide LBBB, **new paroxysmal AF, BB+OAC**
 - 2015. Control: Echocardiography: Inferior-lateral ischaemia , paradox septal movement, slightly decreased LVF, , **EF 45 %**, EDD 62 mm, ESD 52 mm; Coronarography: RCA non-significant 40% stenosis
 - 2017.05. Echocardiography: sinus rythm, decreased LVF, **EF 38%**, dilated ventricles, Grade I MI
- **Current medication:** ACEi, BB, clopidogrel

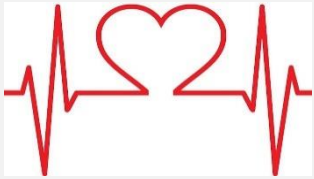
- 2018.01. Sharp right subcostal pain, diagnostic investigation:
- **Abdominal US:** Mpx. hepatic metastases suspect lesions, hepatomegaly
- **Chest-abdominal-pelvic CT:** mpx. Liver metastasis (2-3 cm), mpx. pulmonary nodular metastasis suspect lesions, left adrenal gland metastasis suspect lesion, rectosigmoideal wall thickening

MOA of AVASTIN and Anti-EGFR Agents



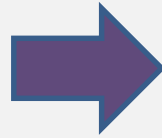
Colonoscopy: sigma exulcerant, non-stenotising tumor

Histology: intestinal adenocarcinoma , KRAS, NRAS, BRAF wild-type



Staging:

- Primary: rectosigm. tumor
- Mpx. hepatic metastases.
Few pulmonary nodules
- Cranial MR: No intracranial metastases



Surgery: not recommended due to increased cardiopulmonary risk

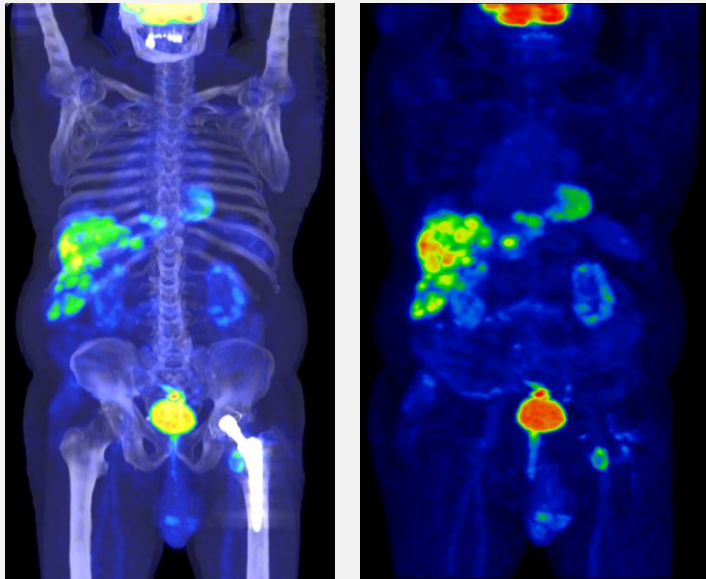
1st line: FOLFOX-Cetuximab is recommended (KRAS NRAS wild)

Cardiologist opinion: **EF 40%**, Grade I MI.

Initiate dose reduced chemotherapy with regular cardiology check-ups

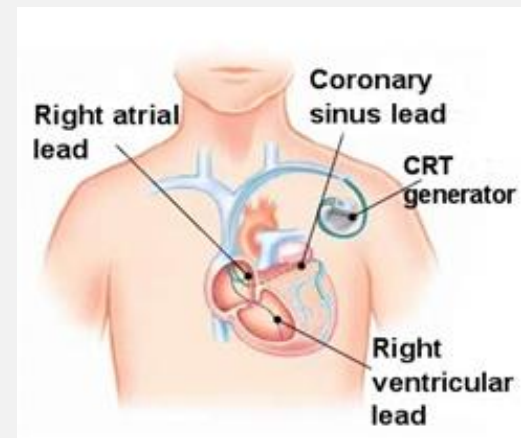
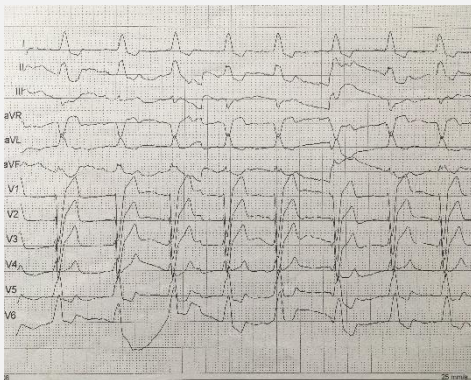


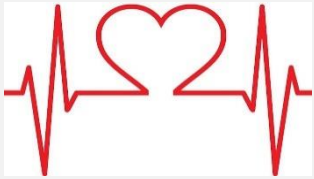
Initiate dose reduced chemotherapy with regular cardiology check-ups
FOLFOX+Cetuximab treatment, 66% dose reduction



Regular cardiological follow-up

- After C03
 - **Echocardiography after 3 cycle** : Diffuse hypokinesia, DCM, grade I diastolic dysfunction, **EF 32%**, EDD 60 mm, ESV 48 mm.
 - **Coronarography**: no intervention is needed
 - **ECG**: normofrequent sinus rhythm, **LBBB, QRS 170 ms**
- **Cardiologist's opinion**: Regarding the decreasing ejection fraction, and known left bundle branch block and ventricular dyssynchrony, implant of CRT-D device is recommended
- CRT-D device implantation is successfully performed immediately

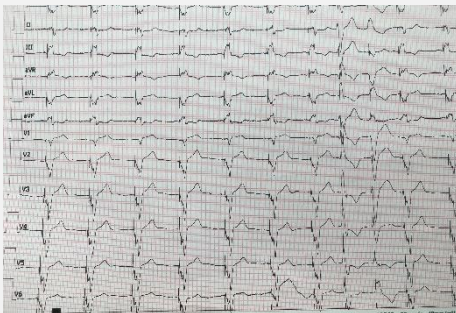




In summary **14 cycle of FOLFOX-Cetuximab in reduced dosage** can be completed after cardiological intervention

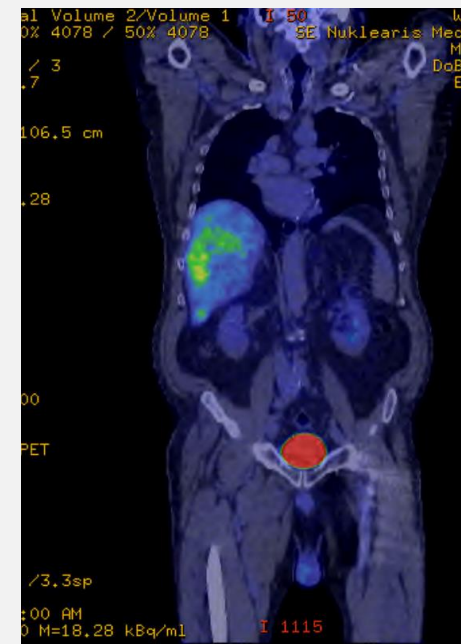
Angina, dyspnoe: did not onset since CRT implant

ECG: normofrequent sinus rhythm, non-PM dependent, PM good sensing and pacing funktion, QRS 160 ms



Restaging:

- Rectosigm. Tumor: **Morphometabolic regression**
- Mpx. hepatic metastases., pulmonary nodules: **Stable disease:**

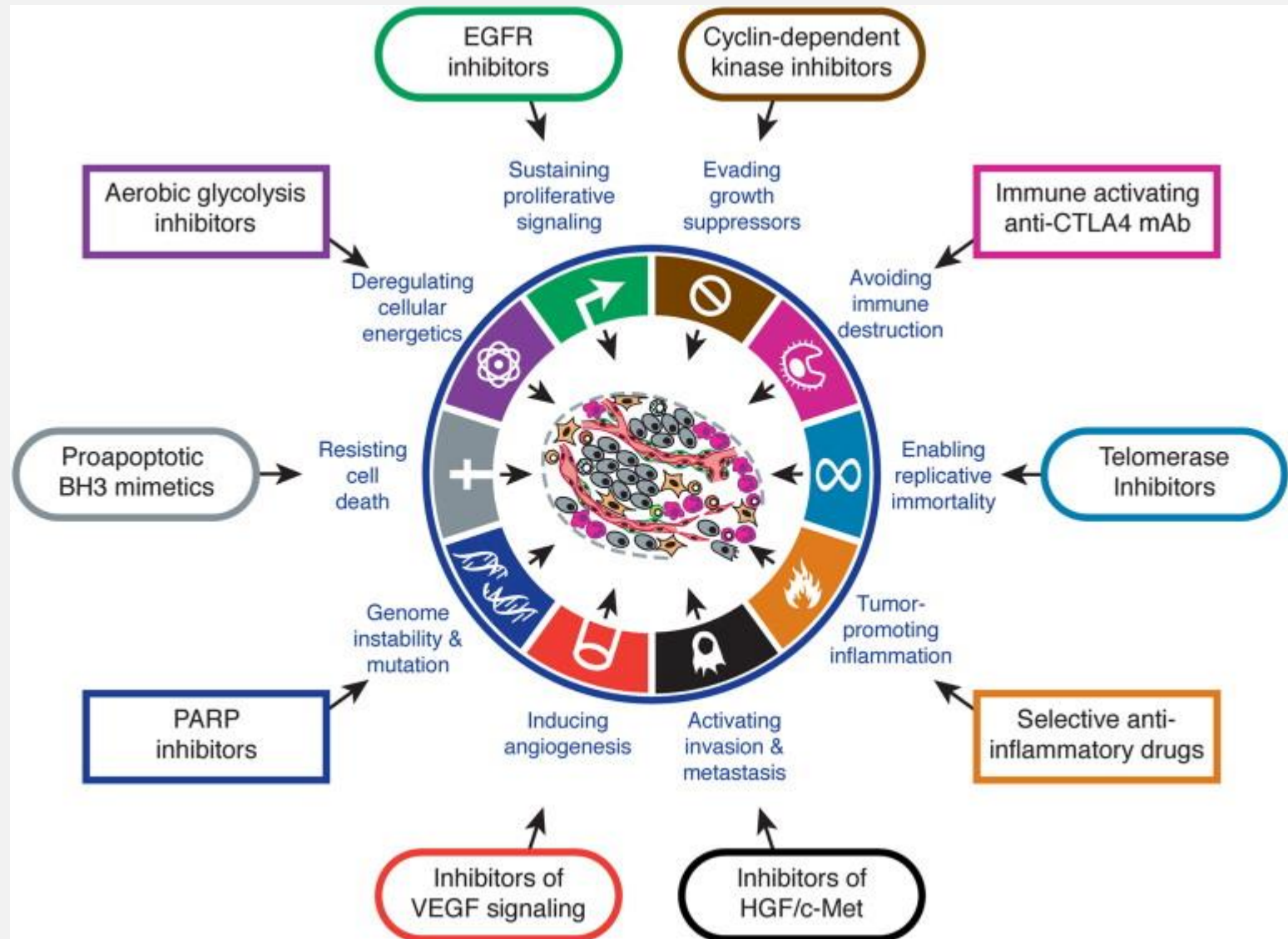


She is a BC pts, with mtpl bone mets....
After 10m-long trastuzumab and pertuzumab treatment.



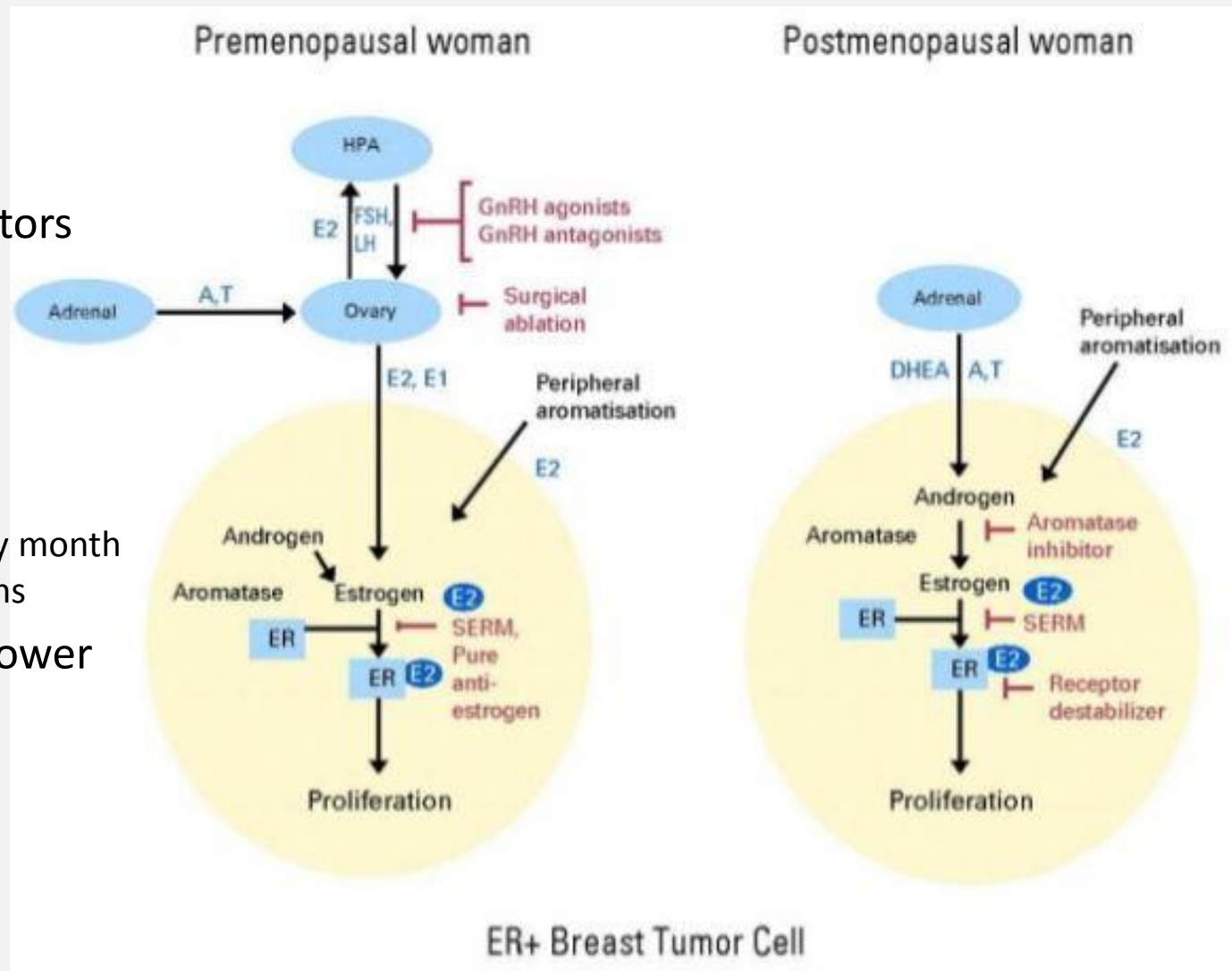
Warm greetings from Erzsébet Linder!!

Personalized medicine



Hormonotherapy: continuously evolving since 50 years

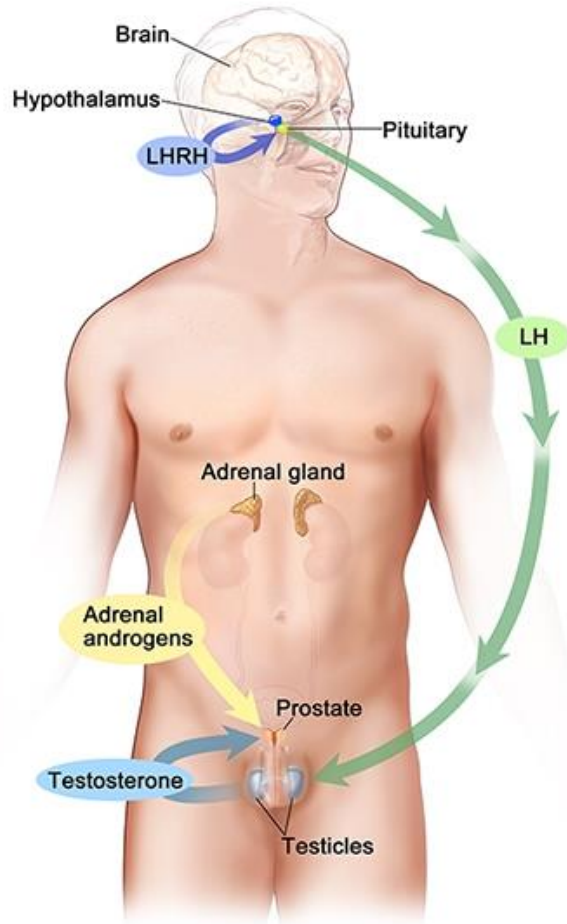
- Antiestrogens
- Aromatase inhibitors
- GnRH analogues
- Easy to apply:
 - daily per os or
 - injection in every month or every 3 months
- New drugs with lower toxicity



Endocrine therapy

- **Digestive system:** constipation or diarrhoea, loss of appetite/ or increased appetite of it which can lead to weight-gain
- **Menopausal symptoms:** vaginal dryness, hot flushes. Sweating
- **Hair thinning**
- **Muscles and bone changes:** pain in the joints
- **Weight gain:** body-exercise is essential
- **Headaches** - mild painkillers are useful
- **Memory problems, mood swings and depression**

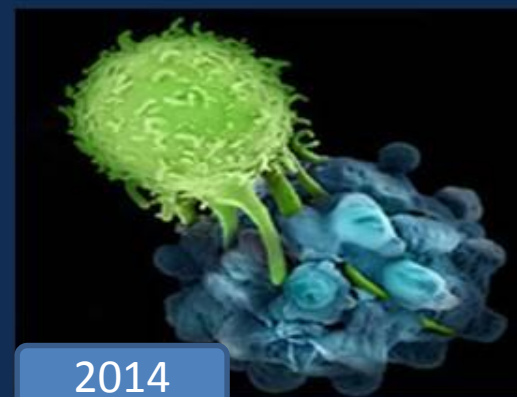
Androgen production in men



- Loss of interest in sex (lowered [libido](#))
- [Erectile dysfunction](#)
- [Hot flashes](#)
- Loss of [bone density](#)
- Bone fractures
- Loss of muscle mass and physical strength
- Changes in [blood lipids](#)
- [Insulin](#) resistance
- Weight gain
- Mood swings
- [Fatigue](#)
- Growth of breast tissue ([gynecomastia](#))

Immunotherapy – The Beginning of the End for Cancer: Transforming Cancer into Chronic Disease

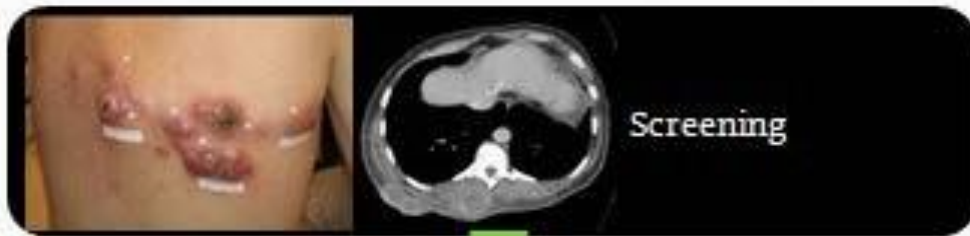
“**Immunotherapies** will likely become the treatment backbone in up to 60% of cancers over the next 10 years compared with <3% today.”



OPDIVO[®]

**MECHANISM
OF ACTION**

Example of Evolution of Response to CTLA-4 Inhibitor



Hamankaya K, et al: EADO 5th Congress / 7th World Congress of Melanoma 2009.

irAE: immune-related adverse event
mWHO: modified World Health Organization (criteria)
PD: progressive disease

Checkpoint inhibitors drugs: adverse and side effects

- Usually are the consequence of the overactive (auto)immune response
- Corticosteroids are often needed in the management of these side effects
- Therapy suspension and/or steroid treatment?
- **Regular laboratory tests are essential! (liver and renal function, thyroid gland function, cholesterol, triglycerides)**

Side effect of immunotherapies

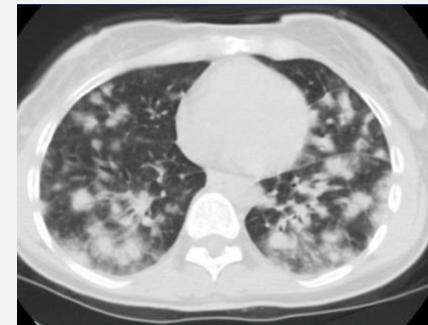
- **Skin:** (immunmediated) dermatitis (erythema, maculopapular rash, etc. Up to 40-50%!), pruritus, alopecia, vitiligo, erythema multiforme, psoriasis, etc.
- **GI tract :** diarrhea, (immunmediated) colitis (diarrhea, tenesmus, melena), stomatitis, nausea, vomiting, pancreatitis, hepatitis (liver function, amylase, lipase!)
- **Pulmonary:** immunmediated pneumonitis, interstitial pulmonary disease: can be asymptomatic, dry cough (!), dyspnoe, GGO,
- **Endocrine :** hypothyreosis, hyperthyreosis, hyperglycaemia, hypophysitis, hypopituitarismus, diabetes mellitus
- **Neurology:** periferial neuropathy, Guillan-Barré sy., mysasthenia gravis, autoimmune neuropathy (n. facialis paresis)
- **Renal:** immunmediated tubulointerstitial nephritis, acute kidney failure
- **Other:** uveitis, hypertension, muscle, joint pain, tiredness



How to Recognize and Manage Ipilimumab-Induced Dermatologic Adverse Events
By Jennifer Nam Choi, MD, October 15 2013



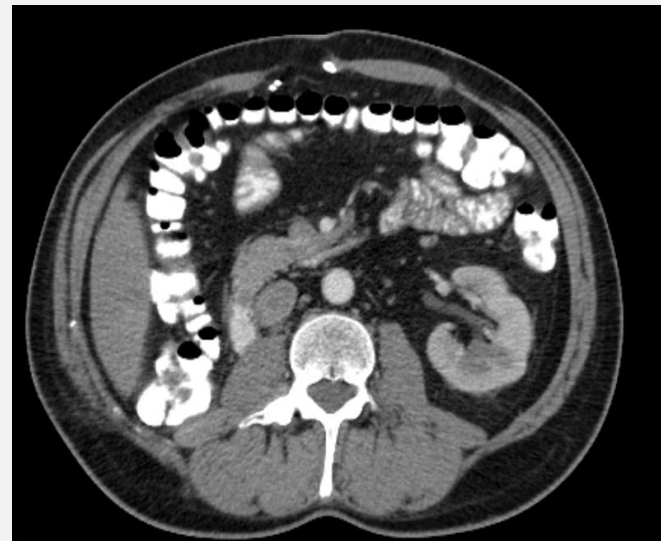
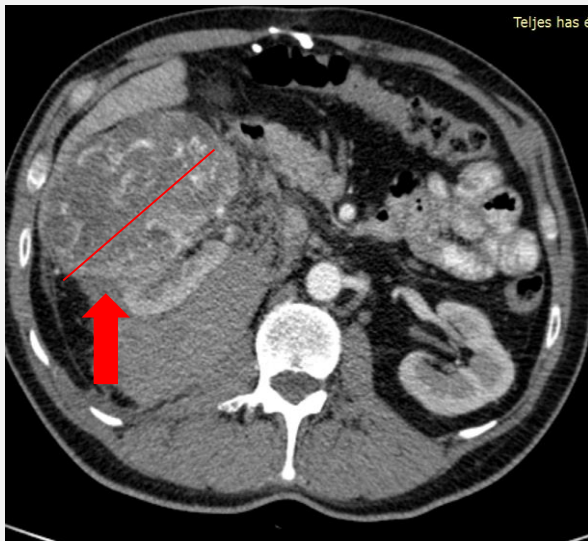
Meng Li, Qiuwei Pan, Maikel P. Peppelenbosch
Should Nivolumab-Induced Colitis Be Treated by Infliximab
Clinical Gastroenterology and Hepatology, Volume 15, Issue 10, October 2017, Pages 1637



Putting Cancer in check with immunotherapy: Melanoma and beyond
Michael Postow MD
Memorial Sloan Kettering Cancer Center

Nivolumab immunotherapy in RCC

- 45 years old, polytrauma+splenectomy,cholelithiasis in history
- 2014.09: **Sudden, sharp pain** in the right subcostal region:
- **CT scan** showed a ruptured kidney tumor and retroperitoneal hematoma
- **Radical nephrectomy** was performed: 14 cm RCC, Fuhrman G3, pT2
- 2014.10. Staging CT scan : St. p. nephrectomiam l.d. Solitary, metastasis suspect lesion in the lower lobe of the left lung



- 2014.11. **Multidisciplinary team:** Patient has good performance status; **pazopanib** (2x400 mg) therapy is recommended, with regular CT scan check-ups
- **Dose reduction** was needed because of diarrhea (400 to 200 mg)
- 2015.07 CT scan): **progressive disease** regarding the pulmonary and retroperitoneal lesions
- 2015.08. **2L therapy:** nivolumab treatment

1st line pazopanib

2nd line nivolumab

Diagnosis

RCC + met pulm

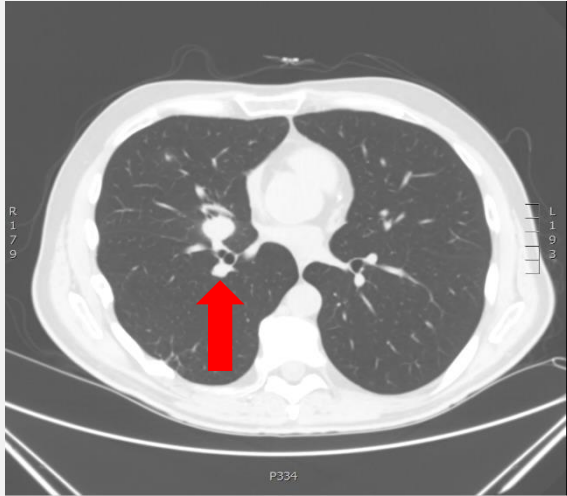


2015.07: PD:
lung +
retroperit.lgl

2015.12:
pseudo-
progression
2016.01:
stable
disease
(lung +
retroperit)

2016.04:
partial
regression

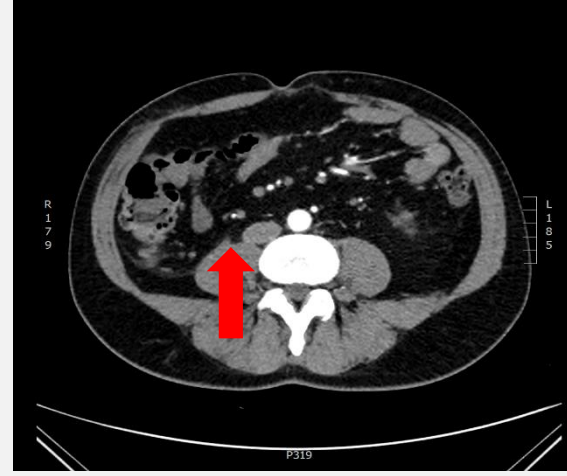
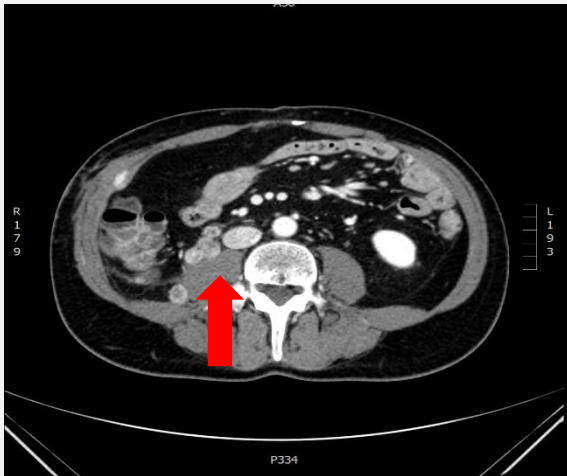
2016.11: further
regression

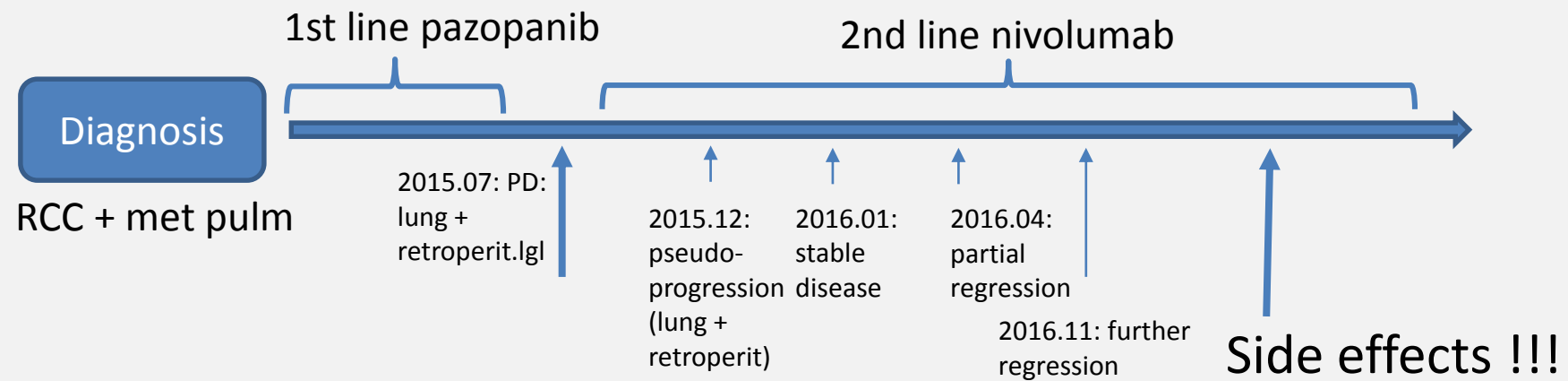


2015.07



2016.11





- 2016.05: Consultation with an Endocrinologist: elevated TSH (12 mU/L) --
→ immunmediated thyreoditis, hypothyreosis is suspected
L-Thyroxin treatment was suggested
- 2017.05.: Persistent upper respiratory complaints, otolaryngist
consultation acute sinusitis
 - Antibiotics, antihistamine and low-dose steroid are initiated: no improvement, immunmediated origin is probable
 - Large- dose steroid treatment is initiated (metylprednysolon 32 mg) ,
Nivolumab therapy is suspended

1st line pazopanib

2nd line nivolumab

Diagnosis

RCC + met pulm

2015.07: PD:
lung +
retroperit.lgl

2015.12:
pseudo-
progression
disease
(lung +
retroperit)

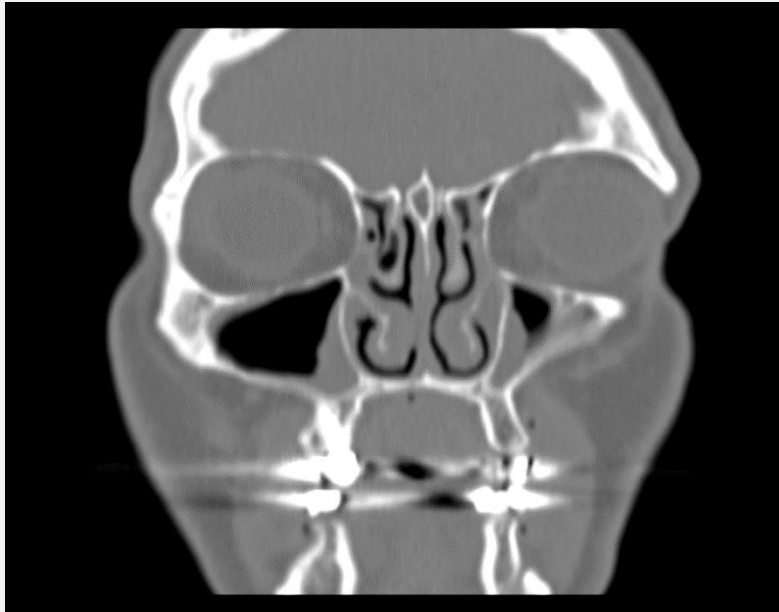
2016.01:
stable
disease

2016.04:
partial
regression

2016.11: further
regression

Side effects !!!

2018: CR



2017.08. CT scan: sinusitis

2017.08: Nivolumab reinduction

CT scan after 42 cycle: **Partial regression** of target lesions
+ Pansinusitis. chronic maxillar and ethmoideal sinusitis
+ Pancreasatrophy, cholecystolithiasis.
- Kreon therapy is started because of steatorrhea , abdominal discomfort

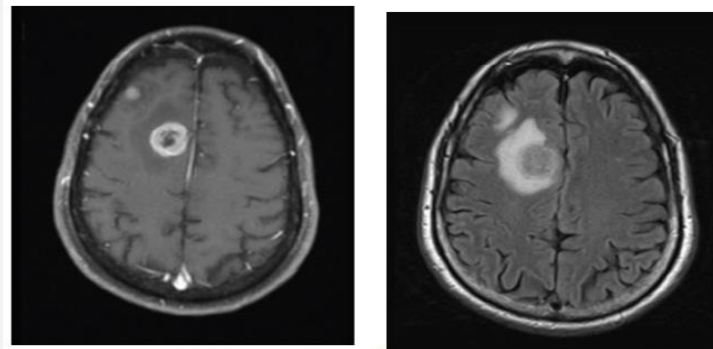
2018.09: C69 Nivolumab!

CT scan showed **no local or distal recurrence**

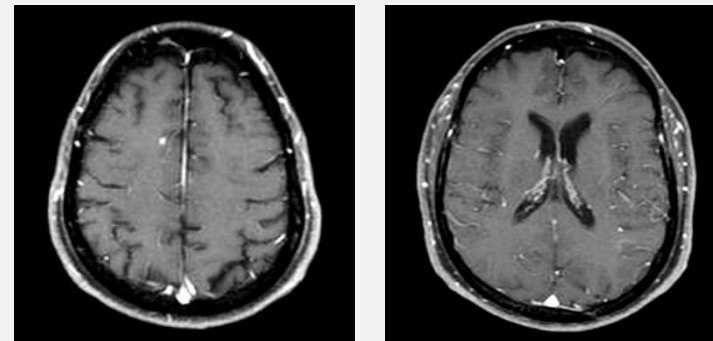
Case report: pts with melanoma malignum AND brain met: treated with combined immun-therapies (Ipilimumab and nivolumab)

71 year old male with *BRAF* V600E-mutated MEL, ~7 brain mets, no steroids or SRT

Baseline



1 year



**One size
does not fit all**

Thank You

