Collaborations between Cancer Centers: Using Lung Cancer as a Successful Model

LCCC Meeting 11/30/12

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Lung Cancer Facts & Figures

- Most common cause of cancer-related mortality in US
- Accounts for more deaths than breast, prostate and colorectal cancers combined
- Histologically and molecularly a very heterogeneous disease
- Unfavorable stage distribution at the time of diagnosis (screening not routinely practiced)
- 25-30,000 never smoking Americans will develop lung cancer this year (more common than esophageal, gastric, ovarian, testis, Hodgkin's, myeloma, CML…ACS Facts & Figures 2010)
- Historically shrouded by therapeutic nihilism

Principles of NSCLC Chemotherapy

Early Stage (Adjuvant Therapy)			
Cisplatin-based chemotherapy			
Locoregional Disease (Stage III)			
Chemoradiotherapy			
Recurrent or Metastatic Disease			
First Line	**Maintenance**	**Second Line**	**Third Line**
Cisplatin- or carboplatin-based chemotherapy ± bevacizumab, pemetrexed, or cetuximab in select patients; single-agent erlotinib or crizotinib in select patients	Bevacizumab, pemetrexed, cetuximab, gemcitabine, docetaxel, or erlotinib in select patients	Single-agent docetaxel, pemetrexed, or erlotinib	Single-agent erlotinib

Major Milestones in the Treatment of Advanced NSCLC

- **1995** – 1st line platinum-based therapy improves survival
- **1999** – 2nd line docetaxel improves survival
- **2004 –** EGFR mutations described
- **2005 –** 2nd/3rd line erlotinib improves survival
- **2006 –** Bevacizumab added to CbP improves survival
- **2007 –** EML4-ALK translocations described
- **2008 –** Pemetrexed effective in non-squamous NSCLC
- **2009 –** Maintenance therapy improves survival
- **2009 –** IPASS ushers in era of genotypic therapy in NSCLC
- **2009 –** Gefitinib approved by EMEA for EGFR mutants
- **2011 –** Crizotinib approved for ALK+ NSCLC
- **2011 –** ROS1, RET, HER2 and BRAF alterations described
- **2012 –** Genotyping of SqC identifies potential therapeutic targets

Lung Cancer – Diagnostic Approach

- **Old Approach**

- Quick, easy and safe
- Often an FNA
- Emphasis on non-invasive approaches
- Bone lesions acceptable
- Goal – Small cell vs non-small cell
- Goal reached in almost 100%

- **Modern approach**

- Core biopsies preferred
- Histology paramount
- Emphasis on more invasive approaches
- Bone lesions unacceptable
- Goal #1 – Small cell vs non-small cell, non-squamous vs squamous
- Goal #2 – genotyping
- Goal reached in <50%

Diagnostic Approach to Lung Cancer

- Ensure initial biopsy is adequate for histology determination and molecular testing
- If not, consider repeat biopsy specifically for molecular testing
- Does require multidisciplinary input/cooperation
- UPCI LTMP implemented routine reflex molecular testing in late 2011

TISSUE SAMPLE FOR MOLECULAR TESTING

- Minimal number of tumor cells
  - 300 for mutation analysis
  - 100 for FISH
- Tumor cellularity
  - 25% tumor cells

Lung Cancer

Lung Cancer

Non-Small Cell (85%)

Small Cell (15%)

Lung Cancer

Non-Small Cell (85%)

Small Cell (15%)

- Adequate biopsy necessary to distinguish between NSCLC and SCLC
- Clinical presentations differ somewhat
- Pathologists almost always agree on this distinction
- Therapeutic paradigms very different

Non-Small Cell Lung Cancer

Non-Squamous (70%)

Squamous (30%)

Non-Small Cell Lung Cancer

Non-Squamous (70%)

Squamous (30%)

- Adequate biopsy or cell block routinely needed
- Much less agreement amongst pathologists in making this distinction **(see Grilley-Olsen et al Arch Pathol Lab Med 2012 epub May 14)**
- Limited use of IHC helpful
- 90% of non-squamous histology is adenocarcinoma
- The remaining 10% is “large cell” carcinoma

Non-Small Cell Lung Cancer

Non-Squamous (70%)

- Bevacizumab
- Pemetrexed
- Genotype-driven

Squamous (30%)

- Platinum doublets
- No bev or pem

Advanced NSCLC – Factors Important in Therapeutic Decision Making

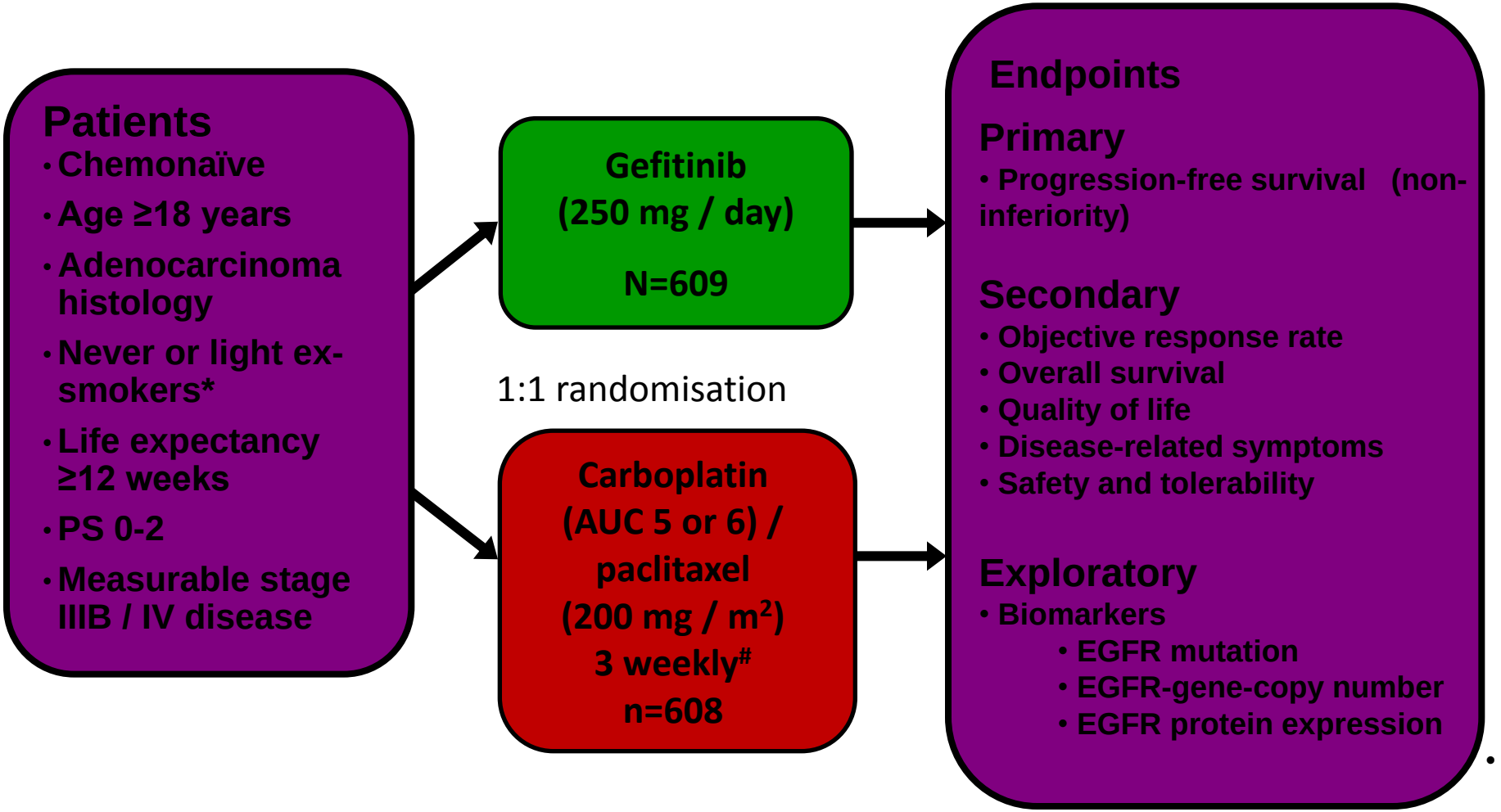
- Prior to 2005
  - PS
  - Age

Advanced NSCLC – Factors Important in Therapeutic Decision Making

- Prior to 2005
  - PS
  - Age

- Since 2005
  - PS
  - Age
  - Histology
  - Bevacizumab eligibility
  - Optimal Platinum doublet
  - ? Role of cetuximab
  - ? Smoking status
  - Genotypically-driven therapy

IPASS Study design



*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years;
#limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok et al, N Engl J Med, 2009

IPASS Study design

Patients

- Chemonaï
- Age ≥18 ye
- Adenocarc histology
- Never or li smokers*
- Life expec ≥12 weeks
- PS 0-2
- Measurabl IIIB / IV dis

Endpoints

vival (non-

ate

otoms y

y number

- EGFR protein expression

Homogeneous Population

100% Asian

100% Adenocarinoma

79% Female

94% Never Smokers

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years;
#limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

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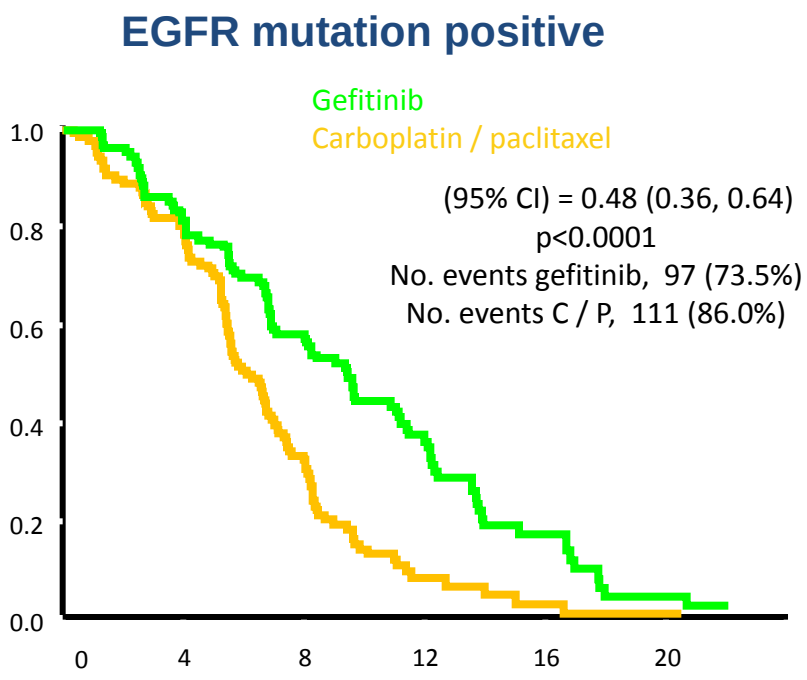
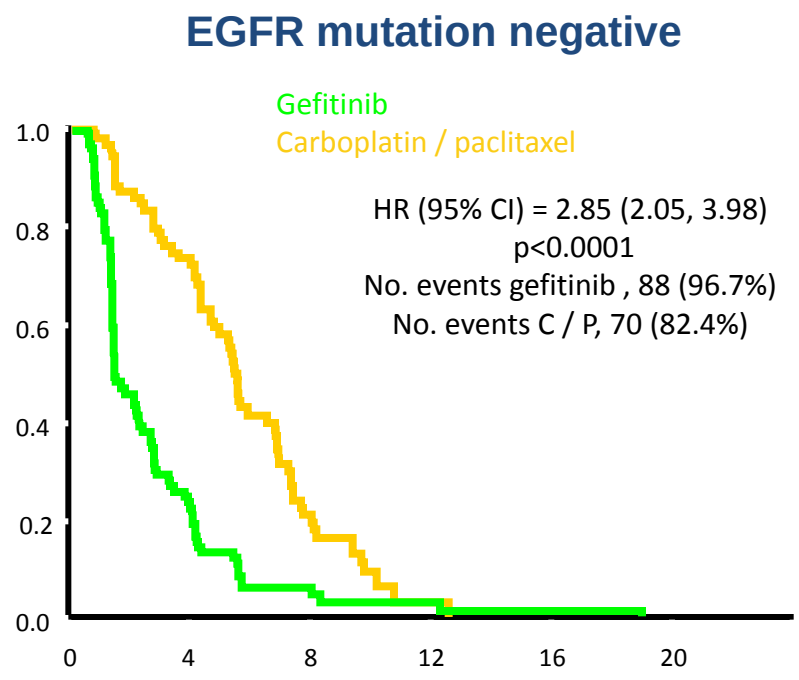
Progression-Free Survival in EGFR Mutation Positive and Negative Patients (n=437)



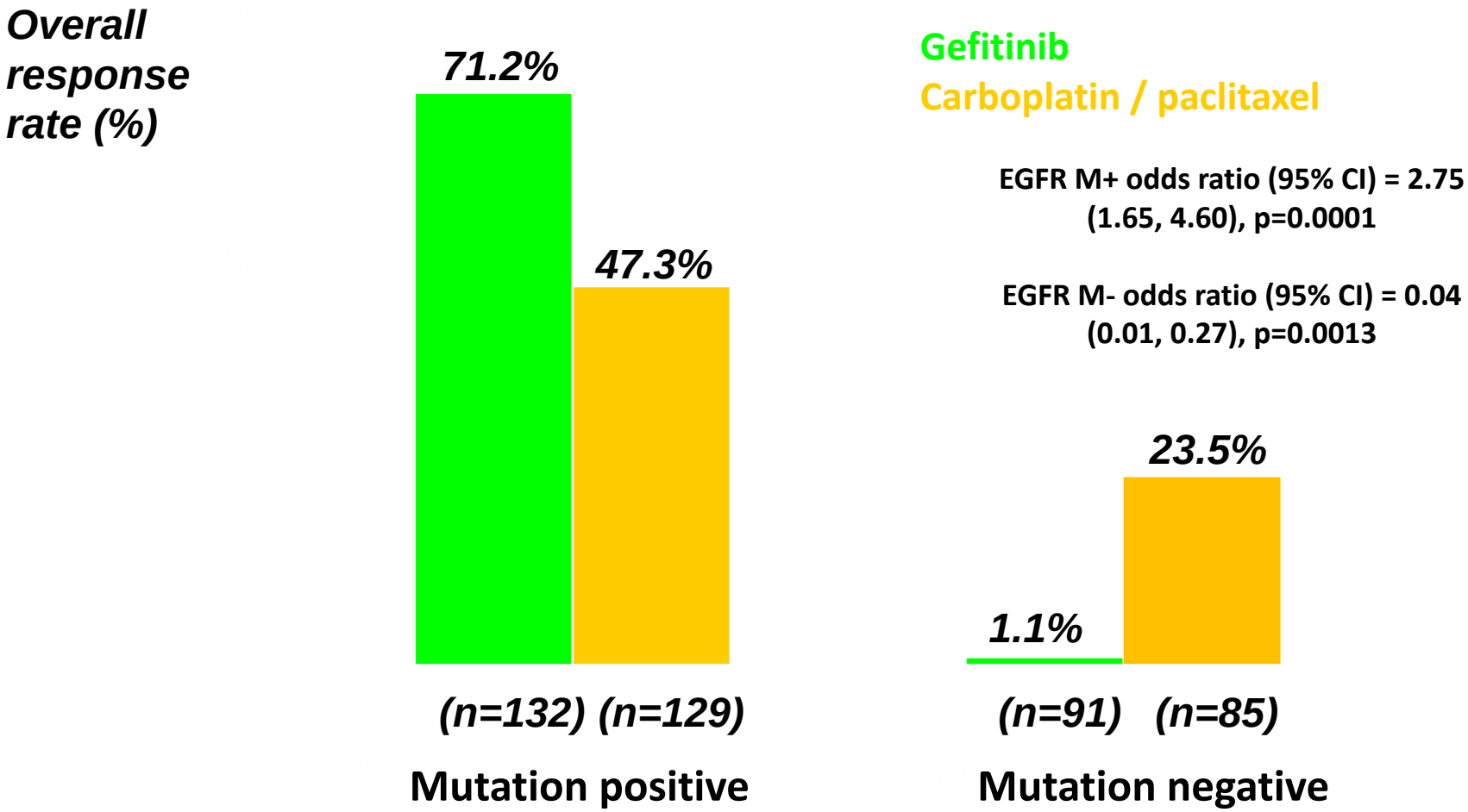


Treatment by subgroup interaction test, p<0.0001

EGFR mutation rate – 60%

Mok et al, N Engl J Med, 2009

Objective response rate in EGFR mutation positive and negative patients



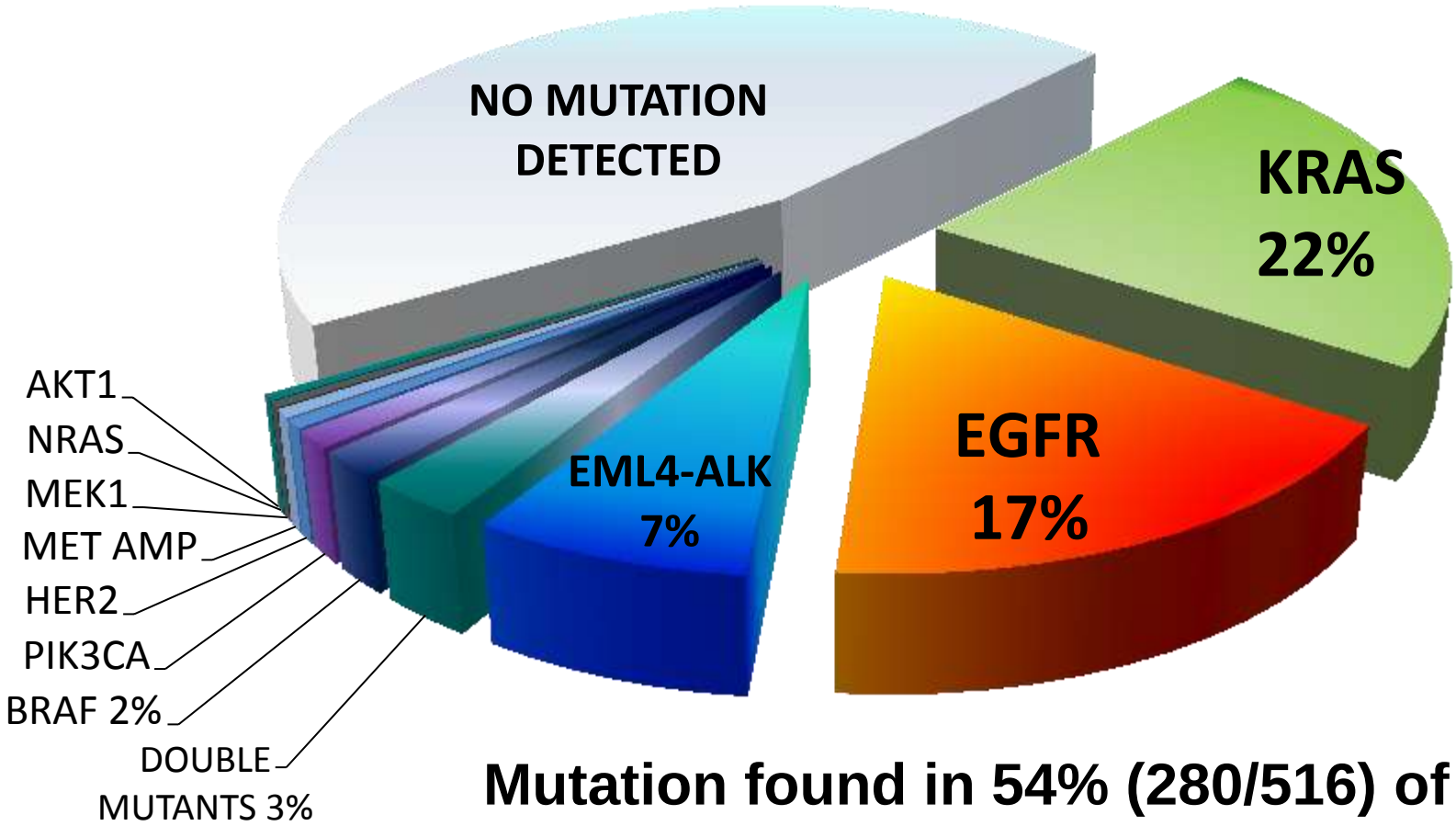
Odds ratio >1 implies greater chance of response on gefitinib

Mok et al, N Engl J Med, 2009

Lung Cancer Mutation Consortium

Lung Cancer Mutation Consortium

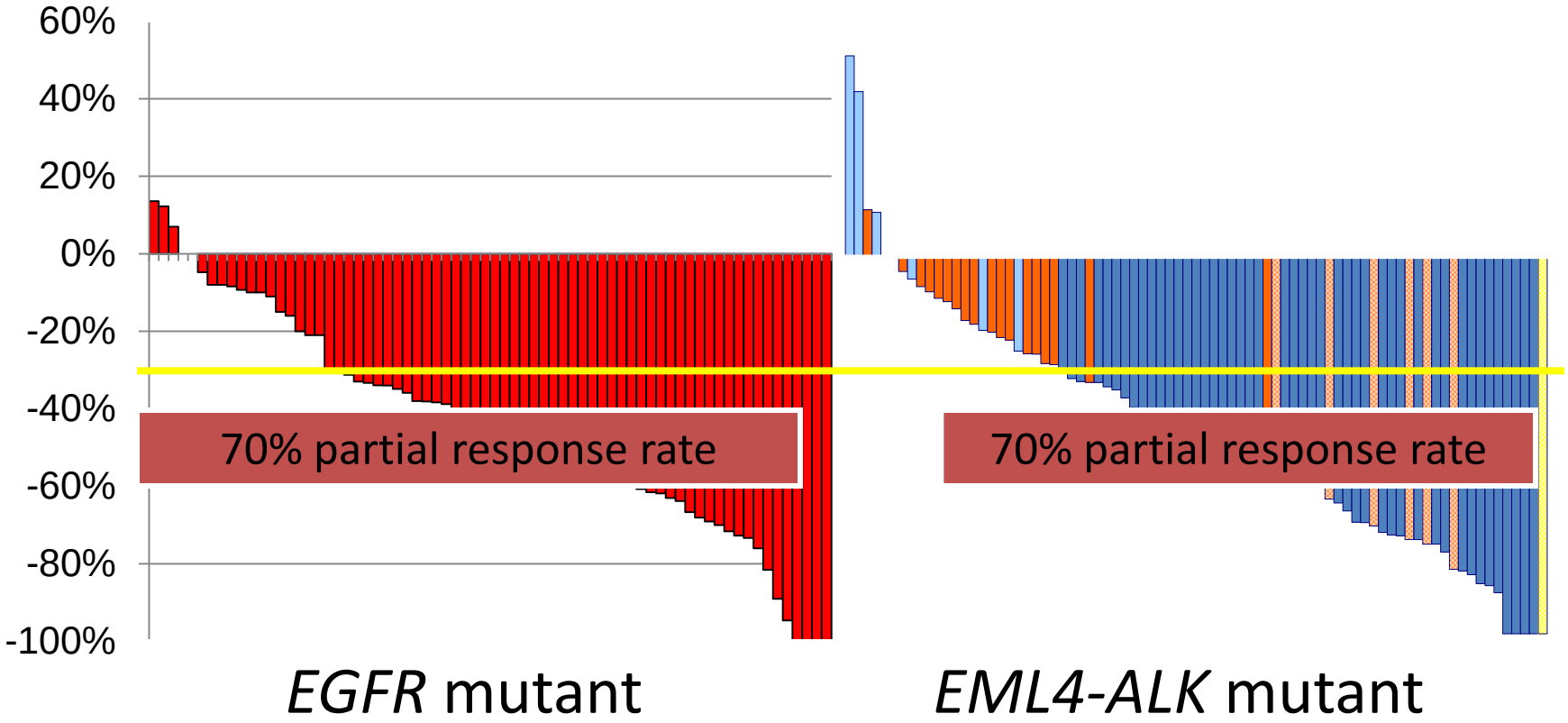
Incidence of Single Driver Mutations in Adenocarcinoma of the Lung



Mutation found in 54% (280/516) of tumors completely tested (CI 50-59%)

Kris MG et al. J Clin Oncol 29:2011 (suppl;abstr CRA7506)

Comparison of Responses *EGFR* mutations with erlotinib vs *EML4-ALK* translocations with Crizotinib

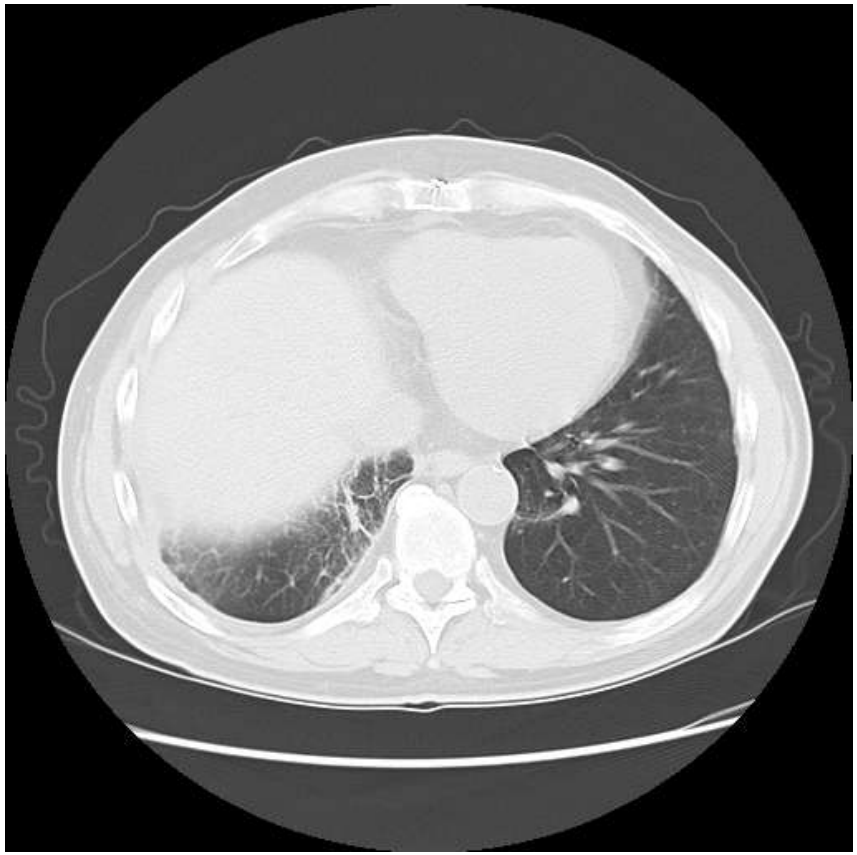


Jackman CCR 2009, Bang ASCO 2010

New Molecular Targets in Lung Cancers in the Last 9 Months

Target	Author	Year	Sensitive to Kinase Inhibition?	Mutually Exclusive?	Incidence
ROS1	Bergethon	2012	Yes	Yes	2%-18/1073
KIF5B-RET	Seok	2011	?	Yes	14%-5/21
HER2 Extracellular Domain Mutations	Gruelich	In press	Yes	Yes	?

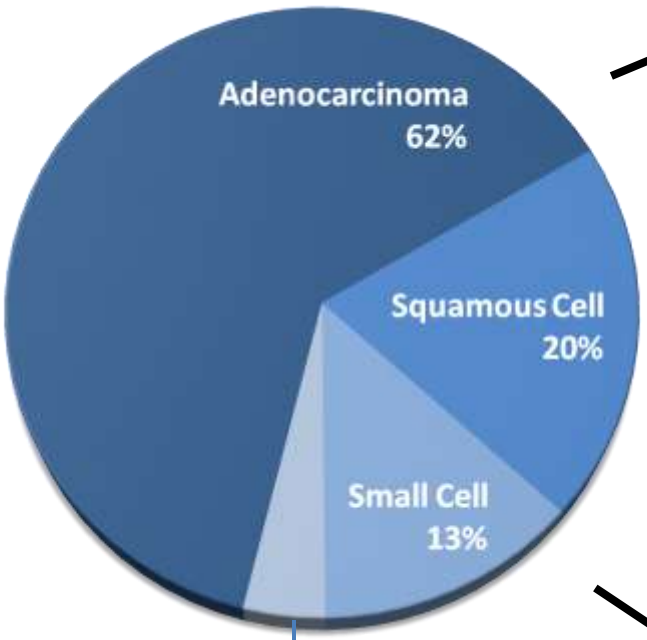
Crizotinib Response in ROS1-positive Non-squamous – 4th Line



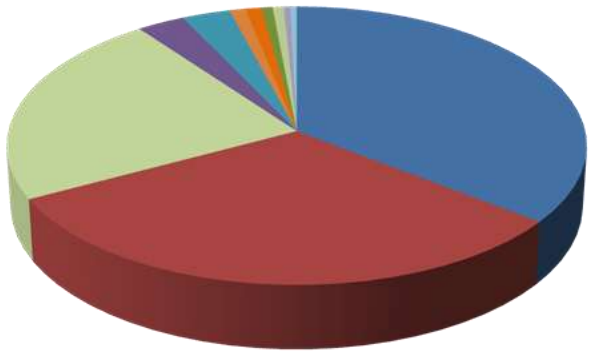
2/1/2012
On O_2, wheelchair-bound, PS 3

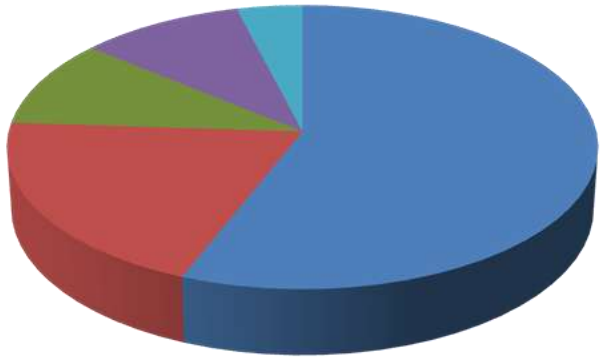
3/19/2012
Fully ambulatory, PS 1

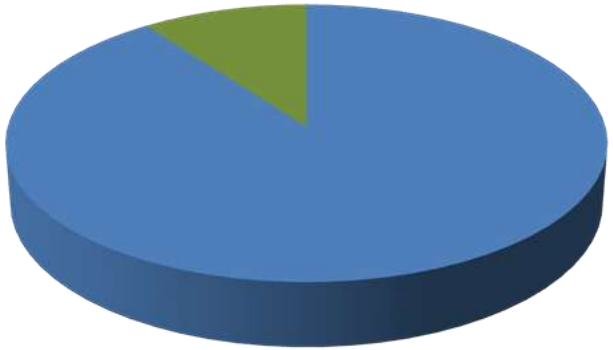
Using Driver Mutations to Classify and Treat All Lung Cancers



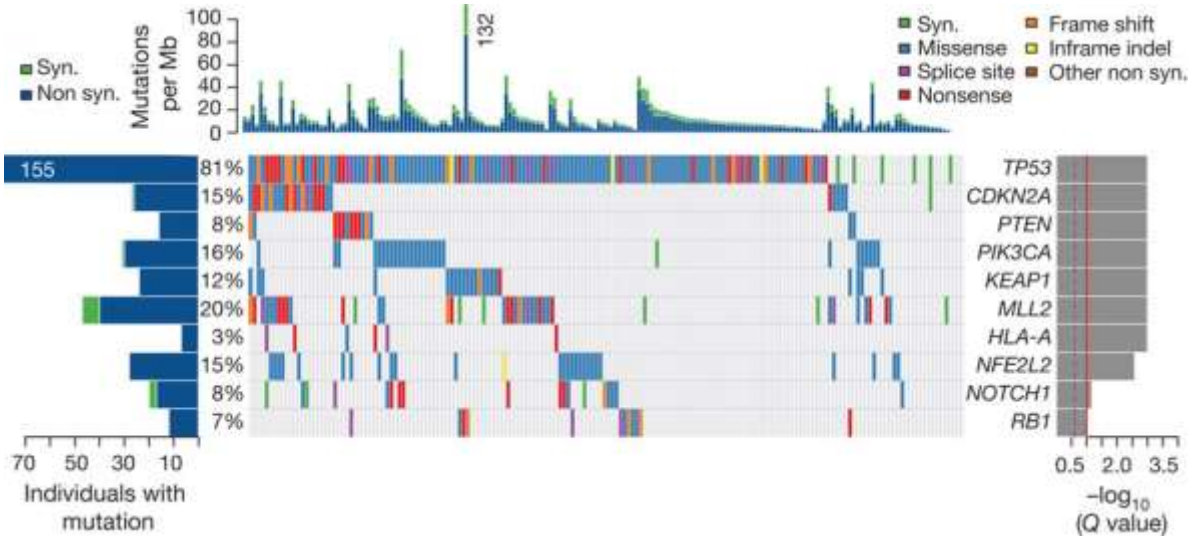
Carcinoid
Large Cell
Large Cell Neuroendocr
5%







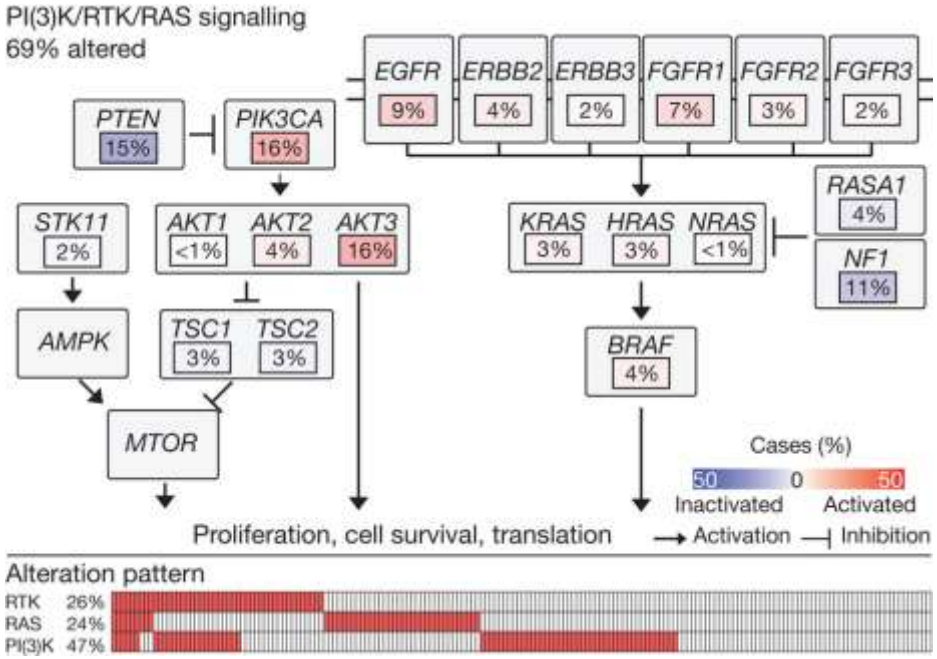
Significantly mutated genes in lung SQCC



PS Hammerman *et al. Nature* 000, 1-7 (2012) doi:10.1038/nature11404

nature

Alterations in targetable oncogenic pathways in lung SQCCs



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nature

UPMC NSCLC "Reflex" Molecular Testing

ADC

EGFR (exons 18-21)
KRAS (G12,G13, Q61)
BRAF (V600)
*PIK3CA (*H1047,E542,E545)

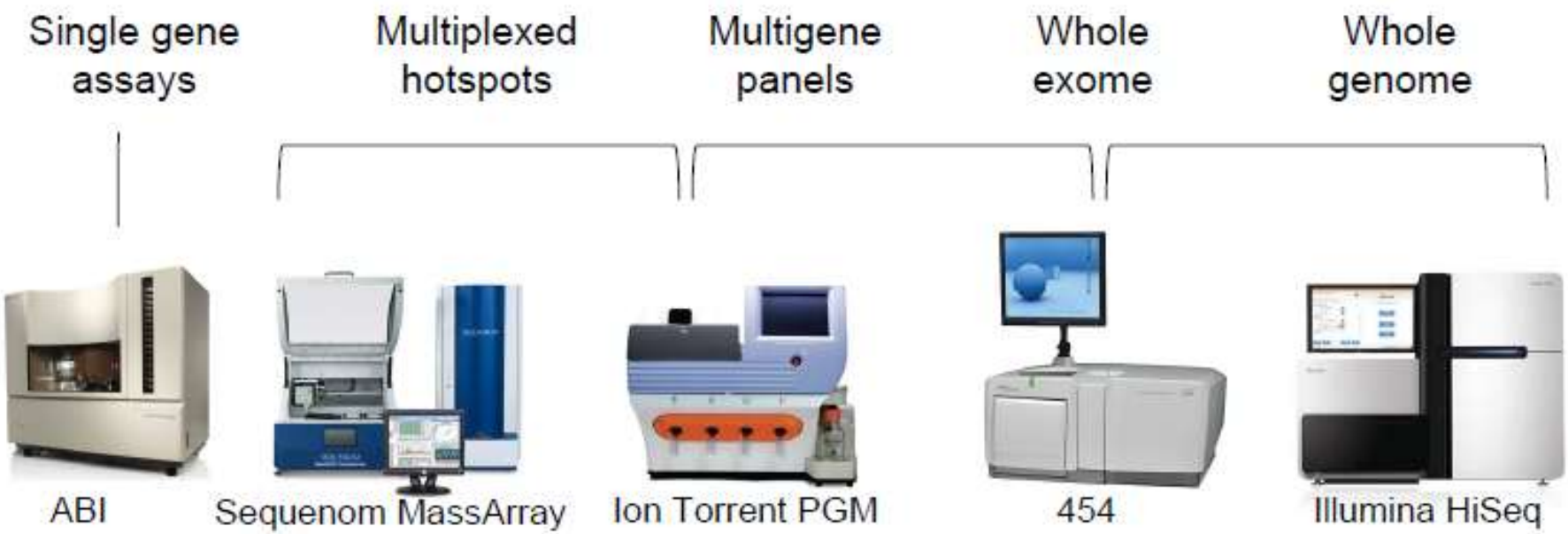
EML4-ALK
ROS1
C-MET
KIF5B-RET

SQC

FGFR1
PIK3CA

What's Next?
Next Generation Sequencing

- Broader coverage
- Better sensitivity, through deeper reads
- Future lower cost, through multiplexing



Clinical Trials in NSCLC

- Issues different in non-squames vs squames
- Targeted therapies in targeted populations
  - bevacizumab an option in non-squames
  - pemetrexed an option in non-squames
- PS 0,1 vs 2
- Expanding genotypically defined populations
  - EGFR, ALK and ROS1 current “actionable” genotypes
  - On the horizon…BRAF, cmet, ret, HER2, others
  - Resistant populations

Ongoing Trials – Molecularly Selected

Study	Design	Comment	Sites
11-109	Ph III Erlotinib +/- MetMAb	Met diagnostic + (Central Lab)	Passavant St. Margaret's Jefferson
12-003	Ph I/II Erlotinib + MM-121	ErbB3 MAb A: EGFR wt, TKI naïve B: EGFR mt, TKI naïve C: EGFR mt, TKI resistant	Passavant
12-020	Ph II Ganetespib	HSP90 inhibitor ALK+	Passavant St. Margaret's Jefferson
11-054	Ph I BKM120	PI3K inhibitor Activated PI3K pathway – Sq only	Hillman
11-119	RPh II Erlotinib + Tivantinib vs SOC	KRAS mt	All
12-040	Ph II GSK2118536	BRAF inhibitor BRAF V600 mt	Hillman
12-068	Ph I Crizotinib	ROS1, c-Met	

Advanced NSCLC

- Given these changes, the approach to advanced NSCLC is no longer “one size, fits all”
- 1st line population now sub-segmented into several distinct subgroups
- This change creates the need for a more diverse clinical trials menu
- This results in more nursing, CRA and regulatory support
- Fewer patients will be eligible for any particular trial

Are Collaborations Necessary?

- Certainly for phase III, yes
- Certainly for uncommon molecularly defined populations (LCMC now in version 2.0)
- For phase I, II…..largely dependent on specifics of the trial as well as institution
- Institutions must be cognizant of their clinical trial population and match trials (good example, AA trial collaboration between OSU and UNC LCCC)

Opportunities for Collaboration

- Institutional
- Networks (within or between institutions)
- Comprehensive cancer centers
- Industry
- Cooperative groups

UPCI and LCCC Collaborations

Trial	Design	Total Accrual Goal	LCCC Accrual	UPCI Accrual
UPCI 11-073 (LCCC 0825)	Cb/Pem/Bev In Never Smokers	40	20 (1 Mission, 1 New Bern)	10
UPCI 11-072 (LCCC 0921)	Pazopanib in Bev-failures	36	9	4
UPCI 11-074 (LCCC 1030)	Cb/Pem + Bavituximab	24	11	1

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Plan to open LCCC XXXX (*nab*-paclitaxel in the elderly) and XXXX (SBRT in EGFR mutants) in near future

The Bottom Line

Collaborations between Cancer Centers

- In my opinion, necessary
- Facilitates accrual and completion of trials
- Requires adequate research nursing, CRA and regulatory infrastructure
- Contracting issues must be anticipated
- Requires unselfish academic initiatives and motivation (authorship, presentation/publication issues should be dealt with prospectively)
- Can be successful as demonstrated by the UPMC and UNC collaboration