EAHP 2016
Seminar PH2
Cancer Therapy: review of the present and a look to the future

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Conflict of interest

- Founder and Scientific Advisor of OncoPeptides AB
- Chief Medical Officer of Vivolux AB

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Three cornerstones in the treatment of cancer

- Surgery
- Radiotherapy
- Pharmacology
  -Chemotherapy
  -Antibodies (tumor associated antigens)
  -Low Mw targeted therapy
  -Immunology adaption
  -Hormonal therapy

  (We will focus on pharmacology today)

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Questions

- Is hematotoxicity the most common dose limiting effect of chemotherapy?
- Is adjustment by BSA an ideal method to reduce variability in PK among patients?
- Does the introduction of targeted agents increase the demands for validated molecular pathology assessments of tumor material for each patient?

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Our case

Case

- A 38 years old woman discovers a tumor in her right breast

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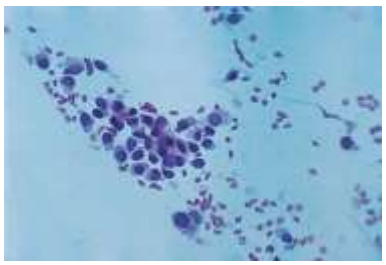
case

Normal

Tumor

Atlas of Breast Cancer, CMG



www.womenshealthsection.com

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Surgery is the most important part of treatment (for most solid tumors)

However, it is not always possible to cut out everything (size, nerves, vessels etc)

Microscopic spread

It is very common that surgery is combined with pharmacologic therapy or radiotherapy, i.e. *"adjuvant treatment"*

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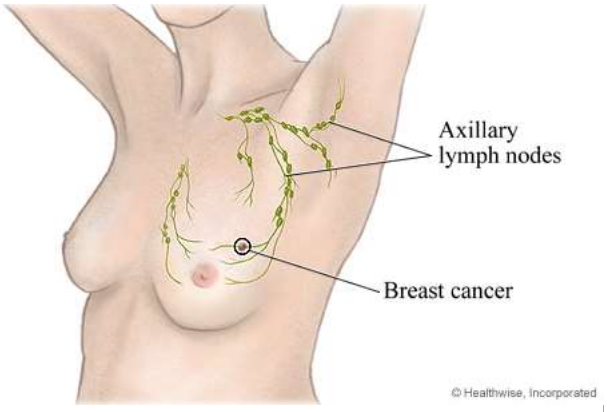

- Breast cancer surgery: lumpectomy and sentinel node biobsy (or axillary clearance if mets)

  In our case patient has a 20 mm ductal cancer; ER+, HER-2 neg, low proliferation (15 %) and 2 lymph node mets (of 9 nodes removed). The PATHOLOGY REPORT is very important for the decision of further therapy.

- The prognosis have significantly changed; histological a non-aggressive tumor, but pos lgll is a bad prognostic sign

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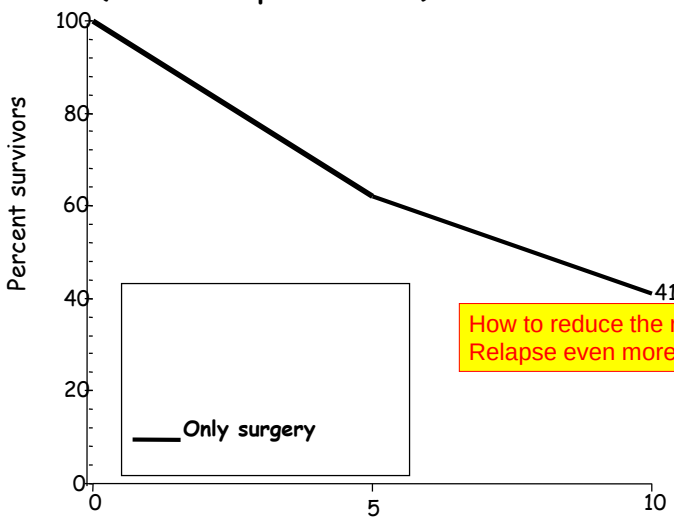
Our case

How will it go? (Premenopausal N1)



How to reduce the risk for Relapse even more?

Prof Carl Blomqvist, Helsingfors Universitetssjukhus, Finland

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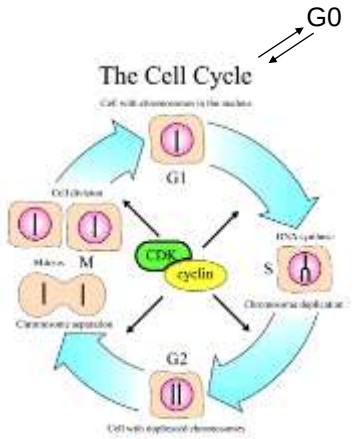
Chemotherapy act on cell division!

- Alkylators/Platinum compounds
- Topoisomerase inhibitors
- Tubulin inhibitors
- Anti metabolites



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CHEMOTHERAPY – Characteristics

Substances delivered into the systemic circulation iv or orally (sometimes used locally) acts on cancer cells by:
- Induction of apoptosis
- Inhibits metastasis
- Inhibits angiogenesis
- Anti inflammatory effect

DNA is the target:
How about selectivity for cancer cells vs normal cells? -> Side effects limit the use

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Different diseses have different sensitivity to cancer drugs

Extremely high sensitivty
Leukemia
Testicular

High sensitivity
Lymphoma
Ovarial
SCLC

Intermedite sensitivity
Breast
Sarcoma
Anal

Low senitivity
Head-neck
Esophagus
GI
Malignant melanoma
NSCLC
Prostate

Resistant
Primary liver (HCC)
Renal

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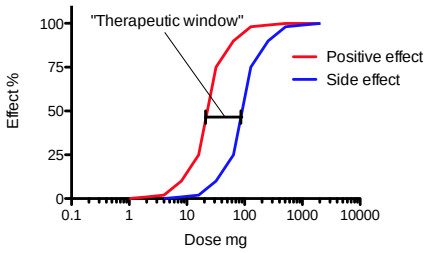
Chemotherapy – Narrow therapeutic window



Acceptable side effects, e.g.:
-hair loss
-nausea
-stomatitis

Unacceptable
-Death
-Irreversible neuropathy
-Renal failure
-Liver failure

Duscussable:
-Secondary neoplasms
-Infertility

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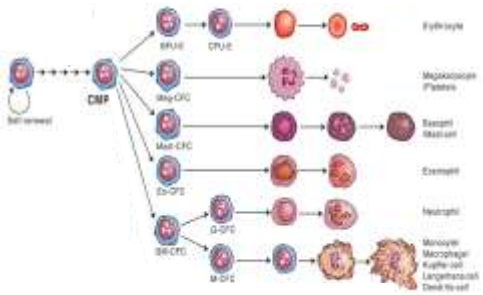
Hematotoxicity is very common



	What can be done:
Anemia	Transfusion, EPO
Thrombocytopenia	Transfusion
Leukopenia	Isolation, Antibiotics, or G-CSF

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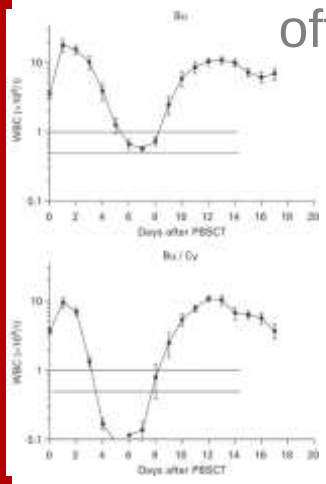
Dose-limiting toxicity often hematotoxicity



Increased risk for severe infections when neutropenia (ANC <0,5 x 10^9/L)

”Neutropenic fever”

Bone Marrow Transplantation (2006) 37, 1087–1091. T Kiefer1, W H Krüger1, F Schüler1, C Lotze1, C Hirt1 and G D

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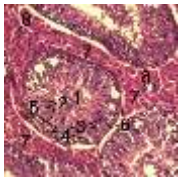
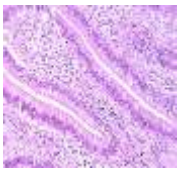
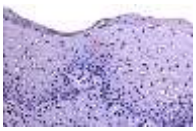
Side effects from organs with high cellular turnover



Gonads



Intestines



Oral epithelium

Hair and Skin

SIDE EFFECTS from CHEMOTHERAPY

-Hematology (low blood cell counts)
-Gastrointestinal: nausea, mucositis, diarrea
-Alopecia, Dry skin
-Fatigue
-Cardiac
-Neurological
-Central nervous: Fatigue, Nausea
-Psycho/neurological: cognitive impairment
-Renal
-Hypersensitivity reactions

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Nausea

ANTIEMETIKASCHEMA VID FÖRDRÖJT ILLAMÅENDE

Nr	1	2	3	4		5		6	
Läkemedel	T/S Primperan 10/20 mg	T Betapred 0.5 mg	T Betapred 0.5 mg	T Betapred 0.5 mg	K Navoban 5 mg	T Betapred 0.5 mg	K Navoban 5 mg	T Betapred 0.5 mg	K Navoban 5 mg
Dag 1	vb	4 st	6 st	8 st	1 st	10 st	1 st	8 st x 2	1 st
2	vb	2 st	4 st	6 st	-	8 st	-	8 st x 2	1 st
3	vb	-	2 st	4 st	-	6 st	-	8 st	-
4	vb	-	-	2 st	-	4 st	-	6 st	-
5	vb	-	-	-	-	2 st	-	4 st	-

Dag 1 = första dagen efter given cytostatikabehandling

Vid otillräcklig antiemetikabehandling: S/T Primperan vb, max 60 mg /dag. Vid kur 1 ska patienten få recept på detta

Vid otillräcklig antiemetikabehandling samt patienten önskar viss sedering: T Emcos 10 mg, 1-2 tabl vb
alternativt T Temesta 1 mg, 1 tabl vb

Basic treatment: corticosteroids and methoclopramide
+5HT3 receptor antagonists
+NK1 receptor antagonist

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Our case

A young patient with lymph node metastases is considered a ”risk patient” is invariably offered adjuvant chemotherapy (and radiotherapy and antihormonal therapy).

She is (in Sweden 2005) treated with six cycles of chemotherapy every three weeks;
FEC x3 followed by Docetaxel x 3.

3-4 weeks after the first cycle she looses her hair, she is nauseous and uses methoclopramide in addition to 5HT3 blocker and aprepitant during FEC. With docetaxel she has muscle and joint pains, fatugue and a discoloration of her nails.
She is informed to be very observant for increased body temperature, but completes her chemo without infections.

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Typical chemotherapy chart

$FE_{75}C$

Inf Epirubicin	75 mg/m²	Dag 1
Inj 5-FU	600 mg/m²	Dag 1
Inf Cyklofosfamid	600 mg/m²	Dag 1

Dosreduktion: Om LPK <2.5 x 10^9 alternativt TPK <75 x 10^9, vid provtagning dag 21 eller 22 skall behandlingen skjutas upp tills dessa värden uppnåtts. Om kuren skjuts upp 2 veckor eller mer, skall dosreduktion övervägas för efterföljande kurer. Om LPK <1.0 x 10^9 uppmätts under mellanperioden, så skall dosreduktion övervägas för efterföljande kurer.
Ta blodstatus dag 12 (nadir).
Cykelintervall 21 dagar.
Efter kur: Antiemetikaschema nr 4

DAG 1 beställt till kl ________ avvakta ja nej — **Ssk.sign** **Läk.sign**

Inj Navoban 5 mg iv
Inj Betapred 8 mg iv

Inf Epirubicin__________ mg iv i 500 ml NaCl. Inf tid 1 tim — Start

Inj 5-FU________ mg iv bolus. Inj tid 2 min

Inf Cyklofosfamid__________ mg iv i 250 ml NaCl. Inf tid 15 min — Start

Dose reduction or delay allowed for low blood cell counts

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Dosing of Chemo based on BSA….

1

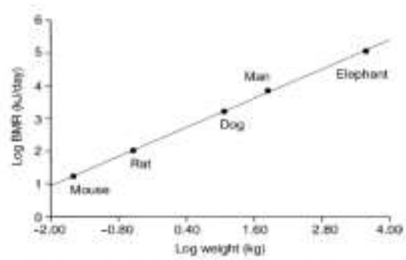

Fig. 2. Linear correlation between basal metabolic rate (BMR) (expressed in kJ/day) of several species and their weight (expressed in kg), known as the 'mouse-elephant curve'.

2

Crawford JD *et al*. Simplification of drug dosage calculations by application of the Surface Area principle. *Pediatrics* 1950, 5, 783-790.
Pinkel D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. *Cancer Res* 1958, 18, 853-6.
->Determination of pediatric and adult dosing

3

Pharmaceutical Industry; need to find model to transfer Preclinical tox data (LD10 or LD50) to phase 1 dosing

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Table I. Frequently used BSA formulas (in chronological order)

Study	Population size	Formula
DuBois and DuBois (1916) [1]	9	BSA (m²) = 0.20247 × height (m)$^{0.725}$ × weight (kg)$^{0.425}$ or BSA (m²) = 0.007184 × height (cm)$^{0.725}$ × weight (kg)$^{0.425}$
Boyd (1935) [2]	147	BSA (m²) = 0.0003207 × height (cm)$^{0.3}$ × weight (g)$^{(0.7285 - 0.0188 \times \log g)}$
Gehan and George (1970) [3]	401	BSA (m²) = 0.0235 × height (cm)$^{0.42246}$ × weight (kg)$^{0.51456}$
Haycock et al. (1978) [4]	81	BSA (m²) = 0.024265 × height (cm)$^{0.3964}$ × weight (kg)$^{0.5378}$
Mosteller (1987) [5]	na*	BSA (m²) = √([height (cm) × weight (kg)]/3,600) or BSA (m²) = √([height (in) × weight (lbs)]/3,131).

* This formula is a modification of the Gehan and George [3] formula.
This information has partly been derived from http://www.halls.md/body-surface-area/bsa.htm

Nomogram (from DuBois and DuBois)
Simple dosage/BSA calculator rulers
Smartphone or web apps

Ron H.J. Mathijssen *et al.* The Oncologist 2007;12:913–923

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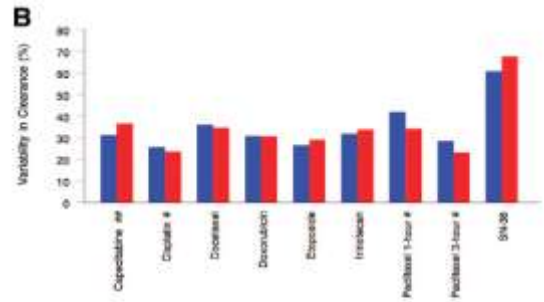
Variability – effects of BSA correction

Table 2
Variability in absolute and BSA-corrected clearance of several anticancer drugs

Drugs	Absolute		BSA-corrected		Patients (n)	References
	CV%	Clearance* (l/h)	CV%	Clearance* (l/h/m²)		
Cisplatin	25.6	87.1 ± 14.7	23.6	50.7 ± 7.25	268	[10]
Cisplatin	26.8	86.3 ± 13.1	24.5	50.8 ± 7.54	391	*
Cyclophosphamide	54.8	4.10 ± 2.25	59.2	2.38 ± 1.41	16	*
Doxorubicin	26.9	74.2 ± 20.0	24.4	38.9 ± 9.51	44	*
Etoposide	22.8	2.25 ± 0.51	21.0	1.36 ± 0.29	25	*
Irinotecan	32.1	33.6 ± 10.8	34	17.9 ± 6.1	82	[15]
Methotrexate	36.6	0.14 ± 2.98	34.9	4.45 ± 1.56	23	*
Topotecan	42	194 ± 80.4	38	103 ± 39.0	112	[17]

Interpatient variation in clearance was calculated as the standard deviation divided by the mean and expressed as a percentage (CV%). CV, coefficient of variation.
* All data are represented as means ± standard deviation.
* Unpublished work by Sparreboom and colleagues.



B: Ron H.J. Mathijssen *et al.*
The Oncologist 2007;12:913–923

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Guidelines for dosing from FASS

Drug	Dosing by				Adjustment for		
	Fixed	BSA	Weight	GFR	Renal	Liver	Other
Cyclophosphamide		x	x				
Chlorambucil			x		(x)	(x)	
Melphalan		x	(x)		x		
Iphosphamide		x	(x)		(x)	(x)	
Busulfan			x				
Lomustin		x					
Temozolomid		x					
Dacarbazine		x			(x)		
Metotrexat		x			x		
Pemetrexed		x			(x)	(x)	
Fludarabin		x			x	(x)	
Cytarabin		x				x	
Fluorouracil		x			x	x	
Gemcitabin		x			(x)	(x)	
Capecitabin		x			(x)	(x)	
Vinkristin		x				(x)	
Vinorelbin		x				(x)	
Paclitaxel		x				(x)	
Docetaxel		x				(x)	
Irinotekan		x			(x)	x	
Etoposid		x			x		(Alb)
Doxorubcin		x					
Epirubicin		x				x	
Bleomycin		x			x		
Mitomycin		x			(x)	(x)	
Cisplatin		x			CI	(x)	
Carboplatin		(x)		X	X	(x)	
Oxaliplatin		x			(x)		
Imatinib	x					x	
Bortezomib		x			(x)	(x)	
Erlotinib	x					(x)	
Sunitinib	x						
Sorafenib	x						
Rituximab		x					
Trastuzumab			x				
Alemtuzumab	x						
Cetuximab		x					
Bevacizumab			x				

Note:
All doses of drugs may be reduced if side effects occur.
Only Temozolomide (and maybe cetuximab) may be increased in the absense of side effects (according to the label)

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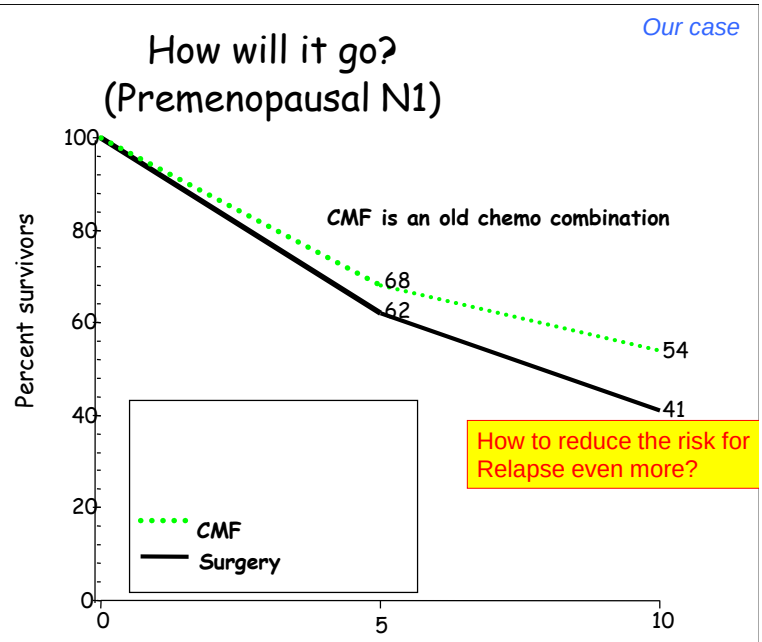
Our case



How to reduce the risk for Relapse even more?

Prof Carl Blomqvist, Helsingfors Universitetssjukhus, Finland

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Figure from http://evb.kleska.com

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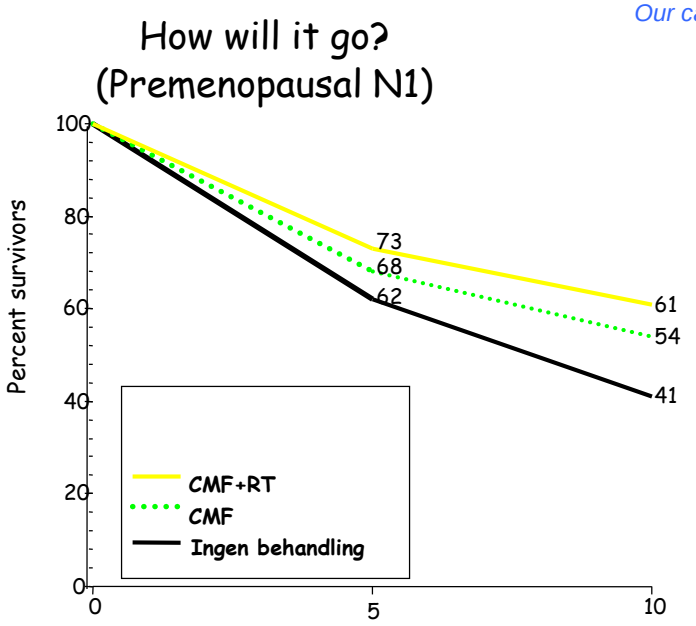
Our case



Prof Carl Blomqvist, Helsingfors Universitetssjukhus, Finland

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There is a slow but steady progress in the treatment results

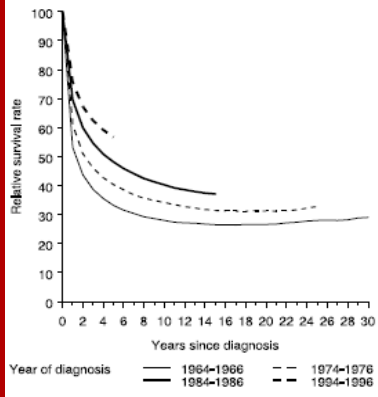

Fig. 3. All sites combined, cumulative relative survival rates by year of follow-up. Males 0–89 years of age.

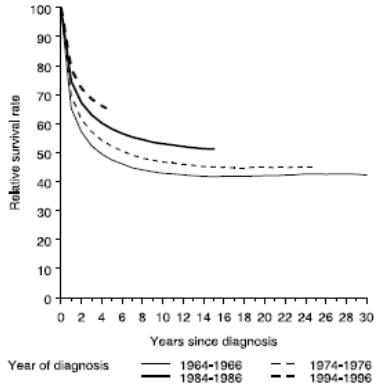

Fig. 4. All sites combined, cumulative relative survival rates by year of follow-up. Females 0–89 years of age.

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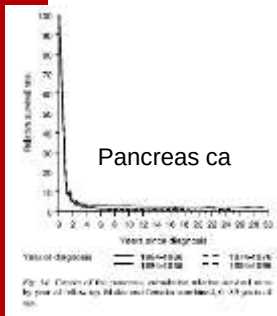
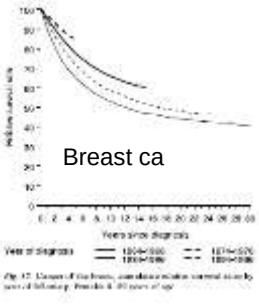
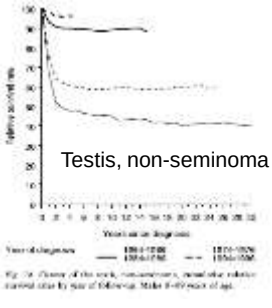
Different diseases have different results



Pancreas ca



Breast ca



Testis, non-seminoma

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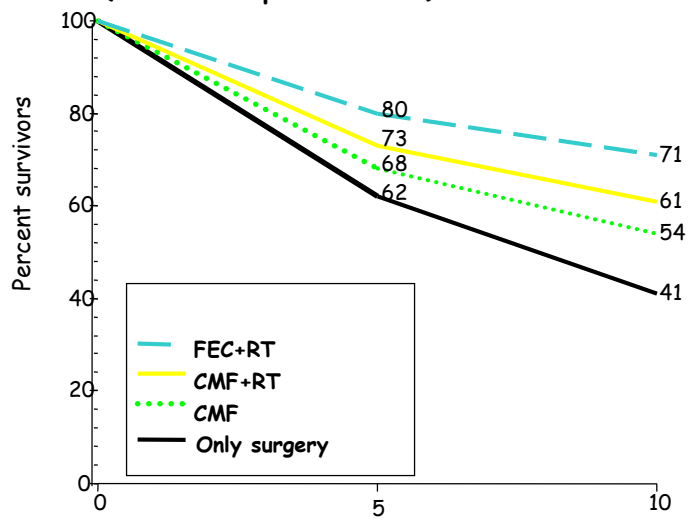
Our case

How will it go? (Premenopausal N1)



Prof Carl Blomqvist, Helsingfors Universitetssjukhus, Finland

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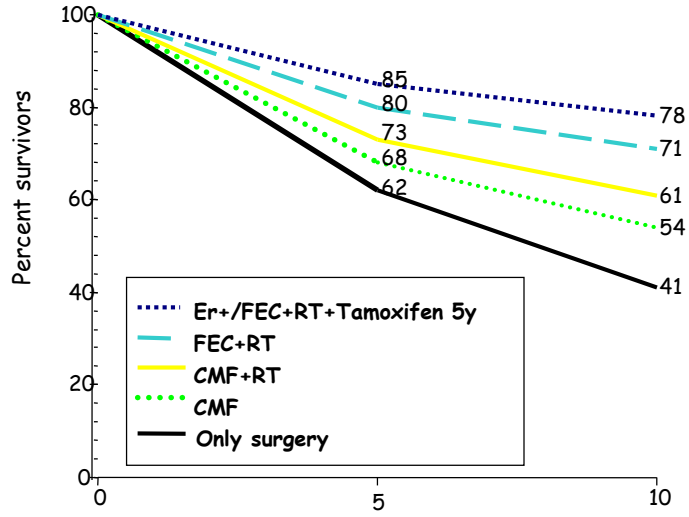

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Our case

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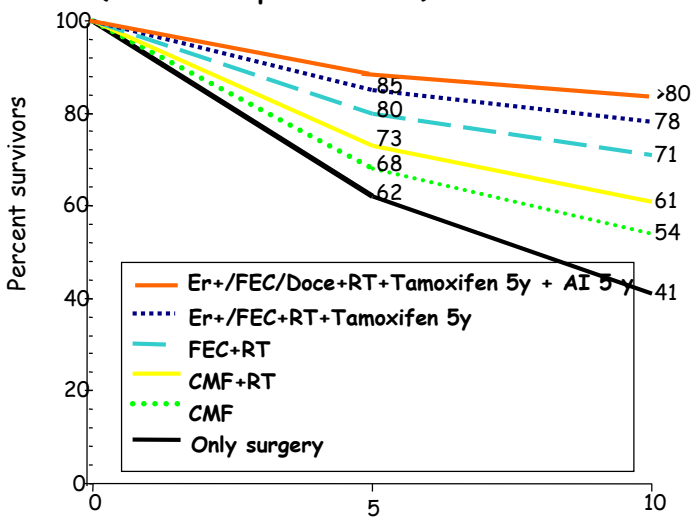

Prof Carl Blomqvist, Helsingfors Universitetssjukhus, Finland

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Yesterday´s therapy?

-Surgery and radiotherapy are very important options for localized disease
-Chemotherapy curative for some (leukemia, lymphoma, testicular ca), very important as adjuvant treatment or in the palliative setting

Side effects are very common; myelosuppression most often dose limiting toxicity and if the cycle intensity important (e.g. R-CHOP14) G-CSF is used

Chemotherapy is most often given
-Intravenously
-In cycles of 3 weeks (1-4)
-With supportive therapy to reduce side effects

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Is the future Target Specific Treatment…

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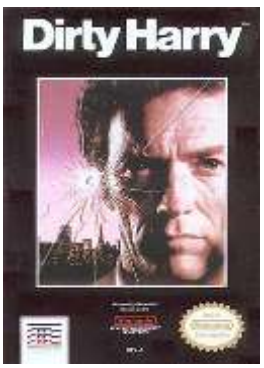
…or Dirty Drugs…



”A dirty disease needs dirty drugs”

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…or both?

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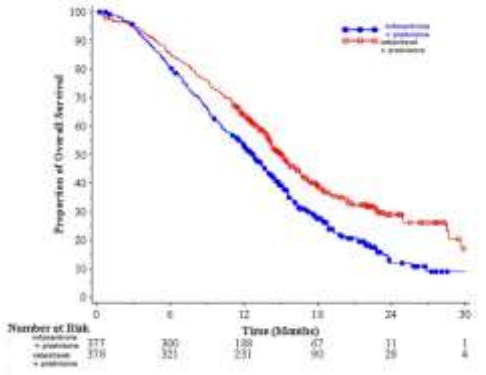
Tomorrows therapy?

Still chemotherapy is needed!

New chemo is developed and marketed, but not as frequently as new targeted agents

E.g.
Bendamustin
Cabazitaxel
Vinflunine
Eribulin
Trabectidin

Abraxane



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Todays/Tomorrows therapy? Targeted therapies

-Tyrosin kinase inhibitors (TKI) and downstream targets, including mTor-inhibitors

-Angiogenesis inhibitors

-Antibodies
i) Surface antigens
ii) Receptors

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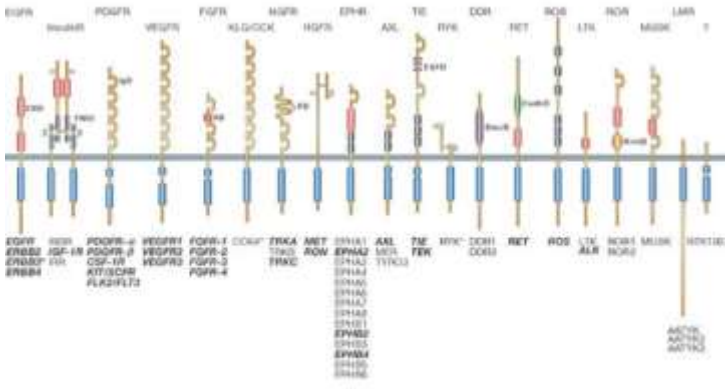
Tyrosine kinase coupled receptors



Blume-Jensen and Hunter, Nature, 2001

Membrane bound TK-R are often mutated in cancers – gives a mitotic signal to the cancer cell

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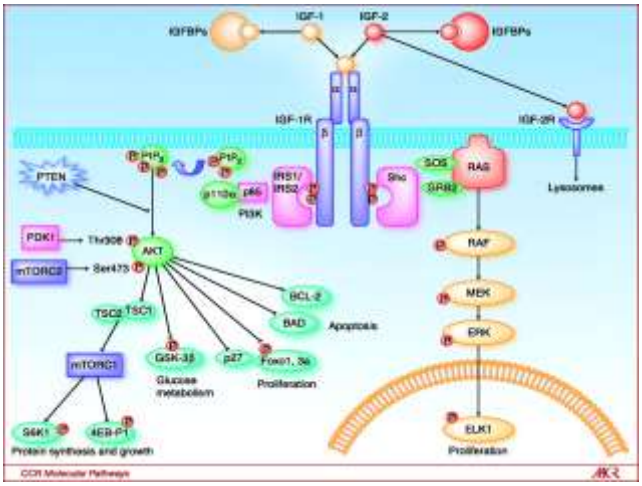
Downstream signalling from RTK -Novel targets!



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Examples of TKI (growing field)

Imatinib: bcr/Abl, PDGFR, cKit (Ph+KML, Ph+ ALL, cKit+ GIST)
Gefitinib: EGFR (NSCLC EGFR+)
Erlotinib: EGFR (pancreas cancer, NSCLC)
Sunitinib: multi TKI (GIST, renal cancer, pNET)
Sorafenib: multi TKI (renal and liver cancer)
Dasatinib: bcr/Abl, PDGFR, cKit (KML, Ph+ ALL)
Lapatinib: HER-2 (Herceptin resistant HER2+ breast ca
Nilotinib: bcr/Abl, PDGFR, cKit (imatinibresistant KML)
Pazopanib: multi TKI (renal cancer)

Some TKI are well tolerated (e.g. Imatinib); some have problematic side effects (hematotoxicity, nausea, diarrhea, skin and hair, cardiac etc).
Oral treatment continuous or with drug free íntervals

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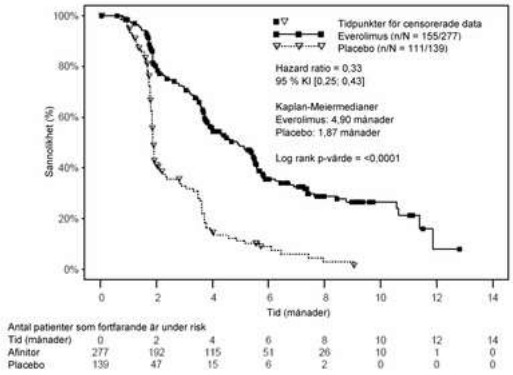
mTor-inhibitors

Everolimus (Afinitor), Temsirolimus (Toricel)
renal cell cancer, mantle cell lymphoma
and some sarcomas



Afinitor second line
PFS renal cell after
TKI

Side effects comparable to chemotherapy

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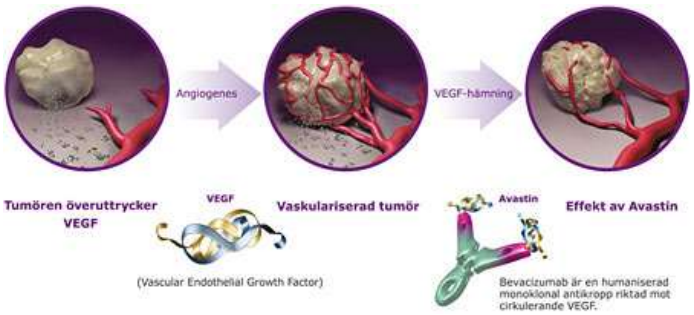
Angiogenesis inhibition e.g. bevacizumab



TKI inhibiting VEGF-R
Sunitinib, Sorafenib

Talidomid
Lenalidomid
Myeloma, lymphoma.
Studies for solid tumors

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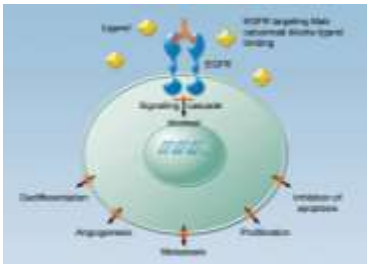
Antibodies

-Surface antigens – cell specific

Rituximab binds to CD20 on B-lymphocytes and activates both the complement system and the cell mediated cytotoxicity to destroy the B-cell

– receptors (e.g. EGFR)



MOA
-blocking the TKR signal
-complement activation
-cell mediated cytotoxicity

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Tomorrows therapy today – where are we going?

- Individualized therapy
- Genomics and proteomics are incorporated in the clinic
- Biomarkers
- New targets
- Antibody conjugates
- IMMUNOTHERAPY

Still very few cures after disseminated disease (?) but tendency to establish 'chronic disease'

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Therapy adapted for each individual patient (tumor)

- To some extent used already
  -ER status, HER-2 status
  -EGFR-status (+/-, mutated/un)
  -KRAS (colorectal)
  -bcr/abl (CML, AML)
  -cKit
  -CD20 (lymphoma)

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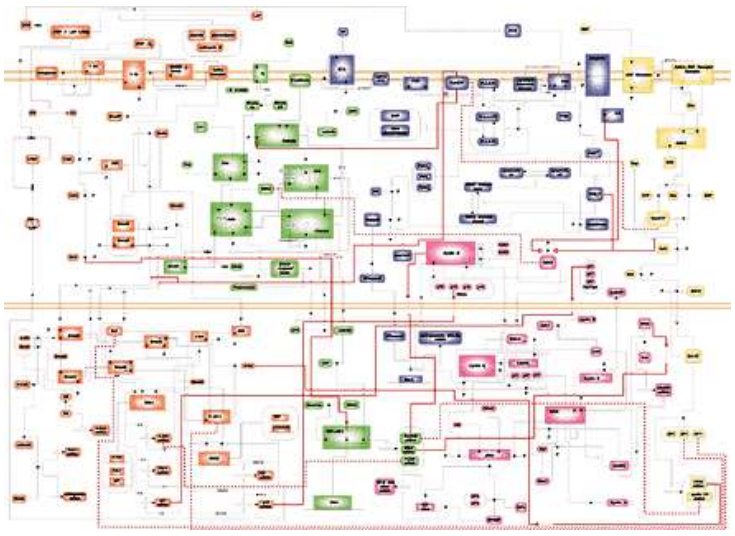
What every Oncologist should know for each patient ?



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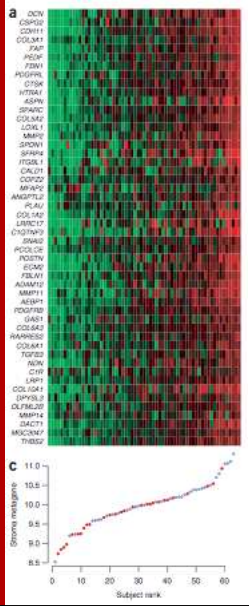
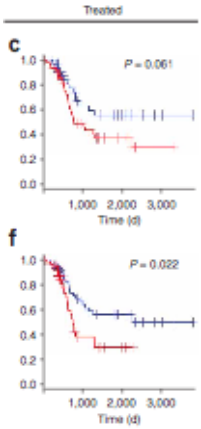
Multivariate analysis

Breat cancer – use of neoadjuvat chemo





Proliferation genes

Stroma genes

Nat Med. 2009 Jan;15(1):68-74. A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. Farmer P, et al

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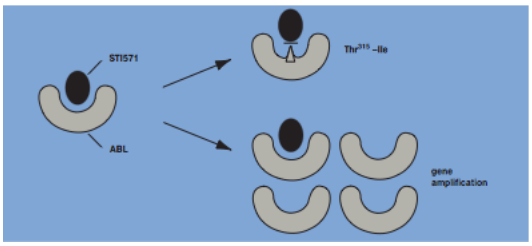
Therapy adopted to each situation



Point mutation
=
Change TKI

Increased expression
=
Increase the dose

Detailed analysis of each patient at diagnosis and progression
The techniques are available…

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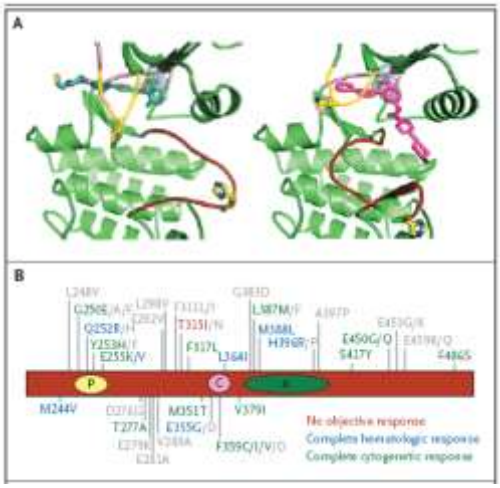

Dasatinib in Imatinib-Resistant Philadelphia Chromosome–Positive Leukemias
Moshe Talpaz et al. N Engl J Med 2006; 354:2531-2541

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Some examples of novel targeted agents accompanied by biomarker assays

- ALK-inhibitors (crizotinib)
- BRAF-inhibitors (vemurafenib, dabrafenib)
- PARP-inhibitors
- Antibody conjugates (potent cytotoxins or radioisotopes)

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ALK

- Anaplastic Lymphoma Kinase (EML4-ALK), fusion mutated oncogene
- 10 % NSCLC
- Found also in lymphoma, sarcoma

- In development: PF02341066 (crizotinib), AF802, LDK378, TAE684

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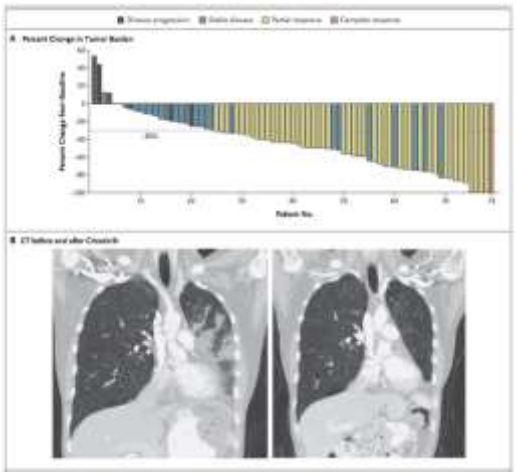
N Engl J Med. 2010 Oct 28;363(18):1693-703.
Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer.



Crizotinib
1500 pat screened,
82 ALK-positive
Dose esc phase I

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PARP

- DNA-repair
- Olaparib, Iniparib, Veliparib, MK-4827
- Single agent treatment or combos with DNA damaging chemo (e.g. platinum)
- In particular with BRCA mutated breas- and ovarial cancer (”synthetic lethality”)

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Lancet. 2010 Jul 24;376(9737):245-51. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial.

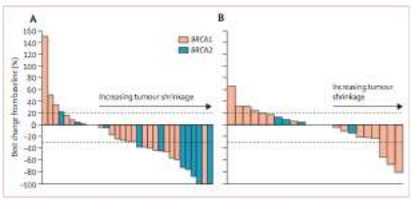

Figure 2: Best percentage change from baseline in target lesion size by BRCA mutation genotype in the intention-to-treat population
(A) Olaparib 400 mg twice daily. (B) Olaparib 100 mg twice daily. Two patients on olaparib 400 mg twice daily and one patient on olaparib 100 mg twice daily have been excluded because they died before Response Evaluation Criteria In Solid Tumors assessment. Reference lines indicate boundaries for progressive disease (20%) and partial response (–30%).

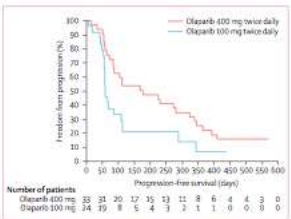

Figure 3: Kaplan-Meier curves of progression-free survival for the intention-to-treat population
Progression-free survival is shown for each of the two cohorts, which ran in sequence.

One-armed phase II study in 33 (300 mg) + 24 (400 mg) patients

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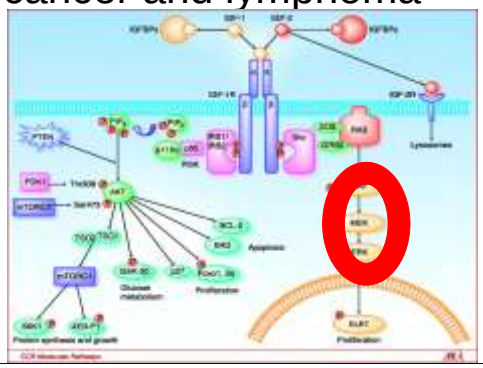
B-RAF

- Oncogene in growth factor signalling cascade, often mutated in melanoma, colorectal ca, NSCLC, papillary thyroid cancer and lymphoma



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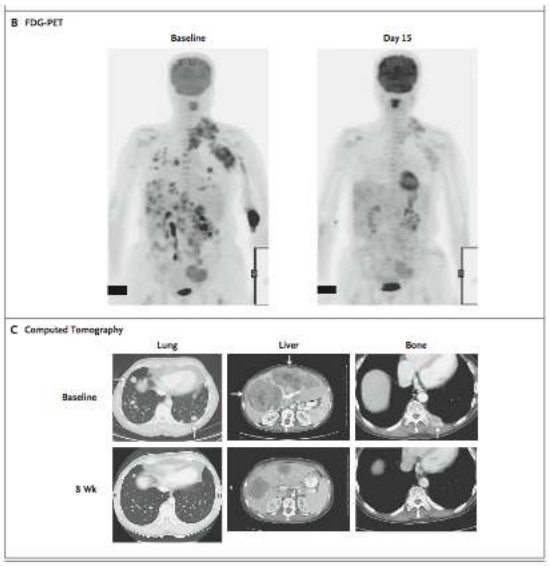
N Engl J Med. 2010 Aug 26;363(9):809-19.**Inhibition of mutated, activated BRAF in metastatic melanoma.**



PLX4032
Vemurafenib

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Antibody conjugates

- Tumor antibody coupled to very potent cytotoxin or radionuclide
- Most results with DM1 (=Emtansine) or Mertansine

-Bivatuzumab mertansine (CD44 SCC)

-Cantuzumab mertansine (CanAg colorektal)

-Lorvotuzumab mertansine(CD56 myeloma, Ovarial ca, NSCLC)

-Trastuzumab-DM1 (HER-2 breast ca)

-Brentuximab vedotin = SGN-35 (CD30 lymphom)

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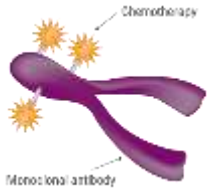

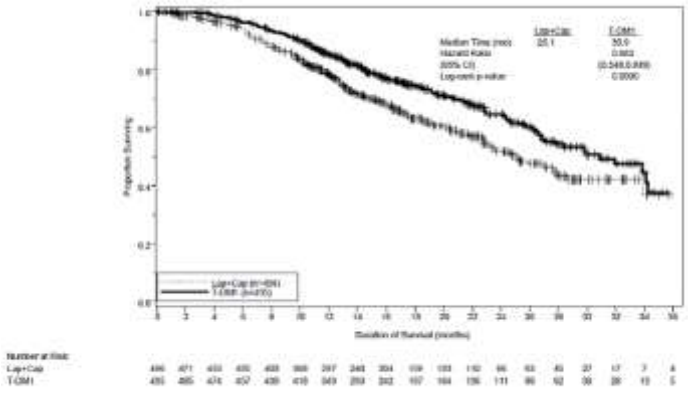

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Immunooncology

- The most rapidly expanding area of oncology right now.
  - BCG-instillation for bladder cancer
  - Allogenic stem cell transplantation
  - Interferon
  - Low dose radiotherapy or chemotherapy
  - Vaccines (HPV16 etc)
  - Monoclonal antibodies
  - CAR-T and other T-cell therapies
  - Immun-checkpoint inhibitors

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Immune-checkpoint

- Regulates the immune defence
- Interplay between several co-stimulatory and inhibitory factors
- Essential to suppress autoimmunity
- But also a way for tumor cells to evade the immune system ”camouflage”

Tumor cells make themselves invincible (”tumor escape”)

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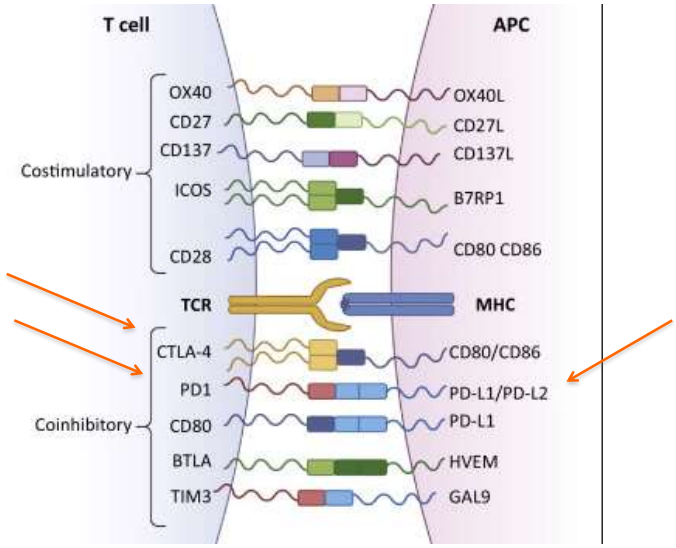
Immune checkpoints



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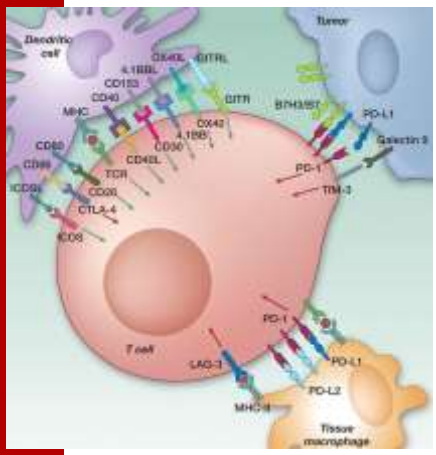
PD-1



•PD1-is a co-inhibitory factor expressed on activated T-cells

•When PD-1 interacts with PD-L1 and PD-L2 the effector T-cells are inhibited

•Expression of PD-L1 on tumor cells and/or stroma cells (macrophages) may supress ”immune surveillance” and facilitate cancer growth

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Immune checkpoint inhibitors

- Ipilimumab – CTLA4
- Nivolumab – PD1
- Pembrolizumab – PD1

- Approved for malignant melanoma, squamous cell lung carcinoma
- Likely approved for many more indications during 2016-2017
- Numerous of antibodies in development incl those targeted against PDL1/L2

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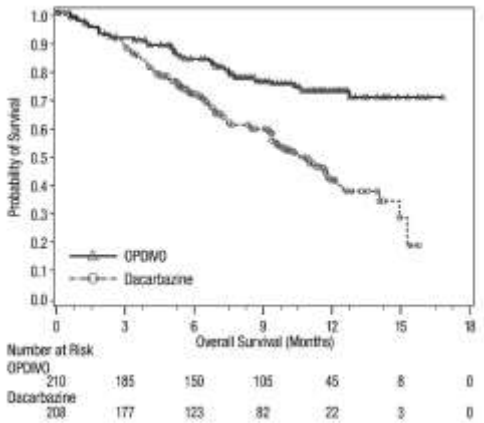

-Dramatic effects in some tumors
-Side effects common and may be problematic (pneumonitis, hepatitis, colitis, nephritis hypophysitis)
-Cost issue!

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Questions

- Is hematotoxicity the most common dose limiting effect of chemotherapy?
- Is adjustment by BSA an ideal method to reduce variability in PK among patients?
- Does the introduction of targeted agents increase the demands for validated molecular pathology assessments of tumor material for each patient?

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Thanks for listening!