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BETTER MEDICINE
BEST PRACTICE

THE TWENTY LESSONS LEARNT FROM THE DEVELOPMENT OF MOLECULAR-TARGETED THERAPIES

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DISCLOSURES

Nuria Kotecki has reported no conflicts of interest

Guillem Argilés has reported no conflicts of interest

Ahmad Awada has reported no conflicts of interest

LESSONS LEARNT

From the development of molecular targeted therapies

Key points

Importance of the target driving carcinogenesis and the selectivity of the new agent

Take into account tumour heterogeneity and mechanisms of resistance

Each patient in a clinical trial should be analysed carefully in particular if efficacy was documented

Perform mainly prospective trials

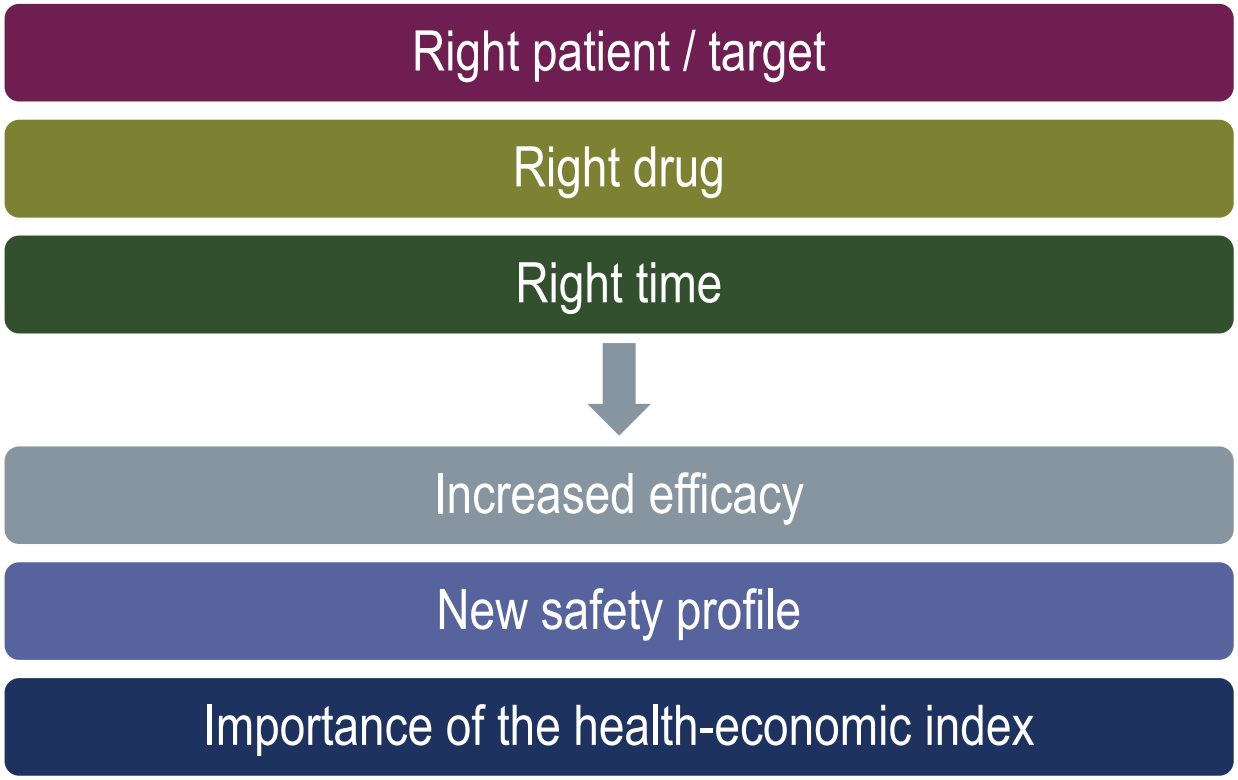
Perform innovative and « smarter » clinical trials design taking into account:

- The patient
- The tumour
- What it is known about the evolution of the disease
- The characteristics of the experimental drug

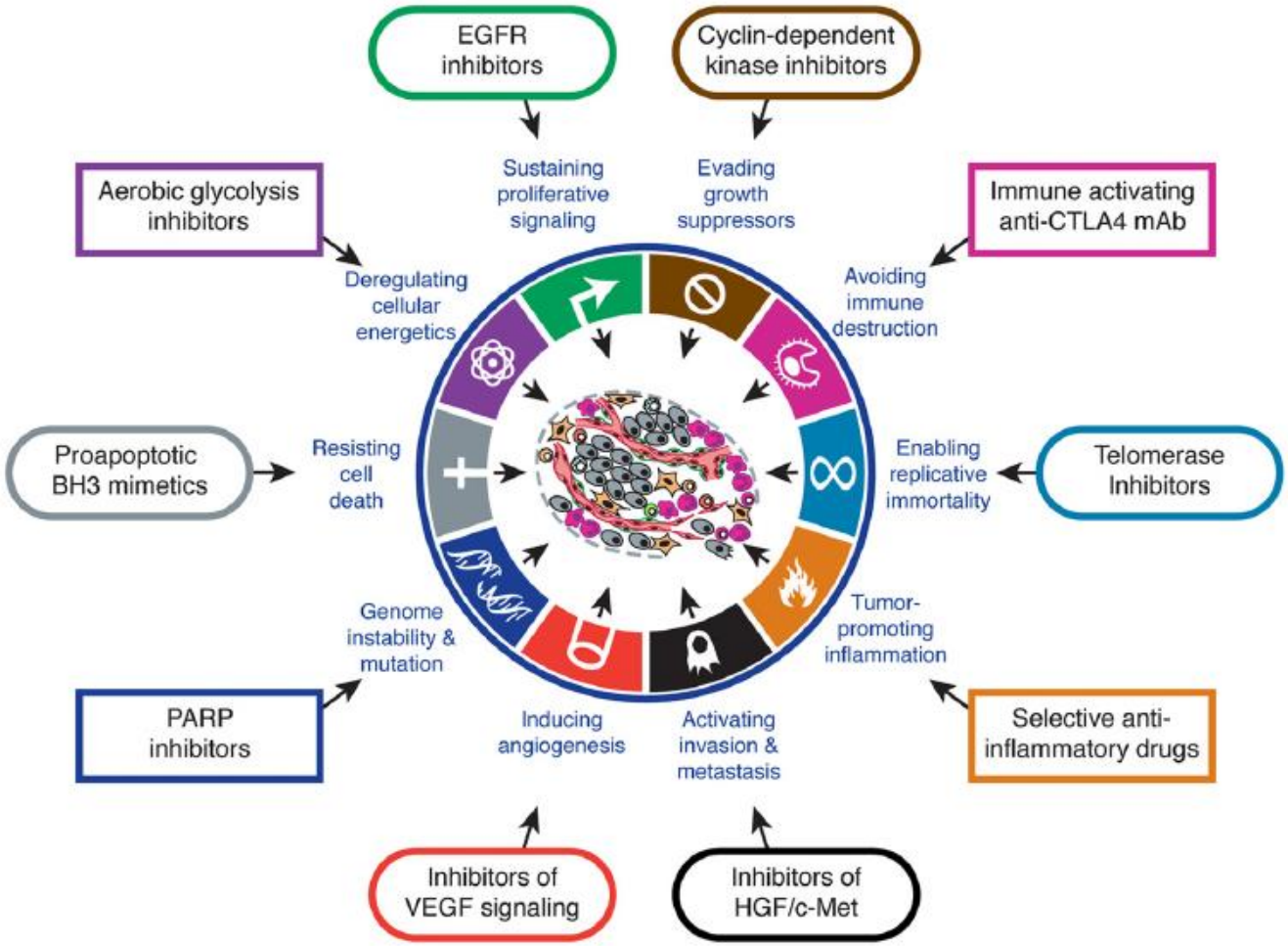
Learn from the past experience in order to avoid mistakes

MOLECULAR BIOLOGY UNDERSTANDING

Changes the approaches of patient care in 2017



BETTER UNDERSTANDING OF THE TUMOUR BIOLOGY



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IMPORTANT TARGETS

Involved in carcinogenesis and their inhibitors (1)

Target	Tumour	Inhibitor	Predictive markers of sensitivity/resistance	Disease setting
ER	Breast	Tamoxifen, AI, fulvestrant	ER expression ER mutation (Resistance)	Adjuvant & advanced disease
EGFR	Head & Neck	Cetuximab	-	Locally/advanced H&N cancer
EGFR	NSCLC	Gefitinib/Erlotinib/ Dacomitinib/Afatinib (Osimertinib)	Mutation of EGFR (T790M)	Metastatic NSCLC
EGFR	Colorectal	Cetuximab Panitumumab	Ras status	Metastatic colorectal cancer
HER-2/neu	Breast, gastric	Trastuzumab, Pertuzumab Lapatinib Neratinib	HER-2/neu amplification	Adjuvant (breast) & advanced disease (breast, gastric)

IMPORTANT TARGETS

Involved in carcinogenesis and their inhibitors (2)

Target	Tumour	Inhibitor	Predictive markers of sensitivity	Disease setting
VEGF	NSCLC, colorectal, renal, breast, ovary, cervix	Bevacizumab, aflibercet (colon)	-	Advanced disease
VEGFR (MAPK and PI3K pathways*)	Hepatocarcinoma Colorectal Gastric	Sorafenib*, lenvatinib* Regorafenib* Ramucirumab	-	Advanced disease
VEGF(R); M-TOR	Renal	MTKs, bevacizumab, everolimus, temsirolimus	-	Advanced disease
VEGF(R); M-TOR	Neuroendocrine Soft tissue sarcomas	Sunitinib, everolimus Pazopanib	-	Advanced disease
VEGFR, RET	Thyroid	Vandatinib, sorafenib lenvatinib	-	Advanced disease
M-TOR	Breast	Everolimus	-	Advanced disease
CDK 4/6	Breast	Palbociclib, ribociclib, abemaciclib	-	Advanced disease

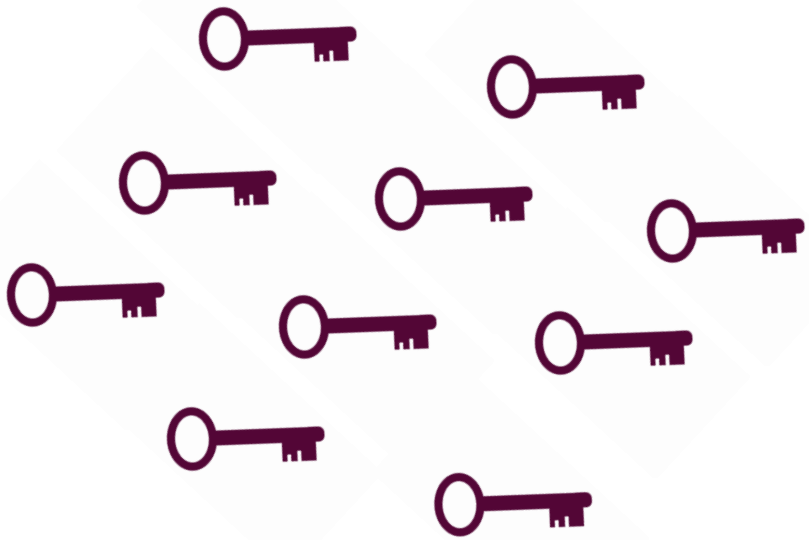
IMPORTANT TARGETS

Involved in carcinogenesis and their inhibitors (3)

Target	Tumour	Inhibitor	Predictive markers of sensitivity/resistance	Disease setting
C-Kit	GIST	Imatinib Sunitinib, regorafenib	C-Kit mutation PDGFR mutation	High risk or metastatic GIST
EML4-ALK R0S1	NSCLC	Crizotinib, ceritinib, Alectinib	EML4-ALK translocation R0S1	Advanced NSCLC
RANKL	Bone metastases; Giant cell tumours	Denosumab	-	Advanced disease
Hedgehog	Basal cell carcinoma	Vismodegib	-	Advanced disease
BRAF, MEK	Melanoma	Vemurafenib, dabrafenib trametinib, cobimetinib	BRAF mutation	Advanced disease
PARP	Breast, ovary (BRCA tumours)	Olaparib, niraparib…	BRCA mutation	Advanced disease
CTLA4	Melanoma	Ipilimumab	-	Advanced disease
PD-1/PD-L1	Melanoma, NSCLC, RCC, H&N, urothelial, MCC	Nivolumab, pembrolizumab, atezolizumuab, avelumab…	(PD-L1 protein)?	Advanced disease
Androgen receptor; immune system; Met	Prostate	Abiraterone, enzalutamide, sipuleucel-T, cabozantinib	Androgen receptor variant 7 (Resistance)??	Advanced disease

LESSON 1:

Identification of a key genetic abnormality in cell carcinogenesis and the discovery of a selective targeted agent leading to a major therapeutic breakthrough



TARGETING BRAF IN ADVANCED MELANOMA

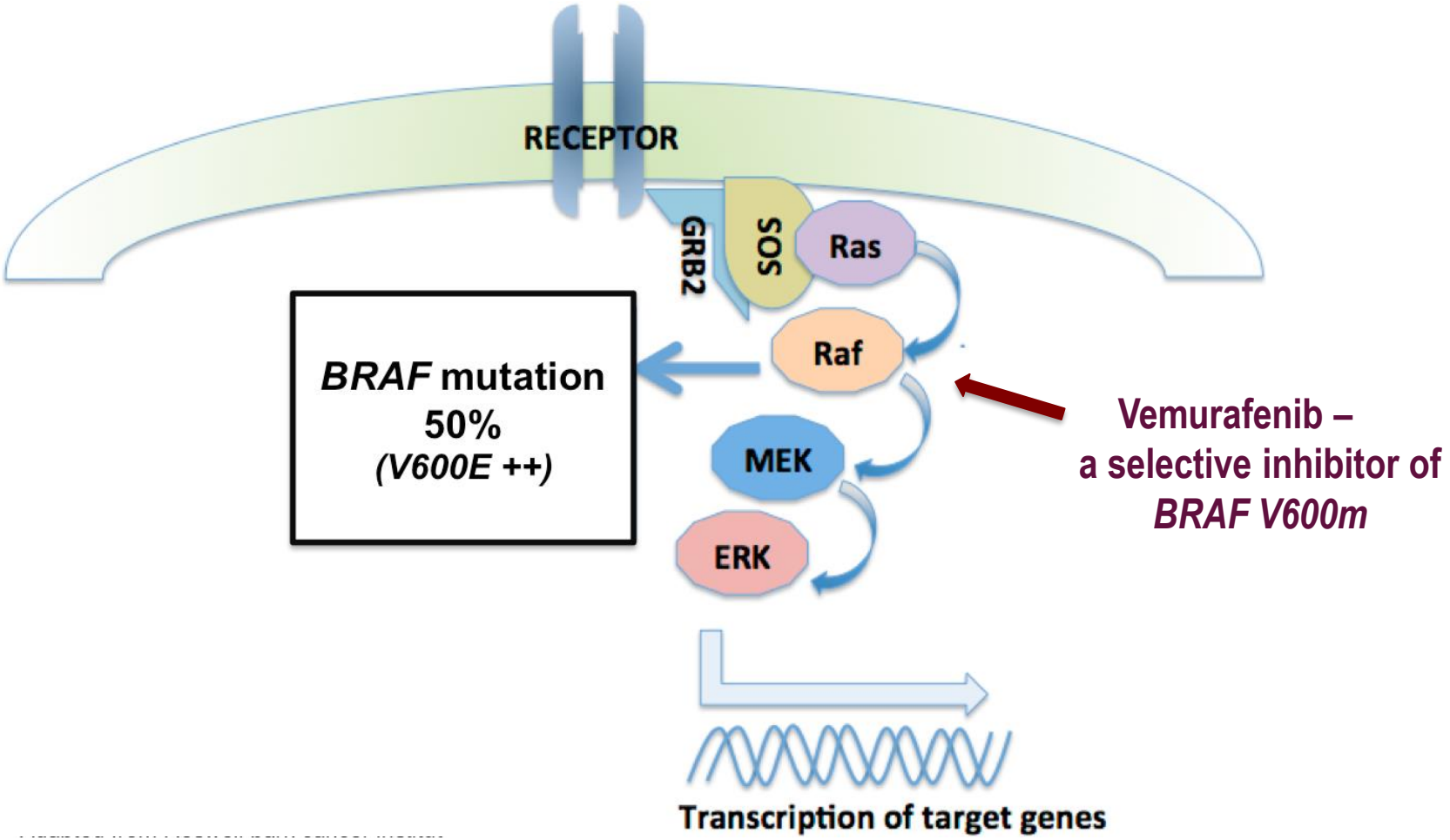
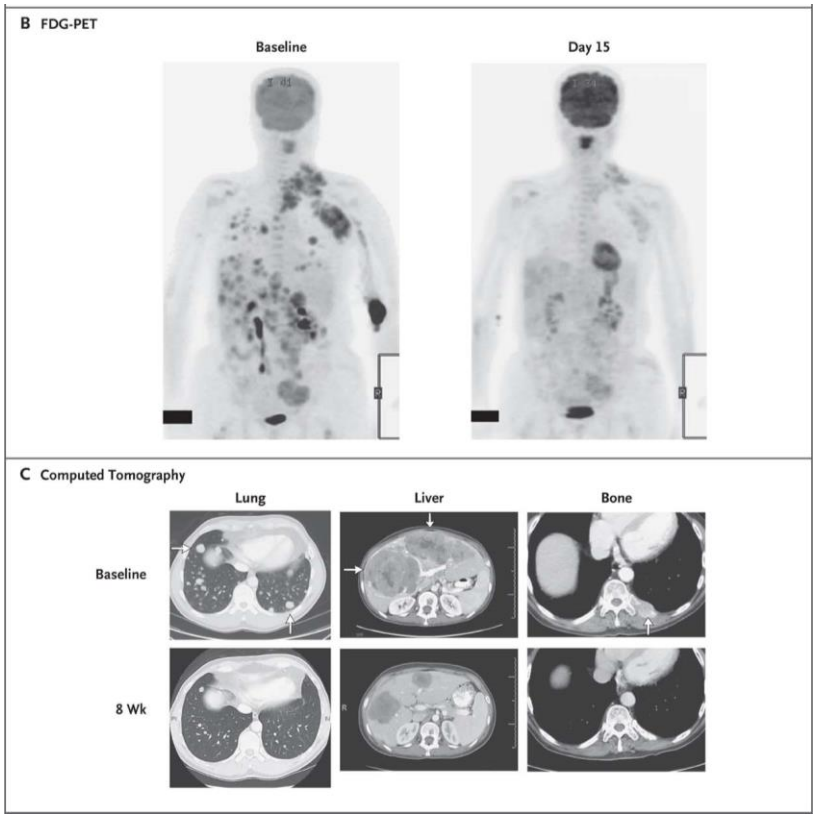


Image adapted from Roswell Park Cancer Institute. Available at: https://www.roswellpark.org/article/targeting-braf-mutation-positive-cancers-melanoma-lung-and-colorectal. Accessed December 2017.

FINDINGS OF THE EFFECT OF VEMURAFENIB

At the recommended Phase 2 dose in patients with melanoma that carried the V600E Mutation



Phase I/II study:

- 16 melanoma pts BRAF V600Em:
- - 10 PR - 1 CR

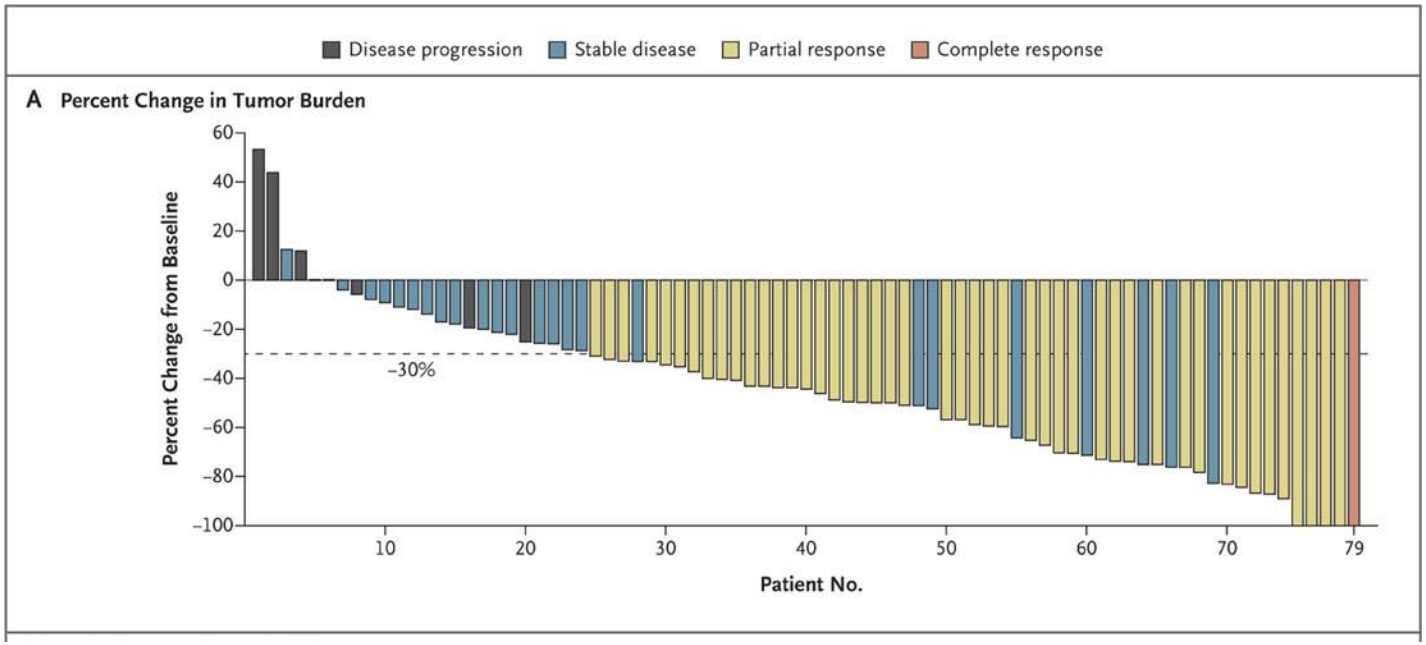
From N Engl J Med, Flaherty KT, *et al.* Inhibition of mutated, activated BRAF in metastatic melanoma., 363, 809–19.

TARGETING EML4-ALK IN A SUBGROUP OF ADVANCED NSCLC

EML4-ALK fusion: 6% of NSCLC patients

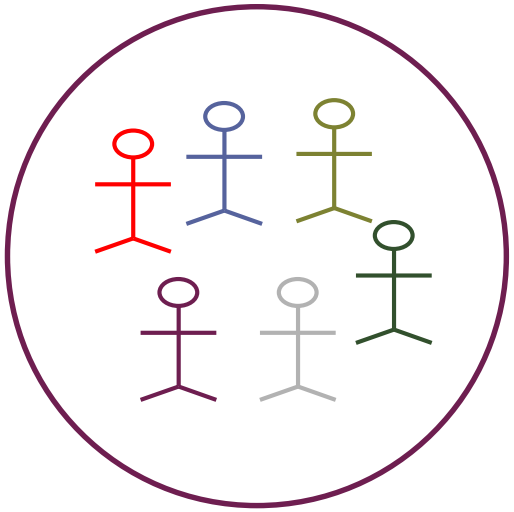
Preliminary data with crizotinib (EML4-ALK inhibitor):

n = 82 patients; RR: 57% of patients; DCR at 8 weeks: 87% of patients

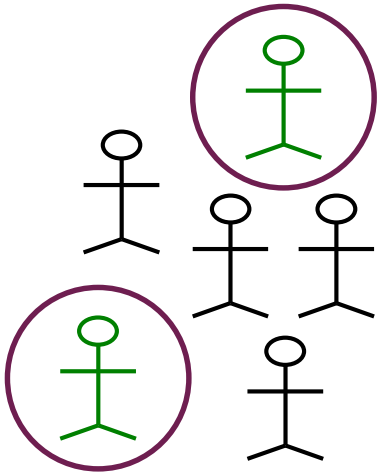


LESSON 2:

Treatment of unselected population with a targeted agent should be prohibited



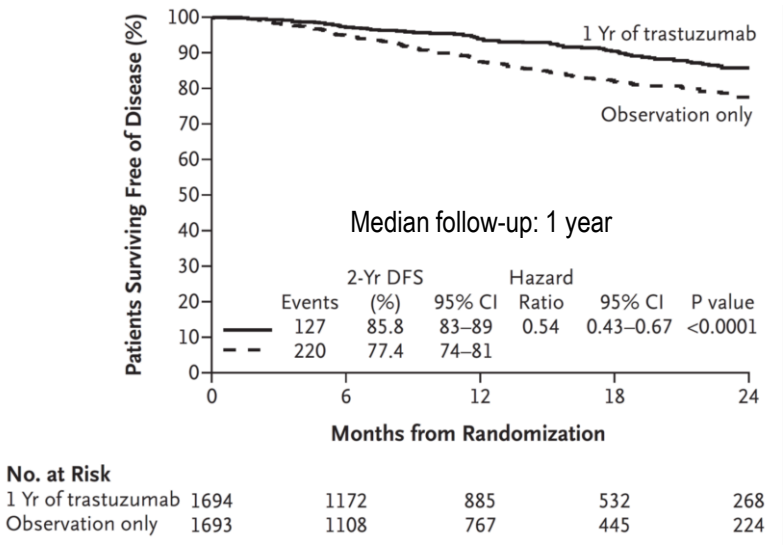
VERSUS



IMPORTANCE OF TARGET FOR THERAPY

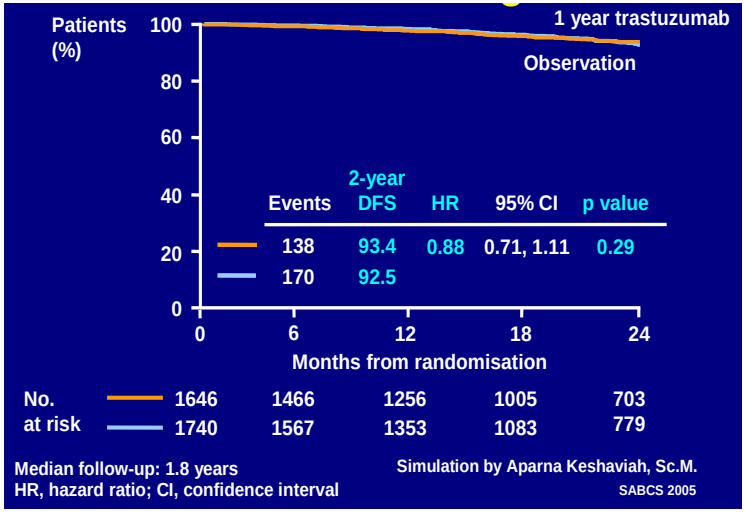
HERA trial (adjuvant trastuzumab) in breast cancer

Disease-free survival[1]



The right subpopulation
The right drug
A huge treatment effect!

Disease-free survival HER2+ and HER2–patients



Simulation of HERA if conducted in unselected patients (HER2 +/–):
HER2+ : HR 0.54
HER2– : HR 0.95

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1. From N Engl J Med, Piccart-Gebhart MJ. *et al.*, Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer, 353(16):1659–72. Copyright © 2005 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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TARGETING EGFR IN ADVANCED NSCLC

1st line erlotinib or gefitinib in combination with chemotherapy (unselected population)

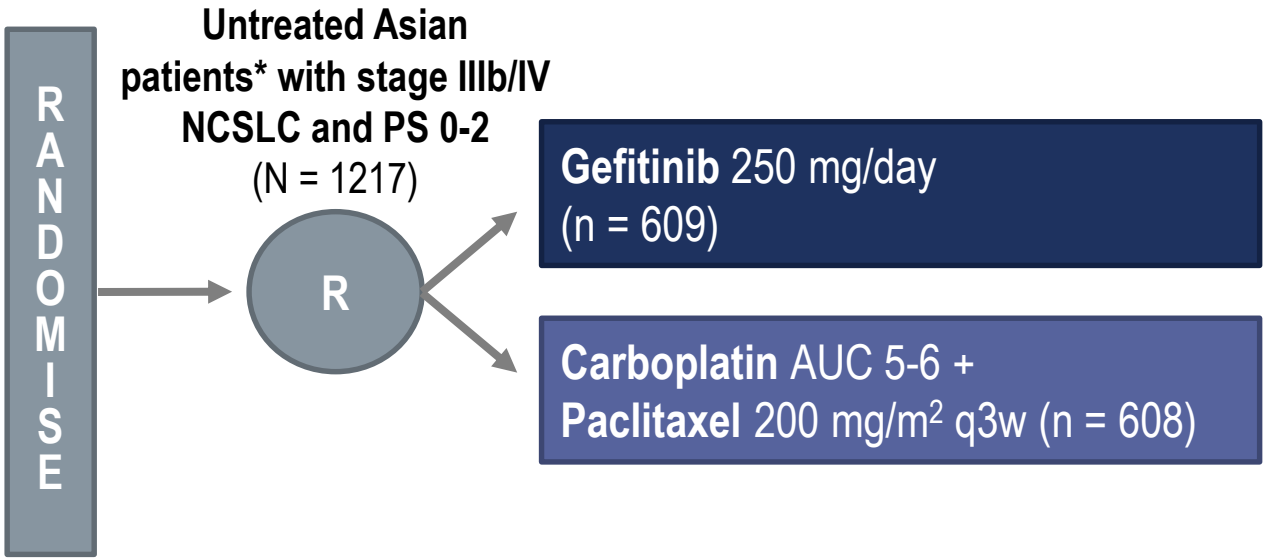
Study	Number of pts	Treatment regimens	TTP (months) (p value)	OS (months) (p value)
TRIBUTE	1059	Carbo/paclitaxel placebo or erlotinib	4.9 *vs.* 5.1 (p =.36)	10.5 *vs.*10.6 (p=.95)
Tarceva lung cancer inv. trial	1172	Cispatlin/gemcitabine placebo or erlotinib	NR	11 *vs.* 10.7 (p =.49)
INTACT-1	1093	Cispatlin/gemcitabine placebo or gefitinib	10.9 *vs.* 9.9 (p = .45)	6.0 *vs.* 5.5 (p =.76)
INTACT-2	1037	Carbo/paclitaxel placebo or gefitinib	5.0 *vs.* 4.6 (p =.56)	9.9 *vs.* 8.7 (p = .64)

4361 patients randomised across four phase III trials

Unselected patients according to EGFR mutation status was probably the main reason of the observed negative results

TARGETING EGFR IN ADVANCED NSCLC

1st line gefitinib *versus* chemotherapy – IPASS study



Primary endpoint: PFS

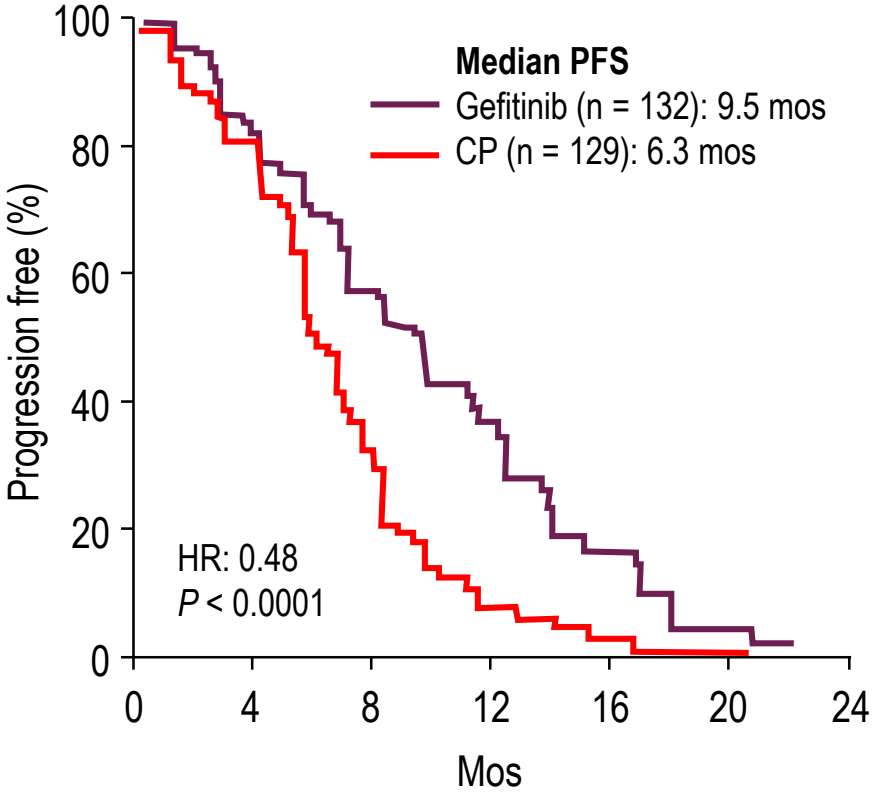
Biomarker analysis: EGFR mutation, expression, and gene copy number

Fukuoka M, *et al*. ASCO 2009. Abstract 8006.

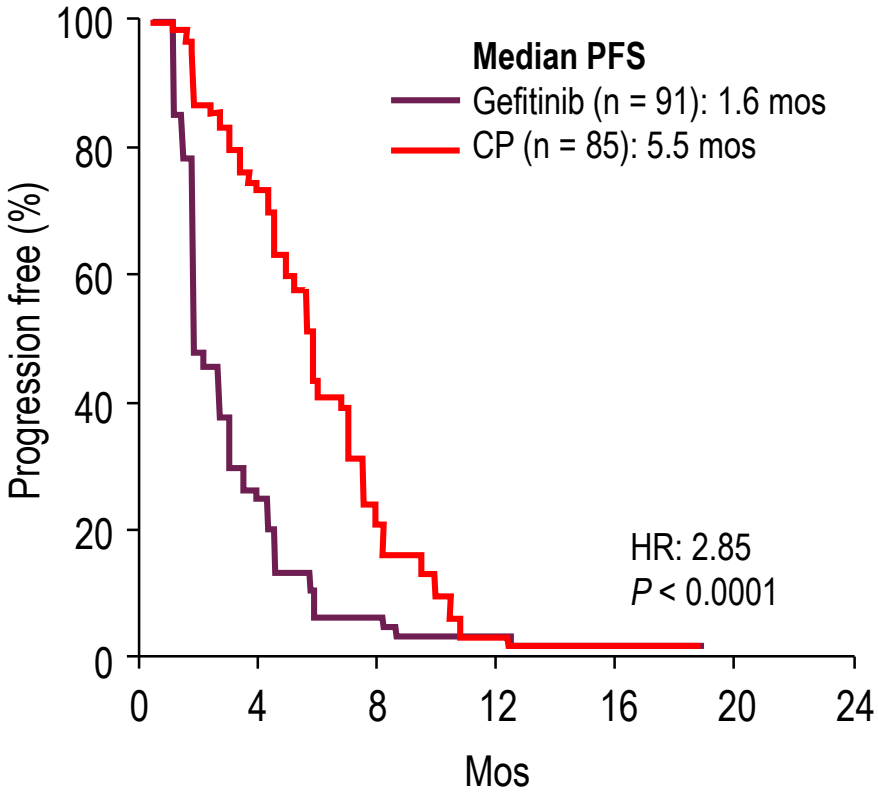
TARGETING EGFR IN ADVANCED NSCLC

1st line gefitinib *versus* chemotherapy – IPASS study

PFS: Mutated *EGFR*



PFS: Wild-Type *EGFR*



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Fukuoka M, *et al*. ASCO 2009. Abstract 8006.

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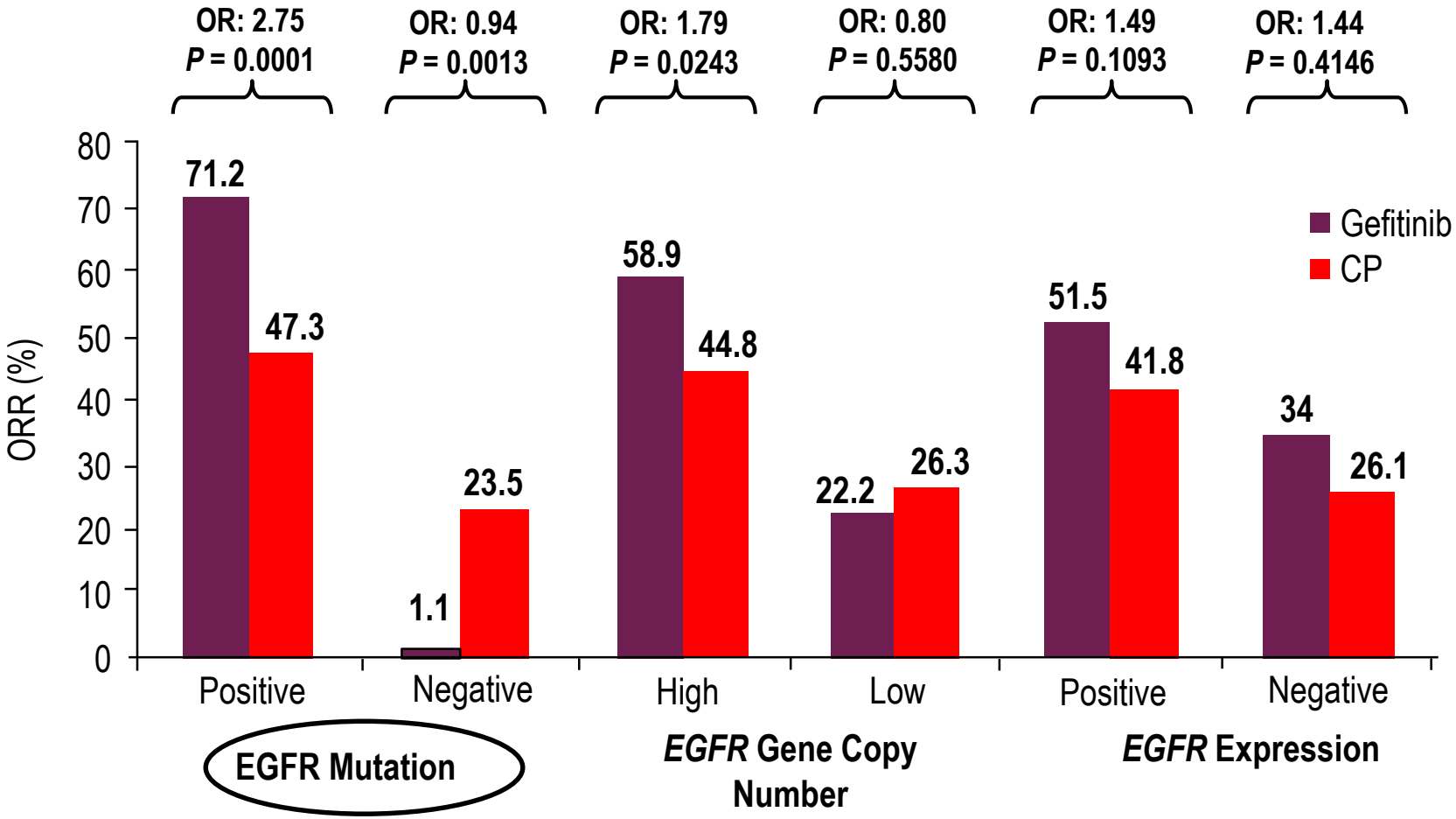
TARGETING EGFR IN ADVANCED NSCLC

1st line gefitinib *versus* chemotherapy – IPASS study

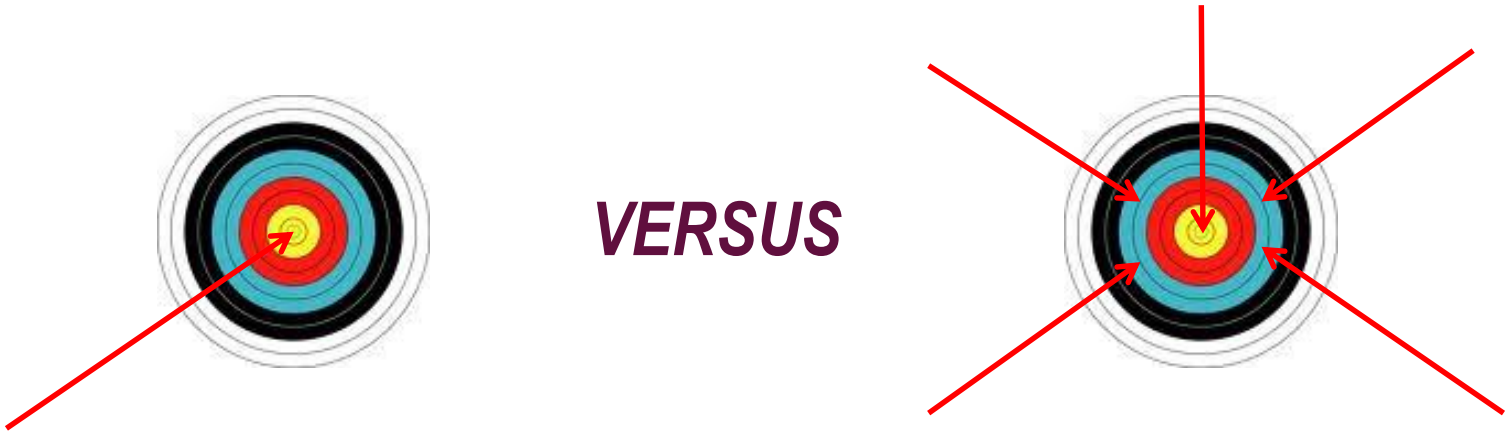


Fukuoka M, *et al.* ASCO 2009. Abstract 8006.

LESSON 3:

Unitargeted or multitargeted kinase inhibitors for solid tumours?:

Tumour dependency

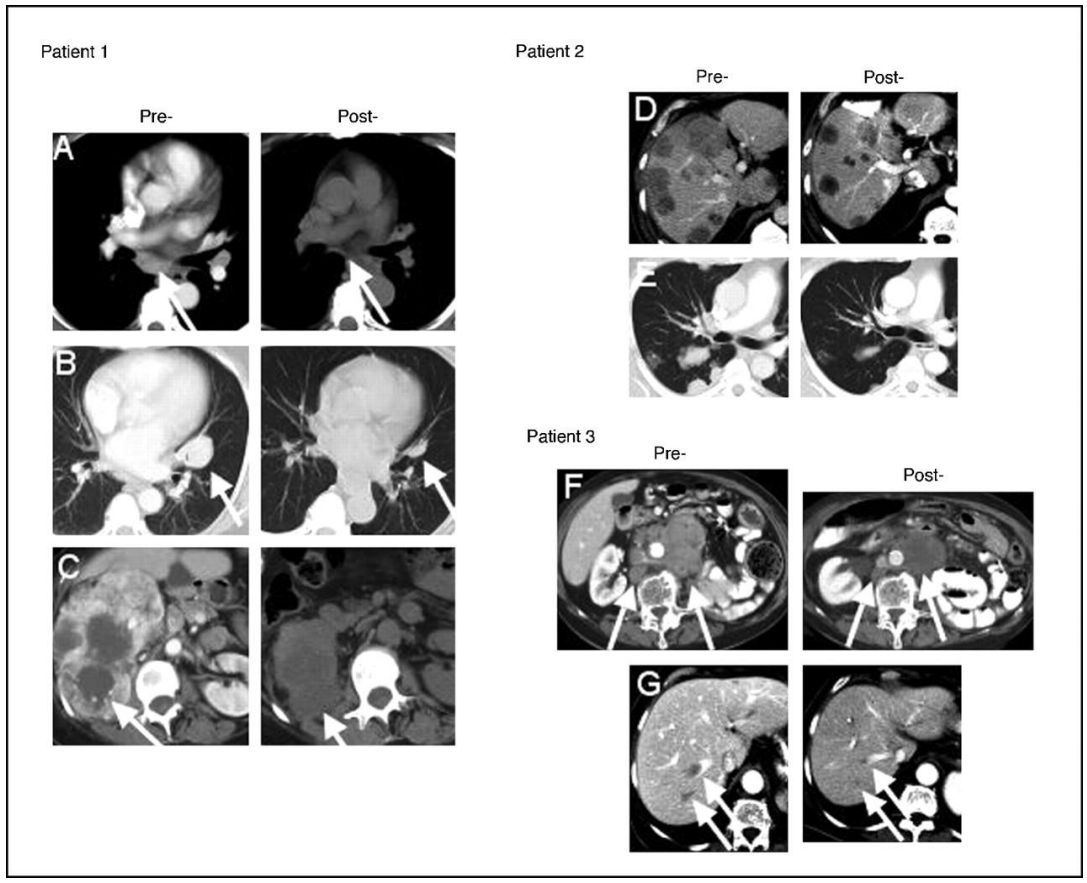


TYROSINE KINASE MAP (KINOME) AND SELECTIVITY OF TARGETED AGENTS

The appropriate approach depends on tumour type and the critical carcinogenesis process

MULTITARGETED KINASES INHIBITORS IN RENAL CANCER:

Tumour responses



A,B,C: responses in patient 1 with multiple metastatic sites from a large primary RCC.

D,E: responses in patient 2 with multiple hepatic, lung, and pleural metastases.

F,G: responses in patient 3 with large retroperitoneal lymphadenopathy and hepatic metastases.

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LESSON 4:

Different tumour types might share common molecular aberrations that could be targeted (such as BRAF mutations) but responding differently to the same targeted therapy depending on the context

Although BRAF inhibitors have been approved for treating BRAF mutated metastatic melanoma, disappointingly, these drugs had only scant activity when used as a monotherapy in mCRC when constitutively expressed EGFR led to resistances. Therefore the addition of anti-EGFR monoclonal antibodies and MEK inhibitors is needed in mCRC

Drug	Tumour type	ORR	
Vemurafenib	BRAFV600m metastatic melanoma	48%	Chapman PB, *et al.* NEJM. 2011
Vemurafenib	BRAFV600m metastatic CRC	5%	Kopetz S, *et al.* JCO 2015
Vemurafenib + cetuximab	BRAFV600m metastatic CRC	20%	Tabernero J, *et al.* JCO 2014 no. 15_suppl
Dabrafenib + trametinib + panitumumab	BRAFV600m metastatic CRC	18%	Corcoran RB, *et al.* ESMO 2014

Chapman PB, *et al.* N Engl J Med 2011;364(26):2507-16.

LESSON 5:

Rare (orphan) tumours are “good” niches of selected targeted agents

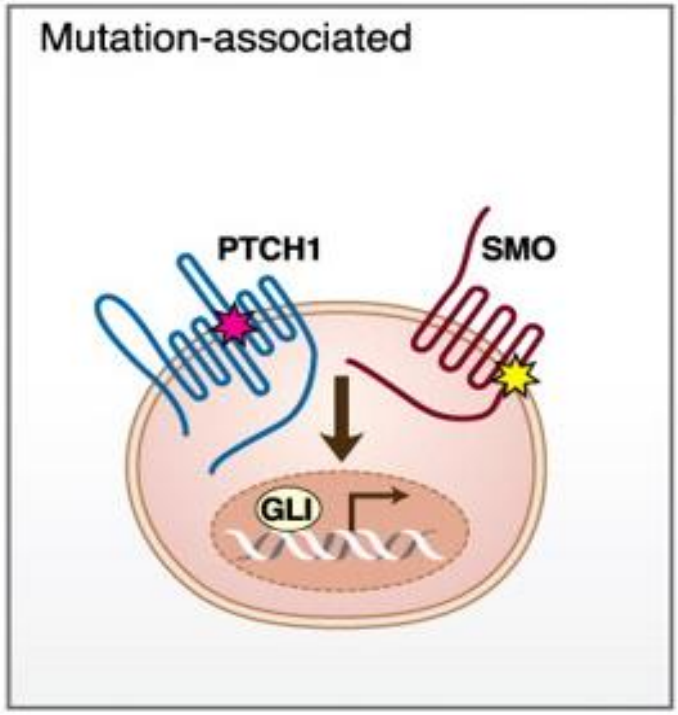
Hedgehog signaling inhibitors and basal cell carcinoma

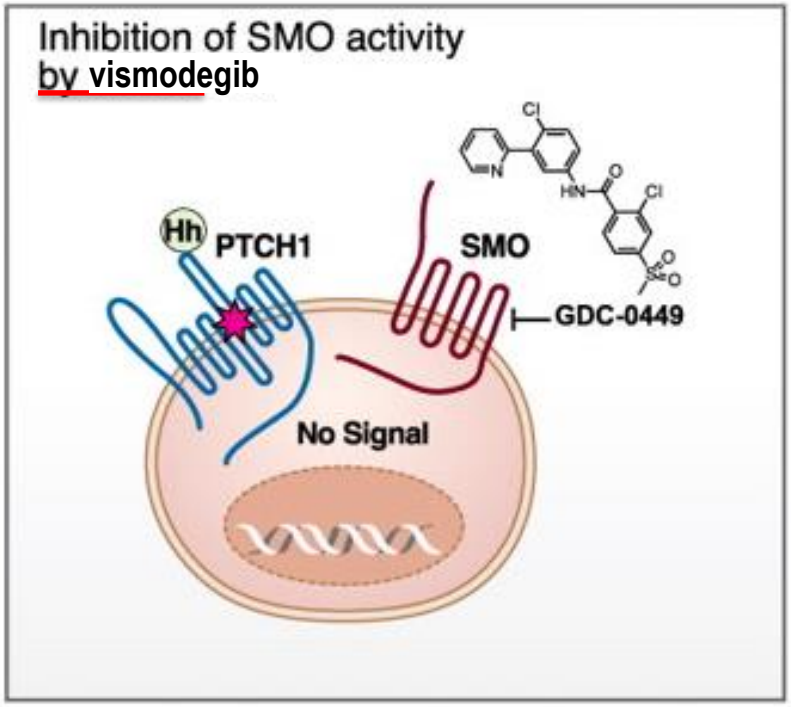
PARP inhibitors in BRCA mutated tumours

Rank ligand inhibition in giant cell tumours

BASAL CELL CARCINOMA

Abnormalities in hedgehog signaling pathway and mechanism of vismodegib activity in basal cell carcinoma





Reprinted from Clin Cancer Res, 2011, 17(8), 2502–11, Lo Russo PM, *et al.*, Phase I Trial of Hedgehog Pathway Inhibitor Vismodegib (GDC-0449) in Patients with Refractory, Locally Advanced or Metastatic Solid Tumors, with permission from AACR.

PHASE II STUDIES WITH OLAPARIB

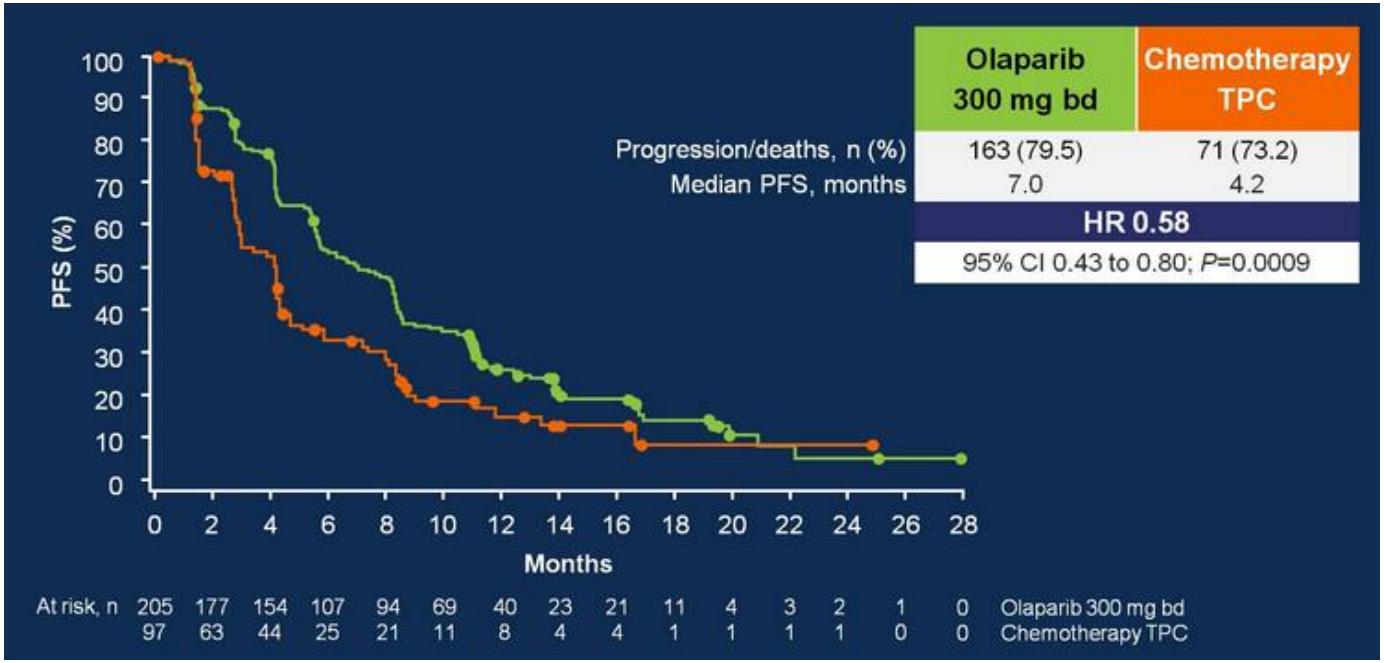
In BRCA-deficient advanced breast cancer

	Tutt *et al.* Lancet 2010 (n=54)	Gelmon *et al.* Lancet Oncol 2011 (n=26; 10 g BRCAm)	Kaufman *et al.* JCO 2015 (n=62)
Patient population	Locally advanced/ metastatic BRCAm BC	Advanced metastatic or recurrent BC, TN or known BRCAm	Advanced BRCAm BC; ≥ 3 previous lines of chemotherapy for locally advanced/metastatic BC
Prior lines of therapies for advanced disease	3 (median, including adjuvant)	3 (median, including adjuvant)	4.6 (mean, metastatic only)
ORR	41%	0% (50% unconfirmed ORR in BRCAm)	13%
Median DoR	144 days	-	204 days

OLYMPIAD TRIAL

Olaparib slows significantly the growth of BRCA-mutated metastatic breast cancer

Primary endpoint: progression-free survival by BICR



Robson M, *et al*. J Clin Oncol 35, 2017 (suppl; abstr LBA4). ASCO 2017. Reproduced with permission from Dr Mark Robson.

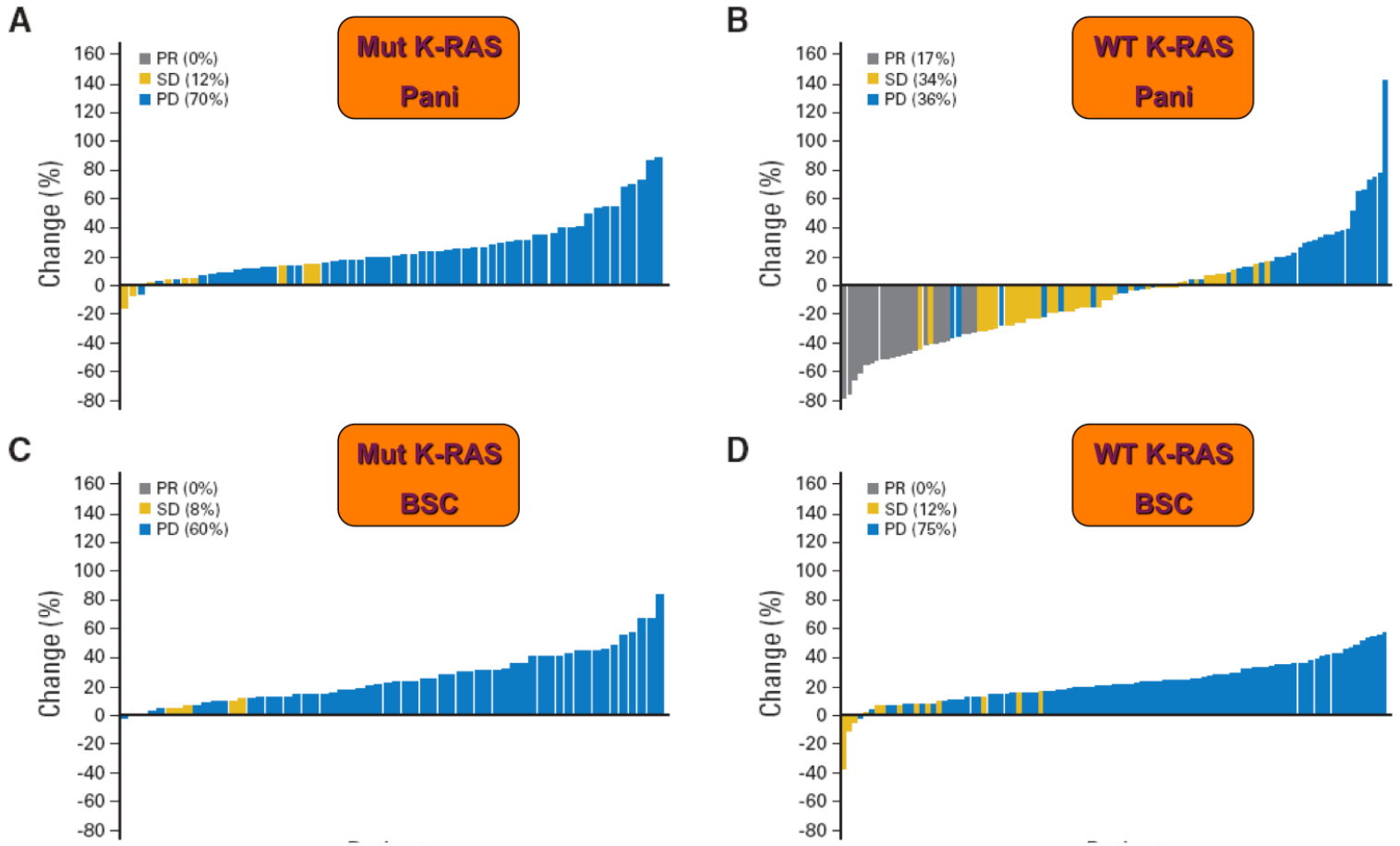
LESSON 6:

One gene could predict resistance to a family of targeted therapy but no single gene, protein, pathway predict full activity of a targeted agent

KRAS wild type/mutation and efficacy to EGFR monoclonal antibodies and colorectal cancer

BENEFIT FROM PANITUMUMAB (EGFR INHIBITOR)

According to K-RAS in mCRC



Amado RG, *et al.* J Clin Oncol 26(10), 2008:1626–34. Reprinted with permission. © 2008 American Society of Clinical Oncology.

THE 4 GOOD REASONS FOR TESTING RAS STATUS

In order to guide anti-EGFR mabs in mCRC

1. Possible benefit if Ras « wild »
2. Avoid potential harm if « mutated »
3. Avoid undue toxicity
4. Avoid extra cost

LESSON 7:

The discovery of resistance mechanisms to targeted agents remains a key field as well as the development of active agents to the resistant mutations

C-Kit resistant mutations to imatinib in GIST

EGFR resistant mutations to gefitinib and erlotinib in NSCLC

→ **New generation of targeted agents are available in clinical practice**

LESSON 8:

Patient and tumour characteristics remain important in selecting systemic targeted therapies: The example of NSCLC

Ethnicity, gender, smoking habit and the efficacy of small molecules EGFR inhibitors in NSCLC

Location of metastatic sites (central *versus* peripheral): Antiangiogenic agents

Histology (squamous *versus* non-squamous)

Tumour EGFR mutational status

LESSON 9:

Mechanism-based and unexpected side effects arose from targeted therapy and could be cumbersome

Side effects of targeted agents were considered as predictive markers of clinical response but not fully validated for clinical practice use

TARGETED AGENTS:

Main side effects

Side effects	Agents
GI, skin	Anti-EGFR; Multi-targeted kinases
Interstitial lung disease	Gefitinib, mTor inhibitors
Hypomagnesemia, hypocalcemia	Monoclonal Antibody Anti-EGFR
Hypophosphatemia	Imatinib
Cardiac dysfunction	Trastuzumab, multi TKI, others
Bleeding, thrombosis, perforation, HTA	Anti-VEGF(R)
Cholecystitis	Motesanib
Proteinuria	Bevacizumab, multi TKI
Reversible posterior Leukoencephalopathy syndrom	Bevacizumab, multi TKI
Hypothyroidism	Sunitinib (Sorafenib)
Auto-immune disorders	Anti-CTLA-4 monoclonal antibodies
Hematological	Sunitinib, mTor inhibitors

« I stopped taking the medicine because I prefer the original disease to the side effects »

CORRELATION OF SKIN REACTION AND EFFICACY OF CETUXIMAB:

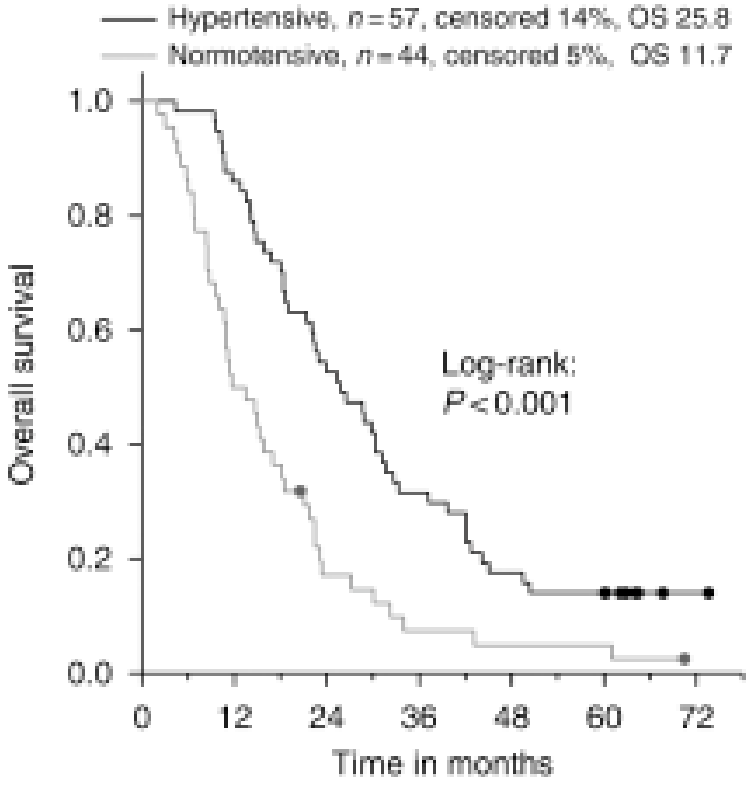
Bond subgroup analysis in colorectal cancer

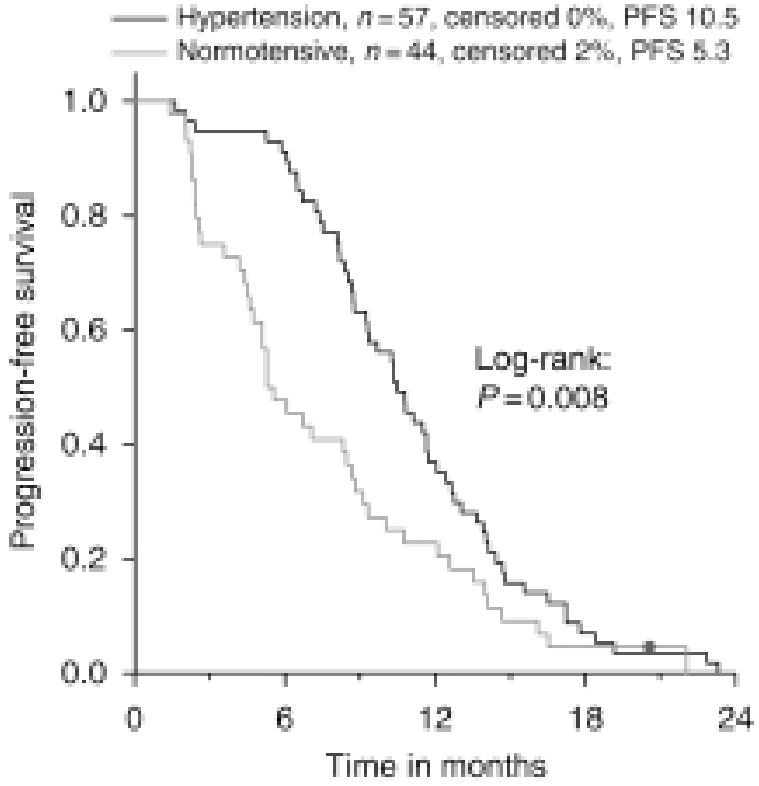
Grade of skin reaction (up to Week 4)	Percentage of patients	Response rate	mTTP	Median survival
0	14.7	6.3%	1.4 months	3.0 months
1	26.6	8.6%	1.5 months	6.5 months
2	45.4	27.3%	4.2 months	10.3 months
3	13.3	55.2%	8.2 months	13.7 months

Cunningham D, *et al.* N Engl J Med (2004).

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL

By hypertension during bevacizumab-containing treatment for metastatic colorectal cancer





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Österlund P, *et al.* Br J Cancer 2011;104(4):599–604.

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LESSON 10:

Even in the presence of targeted therapies, chemotherapeutic agents remain key backbone for successful combinations in selective solid tumours such as breast and GI tumours

Bevacizumab experience in solid cancers (breast and CRC)

HER-2 therapy in breast and gastric cancer

LESSON 11:

Continue the development of new cytotoxics or new formulations of existing anticancer agents is important for improving outcome of our patients

Nab-paclitaxel, ixabepilone, eribulin, etirinotecan

Antibody drug congugates: TDM-1, …

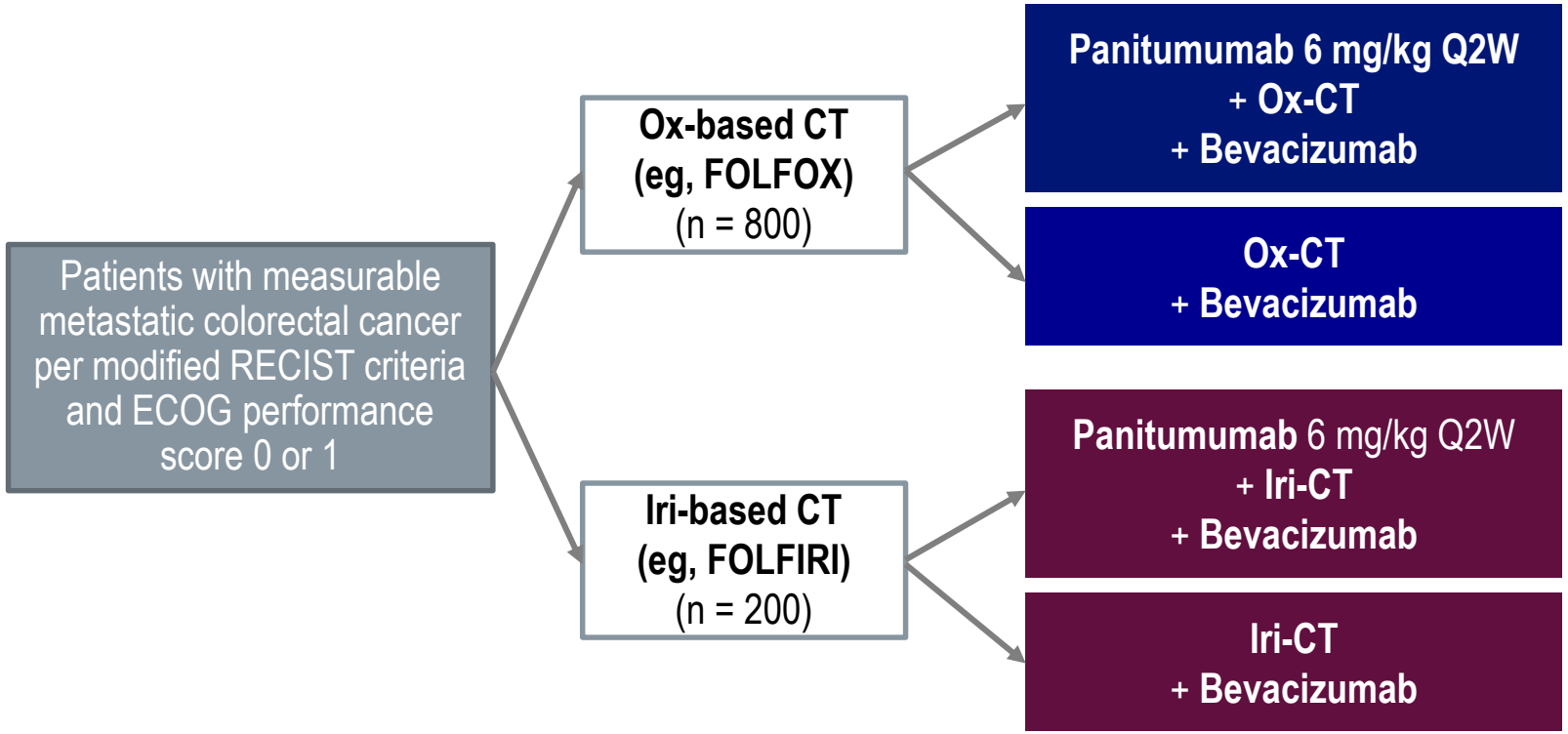
LESSON 12:

Combining different therapeutic approaches in some circumstances could be detrimental for the patient

Bevacizumab + EGFR monoclonal antibodies + chemotherapy in advanced CRC: Negative results

PACCE STUDY:

Panitumumab + chemotherapy + bevacizumab for mCRC



Tumour assessments: Every 12 weeks until disease progression or intolerability

Hecht JR, *et al*. GI Cancers Symposium 2008. Abstract 273.

PACCE TRIAL IN ADVANCED COLON CANCER:

Summary

Adding panitumumab to chemotherapy with bevacizumab did not prolong PFS

Trend toward inferior PFS and OS !

Toxicity frequent in both arms; incidence of serious adverse events higher in patients receiving panitumumab

Hecht JR, *et al.* GI Cancers Symposium 2008. Abstract 273.

LESSON 13:

Targeted therapy in combination with radiotherapy: A major delay in clinical research

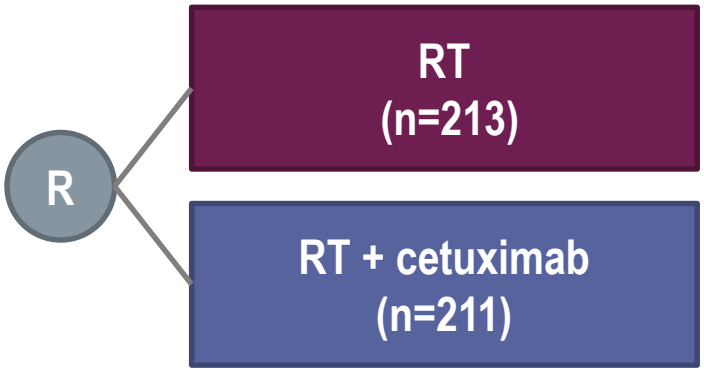
Cetuximab (EGFR inhibitor) in Head & Neck cancer is the only approved agent in combination with radiotherapy

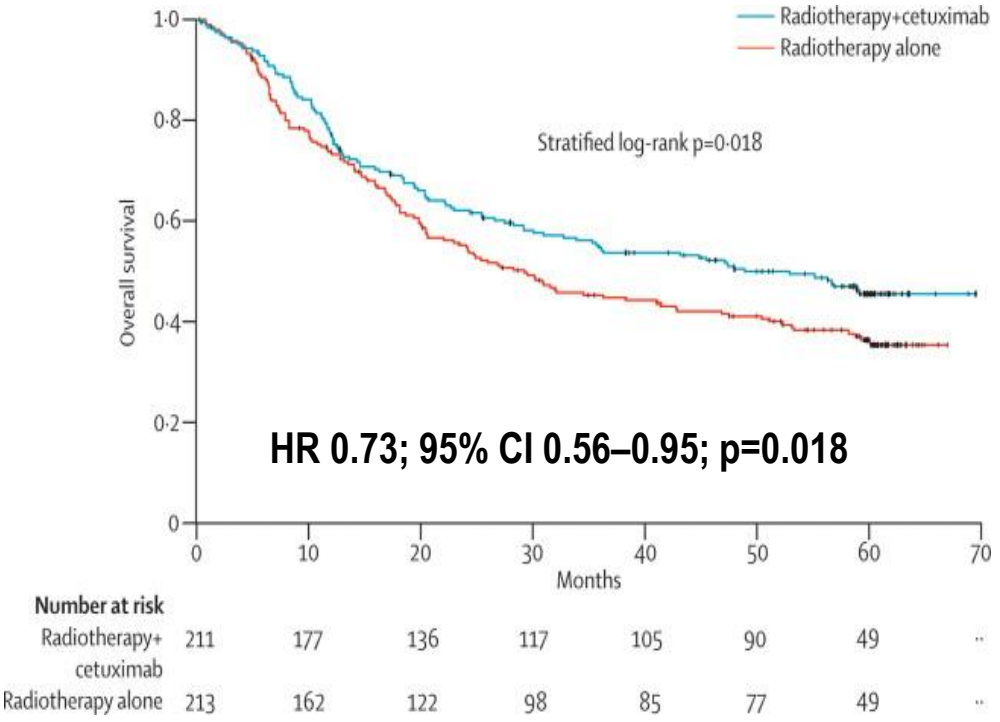
RADIOTHERAPY PLUS CETUXIMAB

For locoregionally advanced head and neck cancer: 5-year survival data from a Phase 3 randomised trial

Overall survival:

- RT cetuximab: 49 months
- RT: 29.3 months





Reprinted from The Lancet Oncol, 11(1), Bonner JA, *et al.* Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival, 21–8, Copyright 2010, with permission from Elsevier.

LESSON 14:

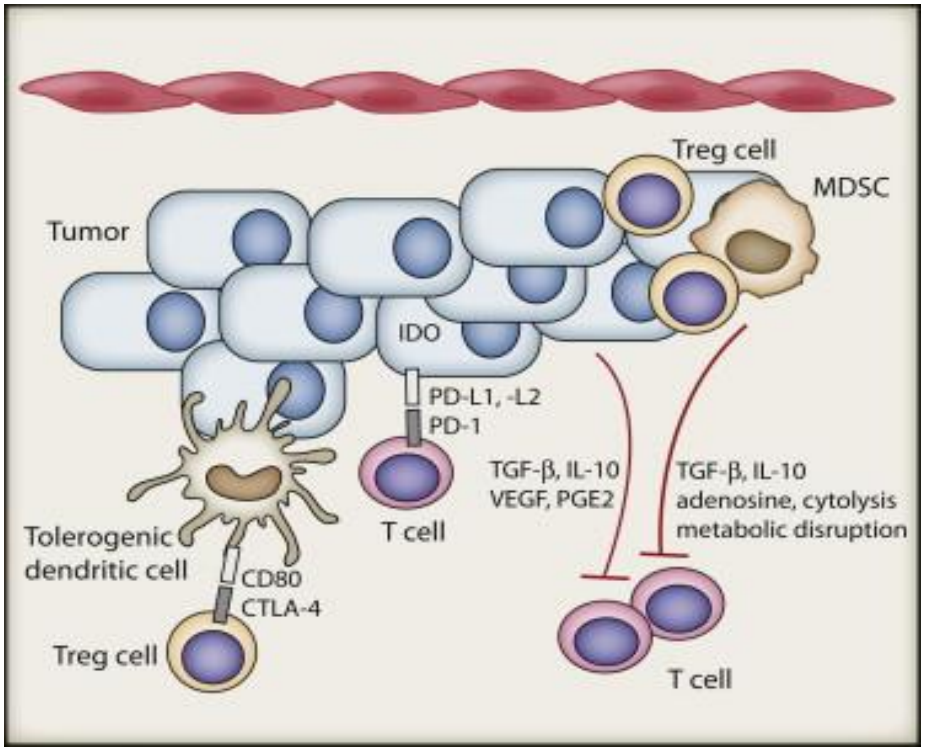
Immune modulation is revisited with success

Checkpoint inhibitors

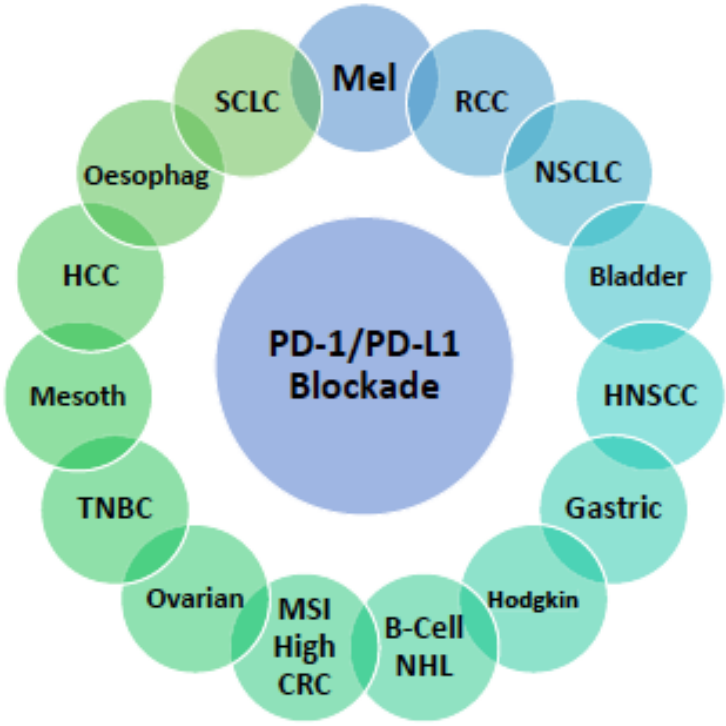
- In melanoma
- In NSCLC
- In Head and Neck SCC
- In bladder cancer and RCC
- MSI-H tumours
- More to come…

Vaccine in prostate cancer

IMMUNOTHERAPIES/ CHECKPOINTS INHIBITORS



Reprinted from Immunity;39(1), Motz GT, Coukos G. Deciphering and reversing tumour immune suppression, 61-73. Copyright 2013 with permission from Elsevier.



Michot JM, *et al.* Eur J Cancer 2016;54:139–48

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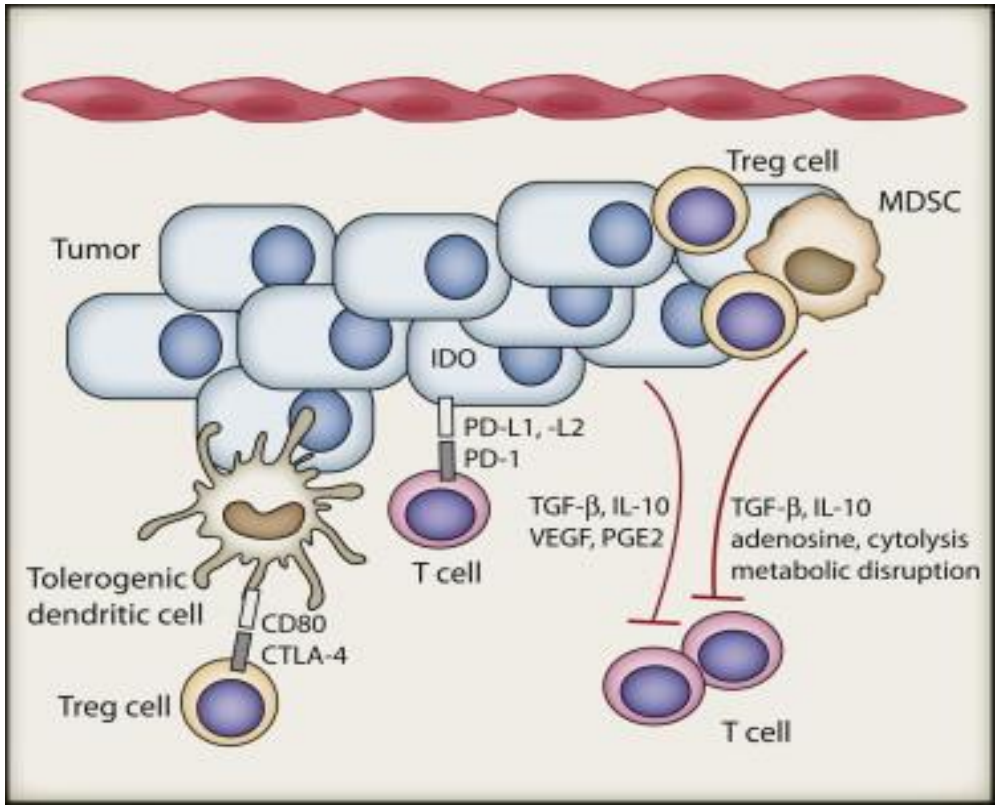
MECHANISMS OF ACTION

Anti-CTLA-4
Ipilimumab, …



Anti PD1: Pembrolizumab, Nivolumab, …

Anti-PD-L1: Atezolizumab, …

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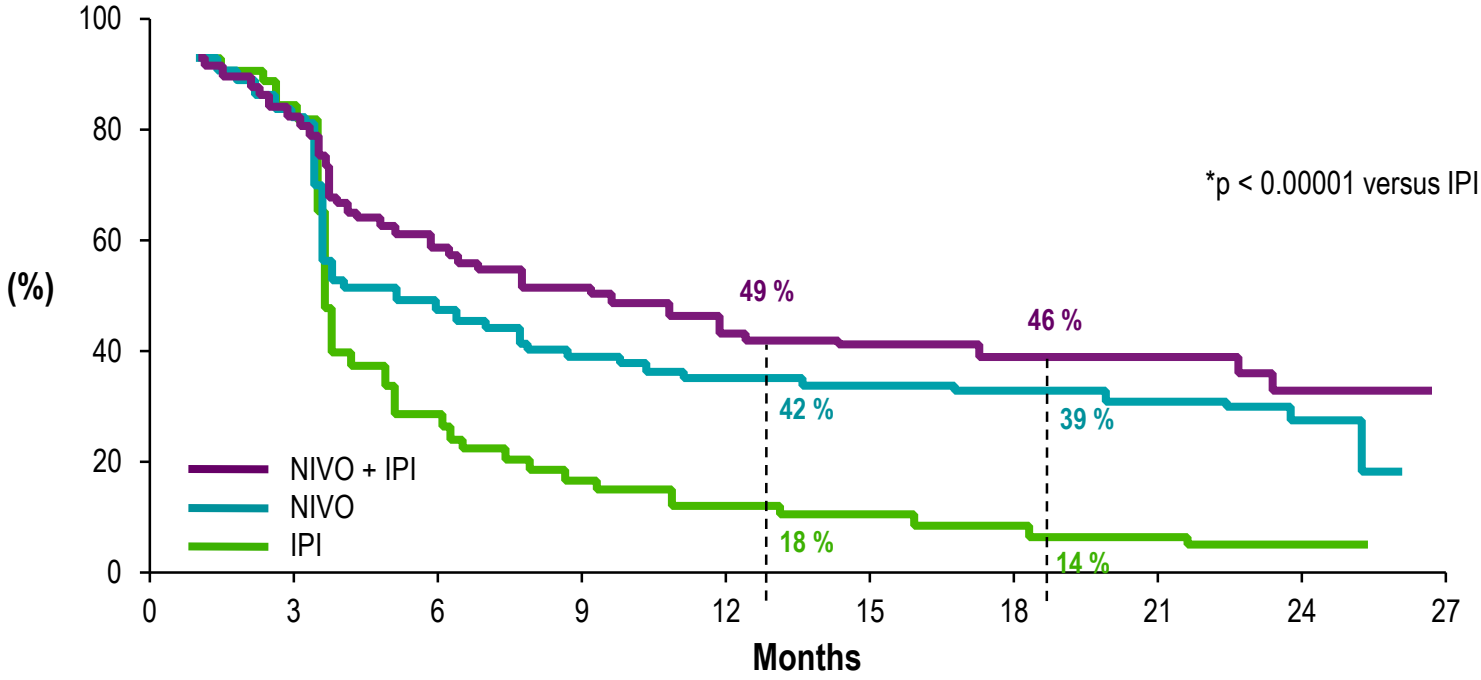
CHECKMATE 067:

Phase 3 study in previously untreated patients with advanced melanoma



	Nivo + Ipi (n=314)	Nivo (n=316)	Ipi (n=315)
Median PFS, months (IC $_{95}$)	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)

Wolchok JD, *et al*. J Clin Oncol 34, 2016 (suppl; abstr 9505). Reproduced with permission from Dr Jedd Wolchok.

LESSON 15:

Targeted therapy in selected tumours failed so far

The example of pancreatic cancer: >30 randomised trials failed to show survival advantage!!!

Absence of effective biomarkers for screening and early detection

Aggressive behaviour and resistance to the currently available chemotherapy

Inter-/intra- tumour genetic heterogeneity

Targeting key dysregulated signaling pathways in advance pancreatic cancers

LESSON 16:

Emergence of brain metastases is a major challenge in some tumours

Brain metastasis are more frequently seen as systemic control through targeted therapies improves

Major clinical problem in patients with advanced breast cancer, lung cancer, melanoma, and renal cell carcinoma

Challenge: Better understand how to optimise the activity of targeted agents in the CNS and how to best incorporate them into the clinical research and the current treatment paradigms

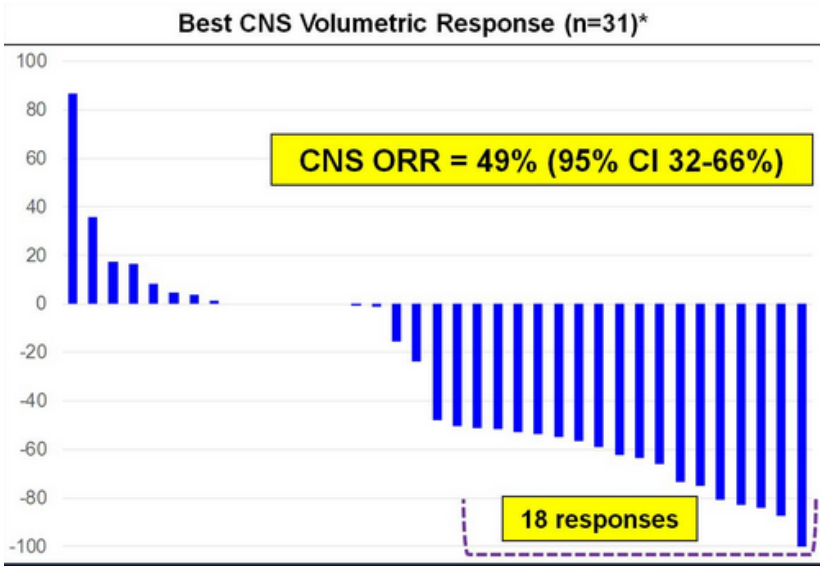
INCIDENCE OF CNS METASTASES

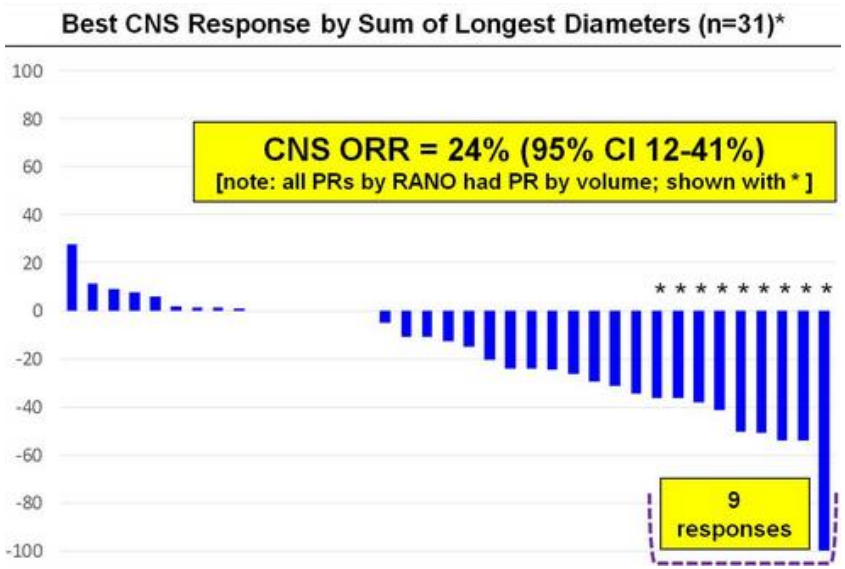
In HER2 advanced breast cancer treated with trastuzumab: 25-50%

Bendell *et al.* Cancer 2003	34%
Heinrich *et al.* ASCO 2003	43%
Brufsky *et al.* ASCO 2003	50%
Clayton et al. Br J Cancer 2004	25%
Altaha *et al.* ASCO 2004	33%
Stemmler *et al.* ASCO 2005	31%
Yau *et al.* Acta Oncol 2006	30% (at 1 y)
Gori *et al.* The Oncologist 2007	35%
Brufsky *et al.* ASCO BCS 2008	33.4%

TBRC 022: NERATINIB/CAPECITABINE

For the treatment of brain metastases in HER2 positive advanced breast cancer





Median survival: 13.5 mo (19 pts)

Freedman RA, *et al.* J Clin Oncol 35, 2017 (suppl; abstr 1005).

LESSON 17:

No single methodology to the development of new targeted agents is available. “Individualising” and “innovative” drug development methodology are a key for success

LESSON 18:

Standard radiological evaluation of tumour responses (RECIST) to targeted therapies could be misleading in some circumstances

RECIST-based criteria, originally developed to assess response to cytotoxic chemotherapeutic agents

Prolong disease stabilisation rather than substantial tumour regression was seen with targeted agents as well as changes in tumour density, …

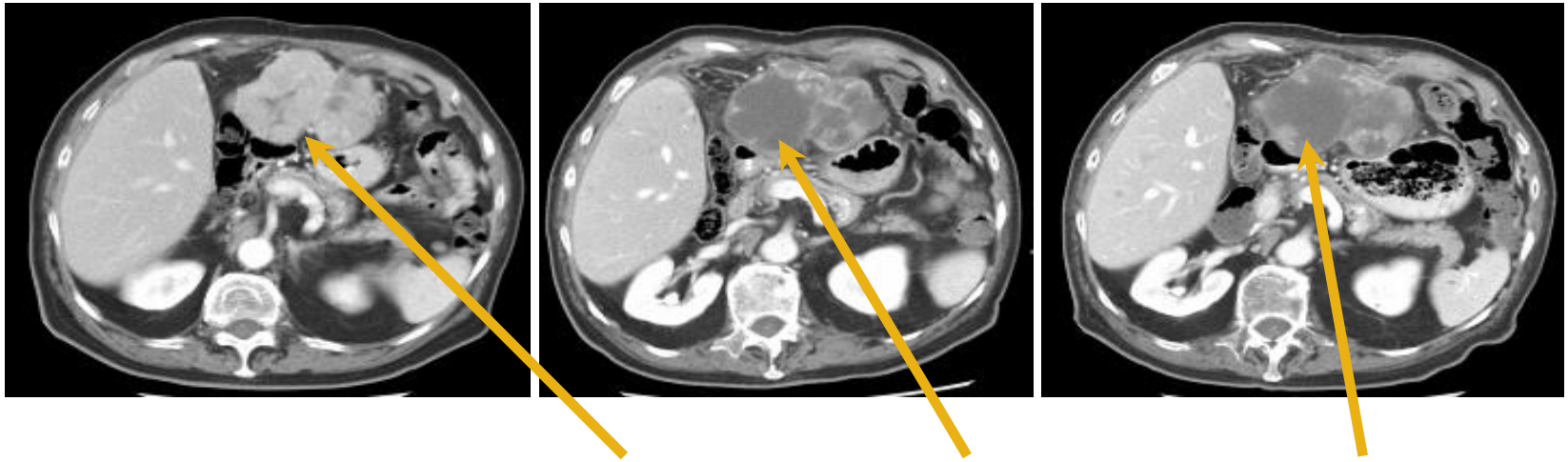
- Development of new response evaluation criteria is needed for selective drugs
  - Tumour growth rate index was proposed

New imaging techniques : PET-CT, DCE, US

DRAWBACKS OF STANDARD RESPONSE CRITERIA

With targeted agents: tumour volume *vs.* tumour necrosis

Sorafenib treatment (400 mg b.i.d.)



	Baseline	8 weeks	16 weeks
Tumour volume (cm^3)*	295	341	285
Tumour necrosis (%)*	2.09	53.07	51.03

*Assessed by modified WHO criteria

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Abou-Alfa G, *et al.* J Clin Oncol 24(26), 2006:4293–300. Reprinted with permission.

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LESSON 19:

Major challenges in the era of targeted therapies

Not to repeat mistakes

To learn from the past history in clinical research

Not to be prisoner of administrative bodies

To be rational and innovative

To individualise clinical research

LESSON 20 AS A CONCLUSION:

What could be done to maximise the patient's chance of benefiting from a new targeted therapy (1)

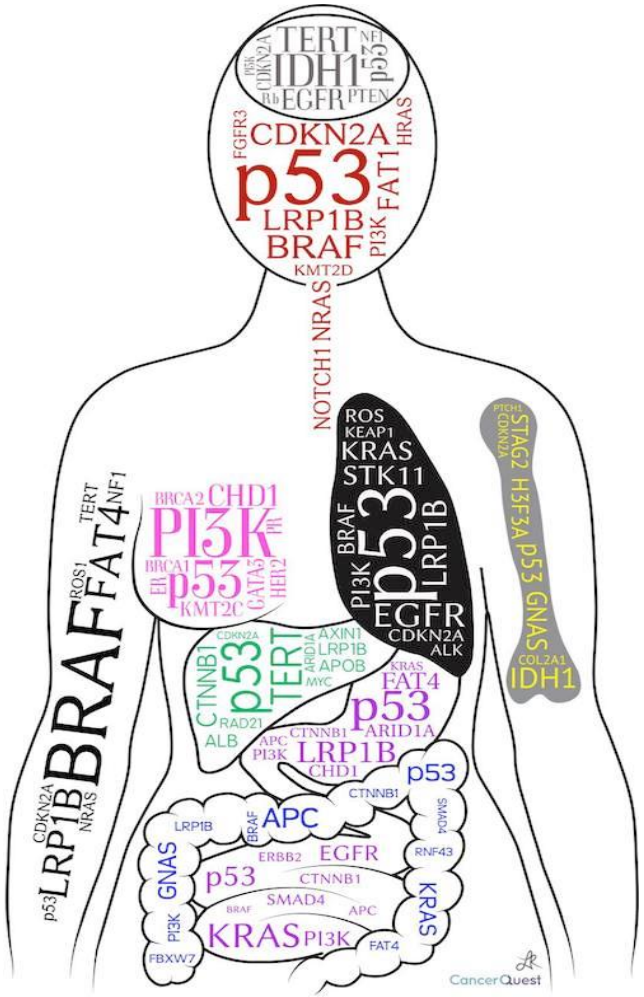
1. Importance of the target and the selectivity of the new agent
2. Keep in mind to find whenever possible the « context of vulnerability » in the host as well as in the cancer cell:
    - Clinical data
    - IHC/FISH, …
    - Genomic (specific gene sequencing, CGH, complete sequencing, …)
    - Other technics to come
3. Use of all available and validated tools to maximise the value of the results from a clinical trial

LESSON 20 AS A CONCLUSION:

What could be done to maximise the patient's chance of benefiting from a new targeted therapy (2)

4. Each patient in a clinical trial should be analysed carefully in particular if efficacy was documented
5. Perform mainly prospective trials
6. Perform innovative and « smarter » clinical trials design taking into account:
   - The patient
   - The tumour
   - What it is known about the evolution of the disease
   - The characteristics of the experimental drug

HYPOTHESIS:



Targeting the molecular mechanisms involved in cancer improves outcome

THANK YOU!

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