National Cancer Institute

Director's Consumer Liaison Group Meeting, September 22, 2011, Washington, DC

From Target Discovery to Therapy - Clinical Development of Single or Combinations of Anticancer Drugs

Helen Chen, M.D.

Associate Chief and Senior Investigator

Investigational Drug Branch

Cancer Therapy Evaluation Program (CTEP)

National Cancer Institute

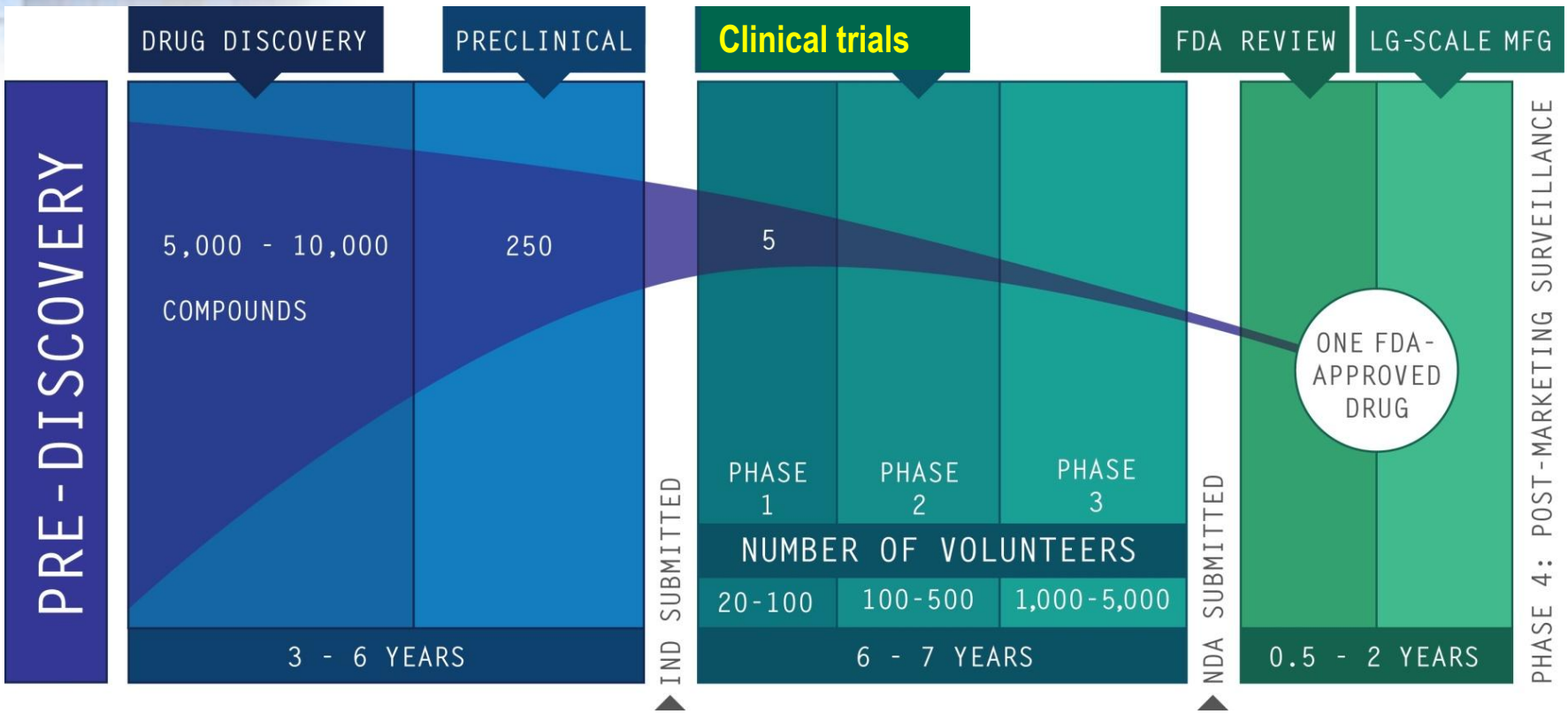
Outline

- Translation from Biology to Therapy
  - Examples of trials, failures and success
- Challenges
- Combination of molecularly targeted agents (MTAs)
- Future directions

A partial list of FDA approvals of molecular targeted agents (MTAs)

	Target (indications)	Drugs	
•Signal transduction	• **BCR-ABL** – *CML*	***Imatinib, Nilotinib***	
	• **C-KIT** – *GIST, Melanoma*	***Imatinib***	
	• **EGFR** – *NSCLC, CRC, SCCHN , pancreatic ca*	***Erlotinib, Cetuximab, Panitumumab***	
	• **PDGFR mutation** – *GIST*	**Sunitinib**	
	• **HER2 amplification** – *breast, gastric ca*	***trastuzumab, Lapatinib***	
	• **mTOR** – *RCC, mantle cell , pancreatic neuroendocrine tumors*	***Temsirolimus, Everolimus***	
	• **EML-ALK translocation** – *NSCLC*	***Crizotinib***	
•Protein/epigenetic modulation	• **BRAFV600 mutation** - *melanoma*	***Vemurafenib***	
	• **Proteosome** – *myeloma, lymphoma*	***Bortezomib***	
	• **HDAC** – *cutaneous T cell lymphoma*	***Vironastat, Romidepsin***	
•Angiogenesis	• **VEGF** – *RCC, CRC, NSCLC, neuroendocrine tumor*	***Bevacizumab, Sorafenib, Sunitinib, Pazopanib***	
•Immunotherapy	• **CTLA-4** – *Melanoma*	***Ipilimumab***	

Drug Development – Traditional Model



One FDA-Approved Drug - Start to Finish

- 10- 15 Years
- 1,000 – 6,000 Patient Volunteers
- $1 Billion

What are required for transition from target discovery to successful therapy

- **Identify the unique target**
  .... define the functional relevance within the appropriate molecular contexts
- **Make the right drug** (potency, specificity, bioavailability)
  ... used at the right dose and schedule, in the right regimen (monotherapy or combination)
- **Use in the right patient** (with susceptible molecular features)
  … in the right clinical setting

Examples for discussion

- **Vemurafenib** (BRAFV600E inhibitor)
- **Erlotinib** (EGFR inhibitor)
- **Crizotinib** (C-MET and ALK inhibitor)
- Antiangiogenic agents, and others

Targeting BRAF activating mutation

- From sorafenib to vemurafenib

… search for the right drug

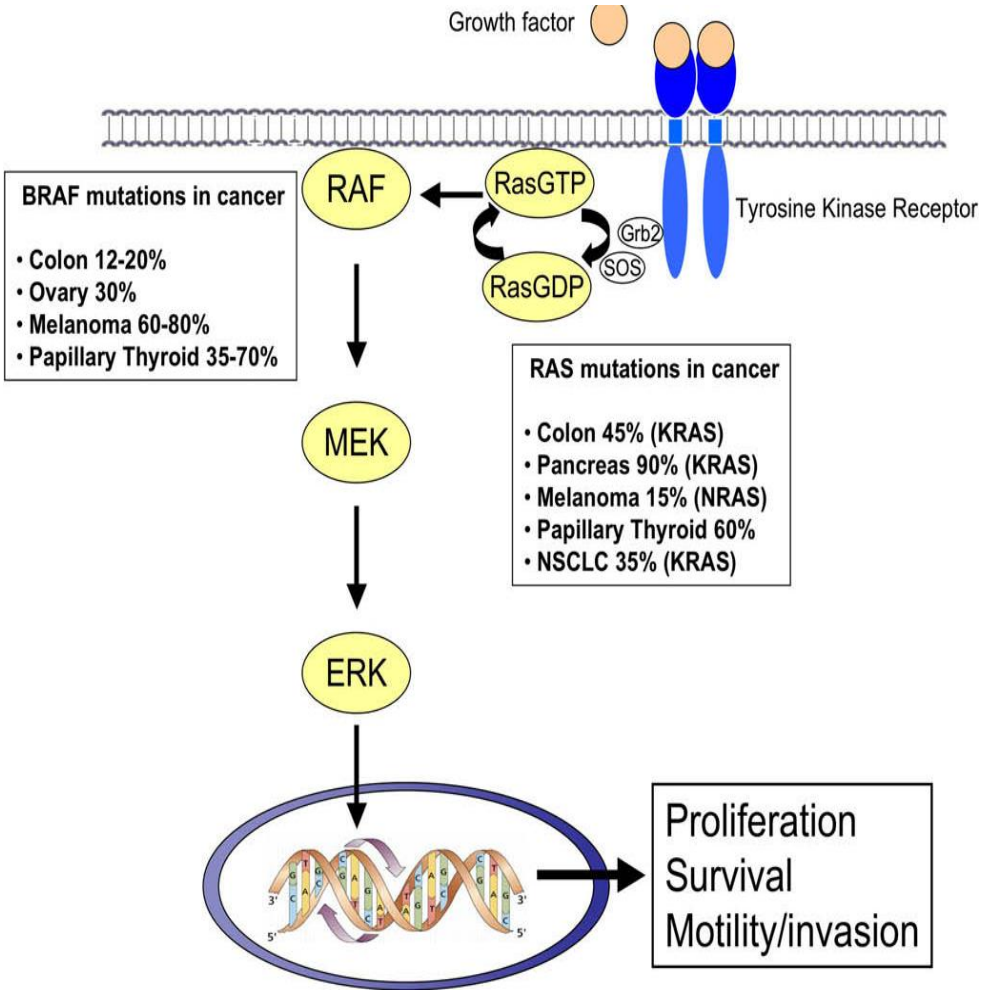
Target discovery – 1980's, 2002

- **19080's: RAS- RAF activation important in cancer**

- **2002: Davies et al, Nature 2002**

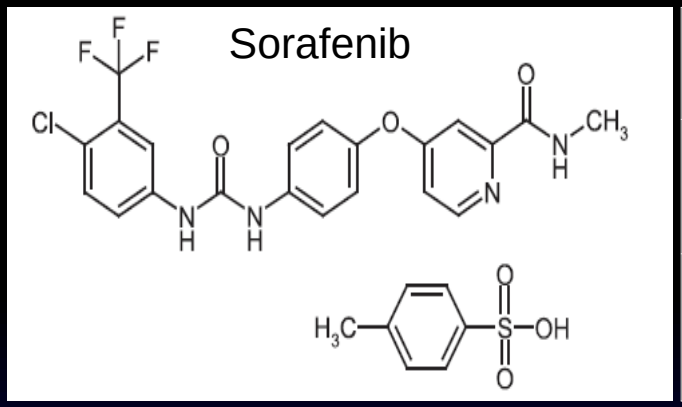
Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]



- Targets that are unique to cancer are ideal
- However, need specific and potent agent to achieve the potential therapeutic window

Drug discovery – against BRAF mutant cancers
- Sorafenib (Phase 1 trial in 2001)

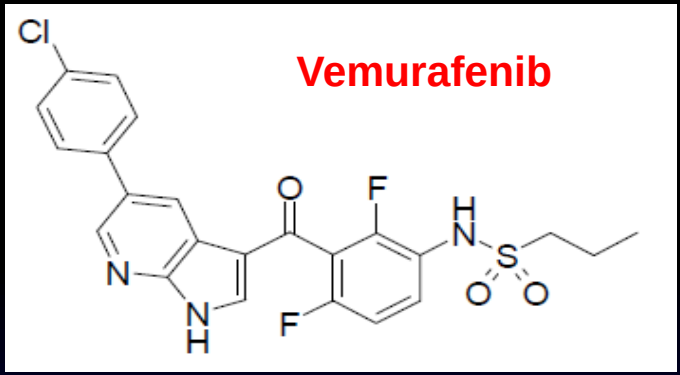


	IC50 (nM)				
	BRAF-V600E	BRAF	PDGFR	C-KIT	VEGFR2
Sorafenib	38	22	57	68	90

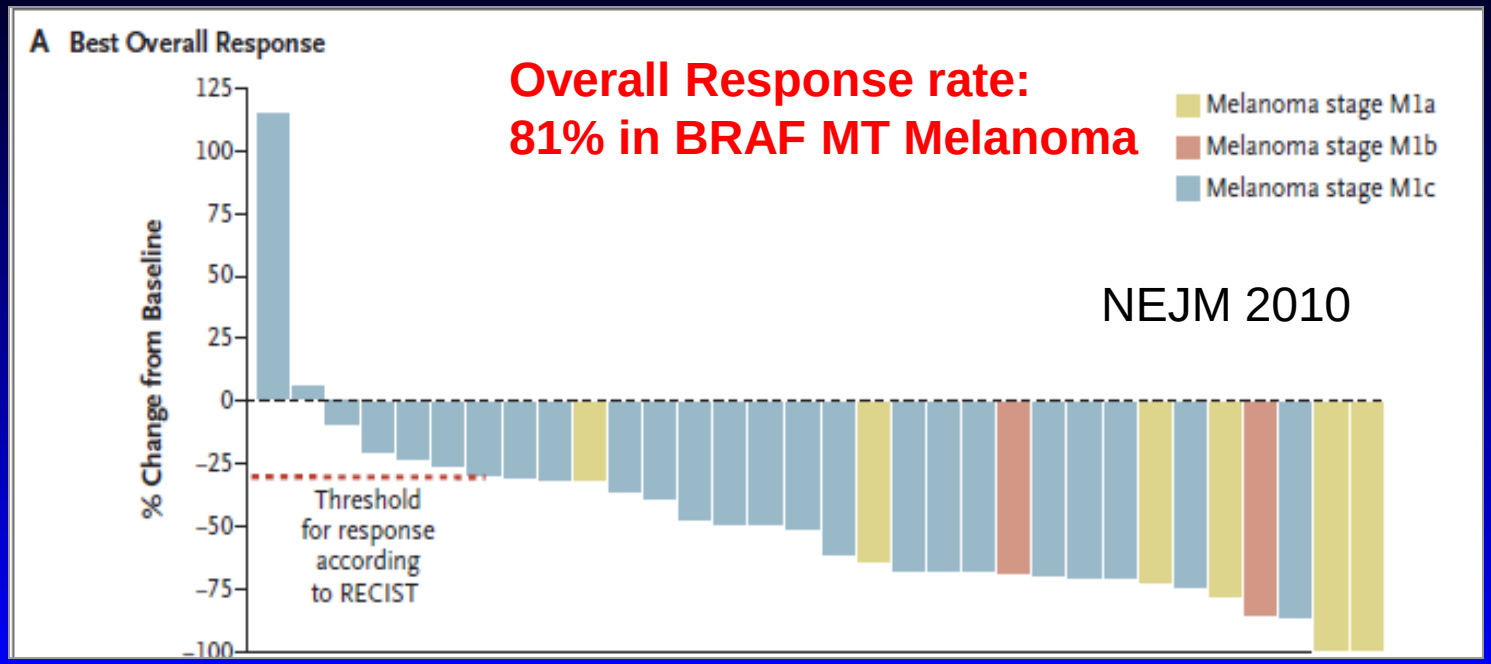
- Designed to target Raf1, however ….
  - Nonspecific and low potency against mutant BRAF
  - High "off-target" toxicities
- Not active in melanoma with B-raf mutation
  - Response rate 1/36, no correlation with the BRAF status
  - Phase III trials in combination with chemotherapy – NEGATIVE!

Drug discovery – against BRAF mutant cancers

- Vemurafenib (PLX4032, ZALBORAF) (phase I in 2006)

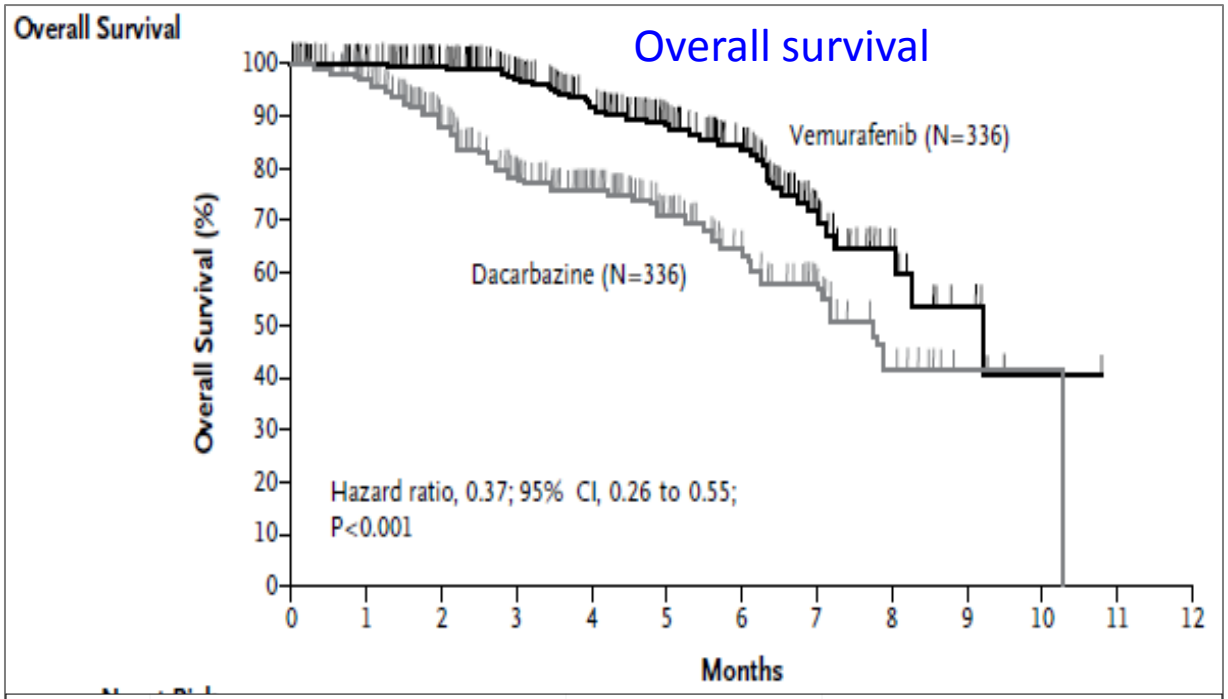


	IC50 (nM)				
	BRAF-V600E	BRAF	PDGFR	C-KIT	VEGFR2
Sorafenib	38	22	57	68	90
PLX4032	13	130	> 1000	> 1000	ND



FDA approval of Vemurafenib - 2011

Phase III trial of Vemurafenib vs. standard chemotherapy in late stag melanoma with BRAFV600E mutation



	Vemurafenib	Dacarbazine	
ORR	48%	5%	
PFS	5.3m	1.6m	HR 0.22 (P< 0.0001)
OS	Not reached at 9.6m	7.9m	HR 0.44 (p< 0.0001)

The NEW ENGLAND JOURNAL of MEDICINE

Chapman et al, NEJM 2011

- **The story of EGFR small molecule inhibitors**
  - » ***Erlotinib (Tarceva)**
  - » ***Gefitinib (Iressa)**

….. Search for the right patients

EGFR TKIs are active in NSCLC

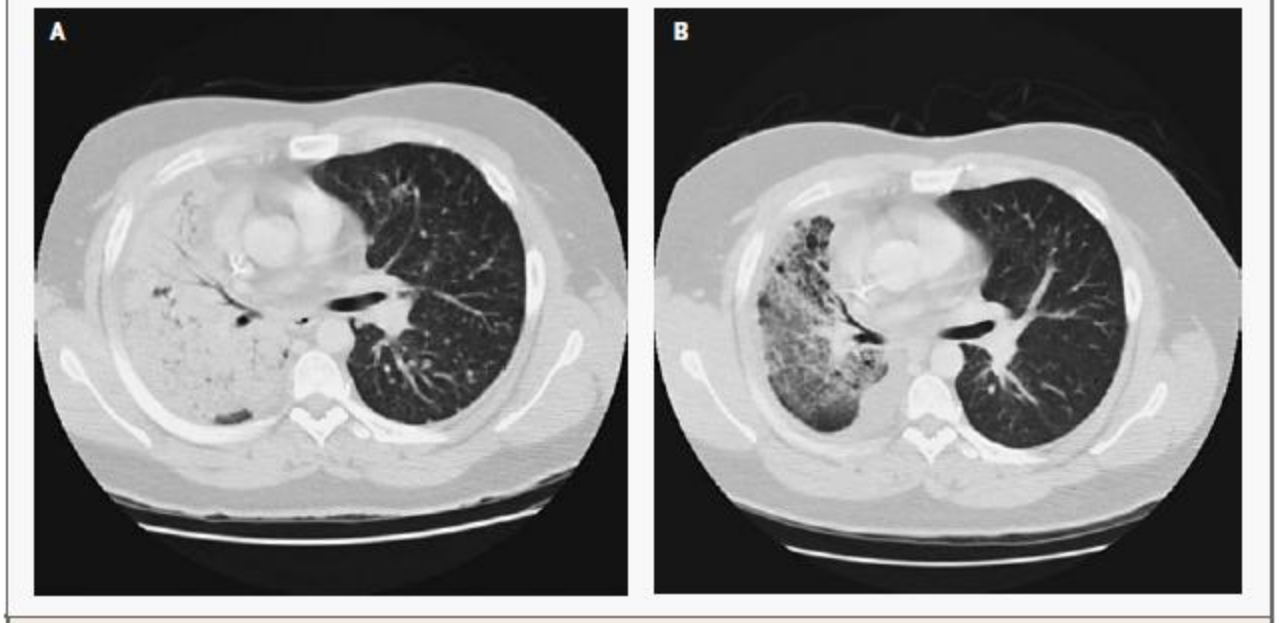


Figure 1. Example of the Response to Gefitinib in a Patient with Refractory Non–Small-Cell Lung Cancer.
A computed tomographic scan of the chest in Patient 6 shows a large mass in the right lung before treatment with gefitinib was begun (Panel A) and marked improvement six weeks after gefitinib was initiated (Panel B).

- Response rate: **10%** in North America patents with Nonsmall cell lung cancer (NSCLC)
- Predictive markers unknown

- **May 2003, FDA granted accelerated approval of Iressa (based on ~10% RR)**
- *Full approval requires positive results from the Phase III trial (based on survival endpoint)*

Phase III trials of Erlotinib or Gefitinib in advanced lung cancers (patient # = 6716)

Trials	N	EGFR TKI	Outcome (Survival benefit)
ISEL	1692	*Gefitinib* vs, Placebo	Negative
INTACT1	1093	*Gefitinib* + Chemo vs. chemo	Negative
INTACT2	1037	*Gefitinib* + Chemo vs. chemo	Negative
TALENT	1172	*Erlotinib* + chemo vs. Chemo	Negative
TRIBUTE	1079	*Erlotinib* + Chemo vs. Chemo	Negative
BR21	638	*Erlotinib* vs Placebo	Positive (marginal benefit: OS 4.7 to 6.7 m)
	6717		

- Iressa did not meet the criteria for full approval by FDA
- Tarceva approved in Nov 2004, based on modest OS improvement

2004 – EGFR mutation in Patients with significant responses to Tarceva/Iressa

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

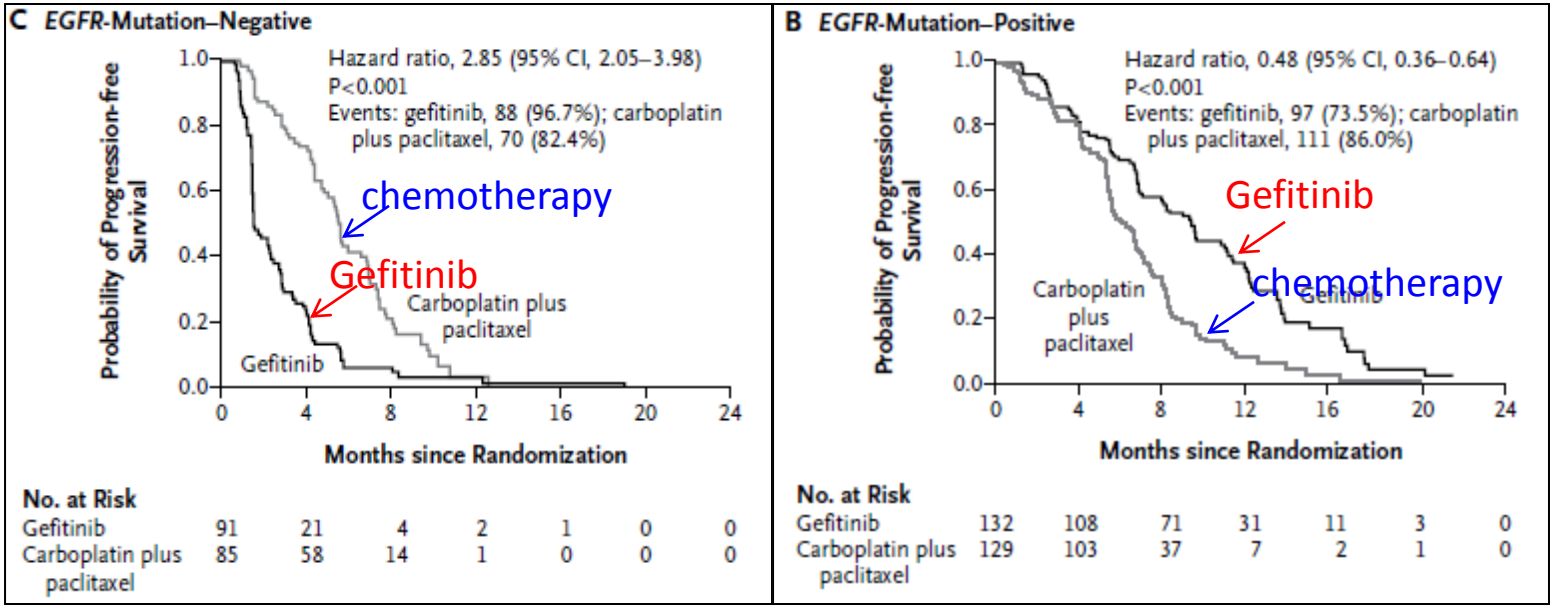
EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

EGFR mutation Predicts tumor response to EGFR TKIs:

- **Tumors with EGFR Mutation: Response rate 53-94%**
- **Tumors with wide type EGFR : Response rate 1%**

EGFR TKI in biomarker-defined patient population, as compared to 1st-line chemotherapy



- ***Without patient selection*** **- no difference between chemotherapy vs. Gefitinib**
- ***In patients <u>without</u> EGFR mutation*****: Gefitinib was <u>worse</u> than chemotherapy**
- ***In patients <u>with</u> EGFR mutation*****: significant benefit with Gefitinib**
  - **Progression free survival at 12 months: 24.9% vs. 6.7%, compared to the standard chemotherapy**
  - **(OS difference difficult to assess due to crossover)**

Crizotinib
- a c-MET and ALK inhibitor

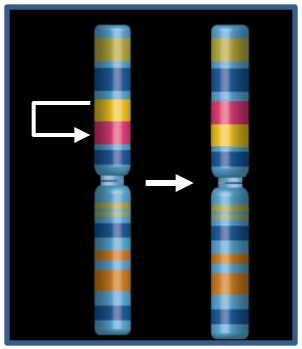
… when everything happens at the same time

The story of Crizotinib – a c-MET and ALK inhibitor

- **2007: Target discovery** (EML4-ALK fusion protein) **in NSCLC**

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

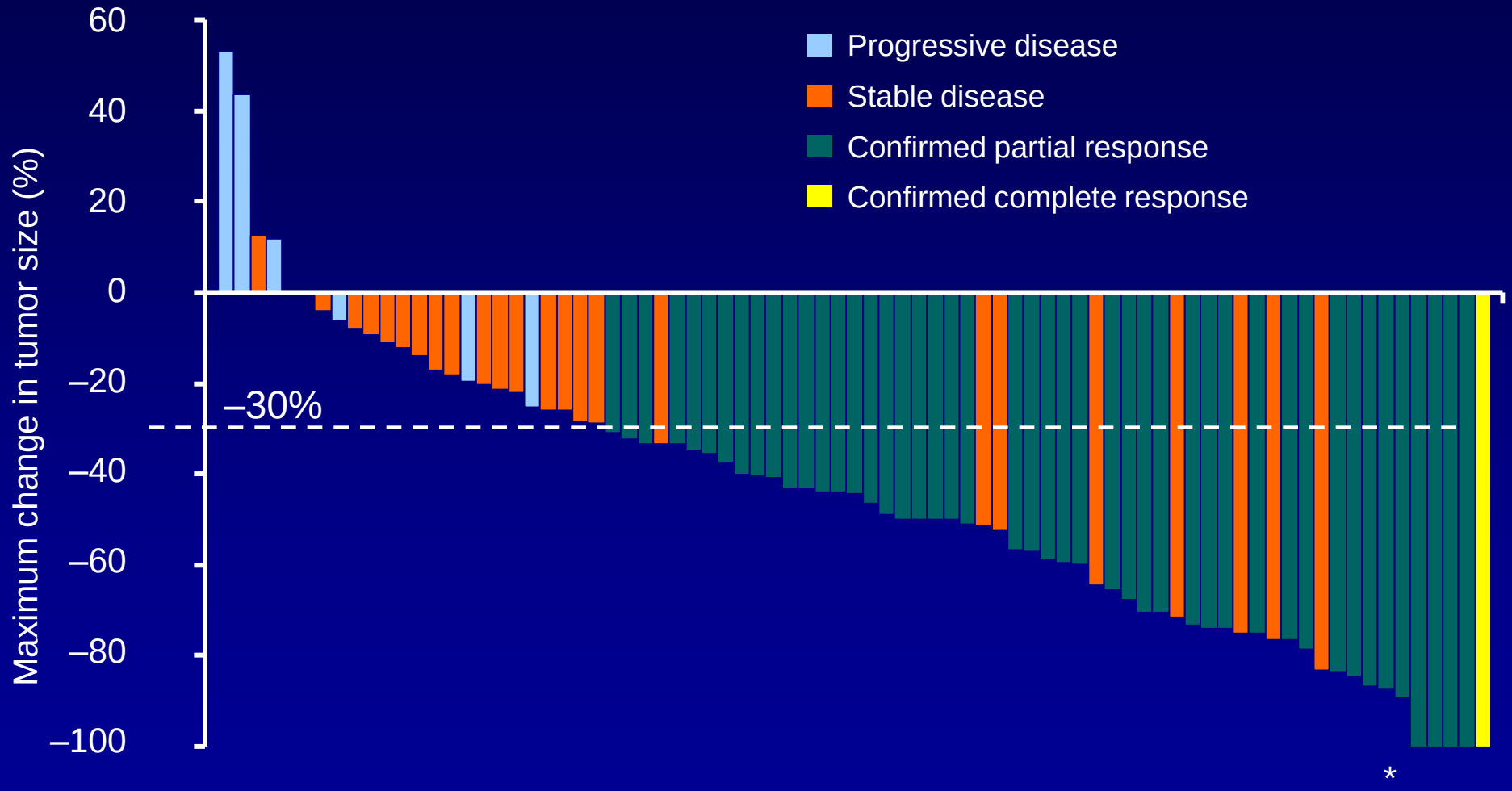
Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



Soda, M *et al.* *Nature* 448: 561-566

- **2011: FDA approval of the agent for patients with lung cancers bearing the genetic alteration**

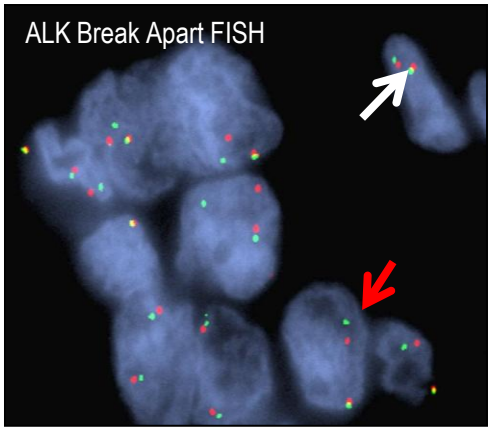
Tumor Responses to Crizotinib for Patients with *ALK*-positive NSCLC (expansion cohort in the phase I trial)

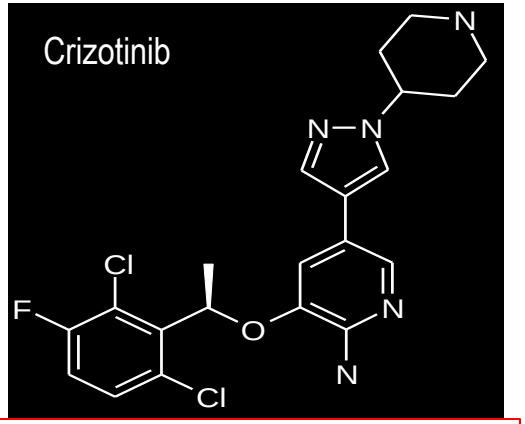


*Partial response patients with 100% change have non-target disease present

Elements critical to success of Crizotinib

- **Strong rationale for the target**
  - Driver single genetic alteration
  - Target unique to cancer cells
- **Rapid development of the diagnostics**
  - FISH (Vysis)
- **Availability of a potent inhibitor at the time of target discovery**
  - Crizotinib (a c-MET and ALK inhibitor)
- **Rapid adaptation of the clinical trial**
  - Protocol modified for ALK+ lung cancer





- Similar rapid translation may occur again with the convergence of scientific, medicinal and diagnostic development
- However, significant challenges must be addressed for the majority of tumors and targets

Challenges

Most cancer therapies, approved or investigational, do not (yet) have predictive markers

- **Targeted Agents with <u>known</u> predictive markers**
  - **Trastuzumab (**HER2 FISH)
  - **PLX4032 or GSK 212** (BRAFV600E)
  - **EGFR TKI (**mutation**)….**
  - **Imatinib** (BCR-ABL; PDGFRA; c-KIT mutations)
  - **PARP** (BRCA1/2)

  (limited tumors and low frequency)

- **Targeted agents <u>without</u> predictive markers**

  Approved
  - **EGFR** (in EGFR WT)
  - **mTORi**
  - **VEGFi**
  - **Proteosome (**Bortezomib)
  - **HDACi** (vorinostat)
  - **CTLA4i**

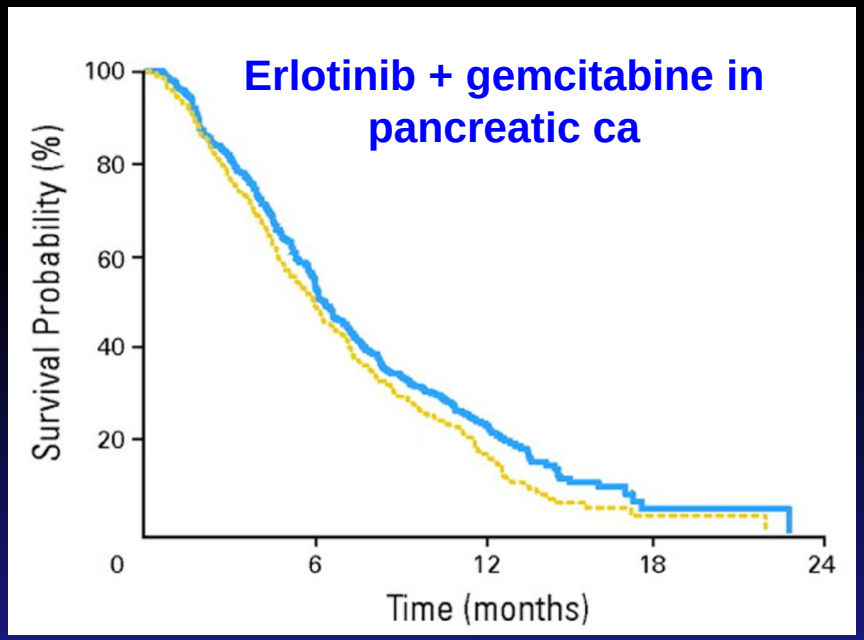
  Investigational
  - **IGF-1Ri**
  - **BCL-2 family i**
  - **SRCi**
  - **Cancer "stem "cell agents**
  - **…..**

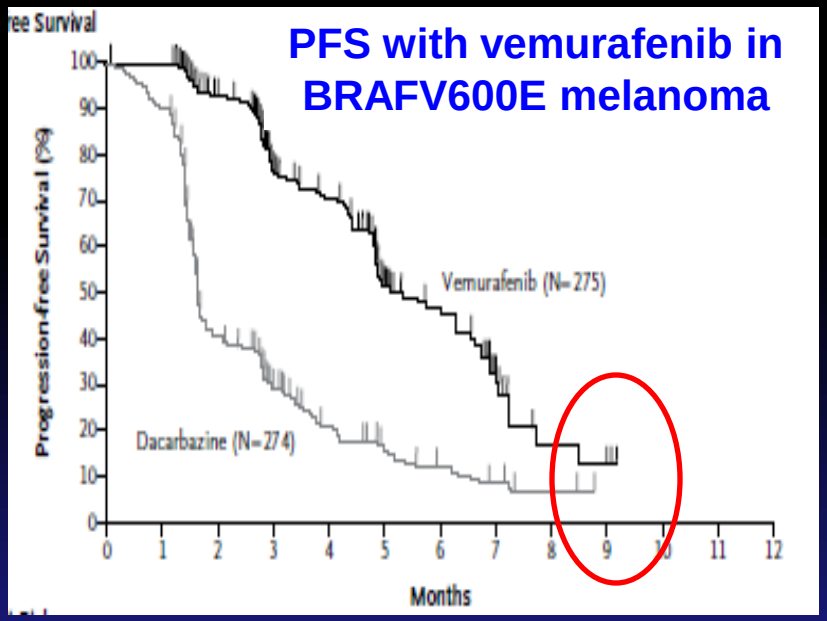
- **Agents with possible but <u>unconfirmed</u> predictive markers**

  Investigational
  - **AKT/PI3K inhibitors** (mutations, activations …)
  - **C-MET/HGF inhibitors** (Mutation, amplification, IHC)
  - **MEKi** (RAS, RAF mutations + other)
  - **PARPi** (for combination)
  - **…..**

- **Tumors driven by a single gene/protein alterations are rare**
- **Development of predictive markers based on multi-gene/multi-analyte assays are statistically and technically difficult**

Disease control with most cancer therapies are either modest or transient





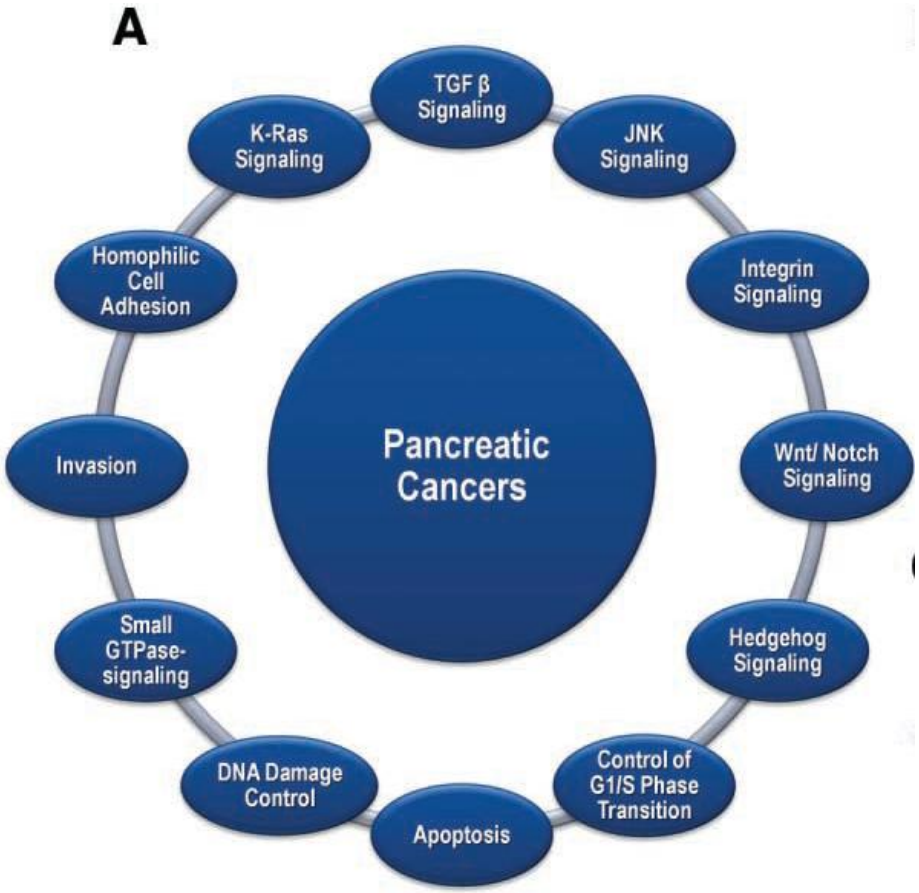
Agents with proven but modest *activities*:

- *Cetuximab (colon ca)*
- *Bevacizumab and VEGF TKIs*
- *mTOR inhibitors in RCC*

Agents with acquired resistance within months despite initial response

- *Crizotinib, vemurafenib, erlotinib,*

Tumor growth/survival pathways are complicated – de novo resistance to single-targeted therapy



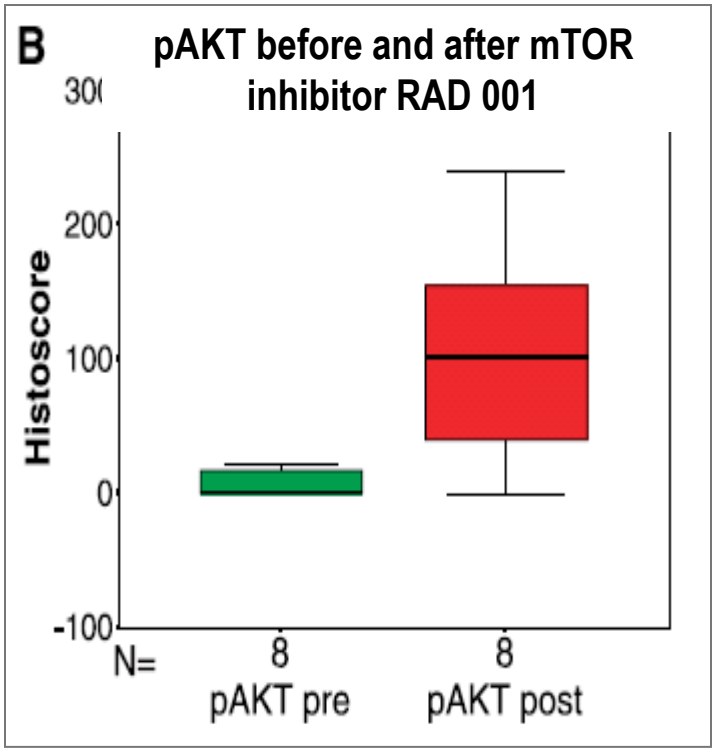
The Cancer Genome Atlas (TCGA) –Pancreatic ca

- **63 genetic alternations**
- **12 core pathway/processes activations in most patients**

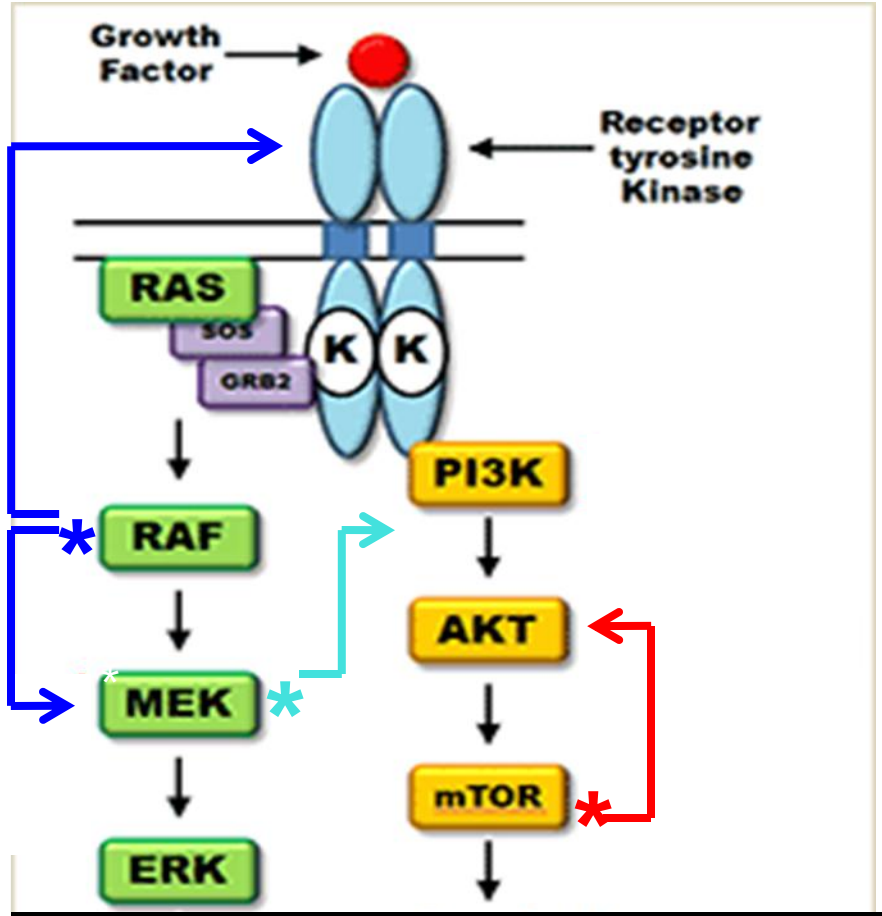
- ***Implication for therapy and targets***
  - ✓Targeting an individual gene may not be sufficient

Tumor growth/survival pathways are adaptive

Clinical observations from post-Rx biopsies …



O'Reilly et al, CR 2006 and others



Escape induced by target inhibitions

- mTOR ↓ → IGF-1R/AKT activation
- BRAFV600E ↓ → C-RAF/MEK activation
- MEK ↓ → AKT/PI3K activation
- EGFRi → new gene mutation,

Strategies to optimize the therapeutic outcome

- **Deeper molecular characterization of the tumors**
  - Define molecular contexts in addition to single gene mutation
    - At baseline and at progression
- **Rational combinations among MTAs**
- **Targeting tumors beyond the complexity of tumor-based pathways**

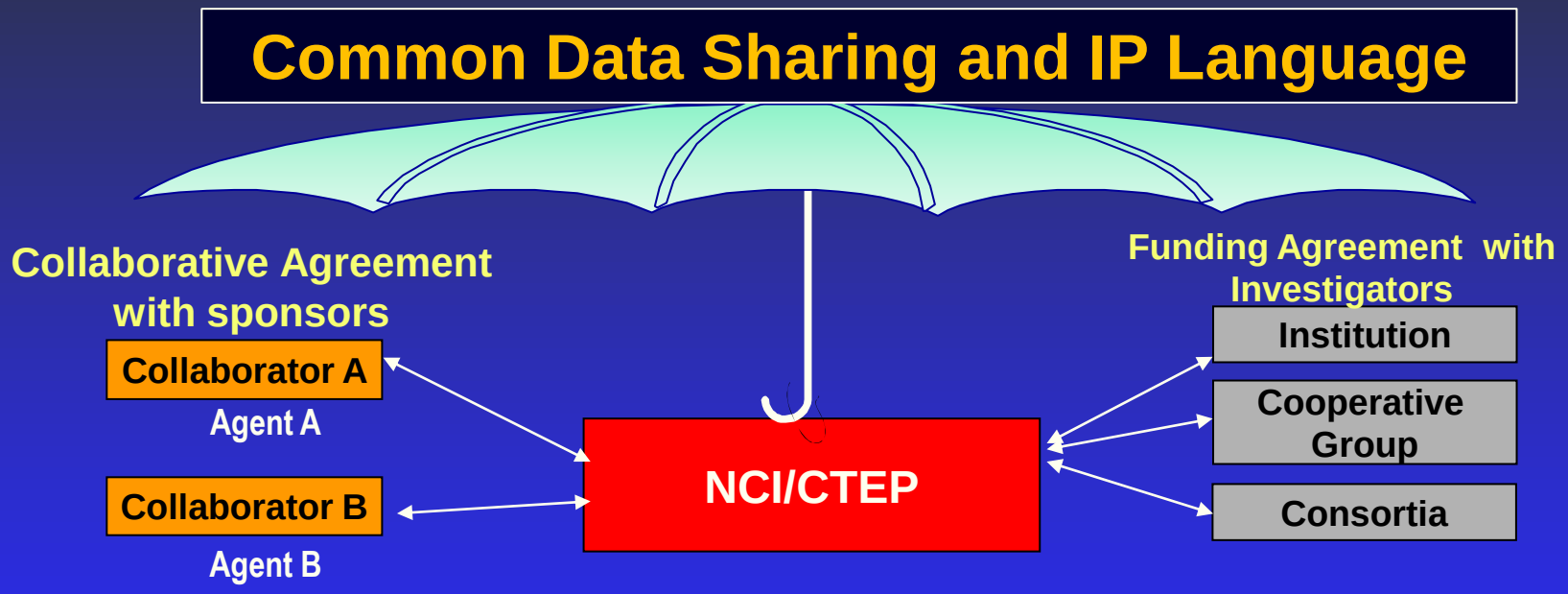
Critical Molecular Pathway Project - a DCTD initiative in 2003

In 2003:

- Emergence of promising agents and validated targets
  - EGFR, VEGF, mTOR in development (not all were FDA approved yet)
  - Clinical benefits were evident but modest
  - Combinations to target parallel pathways, linear signaling molecules and resistance mechanism were high priority

- DCTD, at Wye River Retreat with extramural experts, formulated the pilot project for novel agent combinations
  - **Targets and agents prioritized:** **EGFR** (erlotinib), **RAS/RAF**(Tipifarnib) **VEGF** (bevacizumab, sorafenib) **mTOR** (temsirolimus)
  - **Tumour types:** ***GBM, RCC and melanoma***

Industry-NCI/CTEP-Investigator Agreements for combination studies



CTEP

- Develop scientific strategy; solicit clinical trial concepts
- Sponsor and hold IND for combination protocols
- Device master IP, contract language

Examples of trials from the pilot project in 2003 (VEGF, EGFR, mTOR, RAS/RAF)

ECOG 2804
(BeST)
RCC
(VEGF, mTOR)

- Bevacizumab
- Bevacizumab + Sorafenib
- Bevacizumab + CCI-779
- CCI-779 + Sorafenib

NABTC 05-052
GBM
(VEGF, mTOR, EGFR)

- Sorafenib + CCI-779
- Sorafenib + erlotinib
- Erlotinib + CCI-779

SWOG-0438
Melanoma
(VEGF, mTOR, raf/ras)

- Sorafenib + CCI-779
- Sorafenib + tipifarnib

- Rational treatment and study designed based on best available knowledge
- *However,*
  - *No available patient selection markers*

- **Mandatory baseline tissue collection and central banking**
- **Central depository of imaging data (DCE-MRI)**

MTA combinations can be toxic

Sorafenib + CCI-779 (VEGF + mTOR) *Patnaik, et al, ASCO 2007*

Dose Level	Sorafenib	CCI-779	Pt #
1	200 mg bid	15 mg	6
2	400 mg bid	15 mg	11
3 (full dose)	400 mg bid	25 mg	6
3 (a)	**200 mg bid**	**25 mg**	**10**

→ **Final dose** (50% dose ↓)

DLT: G3 hand and foot syndrome
G3 cytopenia

- G3 renal dysfunction
- G3 rash, G3 typhitis

Most MTAs are not tolerable at full doses with prolonged therapies

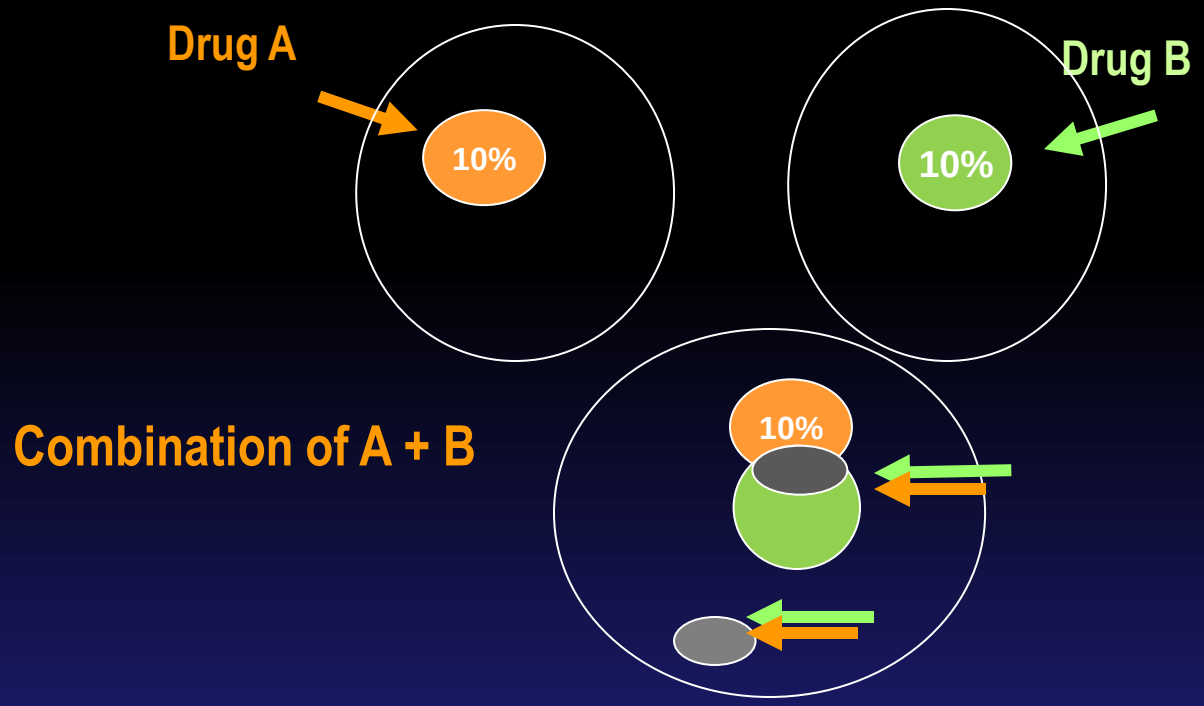
Combinations with dose ↓

- Bevacizumab + VEGF TKIs
- VEGF TKIs + mTORi
- IFNα + CCI-779
- EGFR + MEKi
- Erlotinib + mTOR
- AKTi + MEKi

Combinations with treatment duration ↓

- Bevacizumab + cetuximab (+ chemo)
- Bevacizumab + temsirolimus
- ….. Most MAT combinations

Identification of Patient Selection is Challenging for MTA Combinations



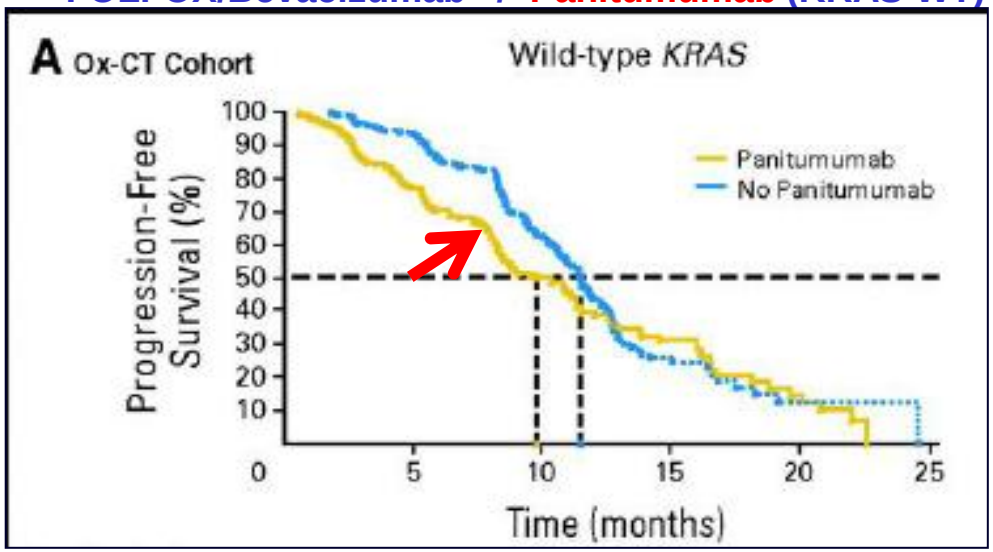
- **Predictive marker for single agents not always known**
- **Marker for combination may differ from that for single agents**
- **<u>Without</u> predictive markers …**
  - A patient may be unnecessarily exposed to both agents, even if only one or neither is working;
  - A trial may miss a true signal of synergism

FOLFOX + BV + *EGFR mAb* *vs.* FOLFOX + BV

More is Less!

PACCE trial

FOLFOX/Bevacizumab +/- Panitumumab (KRAS WT)



	Chemo +BV + Panitumumab	Chemo + BV	*HR*	*P*
RR	50%	56%		NS
PFS	***9.8 m***	11.5m	*1.36*	
OS	***20.7m***	24.5m	*1.89*	*0.045*

Hecht, J. R. et al. J Clin Oncol; 27:672-680 2009; Tol Et al, NEJM 2009

Current status of novel combinations between MTAs

	Therapeutic enhancement? (RR, PFS)	Clinical benefit? (sustained tumor control; significant survival benefit)
• Chemo A + Chemo B	√	√
• MTA + Chemo or RT	√	√
• MTA 1 + MTA 2	√	Not, yet

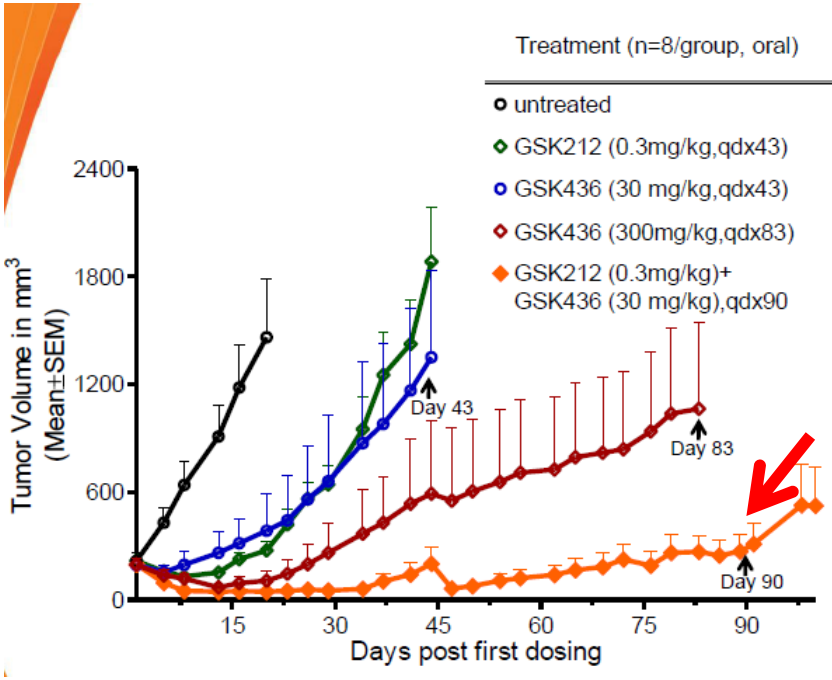
- **True proof of concept of MTA combinations is lacking to date**
  - Modest PFS with a few regimens *(e.g. Bevacizumab-erlotinib; lapatinib-trastuzumab)*
  - Many failed to demonstrate therapeutic enhancement
- **Possible reasons for failure**
  - Lack of patient selection
  - Wrong dose and schedule
  - Inadequacy of preclinical models to guide proper trials
- **New-generation of combination studies may be more promising**

BRAFV600 inhibitor + MEK inhibitor

- from clinical observation, to preclinical MOR studies, to combination strategies

BRAFV600 inhibitor can activate CRAF → MEK/ERK upregulation:

- **Tumor escape**
- **Proliferative skin toxicity (Squamous cell ca)**



Treatment (n=8/group, oral)	Tumor progression*	Tumor free**
untreated	8/8 (d 20)	0/8
GSK212 (0.3mg/kg,qdx43)	7/8 (d 43)	0/8
GSK436 (30 mg/kg,qdx43)	5/8 (d 43)	0/8
GSK436 (300mg/kg,qdx83)	3/8 (d 43)	2/8
GSK212 (0.3mg/kg)+ GSK436 (30 mg/kg),qdx90	1/8 (d 43)	2/8

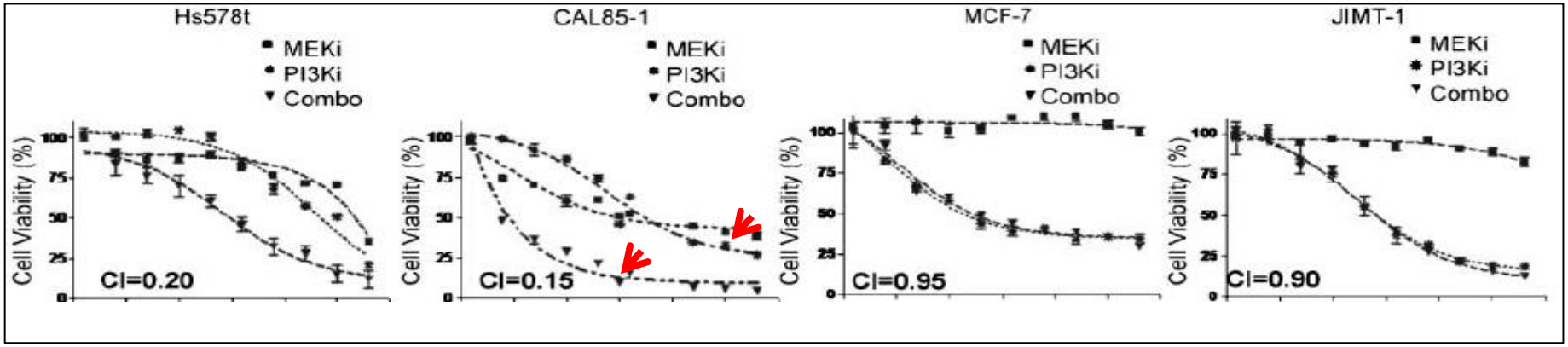
BRAF + MEK I – Clinical experience

- **Study design:**
  - Restricted to patients with BRAFV600 mutant tumors
  - Selected agent that are specific to mutant BRAF
- **Phase I experience**:
  - Combination had lower rate of squamous cell ca
    - <1% (c/w 19% BRAFi alone)
  - Promising PR/CR rate
  - Benefit to be confirmed in randomized phase 2 trial BRAFi +/- MEKi

Infante et al, ASCO 2011

Combination MEK and PI3K inhibitors

–In-depth preclinical studies



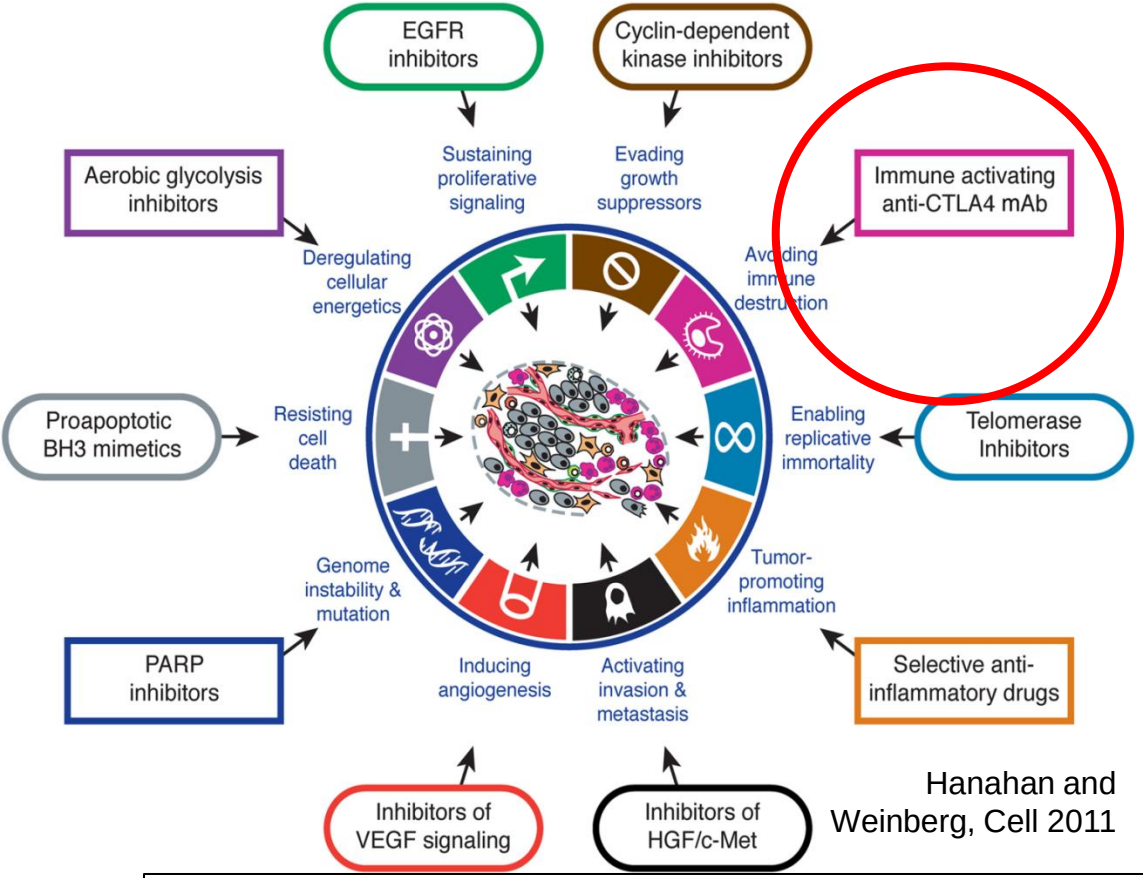
Hoeflich et al, CCR 4653 2009;15(14), 2009; Hoeflich et al, AACR 2010

- **Predictive marker explored in a panel of models** (<u>13 breast ca cell lines tested)</u>
  - *Additive/synergistic* by CI – 7 cell lines
  - *Antagonistic* – 6 cell lines

- **Various schedules explored *in vivo* --intermittent schedules were efficacious**
  - Consistent **BIM elevation** and **cyclin D decline** (associated with apoptosis)

Clinical POP pending

Role of Immunotherapy



Hanahan and Weinberg, Cell 2011

- **Active host immunity** can act beyond the circuitry of tumor signaling pathways
- **Sustained tumor controls** have been achieved, though at low frequency
- ***Challenges:***
  - Predictive markers for patient selection
  - combination to enhance the specificity /spectrum of activity

FDA approved:

- **IL-2**
- **INF-alpha**
- **Ipilimumab** (anti-CTLA mAb) - *melanoma*
- **Provenge -** (GMCSF-transduced DC)

In development:

- **Anti-PD1 mAb**
- **Adoptive cell transfer**
- **CD40 agonist**
- **Vaccines and More**

Summary

- **What have been learned:**
  - Significant progress in the development of molecularly targeted therapies
  - Better tumor characterizations and deeper understanding of tumor biology had been key to success
  - Durable tumor control still rare due to de novo or acquired resistance

- **Remaining gaps:**
  - Some important targets are not easily druggable (e.g. transcriptional factors)
  - Many agents still do not have predictive markers
  - Many tumors do not have “actionable” molecular features identified
  - Analytical and clinical validation of multi-gene or epigenetc markers challenging
  - Incorporation of biomarkers in clinical trails is essential but currently limited by:
    - Scientific issues – nonclinical studies for marker discovery
    - Technical issues – assay validation
    - Logistic issues – resources for tissue acquisition and access to assays

Filling the Gaps

- **Comprehensive preclinical models and studies**
  - Recapitulate the molecular signatures and heterogeneity of tumors in patients
- **In-depth studies on the targets and agents, to better define:**
  - Molecular contexts predictive of sensitivity; of synergism/antagonism
  - Pathway interactions and combination strategies
- **Systematic effort in biomarkers**
  - Assay development, validation and qualification
  - Central or reference labs for assay execution
- **Incorporation of biomarker in clinical trials**
  - Specific or multiplexed molecular characterization for trial allocation
  - Retrospective biomarker studies (on banked specimens from large, randomized therapeutic trials)

Acknowledgement

- James Doroshow, M.D., Director, DCTD
- Jeff Abrams, M.D., Associate Director, CTEP
- James Zwiebel, M.D., Chief, IDB