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# Biology Driven Combination Therapies: How to turn up the HEAT on cancer- a PhRMA perspective

***Richard E. Buller, MD, PhD***
***Pfizer Oncology Clinical Development,***
***San Diego, CA***

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# Disclosures

- I am an employee and  stock holder in Pfizer , Inc.
- Any mention of non-approved (in France) use of regulated products, including pharmaceuticals and diagnostics, is in the context of methodology to improve cancer therapy by determination of molecular abnormalities in individual patient cancers and to utilize this information  to enhance the delivery and or development of personalized medicines.

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# Agenda

- Clinical Vignette
- The Problem
- Rationale – The Hallmarks of Cancer
- Precedent
- Proof of Principal
- Trial Design Issues
- Industry Issues
- Conclusion

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# Clinical Vignette

- 56 yo nonsmoker with stage IV NSCLC containing L858R EGFR mutation per NGS started on erlotinib.
- At about a year, progresses with focal cMET amplification on re-biopsy; crizotinib added.
- Following a 7 month PR, radiographic progression prompted evaluation of cfDNA. T790M EGFR mutation detected; AZD 9291 started, but unable to continue crizotinib due to lack of combination data.
- Brief response followed by progression of lesions with cMET amplification!

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http://en.wikipedia.org/wiki/Sidney_Farber http://ycharts.com/companies/PFE/r_and_d_expense

# The Problem

- Cancer death rates minimally changed since Nixon declared war on cancer 1971
- Human Genome sequenced - 2001
- TCGA 3rd Annual Symposium (3500 samples-12 cancer types) – May 2014
- Costs – High and increasing –not so many drugs
  - NCI budget change 1957-1967: $48M-176M; 2013: $5.07B
  - 2013 R&D budget top 5/50 PhRMA(all TA's): $31.5/88.5B

**Primary and secondary treatment resistance are common**

http://www.totalbiopharma.com/2013/12/10/top-50-pharmaceutical-companies-2013/

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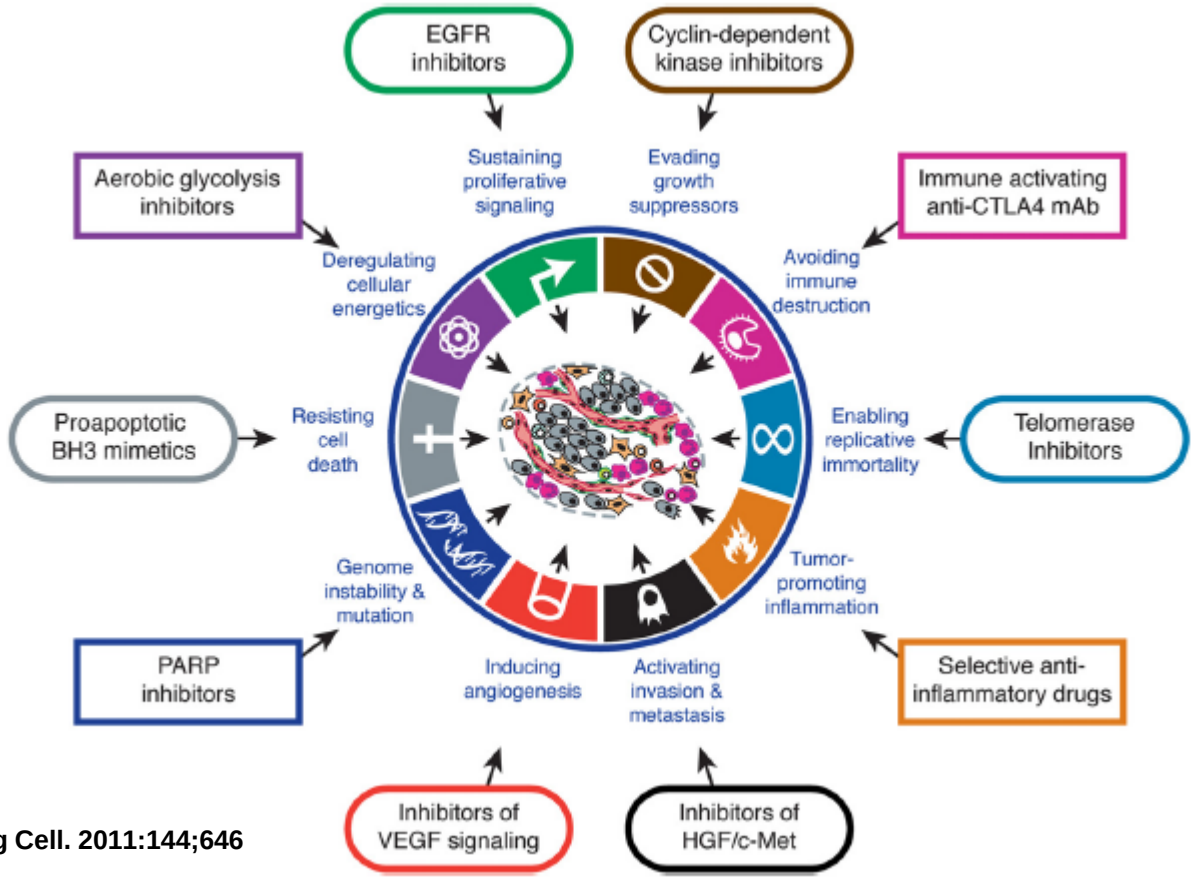
# Therapeutic Targeting of the Biological Hallmarks of Cancer




Hanahan & Weinberg Cell. 2011:144;646

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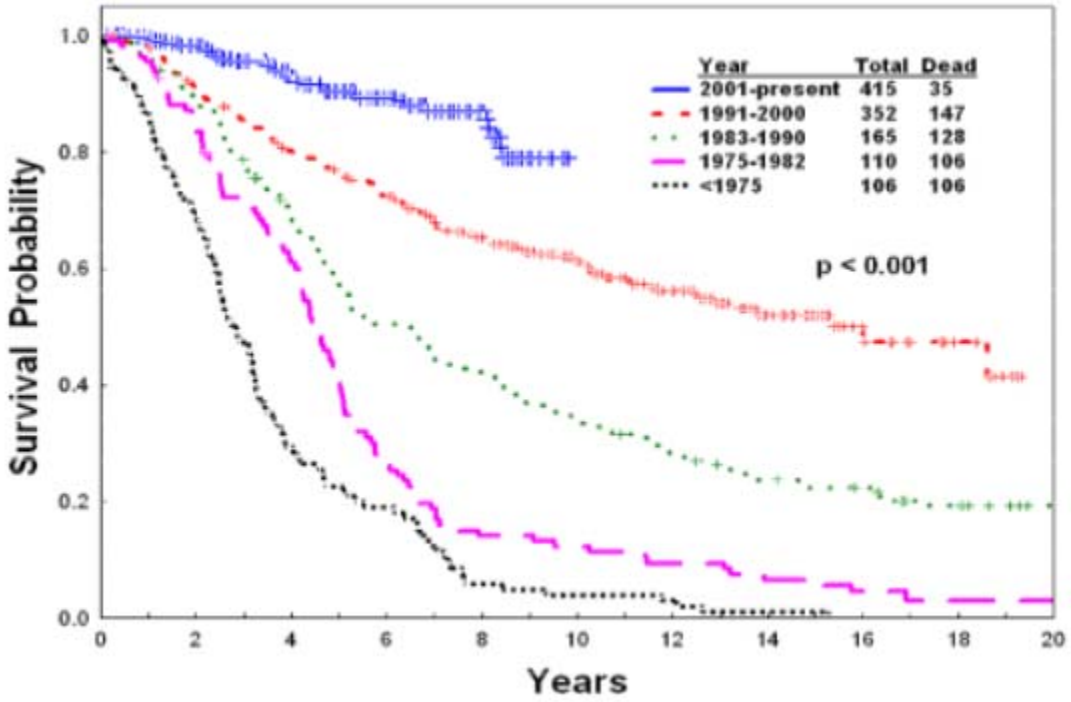
# Impact of Bcr-Abl Targeting on CML Survival




http://dx.doi.org.proxy1.athensams.net/10.1182/blood-2009-11-253294

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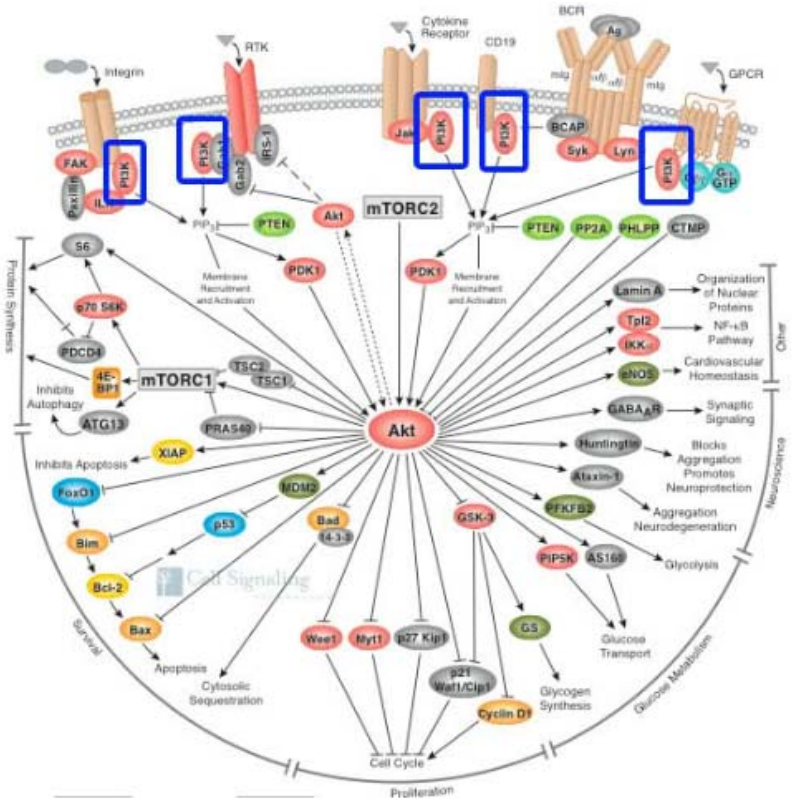
# Signals From the PI3K/AKT/mTOR Pathway




http://i44.tinypic.com/33nhhjt.jpg

- Frequent alterations in many cancers
  - ~20-80% depending on cancer type
  - ~20% of 76 genes
  - Multiple mechanisms
- 30-50 agents in clinic
- Aside from PI3Kδ, little single agent activity
  - Poor chemistry?
  - Incomplete signal blockade?
  - Concomitant changes?
  - Cross talk/feedback loops?

***Pathway not important?***
***Wrong trial designs*?**

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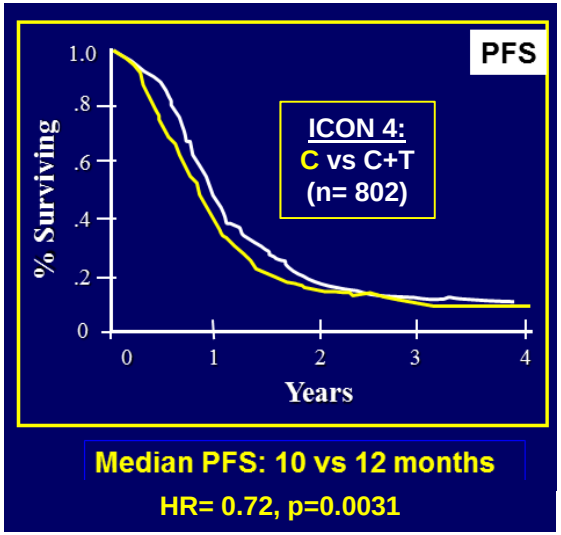
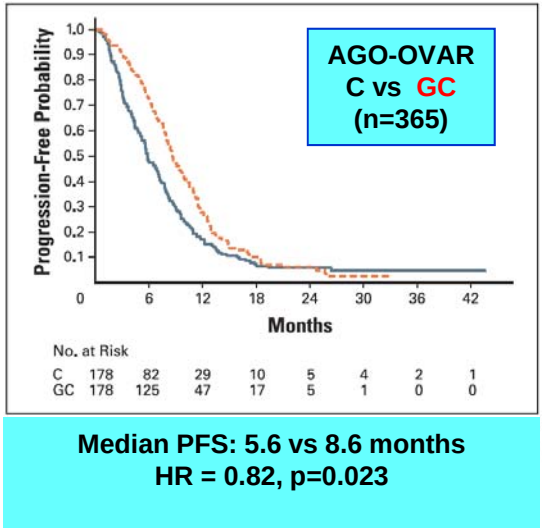
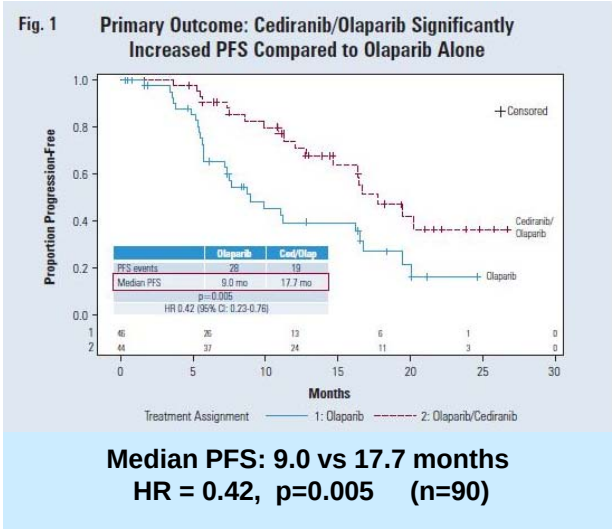
# Proof of Principal: Recurrent Platinum Sensitive Ovarian Cancer




MK Parmer et al Lancet 2003:361;2009




J Pfisterer et al JCO 2006:124,4633




J Liu et al ASCO 2014; LBA5500

- Two is better than one
- Dual targeting of angiogenesis and homologous DNA recombination validated
- Effective combinations impact study size favorably
- Opportunity to replace IV chemotherapy with oral targeted agents
- Even bigger effect in tumors without BRCA mutation detected

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# Elements of Combination Therapy Successes

- Examples of ***REAL*** successes with combination regimens
  - **HAART** Therapy for HIV
  - Cures of multidrug resistant tuberculosis, metastatic GTD, germ cell tumors, acute childhood leukemia - ***complex drug cocktails***
- ***Real time monitoring***
  - CD4 count, HIV- 1 RNA viral load, host genome (HLA-B*5701)
  - M tuberculosis genotype, sensitivity testing
  - β-HCG, AFP
  - PB/ marrow cell types, MRD – ***molecular markers***

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# Patient Selection Caveats

- Tumor genotyping
  - Sample timing
  - How to identify and accommodate tumor heterogeneity
  - Not all cancers have a mutational driver
- "Identical" MPN drivers may not be the same
  - What will this mean for solid tumors?

| TET2 → TET2 +JAK2 | JAK2 → JAK2 + TET2 |
|---|---|
| Disease evolves to ET | Disease evolves to PV |
| Small heterogeneous clones | Large homogeneous clones |
| Delayed disease phenotype | More rapid disease phenotype |
| Transcripts resulting from 2nd mutation dependent upon 1st! | |

David Kent et al :Order Matters EHA 19 Milan 2014 LB6154

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# Useful FDA Guidance for Combinations

- FDA Guidance for Industry Nonclinical Safety Evaluation of Drug or Biologic Combinations http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079243.pdf
- FDA Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

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# Trial Design Issues

| Bottom Up | Top Down |
|---|---|
| Expect some single agent activity | Expect dramatic combination effects |
| Allows stepwise understanding of treatment effects | Requires isolation of treatment effects |
| Probably less time and cost efficient | Absent a large effect, move on |
| Build NCE safety database | Initial focus on interactive safety signals |
| Some advantage with >1 unapproved agent | Most difficult with unapproved agents especially if at different stages of development |

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# Isolating the Treatment Effect: When to Bother

- 2 agent combos = 3 arms
- 3 agent combos = 3 single agent arms + 3 doublets
- How about the standard of care arm?
- Opportunities & Issues
  - True synthetic lethality
  - Overwhelming efficacy – never see CRs and now you do
  - May need PFS or OS

Consider signal finding with a single arm study!
The objective is dramatic clinical benefit.

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# Simultaneous, Intercalated or Sequential?

- Drug – drug Interactions and or synergistic toxicity
  - Bevacizumab + sorafenib – Azad et al JCO 2008
  - Ipilimumab + vemurafenib – (hepatotoxity) –Ribas NEJM 2013
  - Crizotinib + erlotinib -CYP3A4 inhibition by crizotinib – ASCO 2014
- Impact of agents that cause cell cycle arrest on simultaneous chemotherapy
  - Platinum/Gem or Docetaxel vs Erlotinib - Rosell Lancet 2012
    - PFS (EGFR mutant) PFS 9.7 vs 5.2 months; OS 22.9 vs 18.8 months
  - Platinum/Gem D1/8 ± Erlotinib D15-28 NSCLC – Wu Lancet 2013
    - PFS (EGFR mutant) PFS 16.8 vs 6.9; OS 31.4 vs 20.6 months
      PFS (EGFR wt) PFS 6.7 vs 5.9; OS 14.9 vs 12.2 months
- Can sequential targeted or chemotherapy provide antigenic boost prior to PD-1?

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# The Hallmarks Revisited

| Factor | Factorial |
|---|---|
| Ten Hallmarks as Doublets | 10x9 = 180 |
| Ten Hallmarks as Triplets | 10x9x8 = 1440 |
| Sequencing Doublets | X 2 |
| Sequencing Triplets | X 6 |
| Temporal changes | …….????? |
| “Distal” vs “Proximal” blockade | Impact on drug partner for overcoming “escape” |

**Must BALANCE impatience versus overzealous persistence**

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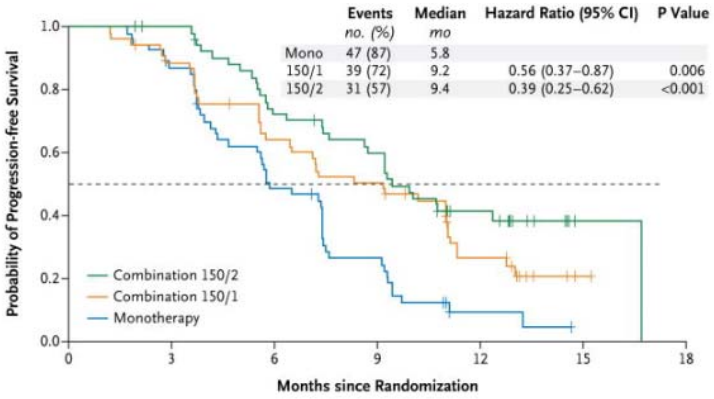
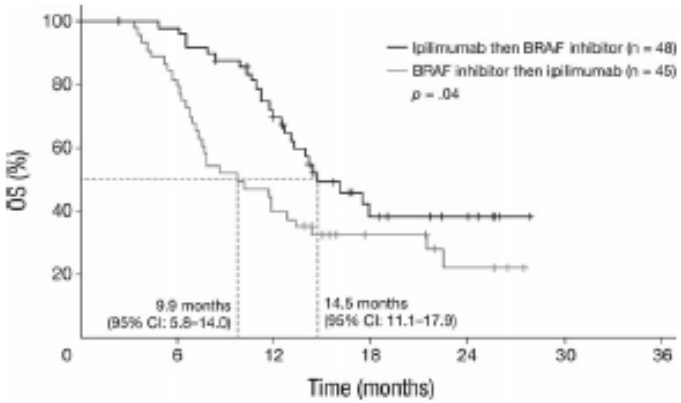
# The Melanoma Laboratory – Generation II




**Flaherty. NEJM.2012:367;1694**




**Ascierto. Ca Invest.2014:32;144**

- **Trametinib + dabrafenib is active** over dabrafenib
- PFS 9.4 vs 5.8 months (HR=0.39, p=0.001)

- Sequential Ipi & vemurafenib can be given
- I->V Median OS 14.5 months (48)
- V-> I Median OS 9.9 months, but 19.3 mo if complete (27/45) vs 5.8 if incomplete
- **Pulse with vemurafenib?**

**Sequence matters!**

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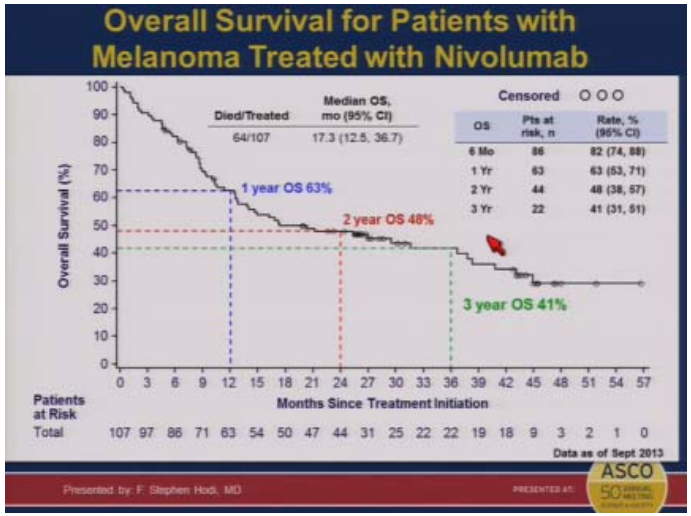
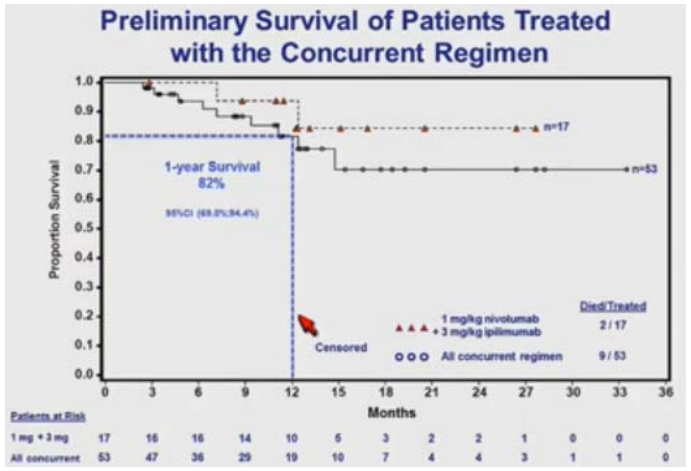
# The Melanoma Laboratory – Generation III




| Agent | 12 Mo Survival | 24 Mo Survival |
|---|---|---|
| Dabrafenib[1] | 10% | N/C |
| Trem + Dabraf[1] | 45% | N/C |
| Ipi[2] | 45% | 24% |
| Ipi→ Vemurafenib[3] | 70% | 40% |
| Nivolumab[4] | 63% | 48% |
| Nivo + Ipi Sequenced[5] | 63% | 48 |
| Nivo + Ipi Concurrent[5] | 82% | NC |

[1] Flaherty. NEJM.2012:367;1694
[2] Hodi. NEJM.2010:363;711
[3] Ascierto. Ca Invest.2014:32;144
[4] Hodi, ASCO 2014, Abs TPS3115
[5] Sznol, ASCO 2014, Abs 9002

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# Industry Issues

- Expectations for single agent activity
- Little patience for sequencing or scheduling
- Standard trials can be a trap
  - Single agent “Head to Head” with SOC or “Add On” approaches
    - EGFR inhibitors in NSCLC
    - Approved drug + NCE is the conservative approach
- Screening cancers with 1 or ***more*** diagnostic platforms
- Competitive philosophy can be an obstacle
- Worry over “Label Contamination” of a one compound with AEs from another
- How to overcome a pricing market hurdle

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# Exelixis Pipeline: Combination Opportunities

| Compound | Target(s) | Outcome |
|---|---|---|
| XL019 | JAK2 | Discontinued |
| XL147 | Pan PI3K | Sanofi |
| XL228 | IGF1-R, Src, Bcr-Abl, FGFR1, Aurora Kinases | Unpartnered (IV) |
| XL765 | PI3K, mTOR | Sanofi |
| XL499 | PI3Kδ | Merck |
| XL518 | MEK | Genentech |
| XL139 | SMO | BMS |
| XL184 | cMET, VEGFR2, RET | BMS |
| XL281 | BRAF, CRAF, BRAF(V600E) | BMS |
| XL880 | cMET, VEGFR2 | GSK |
| XL888 | HSP90 | Un-partnered |

**Your IP Is Not Always Your Friend!**

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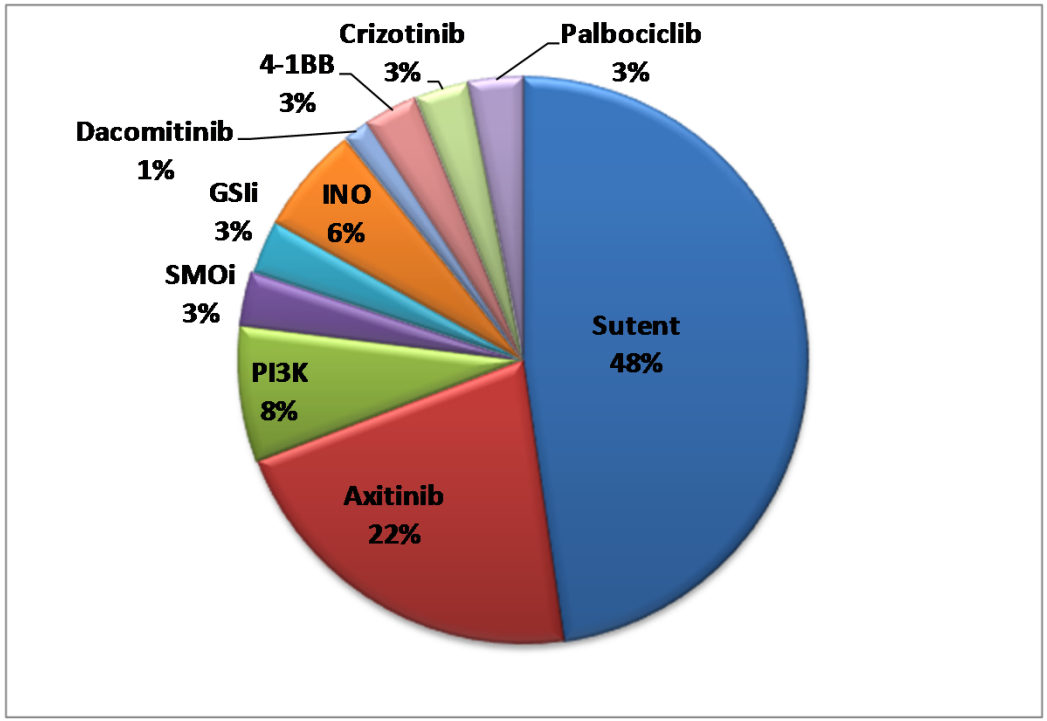
# Pfizer Oncology Combination Studies




| Compound | No of Combos. | Phase 1/2/3 |
|---|---|---|
| Sutent | 31 | 19/6/6 |
| Axitinib | 14 | 6 p12; 1p3 |
| PI3K | 5 | 4 p1; 1 p2 |
| SMOi | 2 | 2 p2 |
| GSIi | 2 | P1; p2 |
| Inotuzumab | 4 | 3p1; 1p3 |
| Dacomitinib | 1 | 1 p2 |
| 4-1BB | 2 | 2 p1 |
| Crizotinib | 2 | 2 p1 |
| Palbociclib | 3 | 1 p12; 2 p3 |
| **Total** | **66** | |

- 10 Compounds (66 combos)
- **Targeted Agent + Chemo**: 48
- **Targeted Agent + Targeted Agent**: 9
- **Targeted Agent + Mab**: 2
- **Targeted Agent + Immunomodulator**: 1

- **Immunomodulator + Immunomodulator**: 1
- **Immunomodulator + Mab :** 1
- **ADC + Mab ± Chemo:** 4
- (**Two new NMEs:** 2)

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# Conclusions

- Let's turn up the HEAT (Highly Effective Anti-Cancer Therapy) on cancer by aggressively testing combination cancer therapies
- Combinations of diverse agents (ADCs, mABs, immuno-modulators, small molecules, & chemotherapy) may be able to minimize toxicity and leverage biology
- Real time monitoring of individual genotypes will be key
- Ongoing evolution of regulatory science will need to accommodate multimodality testing and theranostics
- Partnering will be essential
  - PhRMA, academia, diagnostic companies, payers, patient advocacy groups