EUROPEAN FEDERATION FOR COLORECTAL CANCER

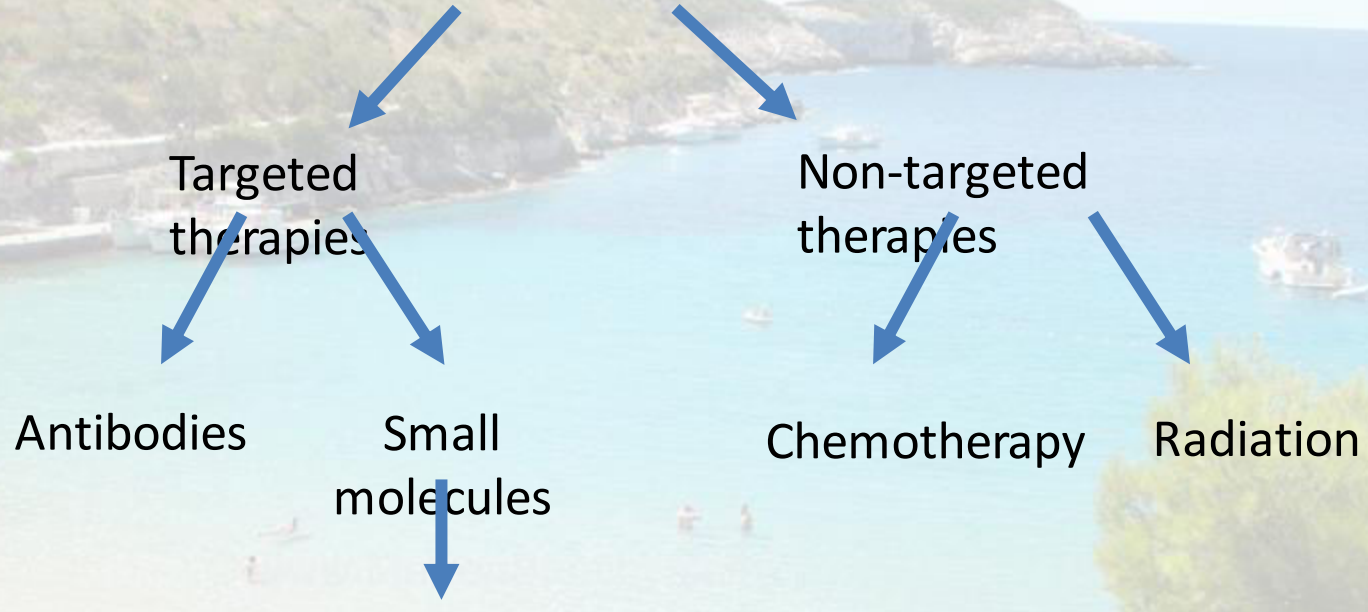
MEDIZINISCHE UNIVERSITÄT WIEN

Targeted Therapy beim Rektumkarzinom - moderne Strategien der systemischen Therapie

Dr. Irene Kührer

MUW, Wien

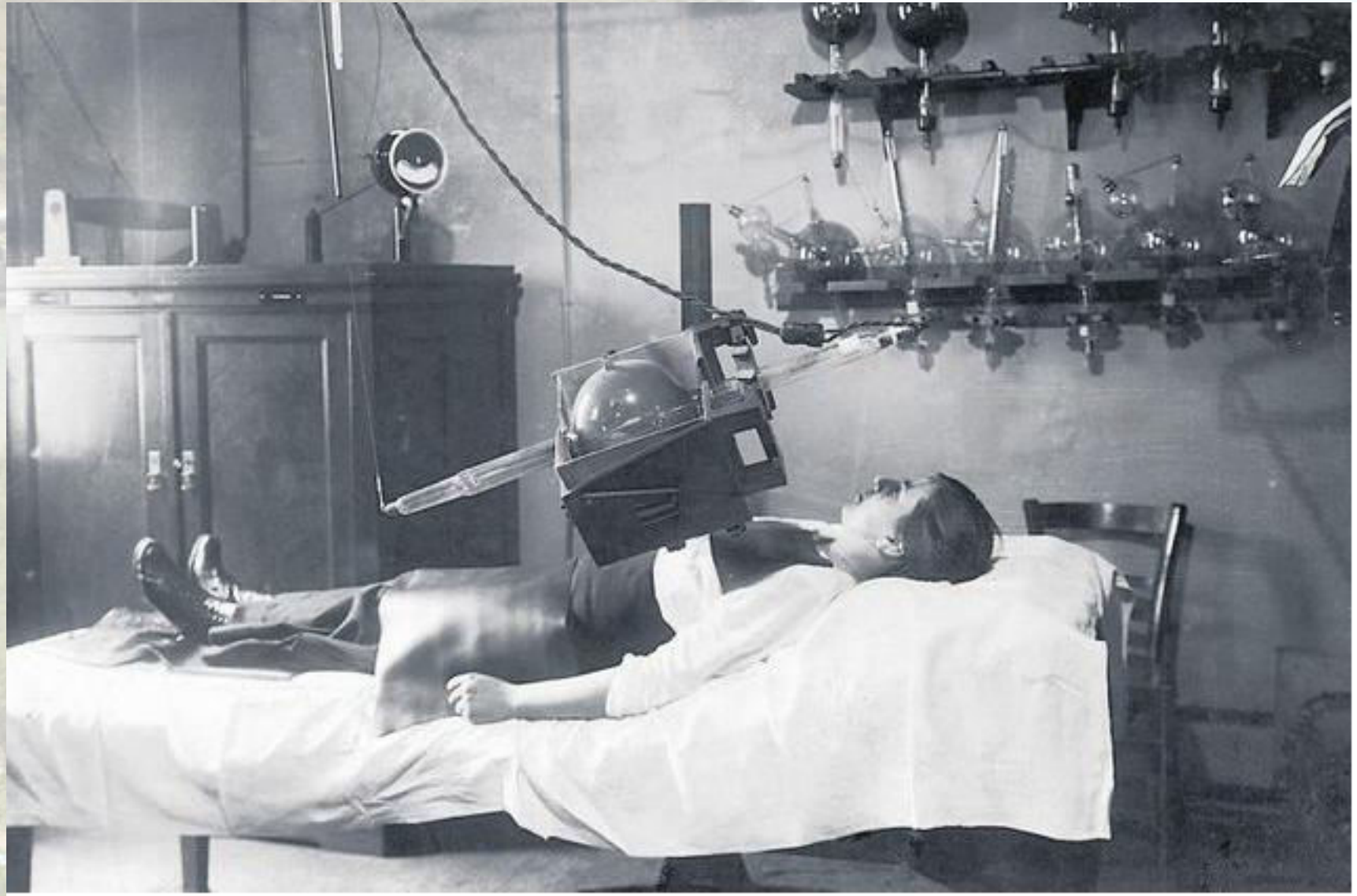
Cancer Treatment



Small molecule compounds are typically developed for targets that are located inside the cell since such agents enter cells relatively

Advantages	Disadvantages
• Low cost of production	• Limited number of small molecules can be synthesized • Not specific • Cancer cells can develop resistance • Multiple side effects

Mediziner stellen 1846 eine der ersten Operationen nach, in der Äther als Narkosemittel eingesetzt worden ist. Die Aufnahme entstand in einem Bostoner OP-Saal mit dem Fotografie-Verfahren der Daguerreotypie. © *Hulton Archive/Getty Images*



Behandlung eines Krebspatienten mittels Röntgenbestrahlung im Berliner Krebsforschungsinstitut, 1917. Bild: «Süddeutsche Zeitung»

5-y Overall Survival

First author, year (reference)	No. of patients	Stage	No. of lymph nodes	5-y overall survival, %	HR or RR* (95% CI)	P
Caplin, 1998 (21)	222	Dukes' B	<7	49	–	.001†
			≥7	68		
		Dukes' C	<7	N/A		.7
			≥7	N/A		
Law, 2003 (24)	115	II	<7	62	2.99 (1.28 to 6.97)	.03†
			≥7	86	‡	
Cianchi, 2002 (22)	140	II	<9	54.9	2.67 (1.26 to 5.67)	<.001†
			≥9	79.9	§	
Yoshimatsu, 2005 (27)	94	Dukes' B	<9	67	–	.028†
			≥9	87		
Gumus, 2005 (23)	80	II	<9	72‡	–	.353†
			≥9	85		
	99	III	<9	55.7		.011†
			≥9	78		
Berberoglu, 2004 (20)	301	II	<11	47	2.8 (1.6 to 5.2) ‖	<.001†
			≥11	81		
Goldstein, 2002 (6)	745	II	≤7	62	–	.018†
			8–12	68		
			13–17	71		
			≥18	76		
Sarli, 2005 (7)	480	II	<10	51	1.50 (1.01 to 2.23)	<.045¶
			10–19	69	¶	
			>19	71		
Wong, 2002 (26)	173	II	11.3	–	–	<.001#
			22.6			
Ratto, 1999 (25)	487	I–II	11.4	83		.04**
			29.4	91		
		IIIA		58.9		.06
				84.2		

Lines of therapy

- Neoadjuvant
- Adjuvant
- Pseudoadjuvant
- First line, 2nd line, 3rd line

- Curative
- Controll of symptoms
- Palliation

- Resectable disease (in lung and liver, peritoneum?)
- Agressive disease
- Indolent disease

*THE MODE OF ACTION OF 5-FLUOROURACIL AND ITS DERIVATIVES**

By Seymour S. Cohen, Joel G. Flaks, Hazel D. Barner,
Marilyn R. Loeb, and Janet Lichtenstein

DEPARTMENTS OF BIOCHEMISTRY AND PEDIATRICS, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, PHILADELPHIA

Communicated by David R. Goddard, August 15, 1958

In 1954 this laboratory described experiments on the lethal consequences of thymine deficiency in growing bacteria.[1] It was shown that when various strains of *Escherichia coli* were permitted to metabolize and grow under conditions of thymine deficiency, which prevented the synthesis of deoxyribonucleic acid (DNA), the cells irreversibly lost the power to multiply. In subsequent explorations of

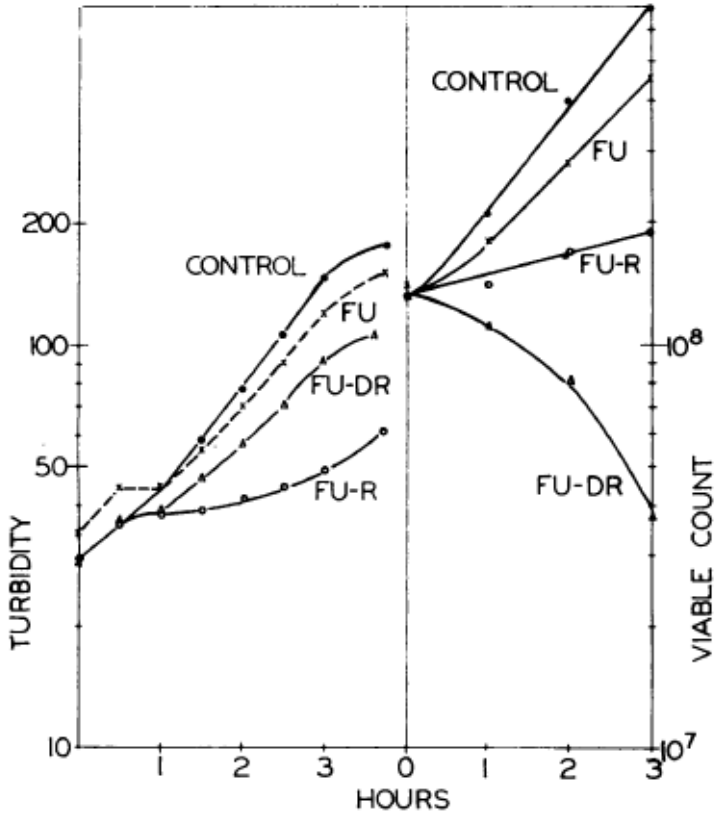


FIG. 2.—The effect of fluorouracil and its nucleosides (0.089 μmoles/ml) on the growth and multiplication of a uracil-requiring strain of *E. coli*.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levamisole and Fluorouracil for Adjuvant Therapy of Resected Colon Carcinoma

Charles G. Moertel, M.D., Thomas R. Fleming, Ph.D., John S. Macdonald, M.D., Daniel G. Haller, M.D., John A. Laurie, M.D., Phyllis J. Goodman, M.S., James S. Ungerleider, M.D., William A. Emerson, M.D., Douglas C. Tormey, M.D., John H. Glick, M.D., Michael H. Veeder, M.D., and James A. Mailliard, M.D.*

N Engl J Med 1990; 322:352-358 | February 8, 1990 | DOI: 10.1056/NEJM199002083220602

THE LANCET

Articles

Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group‡,

‡ Collaborators listed in the webappendix

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

Thierry André, M.D., Corrado Boni, M.D., Lamia Mounedji-Boudiaf, M.D., Matilde Navarro, M.D., Josep Tabernero, M.D., Tamas Hickish, M.D., Clare Topham, M.D., Marta Zaninelli, M.D., Philip Clingan, M.D., John Bridgewater, M.D., Isabelle Tabah-Fisch, M.D., and Aimery de Gramont, M.D., for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators

N Engl J Med 2004; 350:2343-2351 | June 3, 2004 | DOI: 10.1056/NEJMoa032709

ESMO Guidlines – postoperative therapy

1. Postoperative chemoradiotherapy (e.g. about 50 Gy, 1.8–2.0 Gy/ fraction) with concomitant fluoropyramidine-based chemotherapy is no longer recommended but could be used in patients with positive crm, perforation in the tumour area, defects in the mesorectum, or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given

2. Traditionally, postoperative CRT was recommended for all patients with pT3-4 or N+ tumours, but the routine use of this has been questioned for all pT3N0 tumours

3. In Japan, postoperative adjuvant chemotherapy with uracil- tegafur is considered standard therapy since this treatment improved relapse-free and overall survival

Recommendations

- the routine use of infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPEOX) chemotherapy for a total perioperative therapeutic period (including chemoradiotherapy) of 6 months.
- In the most commonly used treatment paradigm for patients with stage II or III rectal cancer, patients receive preoperative chemoradiotherapy or short-course radiation followed by total mesorectal excision (TME) which is then followed by 4 months of an adjuvant fluoropyrimidine with or without oxaliplatin.

JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Adjuvant Chemotherapy for Locally Advanced Rectal Cancer: Is It a Given?

Theodore S. Hong and David P. Ryan

This Article

Published online before print May 4, 2015, doi: 10.1200/JCO.2015.60.8554

JCO May 4, 2015

Adjuvant Chemotherapy for Locally Advanced Rectal Cancer: Is It a Given?

Adjuvant (postoperative) chemotherapy has been accepted as a component of multimodality therapy for locally advanced rectal cancer for two primary reasons. First, postoperative fluorouracil was associated with an improvement in overall survival (OS) in patients with Dukes' B and C rectal cancer from the era preceding total mesorectal excision.

JCO May 4, 2015
JCO.2015.60.8554

EORTC 22921 /2006

In the study, patients had clinical stage T3 or T4 resectable rectal cancer and underwent preoperative radiotherapy, 45 Gy over 5 weeks; these patients served as controls.

Three other groups (with 253 patients in each) received chemotherapy in addition to radiation.

The postoperative group started chemotherapy 3 to 10 weeks after surgery and received four courses delivered every 3 weeks. A third group of patients received chemotherapy both before and after surgery.

5-year survival

- The 5-year overall survival rate was 65.8% vs 64.8% in the groups with and without preoperative chemotherapy (*P* = .84), respectively, and 67.2% vs 63.2% in those with and without postoperative chemotherapy (*P* = .12).
- The 5-year disease-free survival rates were 56.1% vs 54.4% for the groups with and without preoperative chemotherapy (*P* = .52) and 58.2% vs 52.2% for those with and without postoperative chemotherapy (*P* = .13).

Ten-year follow up

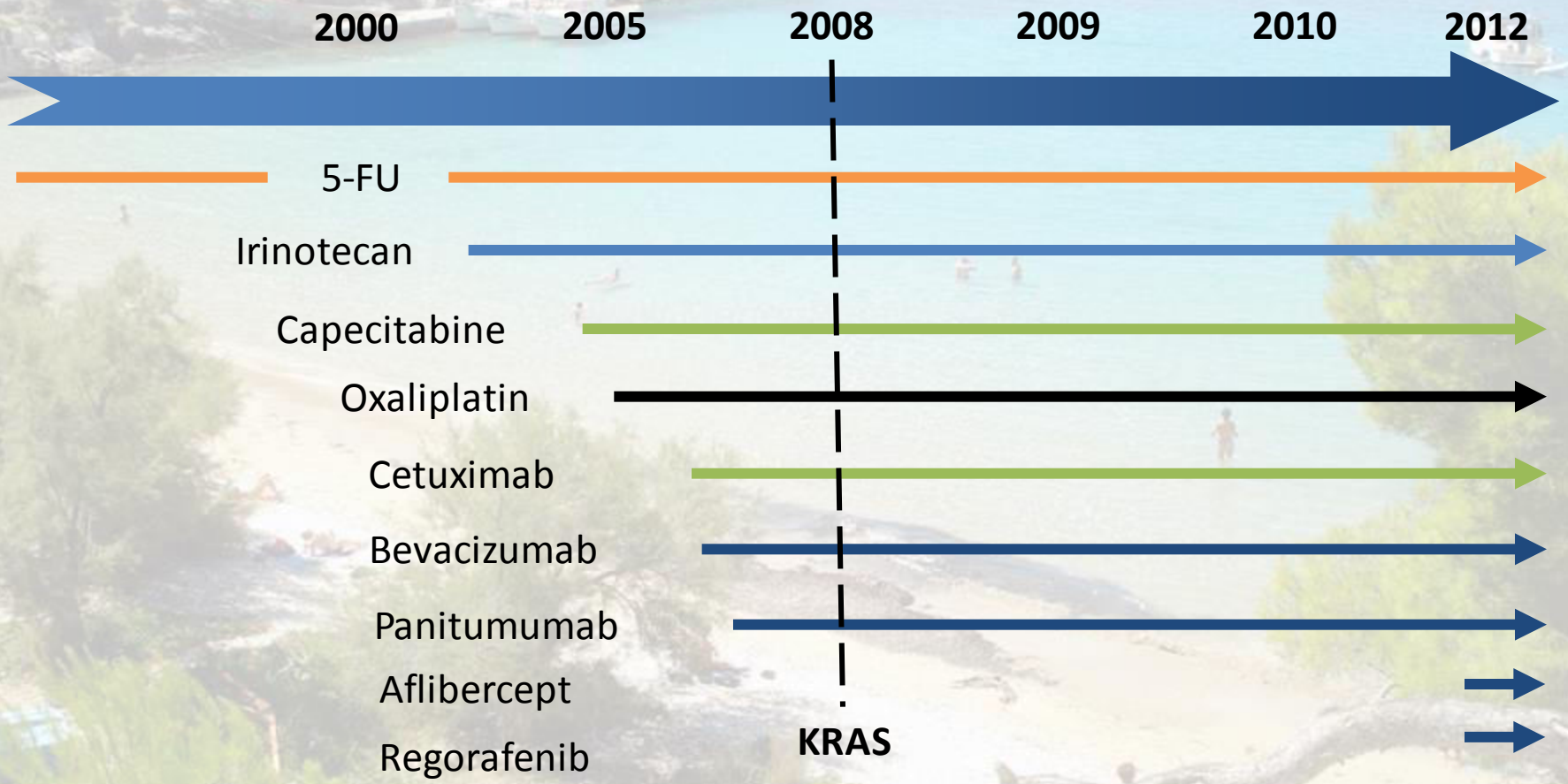
- Ten-year follow-up results, published in 2014, showed that after a median 10.4 years there were no significant differences in either OS (51.8% with adjuvant chemotherapy vs 48.4% without chemotherapy), DFS (47.0% vs 43.7%), or cumulative incidence of distant metastases.

The discussion

There is no decision about postoperative chemotherapy based on what the pathology shows. We base the decision on the clinical stage at the time of diagnosis, and most patients with stage II and III will get adjuvant chemotherapy with FOLFOX or another oxaliplatin-based regimen.

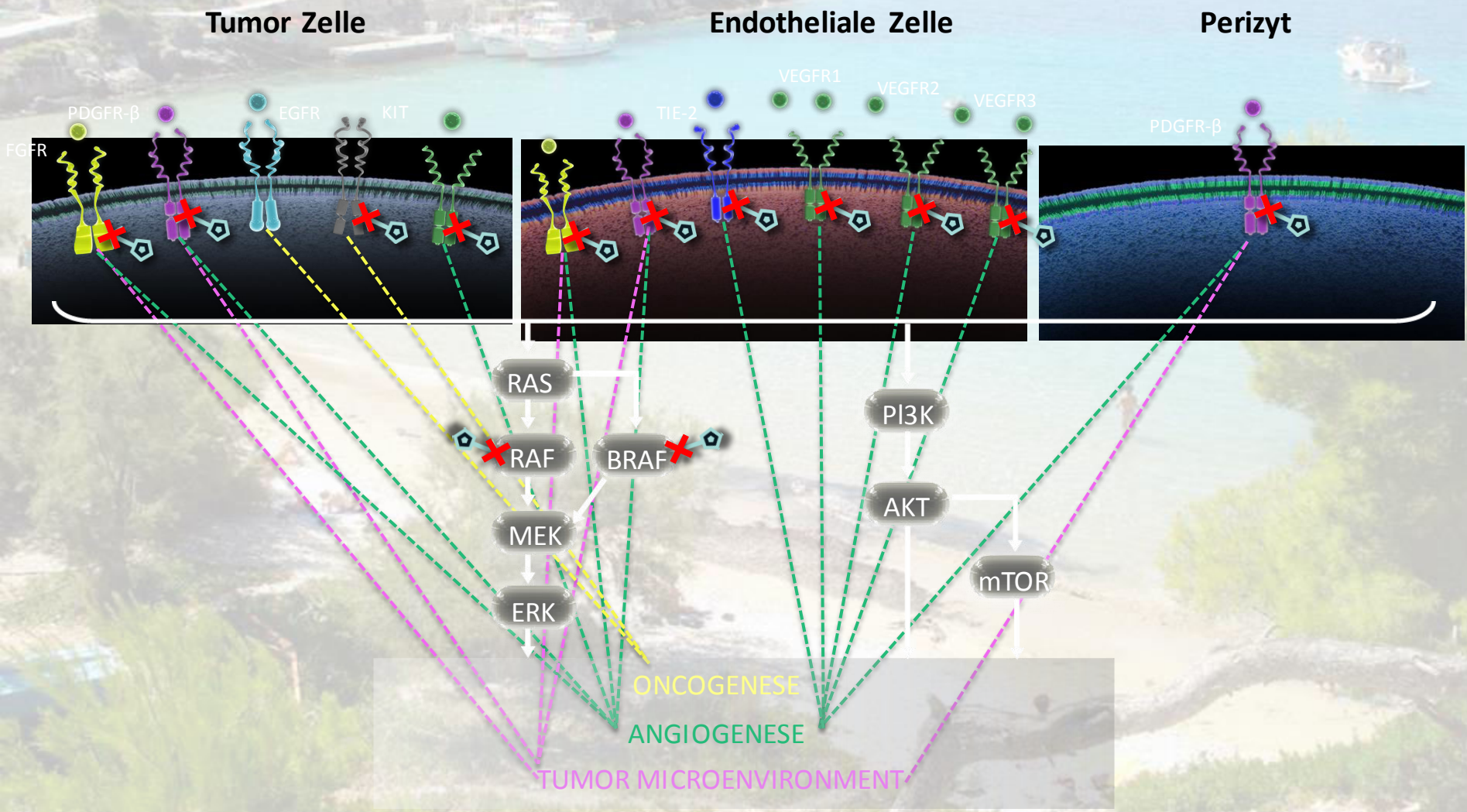
Prognostic markers are needed!

Progress in therapy of CRC



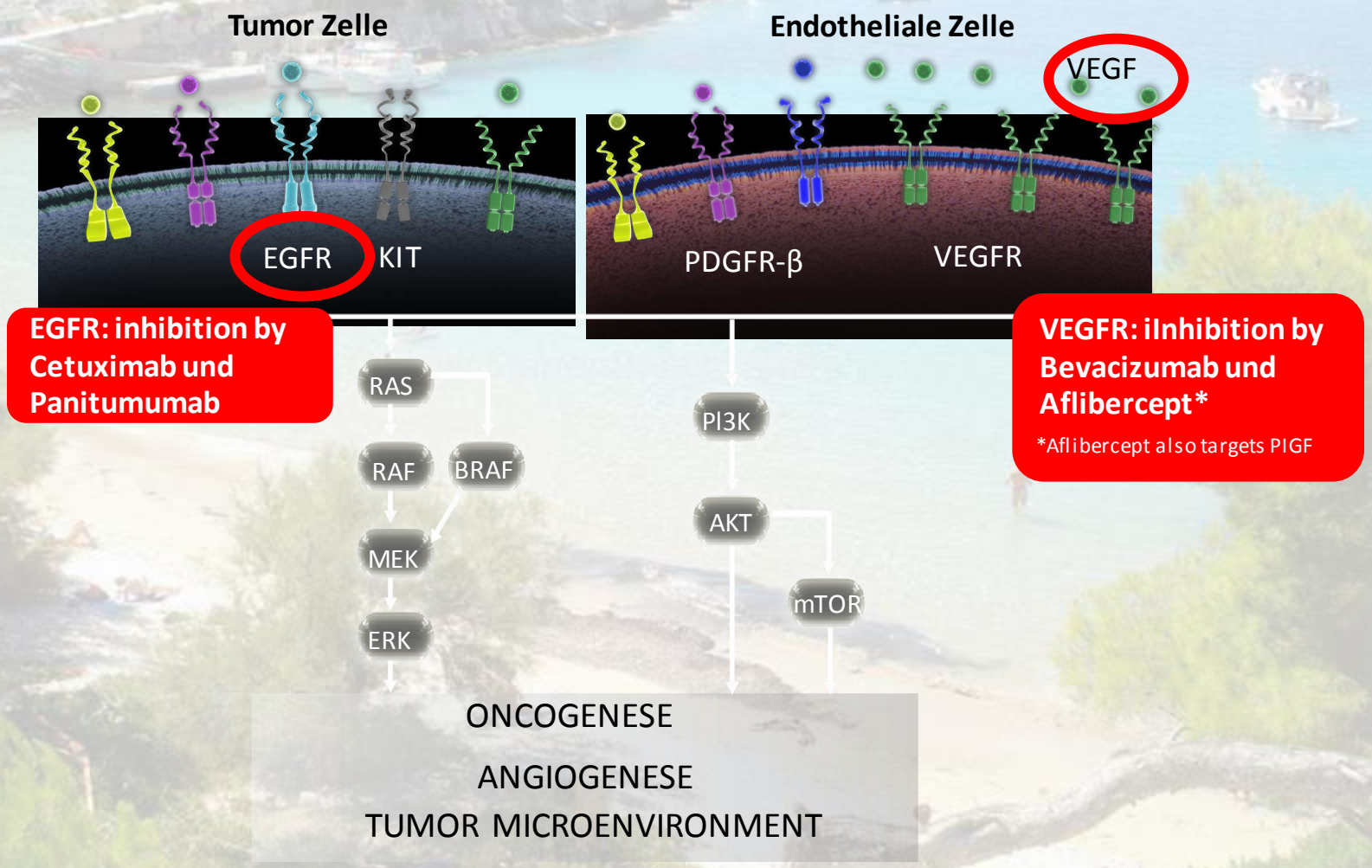
National Cancer Institute. Colon cancer treatment (PDQ). 2012.
National Cancer Institute. Cancer drug information. 2011.

Inhibition of multiple pathways of tumor growth



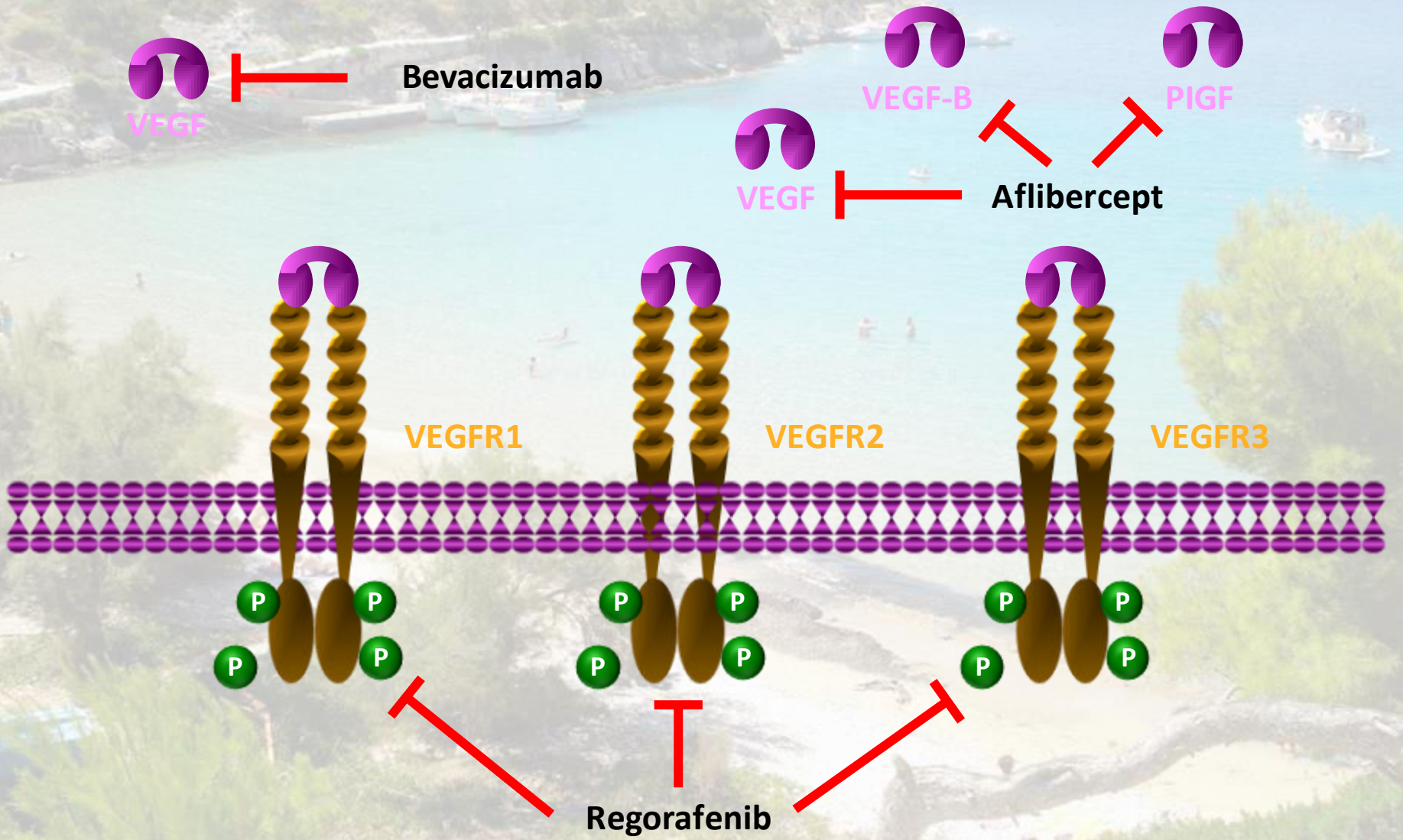
Grothey A, et al. *Lancet*. 2013;381(9863):303-312; Wilhelm SM, et al. *Int J Cancer*. 2011;129:245-255.

AB in the pathway of tumorcontrol



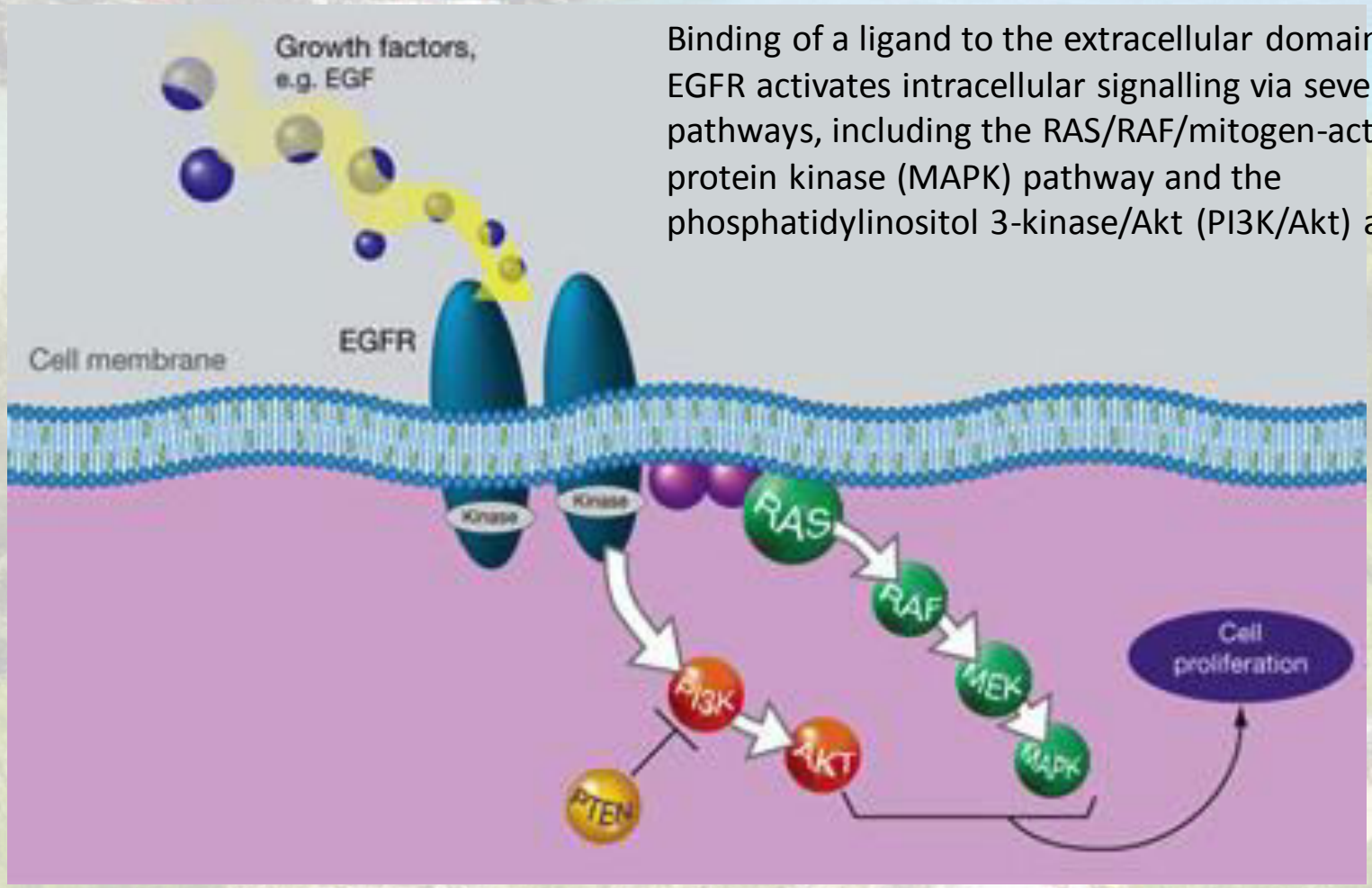
Krasinskas AM. *Patholog Res Int.* 2011;2011:932932; Sitohy B, et al. *Cancer Res.* 2012;72:1909-1914; Bendardaf R, et al. *Anticancer Res.* 2008;28:3865-3870; Kitadai Y, et al. *Am J Pathol.* 2006;169:2054-2065; Lurje G, et al. *J Clin Oncol.* 2005;23:973-981.

Angiogenesis inhibition



Bennen H, et al. *Target Oncol*. 2013;8(2):83-96.

EGFR activation



Binding of a ligand to the extracellular domain of EGFR activates intracellular signalling via several pathways, including the RAS/RAF/mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) axis

Personalization of treatment

- Means the selection of suitable patients

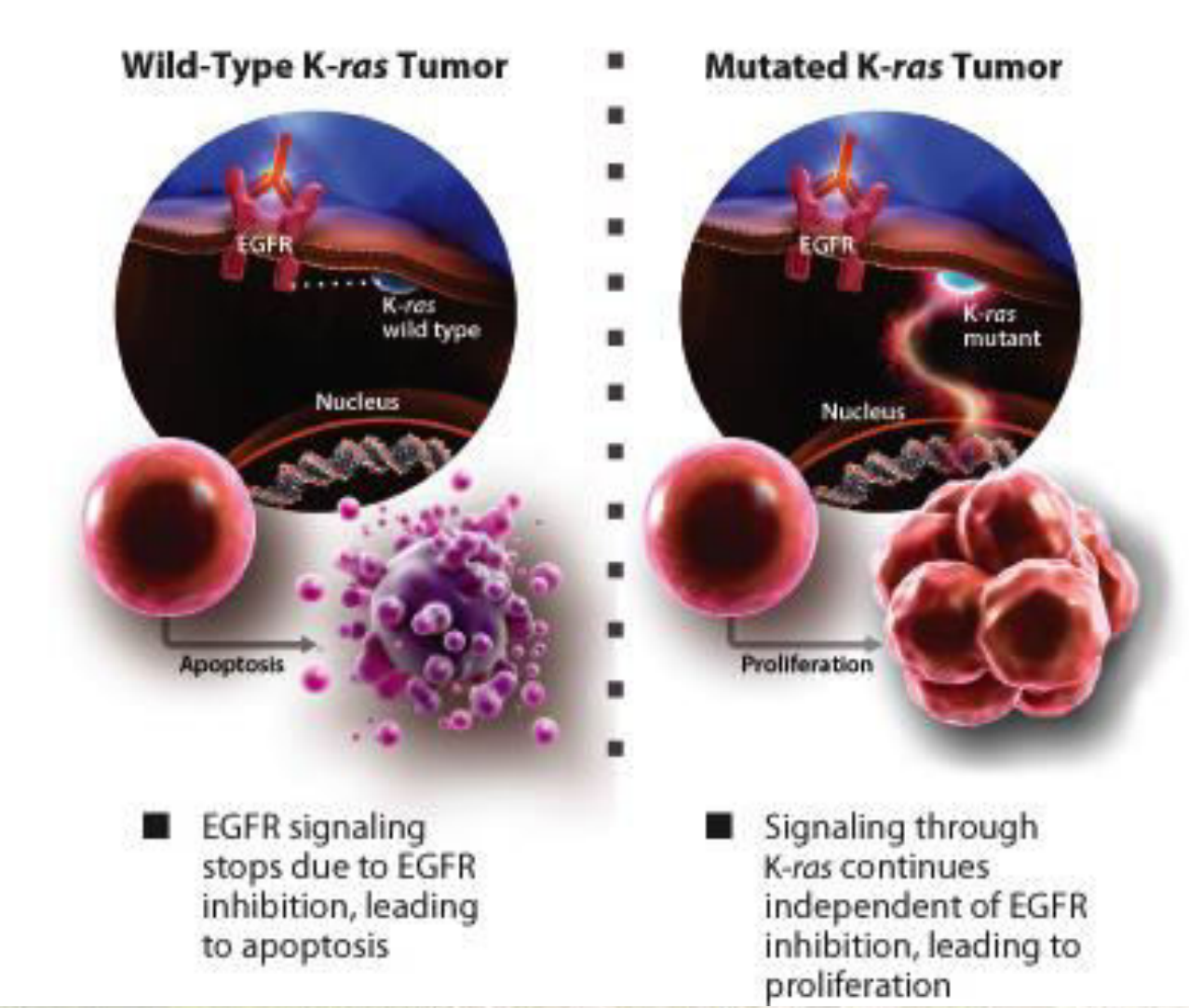
- Prognostic biomarkers identify patients with different disease outcomes.
- Predictive biomarkers help to identify patients who are most likely to benefit from a specific treatment

Table 2: Biomarkers recommended by the European Group for Tumor Markers (EGTM) for use in colorectal cancer (CRC) (Modified from Duffy et al 2013).

Biomarker	Use	Level of Evidence (LOE)	Strength of Recommendation (SOR)
FIT-based FOBT	Screening	I	A
MSI/DMMR	Prescreen for Lynch syndrome	I	A
K-RAS	Predicting response/ Resistance to Anti-EGFR antibodies	I	A
CEA	Postoperative Surveillance	I	A
CEA	Monitoring therapy In advanced disease	III	A
CEA	Prognosis, especially in stage II	III	A
MSI/DMMR	Prognosis especially in stage ii disease	I	A

Mod Modified from Duffy 2013

Predictive marker for response



KRAS status is changing with progression

Autor	Changes in kRAS status
Diaz L et al. 2012	38%
Misale S et al. 2012	60%
Watanabe T et al. 2011	11.6%
Baas J et al. 2011	WT → MT: 14% MT → MT: 5%
Otsuka K et al. 2010	7.4% – 15.4%
Italiano A et al. 2010	5%

Diaz L, et al. Nature. 2012; 486: 537-540. Misale S, et al. Nature. 2012; 486: 532-538.
Otsuka K, et al. Cancer Chemother Pharmacol. 2010; 66(3):605-609.
Watanabe T, et al. Dis Colon Rectum2011;54(9)1170-1178.
Baas JM, et al. Oncologist. 2011;16(9):1239-124
Italiano A, et al. Ann Surg Oncol. 2010;17(5):1429-1434.

The relationship between primary tumor sidedness and prognosis in colorectal cancer

Stage/location of primary tumor	N	Median survival	3-year survival probability %	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Stage IV					
Left	4784	17.0	27	1.0	1.0
Right	7579	8.7	16	1.40 (1.35-1.46)	1.20 (1.15-1.25)
Rectal	4392	17.4	26	0.99 (0.94-1.04)	1.02 (0.97-1.07)
Stage III					
Left	6394	n/a	71	1.0	1.0
Right	13748	59	62	1.39 (1.32-1.46)	1.17 (1.11-1.23)
Rectal	5745	n/a	70	1.02 (0.96-1.08)	1.10 (1.04-1.17)

tumors on the right side are clinically, pathologically, genetically, and molecularly different from those that arise on the left side

Deborah Schrag
J Clin Oncol 34, 2016 (suppl; abstr 3505)

Dr. Kimmie Ng

CALGB/SWOG 80405 Reanalysis ASCO 5.6.2016, abstract 3505

The total patient population with *KRAS* WT mCRC either on the left side (732 patients) or the right side (293 patients)

When the primary tumor location was on the left side of the colon, median survival was significantly longer (33.3 vs. 19.4 months for the right-sided tumors; $p < 0.0001$).

In addition, OS for cetuximab and bevacizumab, each in combination with chemotherapy, were also dependent on the location of the primary tumor.

OS with cetuximab was superior to bevacizumab when the primary tumor was on the left side (36.0 vs. 31.4 months for bevacizumab). A similar trend was seen for PFS (12.4 vs. 11.2 months for bevacizumab).

However, bevacizumab was superior to cetuximab when the primary tumor location was on the right side (OS: 24.2 vs. 16.7 months for cetuximab; PFS: 9.6 vs. 7.8 months for cetuximab).

In an exploratory analysis of patients with *KRAS*-mutant mCRC, location of the primary tumor did not matter.

OS was 23.1 months if the primary tumor was on the right side and 30.3 months when it was on the left; this result was not statistically significant.

Table 3: Predictive and Prognostic Biomarkers for Colorectal Cancer in the Pipeline.

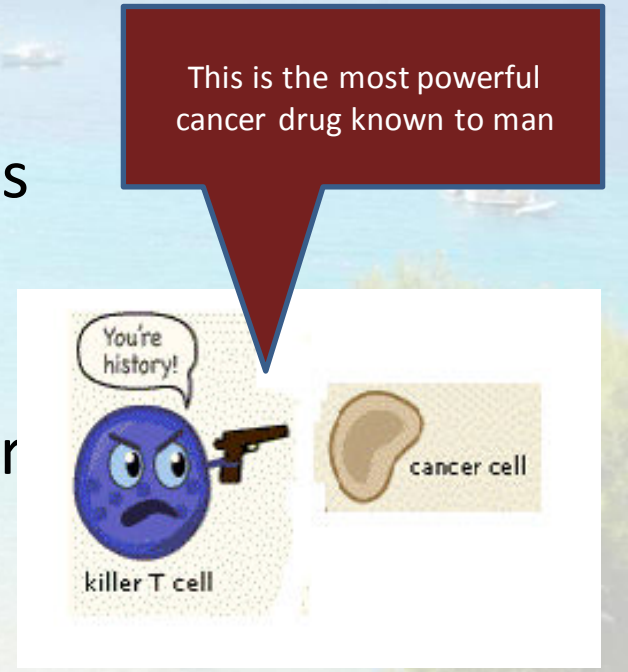
CRC Biomarkers tunder development	Type of Biomarker	Mechanism of action	Role in CRC
KRAS (Kirsten Rat Sarcoma) G13D gene mutation	Predictive	proto-oncogene which encodes a GTP-ase involved incellular response to extracellular stimuli	Indicator of a Better response to EGFR inhibitors with standard chemotherapy
VEGF (vascular endothelial growth factor) Gene expression	Predictive	pro-angiogenic factor	Linked to the aggressiveness of CRC
micro RNAs:	Predictive and Prognostic	short 18-25 nucleotide (non-coding) single-stranded RNA sequences Involved inregulating gene expression. Down regulation of the following: miR-451, miR-624, miR-29c, miR-126, miR-129, miR-133,	Indicators of poor Prognosis in CRC
Microsatellite instability (MSI)	Prognostic	Point mutations in defect mismatch repair system of DNA (15%)	Indicator of poor prognosis Correlate with other significant mutations e.g. KRAS and BRAF
Cycloxygenase 2 (COX-2)	Prognostic	COX-2 inhibitors associated with a lower risk of CRC Risk also strongly correlated with BRAF and VEGF	Associated with worse Outcomes in CRC
CpG Island Methylator Phenotype (CIMP)	Prognostic	Methylation of CpG islands of suppressor promoters	Indicator of poor prognosis Correlate with other significant Mutations eg. KRAS and BRAF
Chromosomal instability (CIN)	Prognostic	Abnormal chromosome Complement or number	Indicator of poor prognosis correlates with other significant mutations eg. KRAS and BRAF
v-raf murine sarcoma viral oncogene homolog B (BRAF)	Prognostic	V600E mutation A serine-threonine protein kinase	Indicator of poor prognosis

Immuno-Oncology

- Usually our immune system keeps us cancer-free by eliminating abnormal cells

- But some cancers can turn off our immune response. Surgery, radiotherapy and most chemotherapy can‘t remedy this ...

- ... However, to restore immune response: **That's the Immuno-Oncology Revolution**



Immunotherapy Landscape

Monoclonal Antibodies:

Herceptin (tratuzumab); Perjeta (pertuzumab)
Keytruda (pembrolizamab); Yervoy (ipilimumab)

T-cell Stimulation – *Ex Vivo*:

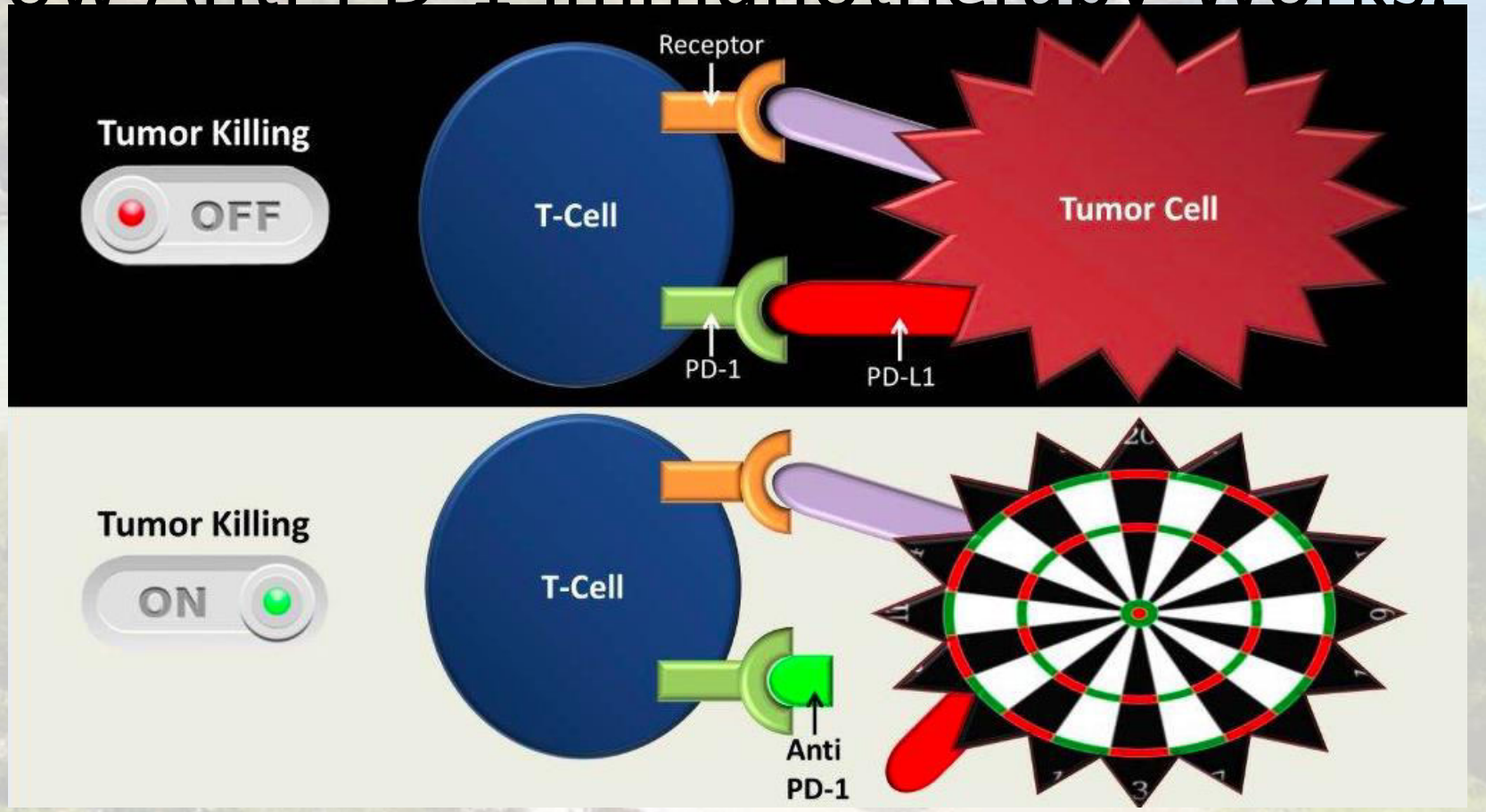
T-Cell Transfer: Lion, Juno, Kite
Dendritic Cell Transfer: Dendreon, NW Bio, Prima BioMed

T-cell Stimulation – *In Vivo*

Antigen Approaches: ONTY, GALE, IMUC
Antigens + Antigen Presentation: TPIV

Marketed Products:
Provenge; Gardasil; Keytruda; Yervoy, Herceptin

How Anti-PD-1 Immunotherapy Works.



Before immunotherapy (top), the tumor cell's PD-1 ligand, or PD-L1, molecule (red) binds to a type of white blood cell called a T-cell in a way that enables the tumor cell to evade destruction by the immune system. During immunotherapy (bottom), an anti-PD-1 inhibitor drug (bright green) blocks PD-L1 binding, enabling the T cell to target the

Pembrolizumab

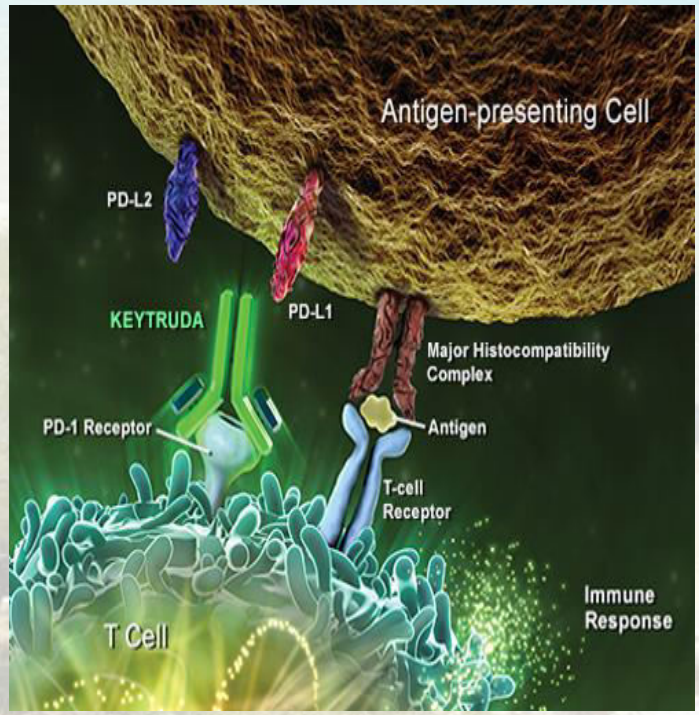
- In a small, proof-of-principle study recently published in The New England Journal of Medicine and presented at the American Society of Clinical Oncology's annual meeting, the Johns Hopkins researchers reported that they could predict the benefit of an anti-PD-1 inhibitor called pembrolizumab (Keytruda®) by scanning patients' tumor samples for defects in mismatch repair.
- Regardless of their type of cancer, patients whose tumors were mismatch repair deficient were more likely to respond to the immune-boosting, anti-PD-1 drug than those with tumors proficient in mismatch repair. In fact, the worse the tumor cells were at repairing DNA, the better the patients fared on anti-PD-1 therapy!

MERCK

KEYTRUDA® (pembrolizumab) for Injection 50 mg

FDA APPROVED

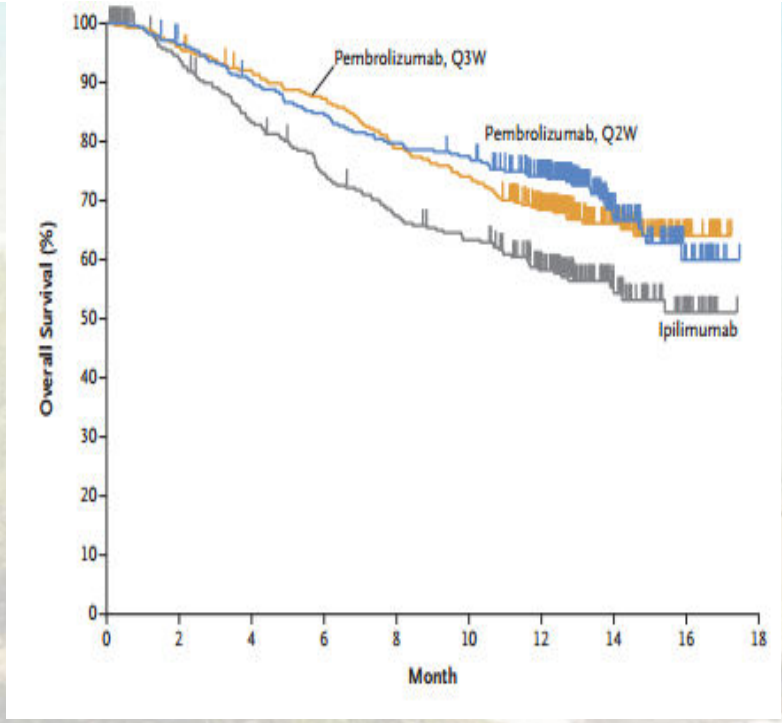
- KEYTRUDA is a monoclonal antibody that binds to the PD-1 receptor and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.



KEYTRUDA Clinical Trial Results

24% (21 of 89 patients) had an overall response to therapy (this means that they had their **tumors partially or completely shrink**).

86% (18 of 21 patients) of those who had an overall response to therapy had an **ongoing response**



Caroline Robert, et al, April 2015

Meeting: **2016 ASCO Annual Meeting**

Programmed death-1 blockade in mismatch repair deficient colorectal cancer.

Author Name: **Dung T. Le**

Abstract Number: **103**

Meeting: **2016 ASCO Annual Meeting**

Preliminary results

- A total of 53 patients (Cohort A: n = 28, Cohort B: n = 25) were treated.
- Median follow up time is 8.7 months.
- RR 89% (25/28) for dMMR the mismatch repair deficient CRC and and 16% for pMMR (mismatch repair proficient) CRC , respectively. Twenty-one of 28 dMMR CRC patients remain on study.
- Median PFS was not reached (NR) for dMMR CRC and 2.4 months for pMMR CRC (HR = 0.135; 95% CI 0.043 to 0.191; p=<0.0001).
- Median OS was NR for dMMR vs. 6 months for pMMR (HR = 0.247; 95% CI 0.117 to 0.589; p=0.001). For dMMR CRC, the PFS rates was 61% at 24 months and the OS rate was 66% at 24 months.

Immuno-Oncology

- One of the ways immune response can be restored is via 'checkpoints' ie inhibitory pathways hardwired into the immune system

- Oncology is now beginning to target these checkpoints

- CTLA-4 and PD-1 are the first two checkpoints to be targeted with approved immuno-oncology drugs

- LAG-3 is an other checkpoint

What is LAG-3?

- LAG-3 (CD223) - "Lymphocyte Activation Gene 3" - expressed on activated T cells, NK cells, B cells and dendritic cells

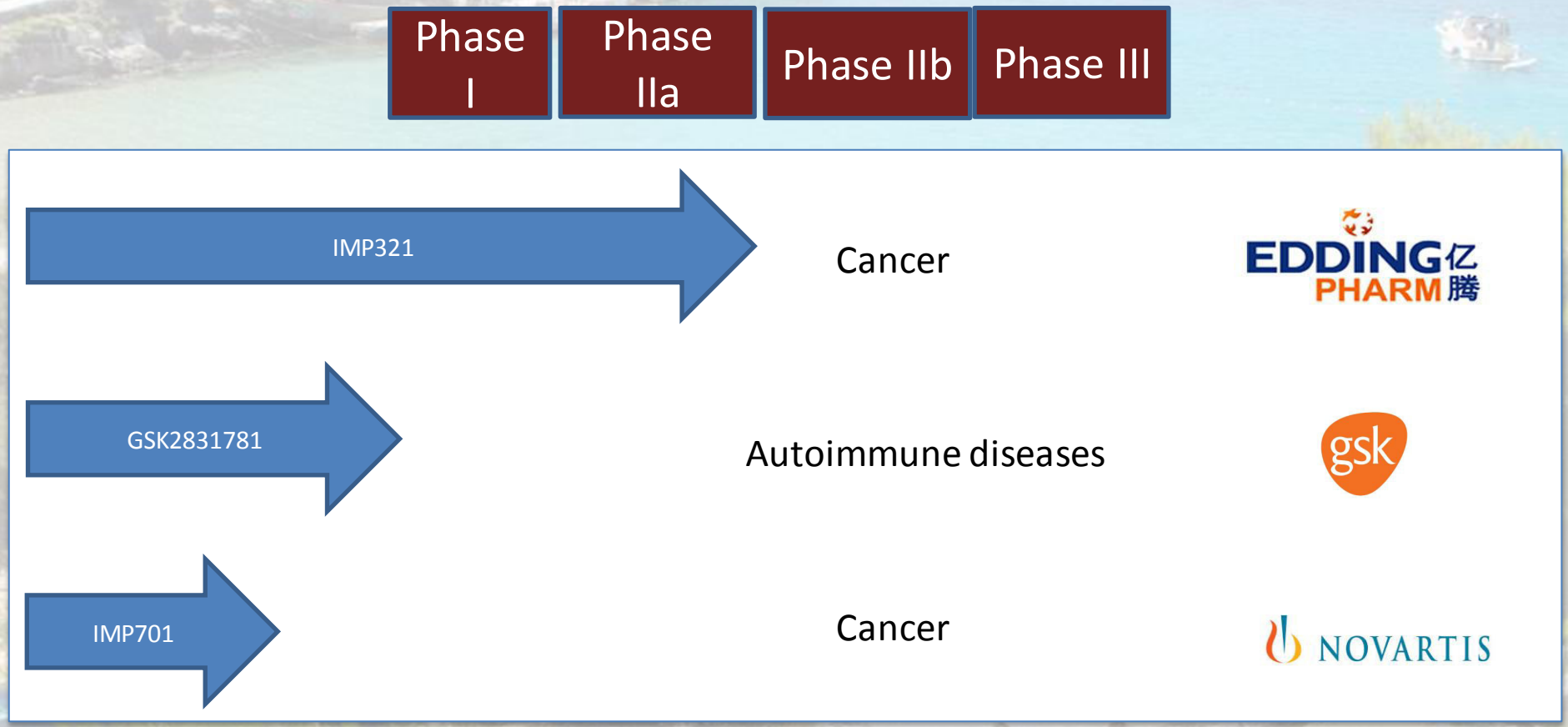
- LAG-3 is a ligand for MHC class II molecules

- On T cells, LAG-3 is an inhibitory receptor that down-modulates (ie turns down) their proliferation and activation. This happens when LAG-3/MHC Class II co-caps (ie crosslinks) with CD3/TCR complex

- Since LAG-3 is widely expressed on T-cells infiltrating human tumours, it is a prime target for an immune checkpoint blocker alongside CTLA-4 and PD-1, with which it is functionally similar

- On dendritic cells LAG-3 is an activator, causing increased antigen presentation when it binds to MHC Class II

Two of our LAG-3 programs have reached the clinic



Working on LAG-3 programs have significant partners

IMP321

One of the fastest-growing specialty pharmas in China

GSK2831781

World's 6th largest pharma*

IMP701

World's largest pharma*

* Ranked by Rx sales for 2013 (source: PharmaExec50 list, June 2014)

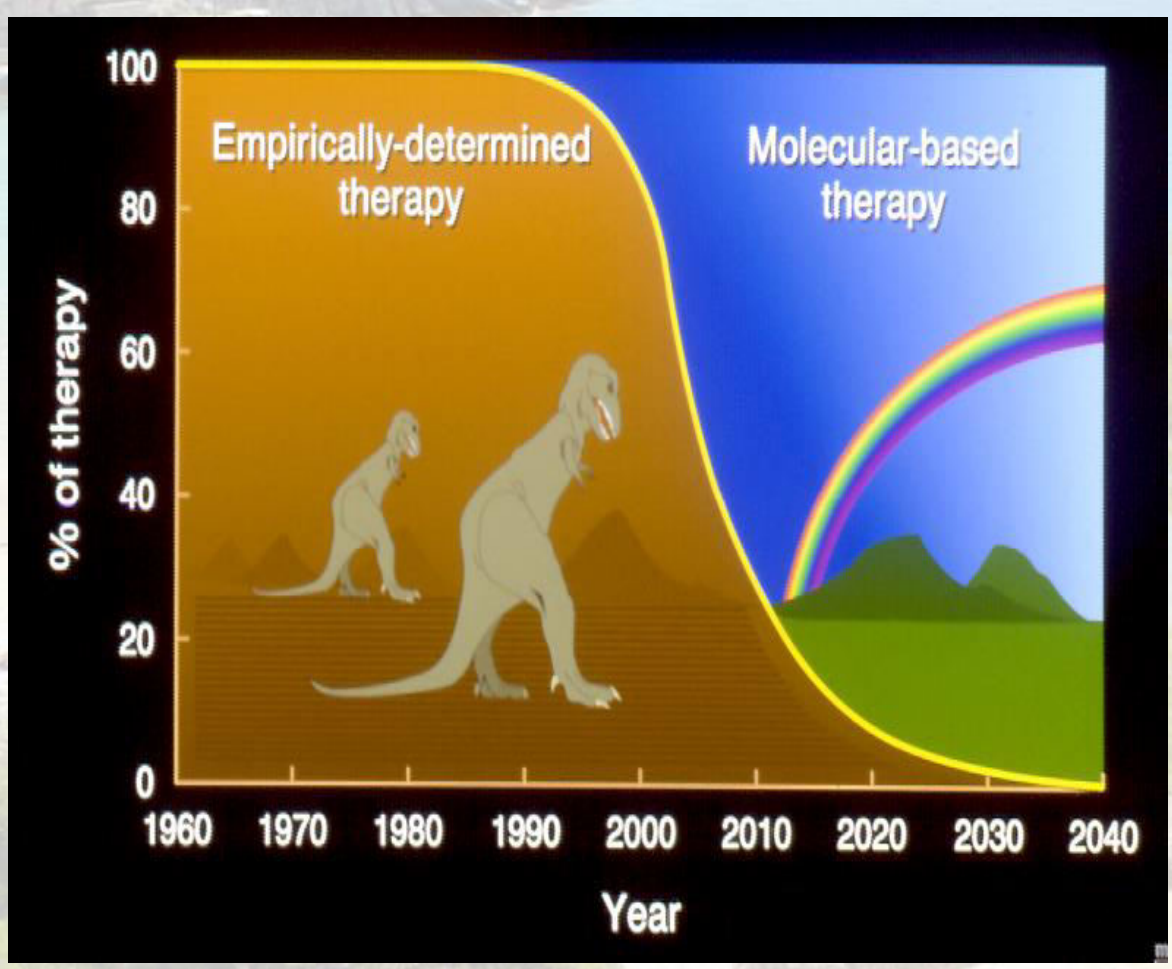
New Targeted Therapies

- Bevacizumab (Avastin)
- Bortezomib (Velcade)
- Ceritinib (Zykadia)
- Ipilimumab (Yervoy)
- Nivolumab (Opdivo)
- Olaparib (Lynparza)
- Pazopanib (Votrient)
- Pembrolizumab (Keytruda)
- Pertuzumab (Perjeta)
- Temsirolimus (Torisel)
- Trametinib (Mekinist)
- Trebananib
- Veliparib
- Rucaparib
- Avelumab
- Binimetinib
- Niraparib
- VB-111
- Vanucizumab
- Selinexor

Emerging therapeutic targets for the treatment of CRC

- Vemutafenib and dabrafenib targeting mutant BRAF;
- Selutmetinib and pimasertib targeting MEK;
- LY294002 and GDC0941 are targeting P13K

Conclusion:
Where we are at in Cancer Therapies?



Adjuvant therapy in colorectal cancer

- The last 30 years have only seen small but progressive improvement in survival for patients with colorectal cancer.

- .... It would be poor medical practice to treat bacterial sepsis without first obtaining the antibiotic sensivity. The same should be the goal for colon cancer

Editorial: Journal of the Royal Society of Medicine 1984

Thank you for listening