New Developments in Lung Cancer Treatment

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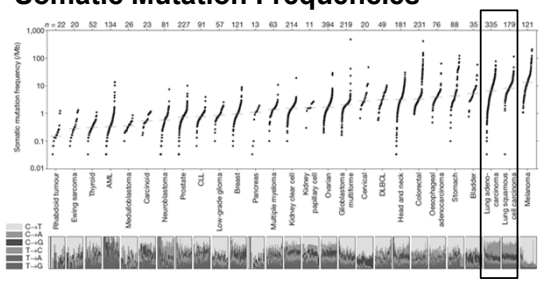
Outline

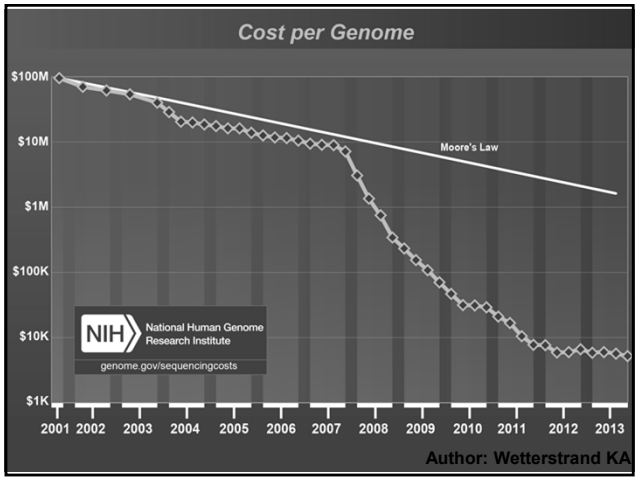
- **Biomarkers/Genomics**
  - **EGFR**
  - **ALK**
  - **ROS**
  - **Others**
- **Immune Therapy**
  - **Checkpoint Inhibitors – antibodies to PD1 and PDL1**

Lung Cancer is Complicated

Somatic Mutation Frequencies



Nature. Jul 11, 2013; 499(7457): 214–218.



Original Investigation

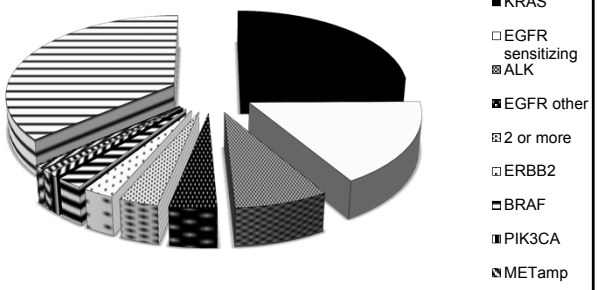
Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

Mark G. Kris, MD; Bruce E. Johnson, MD; Lynne D. Berry, PhD; David J. Kwiatkowski, MD; A. John Iafrate, MD; Ignacio I. Wistuba, MD; Marileila Varella-Garcia, PhD; Wilbur A. Franklin, MD; Samuel L. Aronson, ALM, MA; Pei-Fang Su, PhD; Yu Shyr, PhD; D. Ross Camidge, MD, PhD; Lecia V. Sequist, MD; Bonnie S. Glisson, MD; Fadlo R. Khuri, MD; Edward B. Garon, MD; William Pao, MD, PhD; Charles Rudin, MD, PhD; Joan Schiller, MD; Eric B. Haura, MD; Mark Socinski, MD; Keisuke Shirai, MD; Heidi Chen, PhD; Giuseppe Giaccone, MD; Marc Ladanyi, MD; Kelly Kugler, BA; John D. Minna, MD; Paul A. Bunn, MD

- **Between 2009 and 2012, 14 centers enrolled 1000 patients to test for 10 oncogenic drivers**
- **Lung adenocarcinomas, metastatic, ECOG 0-2**
- **Oncogenic driver found in 64% of testable samples**
- **KRAS, EGFR, ALK, ERBB2, BRAF, PIK3CA, METamp, NRAS, MEK, AKT**

JAMA 2014;311:1998-2006

LCMC results



JAMA 2014;311:1998-2006

LCMC Results

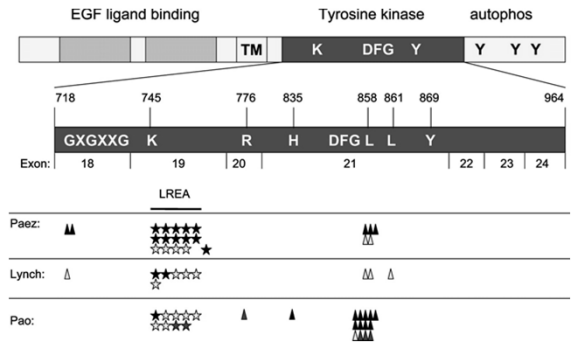
- **733 patients had all 10 assays completed**
- **466 (64%) had identifiable driver alteration**
- **Results used to select targeted therapy in 275 of 1007 patients (28%)**
  - **Median survival of 3.5 years for those with genotype directed therapy**
  - **Median survival of 2.4 years for those with oncogenic driver but no genotype directed therapy**

JAMA 2014;311:1998-2006

What strategy for testing?

Pros	Cons
Sequential, gene specific (KRAS, then EGFR, then ALK, then others)	
- Identify most common mutation first, most "expeditious" use of material	- Time delay, consumption of precious resources
Next Generation Sequencing (Ion Torrent, Illumina)	
- Comprehensive analysis of multiple genes	- Time delay (3-4 weeks for completion/validation of results)
Screening selected genes, then NGS ("Combination" strategy)	
- Quick evaluation of "first line" actionable mutations - EGFR sizing assay – already CLIA certified - ALK FISH (or IHC in some labs)	- Two step process, ? Concerns re billing for same result twice (for example EGFR by sizing and NGS)

Summary of mutations in the TK domain of EGFR in NSCLCs



Pao W et al. PNAS 2004;101:13306-13311

EGFRi vs Chemo

- **Seven + phase III first line studies**
- **In mutation positive patients (exon 19 deletion, L858R)**
  - **Superior response (~ 60-70% vs ~ 30%)**
  - **Superior PFS (~10-12 mos vs ~ 5-6 mos)**
  - **Similar OS**
  - **Improved QoL**

1) IPASS: NEJM 2009; 361:947-57, 2) WJTOG 3405: Lancet Oncol 2010; 11:121-28, 3) OPTIMAL: Lancet Oncol 2011; 12:735-42, 4) EURTAC: Lancet Oncol 2012; 13: 239-46, 5) NEJSG: NEJM 2010; 362:2380-88, 6) LUX-Lung 3: JCO 2013; 31:3327-34, 7) LUX-Lung 6: Lancet Oncol 2014; 15:213-22

Subsequent Treatment

Study (n= mutation pts)	TKI/Chemo	2nd line after TKI	2nd line after chemo
IPASS* (n=261 EGFRmt)	Gefitinib / PC	39% to PC 10% other	40% EGFR TKI 14% other
NEJSG^ (Maemondo n=230)	Gefitinib / PC	68% PC 21% other	95% gefitinib
EURTAC # (n=174)	Erlotinib / Cis or Carbo + Gem or Docetaxel	37% cis/carbo 22% EGFR TKI	76% erlotinib

***IPASS: NEJM 2009; 361:947-57,**
^NEJSG: NEJM 2010; 362:2380-88
#EURTAC: Lancet Oncol 2012; 13: 239-46,

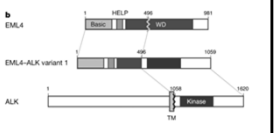
Subsequent Treatment

- **2nd Generation Tyrosine Kinase Inhibitors (TKIs)**
  - **Afatinib**
    - **Effective as initial therapy**
    - **Doesn't "rescue" patients who have progressed on first line TKIs (erlotinib or gefitinib)**
- **3rd Generation TKIs**
  - **Generally active in mutant EGFR, but do not affect WT EGFR**
    - **Less toxicity (rash and diarrhea)**
  - **A number of drugs in clinical testing**
    - **AZD-9291**
    - **CO-1686**

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[3], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[3], Shoji Ohno[3], Yuichi Ishikawa[4], Hiroyuki Aburatani[5-7], Toshiro Niki[3], Yasunori Sohara[3], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

- Echinoderm microtubule-associated protein-like 4 (*EML4*) becomes fused with the anaplastic lymphoma kinase (*ALK*)
  - Inversion within chromosome 2p
- First identified in 2007 from a resected lung adenocarcinoma specimen
- Clinical evaluation
  - Young
  - Never/light smokers
  - ?Male predominance
  - Adenocarcinoma histology



Nature **448**, 561-566 (2 August 2007)
J Clin Oncol 2009;27:4247

Diagnostic Studies

- A) FISH Breakapart
- B) H&E
- C) Sequencing
- D) IHC

NEJM 2010;363:1693

Updated Phase I Results

- Additional follow up of 149 patients
  - 60.8% ORR (77% Asian, 55% non-Asian)
  - Median time to response 7.9 weeks
  - Median PFS 9.7 months
- 69 pts with disease progression
  - 39 continued crizotinib beyond progression (for > 2 weeks)
  - 10 brain, 5 lung, 3 liver

Lancet Oncol 2012; 13:1011-19

Treatment Upon Progression

- Mechanism of progression
  - Pharmacokinetic – Brain
  - Genetic resistance
- "Oligo"-progressive disease
  - Consider stereotactic radiation (brain or elsewhere)
- Diffuse metastatic progression
  - Chemotherapy
  - Clinical trials

Second Generation ALKi

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

NEJM, March 27, 2014; 370:1189-97

LDK 378 Preliminary Results

- Potent activity seen at doses ≥ 400 mg/day
  - ORR 58% in 114 NSCLC pts
  - ORR 56% in Criz treated pts
  - Median PFS 7 months
- Significant activity seen in CNS
- Activity seen regardless of resistance mechanism
- Most frequent toxicities GI
  - Nausea, vomiting, diarrhea

NEJM, March 27, 2014; 370:1189-97

ROS1 Translocations

- ROS1 receptor tyrosine kinase of insulin receptor family
  - Translocations described in GBM (with FIG gene)
  - Targeted by crizotinib (and others)

	All pts (n=1073)	ROS1 (+) (n=18)	ALK (+) (n=31)	ROS(-) (n=1055)
Age (median)	62	49.8	51.6	62.3
Sex % (M/F)	49/51	39/61	55/45	49/51
Smoking % (Never-light/Ever/NA)	28/65/7	84/11/6	45/10/45	27/66/7
Ethnicity % (Asian/non/NA)	4/88/8	28/72	6/58/35	4/88/8
Pathology % (Adeno/Squam/NA)	65/19	100/0	52/3/45	64/19

J Clin Oncol 2012 30:863-870

ROS1 mutant

- In vitro sensitivity to crizotinib
- 50 patients enrolled on standard crizotinib dosing (on original phase I protocol expansion cohort)
- ORR 72% (3 CR, 33 PR)
- Duration of response 17.6 mos
- PFS 19.2 mos

N Engl J Med. 2014 Sep 27 (epub)

Other Molecular Markers

- EGFR – atypical mutations, Exon 20, others
- MET amplification or mutations –ASCO 2014
- BRAF - < 5% of NSCLC patients, ~ 50% of the mutations seen are V600E
- ERBB2 mutations
- FGFR mutations and amplifications
- Other tumors –Squamous?
  - SWOG 1400 "Master Protocol"

Conclusions

- Molecular Directed Medicine is the current standard of care for patients with "Driver Mutations"
- Clinical Trials needed to confirm the preliminary activity seen in MET amp, BRAF, ERBB2 mutant cancers and others
- Expansion of mutation testing to non-adenocarcinoma lung cancers needed

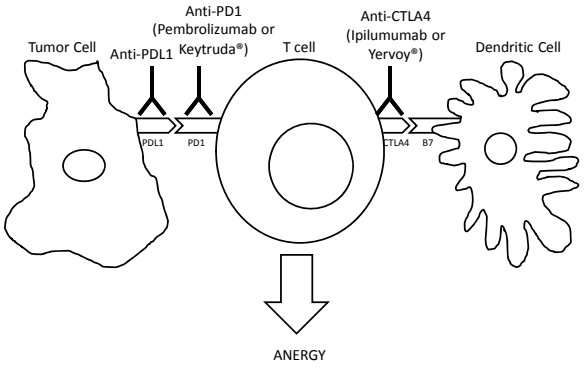
Immune Therapy

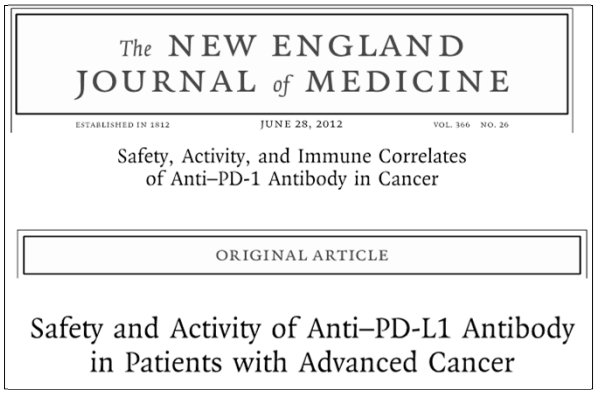
- Attempts for 30+ years
  - Interferons
  - IL-2
  - Vaccines
- Activity seen in Renal Cell Cancer and Melanoma with Interferons and IL-2
- Sipuleucel-T recently approved for prostate cancer
- Disappointment for NSCLC

Checkpoint Inhibitors

- Recent improved understanding of mechanisms of immune suppression in cancer
  - Immune tolerance induced by tumor expression of PDL1 which binds to PD1 on immune (T-cells)
  - When PD1 binds to PDL1, T cells become anergic, blockade of this interaction (with antibodies to PD1 or PDL1) may activate the T-cell

Checkpoint Inhibitors




The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

NEJM 2012; 366: 2443-54 and 2455-65

NEJM 2012 Results

- Phase I studies – both humanized antibodies against PD1 or PDL1
  - 207 patients (PDL1 antibody)
    - NSCLC, Melanoma, Colorectal, Renal Cell, Ovarian, Pancreatic, Gastric, Breasth cancer
  - 296 patients (PD1 antibody)
    - Melanoma, NSCLC, Prostate, Renal, Colorectal Cancer
- Toxicity
  - Well tolerated
  - Immune related toxicity including Pneumonitis (in PD1 antibody)

NEJM 2012; 366: 2443-54 and 2455-65

Responses in Phase I

- PD1 Antibody (Nivolumab)
  - NSCLC – 18% (14 of 76 response evaluable pts)
  - Melanoma – 28% (26 of 94)
  - Renal Cell Cancer – 27% (9 of 33)
- Durability of responses
  - 20 of 31 responses lasted a year or more (in those patients with a year or more of follow up)

NEJM 2012; 366: 2443-54

Phase II Study of Nivolumab

- Phase II study – 3rd line setting (after two prior chemotherapy regimens)
  - 3 mg/kg every two weeks
  - 117 treated patients
    - Median 6 doses
    - OS 6.1 months
    - Time to Response 3 months
  - Toxicity mild – fatigue, diarrhea, pneumonitis
- Response Rate by PDL1 expression
  - 20 % in PDL1 positive tumors
  - 9.8% in PDL1 negative tumors

Chicago Multidisciplinary Symposium in Thoracic Oncology (October 2014)

Immune Therapy Conclusions

- Checkpoint blockade is promising
- Predictive biomarkers unclear
  - PDL1 expression not great at predicting response
- Toxicity is modest and different
  - Autoimmune side effects typical with this class of agents – manageable with steroids
- Duration of response may be most interesting aspect

Targeted Therapy in NSCLC

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Assistant Professor, Internal Medicine
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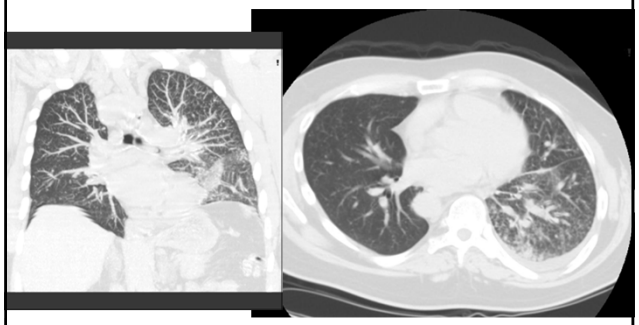
The Ohio State University Wexner Medical Center

Case 1

- 52 yo man, never smoker
- Presented to PCP with 6 months of non-resolving cough
- Medical History – HTN
- Imaging studies were ordered

Baseline scans – spring 2012

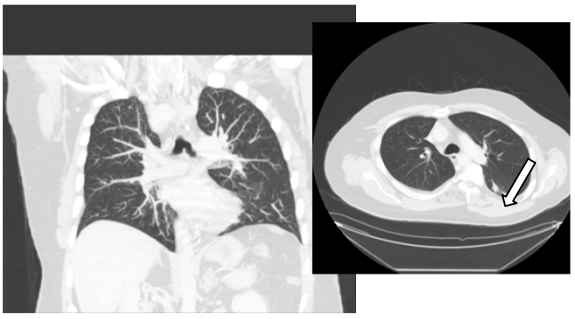


Innumerable small lung nodules throughout both lungs at baseline

Pathology, Staging, and Treatment

- Lung, left lower lobe, biopsy:
  - Primary lung adenocarcinoma
  - Positive for EGFR Exon 19 short-in-frame deletion mutation
- Staging demonstrated bone metastases, brain metastases (7 – all < 1 cm)
- Started Erlotinib 150 mg July 2012
- Brain metastases improved with erlotinib – no brain radiation to date.

Imaging January 2015



Patient on erlotinib alone over 2 years with near complete response.

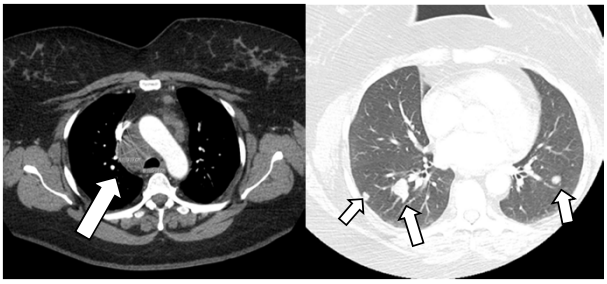
Case 2

- 56 yo woman, never smoker
- Presented with 12/2012, w/ symptoms of SOB, non-productive cough and chest tightness. She was treated with antibiotics, but the symptoms did not improve.
- In 1/2013 she noted an enlarged L neck lymph node (supraclavicular).

Case 2

- 2/2013: Neck CT was performed which revealed a superior mediastinal mass w/ necrosis, as well as a R lung apex lung mass. Bilateral supraclavicular lymph nodes were also seen.
- 2/2013: CT c/a/p: numerous pulmonary nodules throughout both lungs; bulky LAD in the R paratracheal region w/ enlarged LNs in the prevascular space, azygoesophageal recess and lower neck.

Baseline imaging – spring 2013

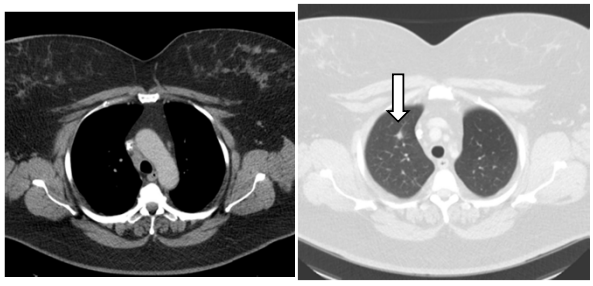


Large mediastinal mass as well as multiple bilateral lung nodules at baseline

Pathology, Staging, and Treatment

- Mediastinal lymph node biopsy: Metastatic adenocarcinoma.
- FISH testing for ALK performed outside – positive for rearrangement
- Started Crizotinib 250 mg BID 3/2013
  - Mild transaminitis in first 4 weeks, resolved without dose adjustment
  - Enrolled in clinical trial after response 8 weeks into therapy

Imaging January 2015



Mediastinal mass has resolved. Minimal residual lung nodules.

Patient did develop new brain metastases – treated with radiation.

She has been started on second generation ALK inhibitor – ceritinib – due to progressive brain disease not amenable to further radiation.

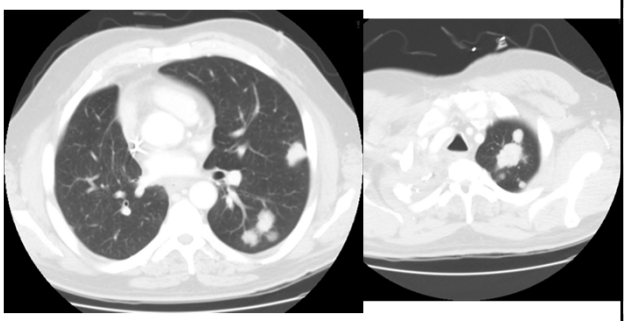
Case 3

- 51 yo man – 30+ pack year tobacco user - with recurrent metastatic NSCLC
- Initial surgical resection for 2/2012 - he was found to have adenocarcinoma 3.5 cm - T2N0. No adjuvant chemotherapy was given. KRAS mutation positive.
- January 2013 – Mediastinal recurrence

Case 3

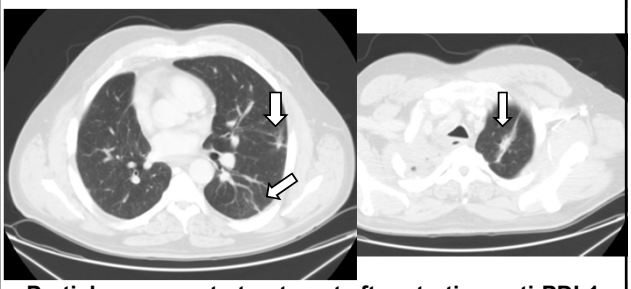
- Treatment History:
  - Spring 2013: Concurrent chemoradiation with carboplatin-paclitaxel
  - Fall 2013: New contralateral lung nodules
  - Fall 2013: Carboplatin-gemcitabine – stopped due to progressive disease
  - Spring 2014: Pemetrexed – stopped due to progression
- Evaluated at OSU for clinical trial – PDL1 positive

Baseline Imaging April 2014



Progression after chemoradiation and 2 lines of chemotherapy – multiple growing lung nodules

Imaging August 2015



Partial response to treatment after starting anti-PDL1 therapy on clinical trial. Remains on trial as of January 2015 with sustained response > 8 months.

No drug-related toxicity observed to date

Conclusions

- **Targeted therapy can produce durable and clinically meaningful responses which translate into improved quality of life and survival for our patients.**