Novel Therapies and Therapeutic Targets in Non-Small Cell Lung Cancer

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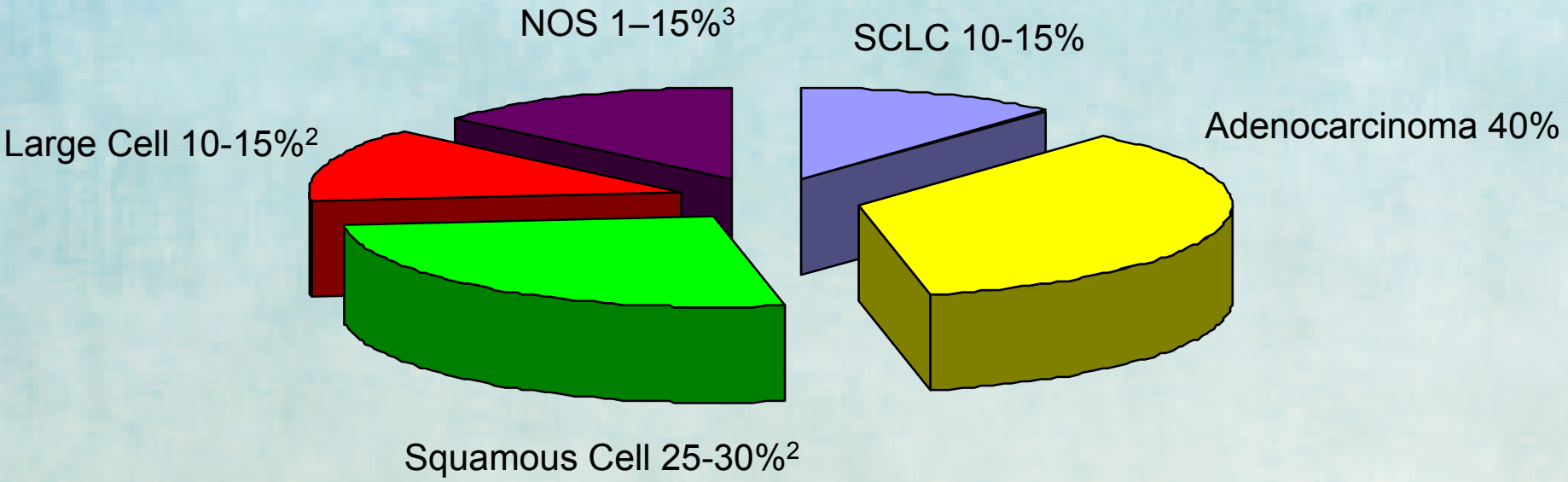
2014

Non-Small Cell Lung Cancer (NSCLC): Background

- Lung cancer continues to be a leading cause of cancer-related mortality worldwide, 1.4 million deaths annually.[1]
- Lung cancer is the leading cause of cancer-related deaths in the U.S..[2]
- In the U.S., the annual number of lung cancer deaths equals the deaths due to breast, prostate, colorectal, and pancreas cancer combined (159,810).[2]
- Poor prognosis. Overall 5-year survival = 15%. Distant metastatic disease, 5-year survival < 5%
- Most patients present with advanced disease
  - 55% of patients present with stage IIIB or IV[3]

1. WHO. Cancer: fact sheet no. 297, World Health Organization website. 2011. http://www.who.int/mediacenter/factsheets/fs297/en. Accessed September 10, 2011; 2. Siegel, R et al. American Cancer Society. Cancer Statistics, 2014 CA Cancer J Clin 64:9-26, 2014; 3. Schrump et al. Non-small cell lung cancer. In: Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

Lung Cancer Histologic Types



American Cancer Society. Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer. Accessed March 24, 2014.

NON-SMALL CELL LUNG CANCER STAGING (seventh edition)

M (Distant Metastasis)

M0 None

M1a: Separate tumor nodule(s) in contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion

M1b: Distant metastasis

Goldstraw et al. J Thorac Oncol. 2007;2:706–714

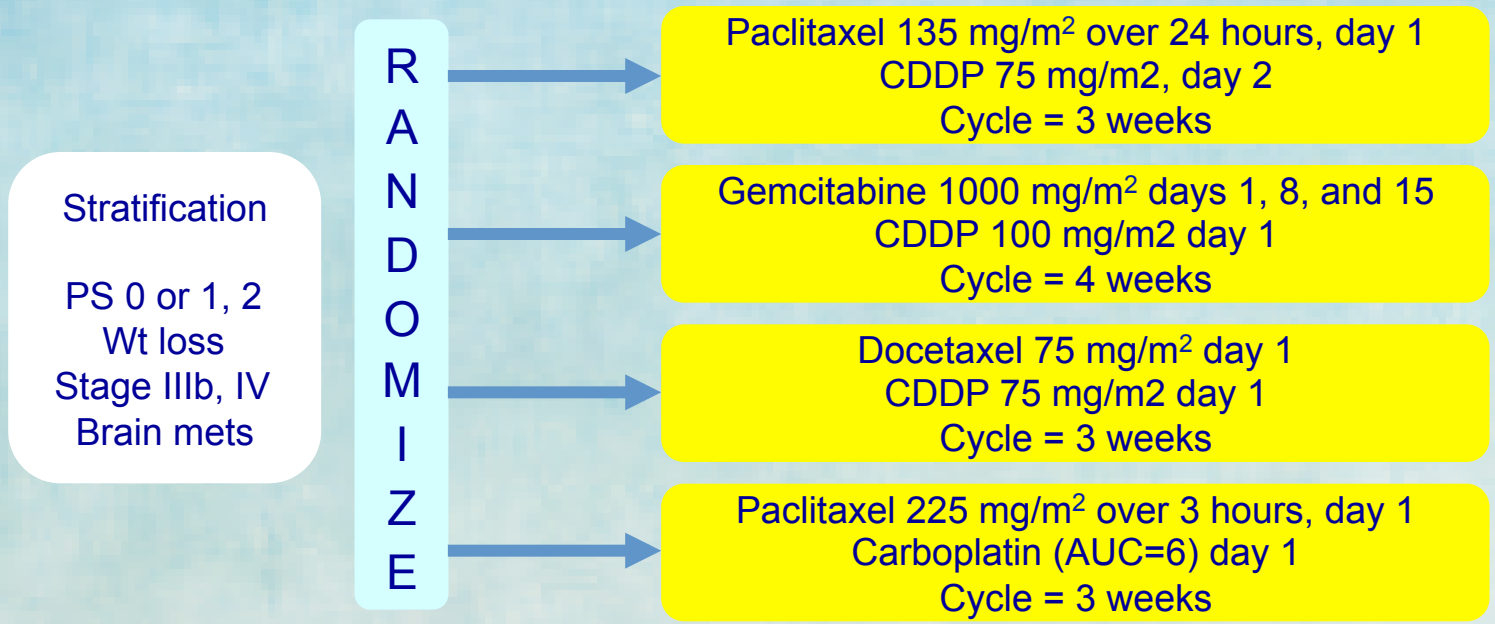
Systemic Therapy for Metastatic NSCLC

- Goal
  - Tumor reduction, palliation of symptoms, QoL
  - Improve survival
- Meta-analyses demonstrate 27% reduction in risk of death with cisplatin-based chemotherapy (worse with alkylating agents)
- Carboplatin easier to administer and less toxic than cisplatin; may have slightly lower RR

Systemic for Metastatic NSCLC (cont'd)

- Platinum doublet standard.
- Non-platinum options
- 4 – 6 cycles
- Performance status, weight loss, smoking status associated with degree of toxicity
- For a minority of patients, molecular targeted therapies have become new treatment options

ECOG trial 1594: Randomised four-arm Study in Advanced NSCLC

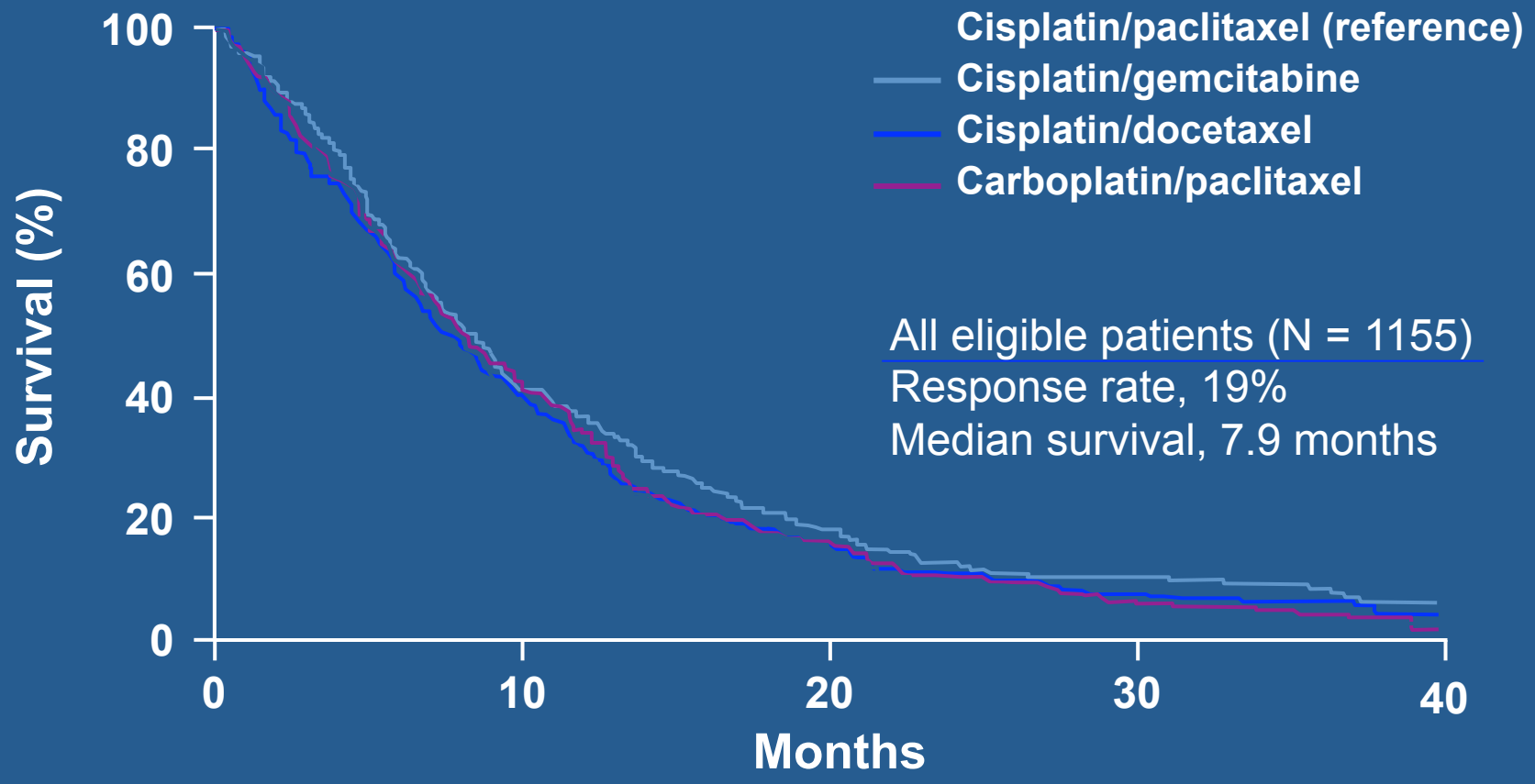


Parameter	PC	GC	DC	PCb
RR (%)	21	22	17	17
Median TTP (months)	3.4	4.2*	3.7	3.1
Median survival (months)	8	8	7	8
1-year survival (%)	31	36	31	34
2-year survival (%)	10	13	11	11

Schiller, et al. N Engl J Med. 2002; 346:92-8.

*p = 0.001 vs PC arm; CDDP = cisplatin

ECOG 1594



Carboplatin/paclitaxel became the ECOG reference standard for its future studies on the basis of the safety results observed in this study.

Schiller et al. *N Engl J Med*. 2002;346:92.

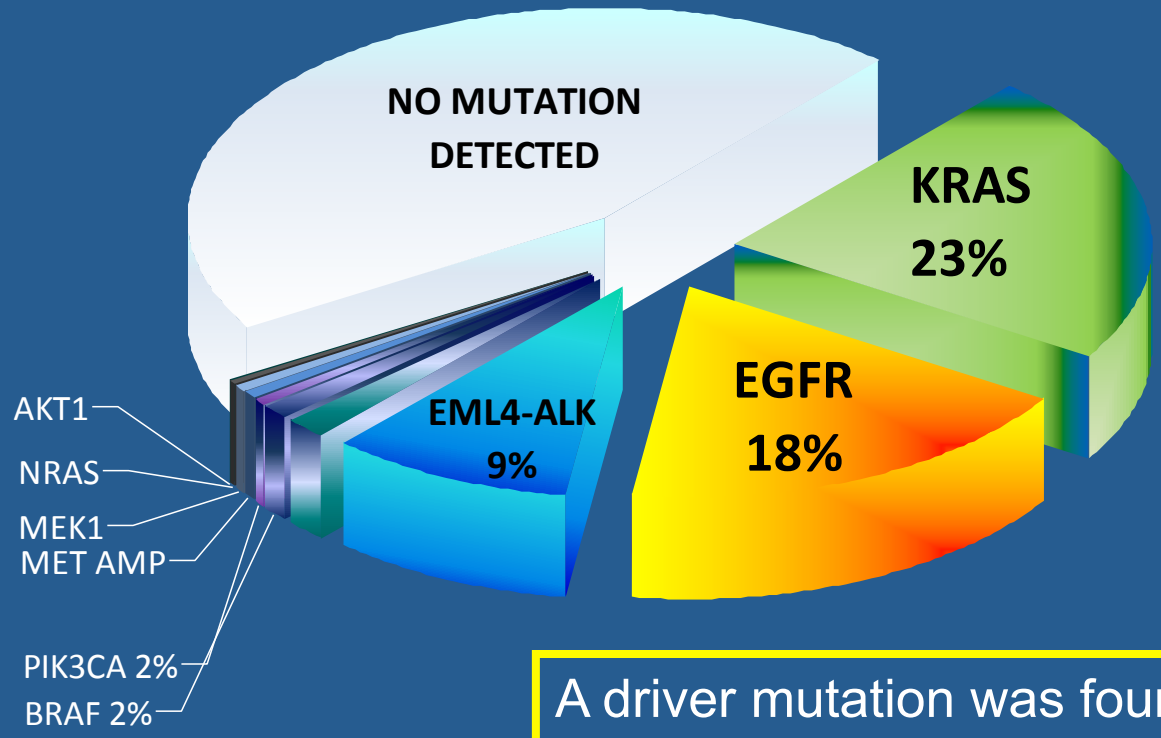
Systemic Therapy for Metastatic NSCLC: Non-Squamous vs Squamous Carcinoma

- Until 2006, NSCLC histologic subtype did not impact choice of chemotherapy
- Bevacizumab approved in 2006 in combination with carboplatin, paclitaxel for non-squamous NSCLC
- Pemetrexed approved 2008 in combination with cisplatin for non-squamous.

Which of the following statements are true for molecular testing of NSCLC tumors?

A. Molecular testing is considered research
B. EGFR mutation and ALK gene rearrangement testing is standard of care for adenocarcinomas
C. Heavy smokers are more likely to have targetable molecular abnormalites
D. P53 and K-RAS mutation testing is standard of care for all NSCLC subtypes

Targeted Therapy: Driver Mutations in Lung Adenocarcinomas



A driver mutation was found in 54% (280/516) of tumors completely tested (CI 50-59%)

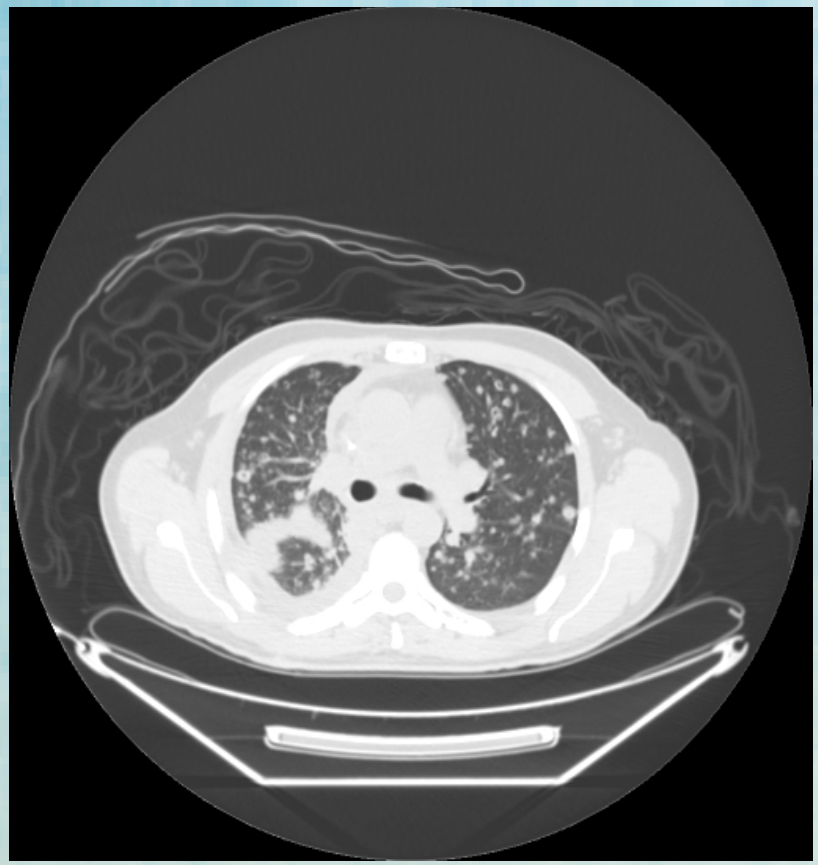
Johnson et al on behalf of LCMC investigators, WLCC July 2011 Abstract #O16.01
Kris et al. on behalf of LCMC investigators, ASCO June 2011 Abstract #CRA7506

EGFR mutations

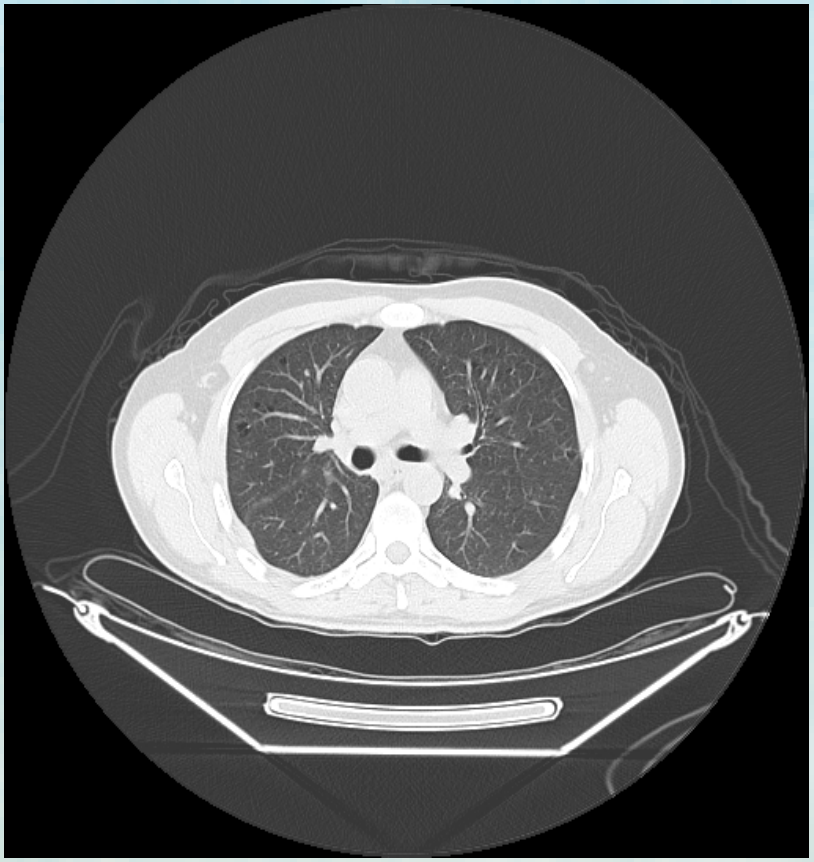
- Found in 10% - 15% of all lung cancer patients and 85% who clinically respond to EGFR TKIs (gefitinib, erlotinib, afatinib)
- Found more commonly in never-smokers, adenocarcinomas, BAC, women, Asians
- Predominantly located in EGFR exons 19 - 21
- EGFR mutations may be associated with sensitivity or resistance (T790M) to EGFR TKIs.
- 85-90% of EGFR TKI sensitive mutations are either exon 19 deletions or exon 21 L858R mutation.

Pao, Miller. *J Clin Oncol*. 2005;23:2556-2568; Wu et al. *J Thorac Oncol.* 2007;2:430-439.

Patient with L858 EGFR mutation



Newly diagnosed
3-16-07



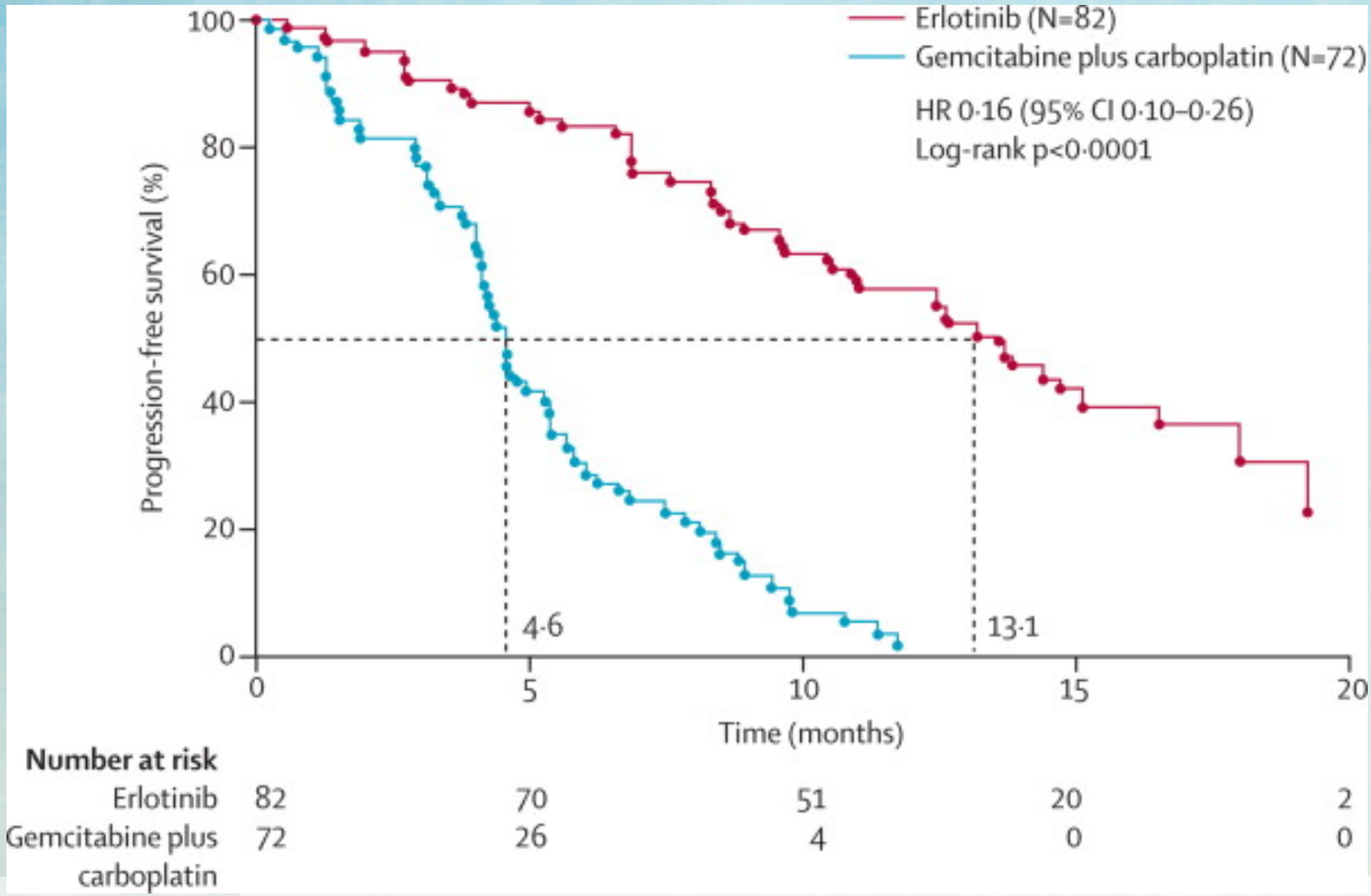
3 months of erlotinib
6-18-07

EGFR Tyrosine Kinase Inhibitors: Phase III First-line Trials in EGFR Mutation-positive NSCLC

Agents	N	PFS (mo)	ORR
Gefitinib vs carboplatin, paclitaxel (NEJ002)[1]	230	10.8 vs 5.4 (HR 0.30, P<0.001)	74 vs. 31% (P<0.001)
Gefitinib vs cisplatin, docetaxel (WJTOG3405)[2]	172	9.2 vs 6.3 (HR 0.49, P<0.0001)	62 vs 32.% (P<0.0001)
Erlotinib vs carboplatin, gemcitabine (OPTIMAL, CTONG-0802)[3]	165	13.1 vs 4.6 (HR 0.16, P<0.0001)	83 vs 36% (P<0.0001)
Erlotinib vs cisplatin/carboplatin, gemcitabine or docetaxel (EURTAC)[4]	173	9.7 vs 5.2 (HR 0.37, P<0.0001)	63 vs 18% (P<0.0001)
Afatanib vs cisplatin, pemetrexed (LUX-Lung 3)[5]	345	11.1 vs 6.9 (HR 0.58, P=0.001)	56 vs 23% (P=0.001)
Afatanib vs cisplatin, gemcitabine (LUX-Lung 6)[6]	364	11 vs 5.6 (HR 0.28, P<0.0001)	67 vs 23% (P<0.0001)

1. Maemondo et al. NEJM 362:2380, 2010; 2. Mitsudomi et al. Lancet Oncol 11:121, 2010; 3. Zhou et al. Lancet Oncol 12:735, 2011; 4. Rosell et al. Lancet Oncol 13:239, 2012; 5. Sequist et al. JCO 31:3327, 2013; 6. Wu et al. Lancet Oncol, Jan 15, 2014

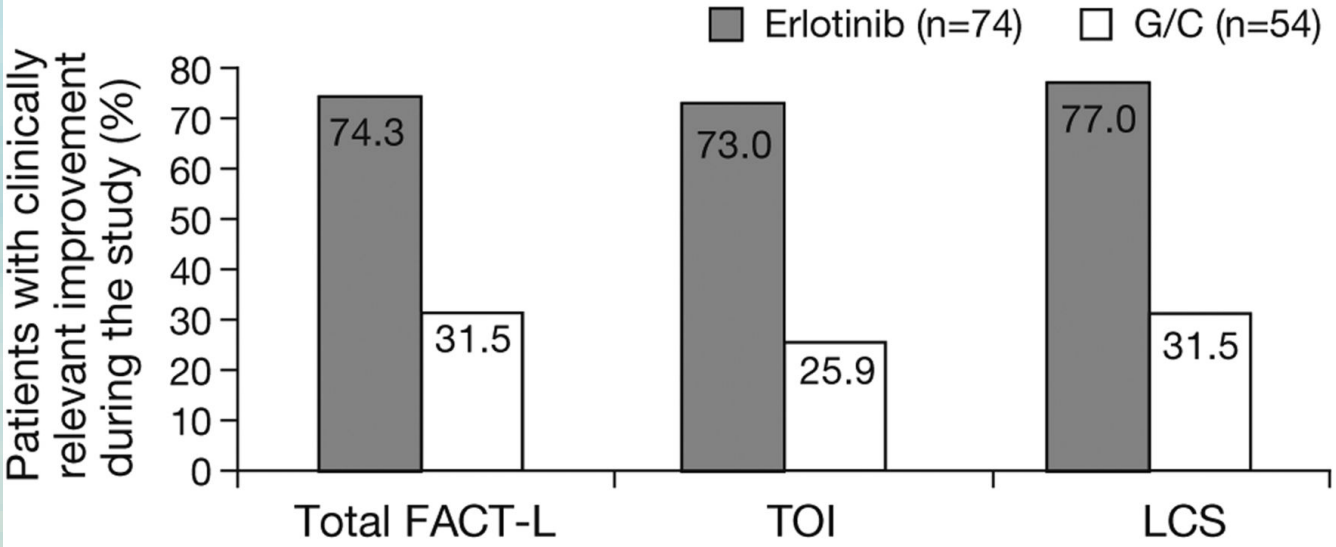
OPTIMAL, CTONG-0802 Study: PFS



Zhou et al. Lancet Oncol 2011, 12(8):735.

OPTIMAL, CTONG-0802: QoL and Symptoms

	Odds ratio (95% CI)		
Covariates	Total FACT-L	TOI	LCS
PS, smoking history and gender	6.73 (3.01–15.04), $P < 0.0001$	7.46 (3.33–16.72), $P < 0.0001$	7.22 (3.23–16.13), $P < 0.0001$
EGFR mutation type, smoking history and histological type	6.69 (3.01–14.85), $P < 0.0001$	8.07 (3.57–18.26), $P < 0.0001$	7.54 (3.38–16.85), $P < 0.0001$



Includes all patients with a baseline and ≥1 post-baseline QoL assessment.

FACT-L = Functional Assessment of Cancer Therapy-Lung. G/C = gemcitabine/carboplatin treatment group. LCS = Lung cancer subscale. PS = performance status. QoL = quality of life. TOI = Trial Outcome Index.

Chen G et al. Ann Oncol 2013;24:1615-1622

ALK Gene Rearrangement-Positive NSCLC

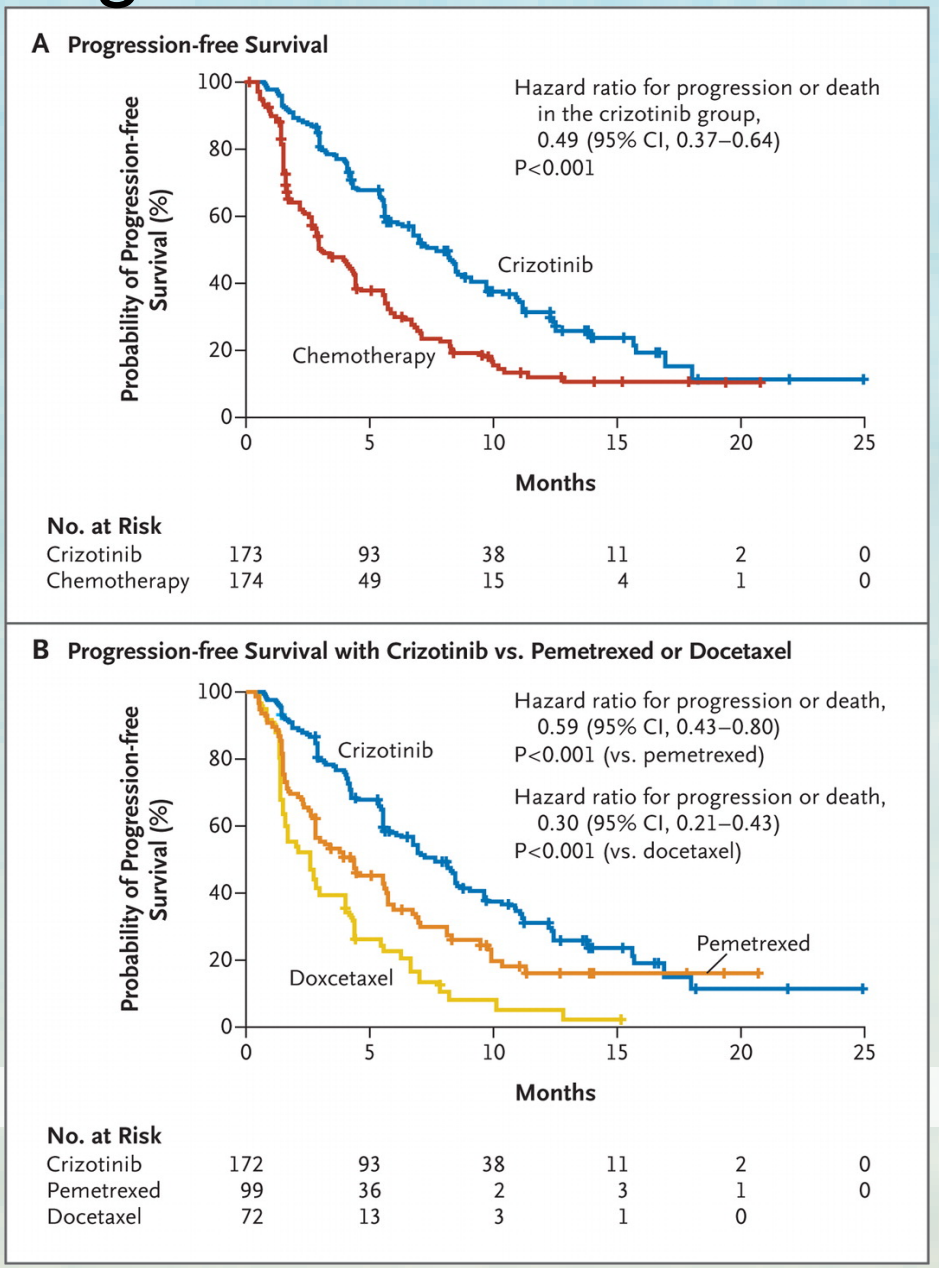
- ALK gene-rearrangement in NSCLC first reported in 2007. Most common fusion gene EML4-ALK. Estimated prevalence 3-5%.
- Associated with adenocarcinoma histology, never- or light smoking history, EGFR and KRAS WT, younger age
- EML 4 ALK is not a favorable prognostic factor (unlike EGFR mutations)
- Crizotinib, an oral TKI targeting ALK, c-Met, ROS1
  - US FDA-approved 2011 crizotinib, based on Phase II trial ORR 61%, low toxicity
  - Recent Phase III trial vs 2nd-line chemotherapy positive.
  - 3/2014: Phase III trial vs 1st-line chemotherapy positive.

Koivunen et al. CCR 14 (13): 2008; Shaw et al. JCO 31(8):1105, 2013; Shaw et al. NEJM 368(25): 2385, 2013

Primary Endpoint: Progression-free Survival

Median PFS 7.7 vs 3.0 mo (HR 0.49, P<0.0001)

ORR 65% vs 20% (P<0.001)



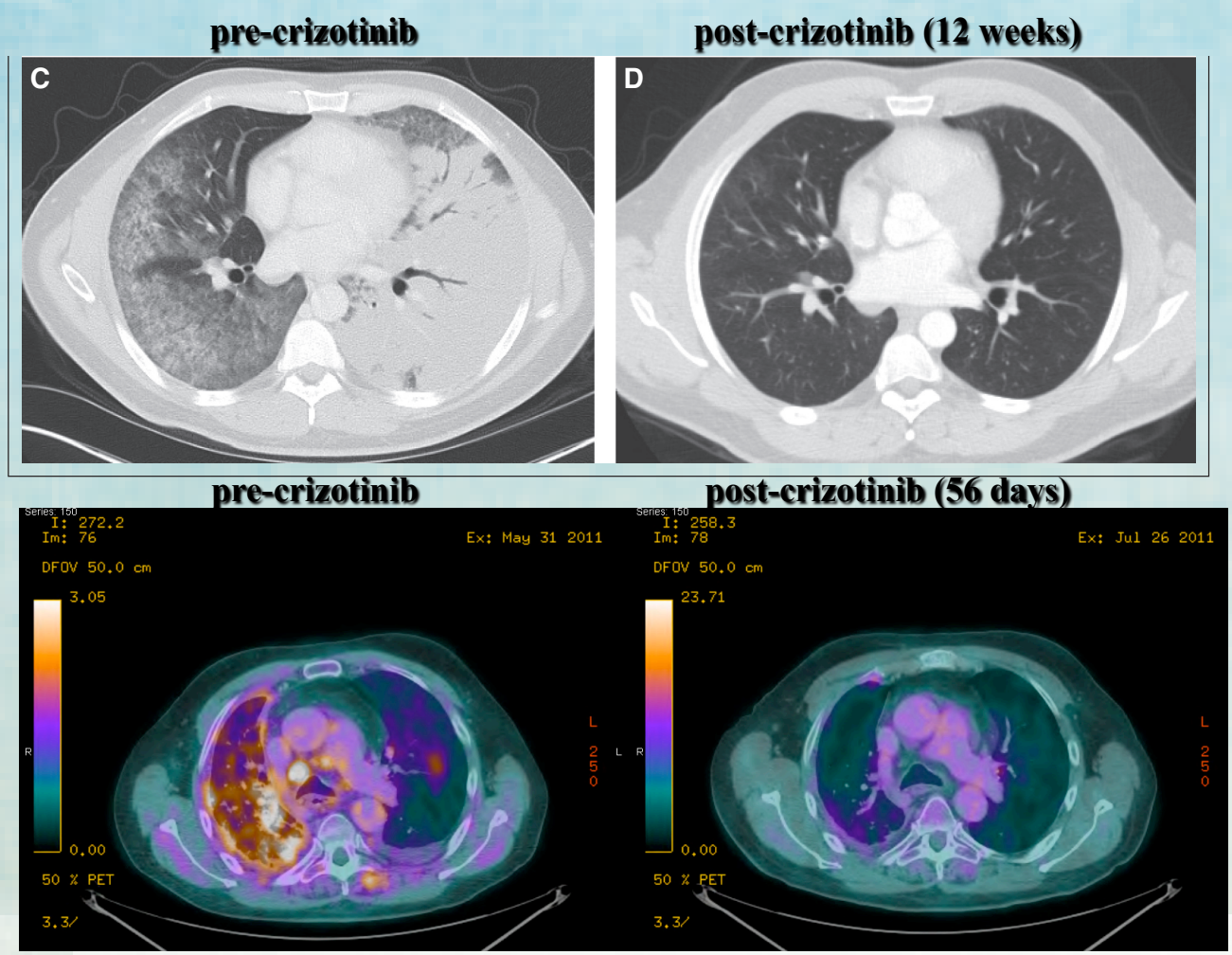
Shaw AT et al. N Engl J Med 2013;368:2385-2394.

ROS1 Rearrangement-Positive NSCLC

- ROS1 – a tyrosine kinase of the insulin receptor family.
- ROS1 gene-rearrangement reported in 1.7% - 2.6% NSCLC.
- Associated with adenocarcinoma histology, never- or light smoking history, younger age, higher grade
- Crizotinib Phase I trial expansion cohort included 33 ROS1-positive NSCLC patients.
  - Median age 51 yr, 79% never-smokers, 97% adenoca
  - RR 56%

Bergeron et al. JCO 2012, 30:863; Ou et al JCO 2013 (suppl; abstract 8032).

Clinical tumor responses in *ROS1*+ NSCLC treated with crizotinib



Bergethon et al. JCO 2012
Davies et al. AACR 2012
Doebele IASLC Targeted Therapy 2012

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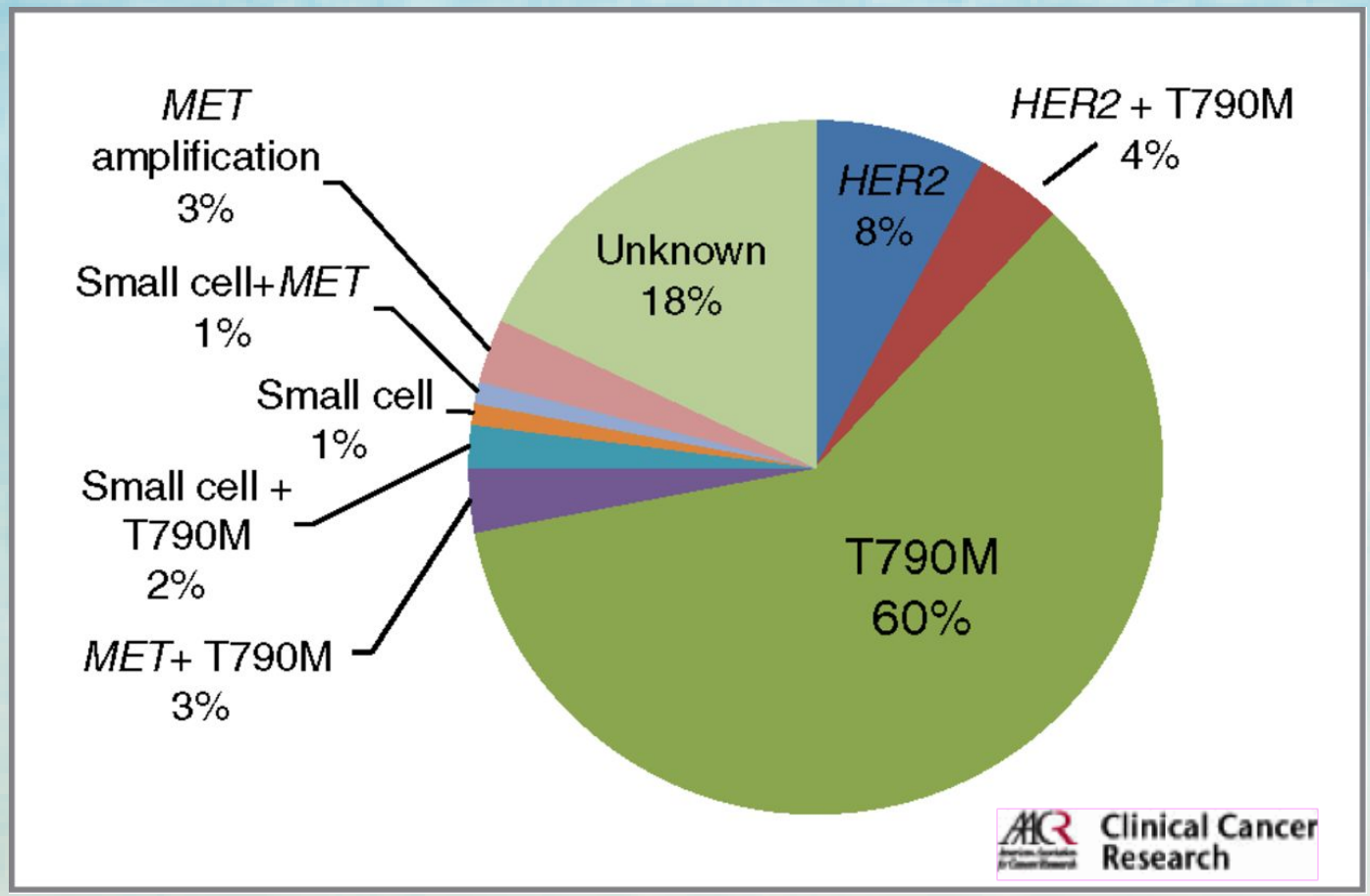
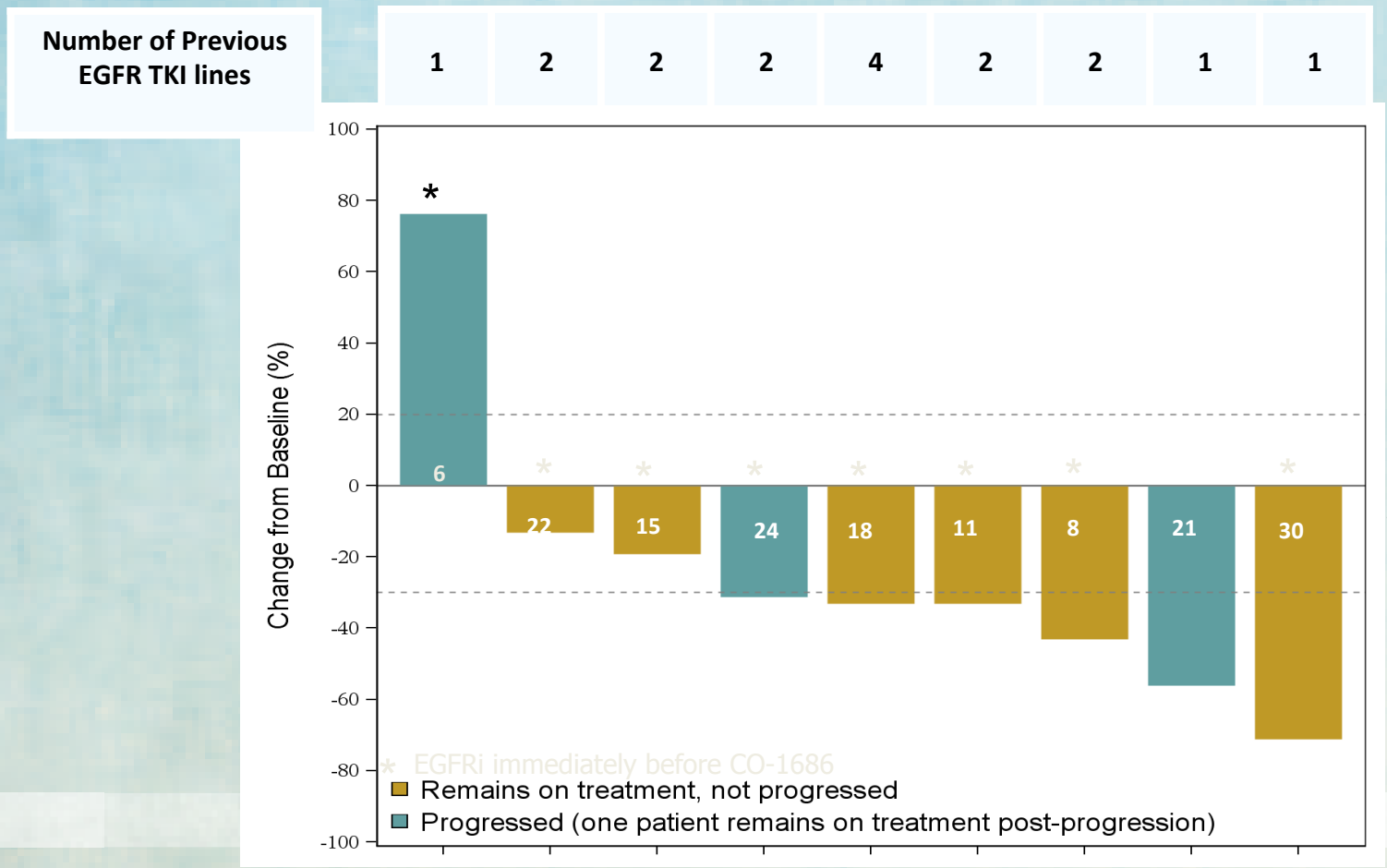
EGFR TKI Mechanisms of Acquired Resistance.



Yu H A et al. Clin Cancer Res 2013;19:2240-2247

CO-1686 Targets EGFR T790M: Preliminary Efficacy Data in T790M+ NSCLC

- 6 of 9 patients with PR



Ceritinib (ZYKADIA): Clinical Activity

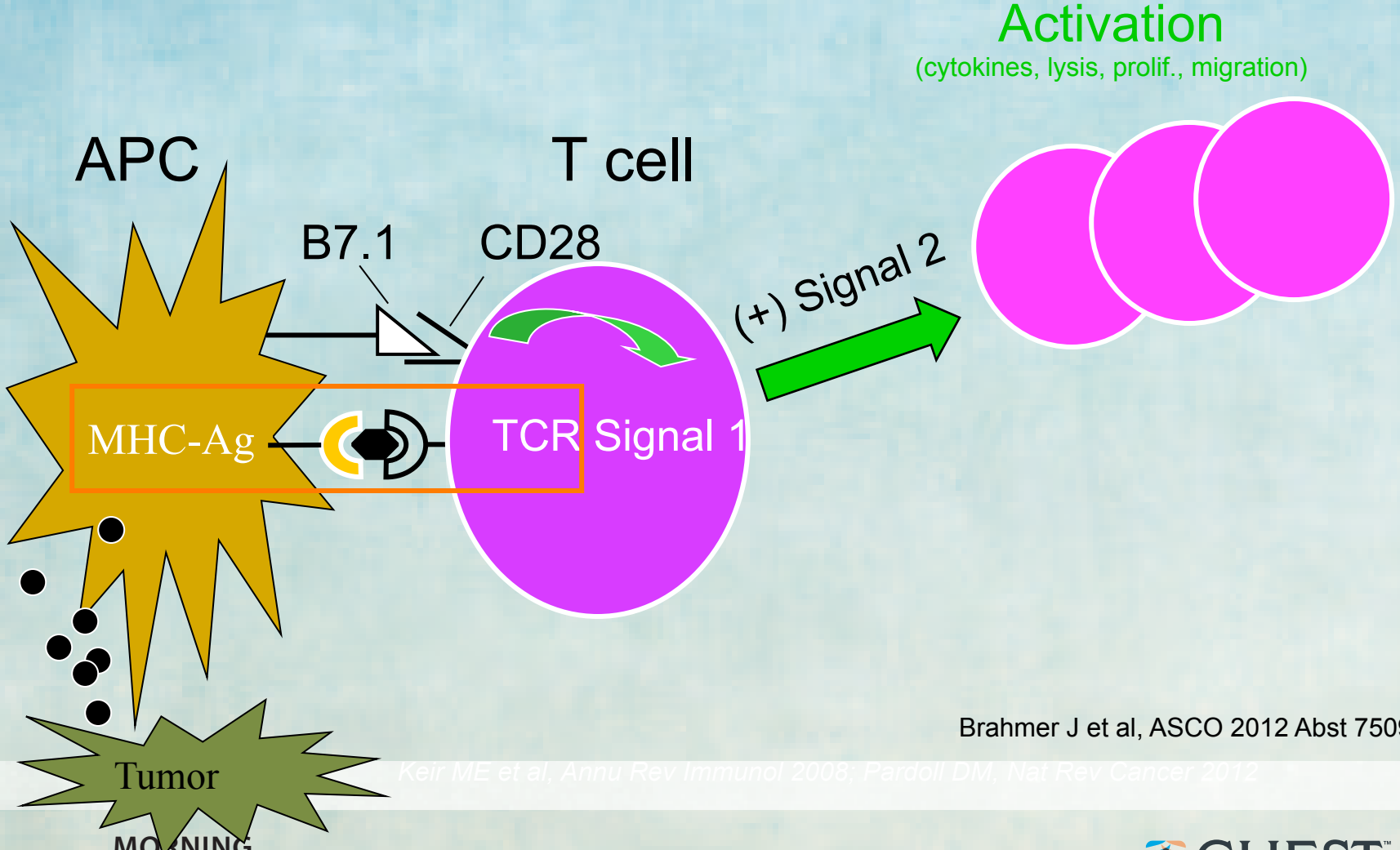
- Phase 1 studies examined doses of 50 to 750 mg daily.
- Multicenter trial, dose 750 mg daily
- N = 163, ALK-positive, previously treated with crizotinib
- Median age 52 years. Adenoca (93%), female (54%), never/former smoker (97%)
- RR 44%
- FDA accelerated approval 4/29/14.

ras/*raf*/MAPK Pathway

- *RAS* mutations seen in 20-30% of NSCLC[1]
- *RAS* mutations associated with a worse prognosis[2]
- Tumors harboring *RAS* mutations do not respond to EGFR inhibition[3]
- Encouraging data combining MEK inhibitors with chemotherapy

1. Massarelli E, et al. Clin Cancer Res. 2007 May 15;13(10):2890-6; 2. Mitsudomi T, et al. Cancer Res. 1991 Sep 15;51(18):4999-5002; 3. Pao W, et al. PLoS Med. 2005 Jan;2(1):e17.

Role of PD-1 in Suppressing Antitumor Immunity



Brahmer J et al, ASCO 2012 Abst 7509

Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

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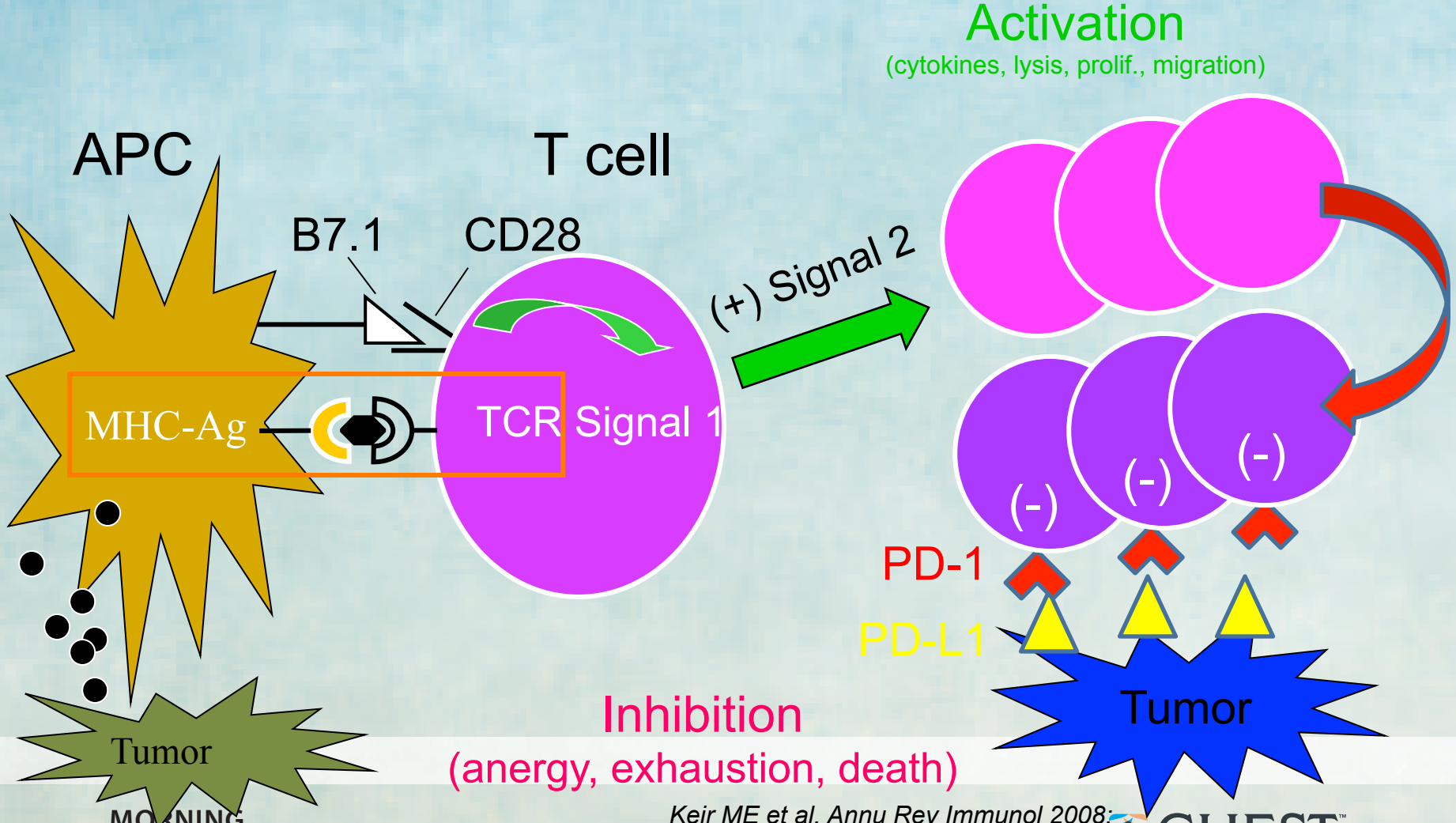

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Brahmer J et al, ASCO 2012 Abst 7509

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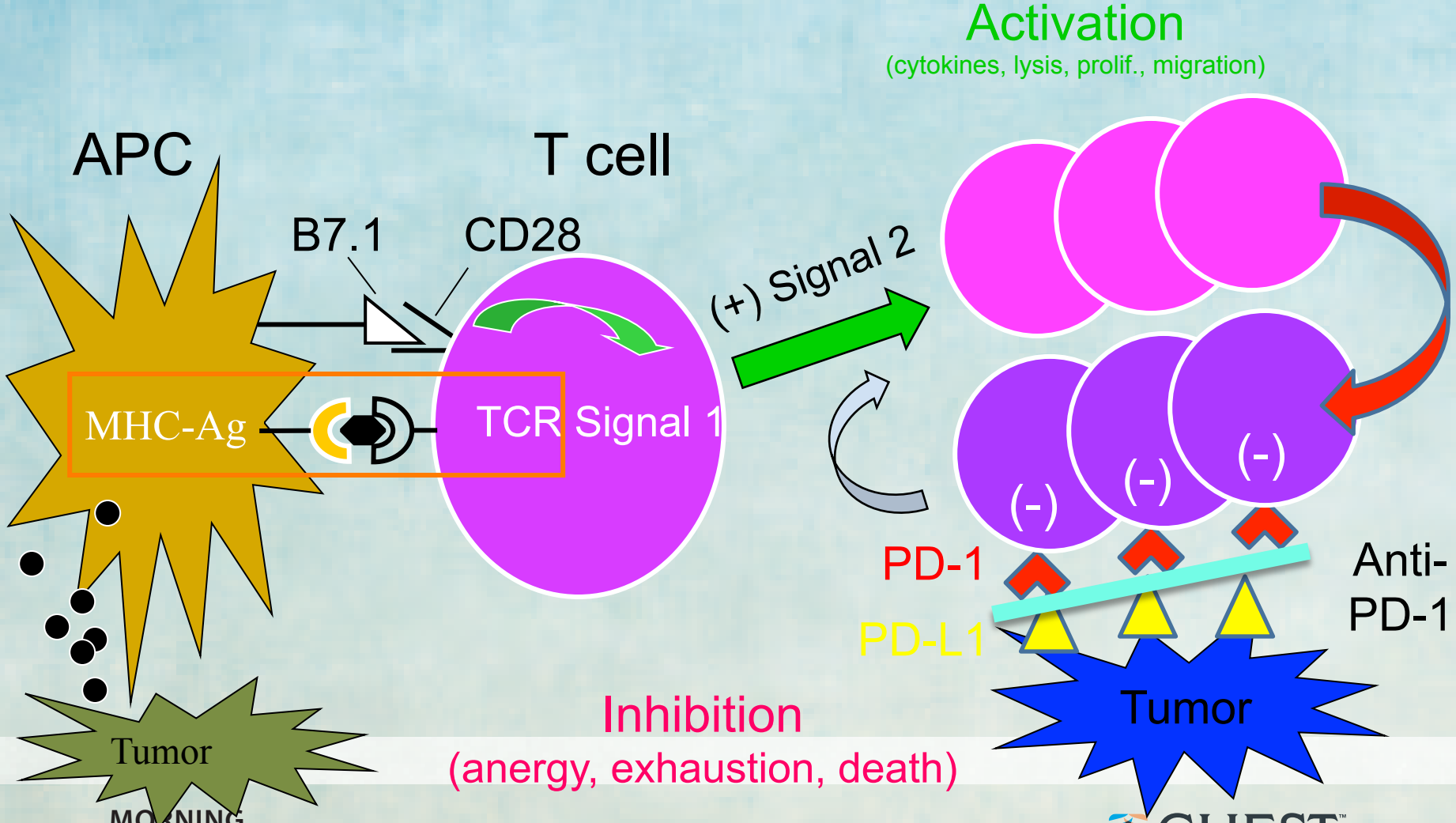
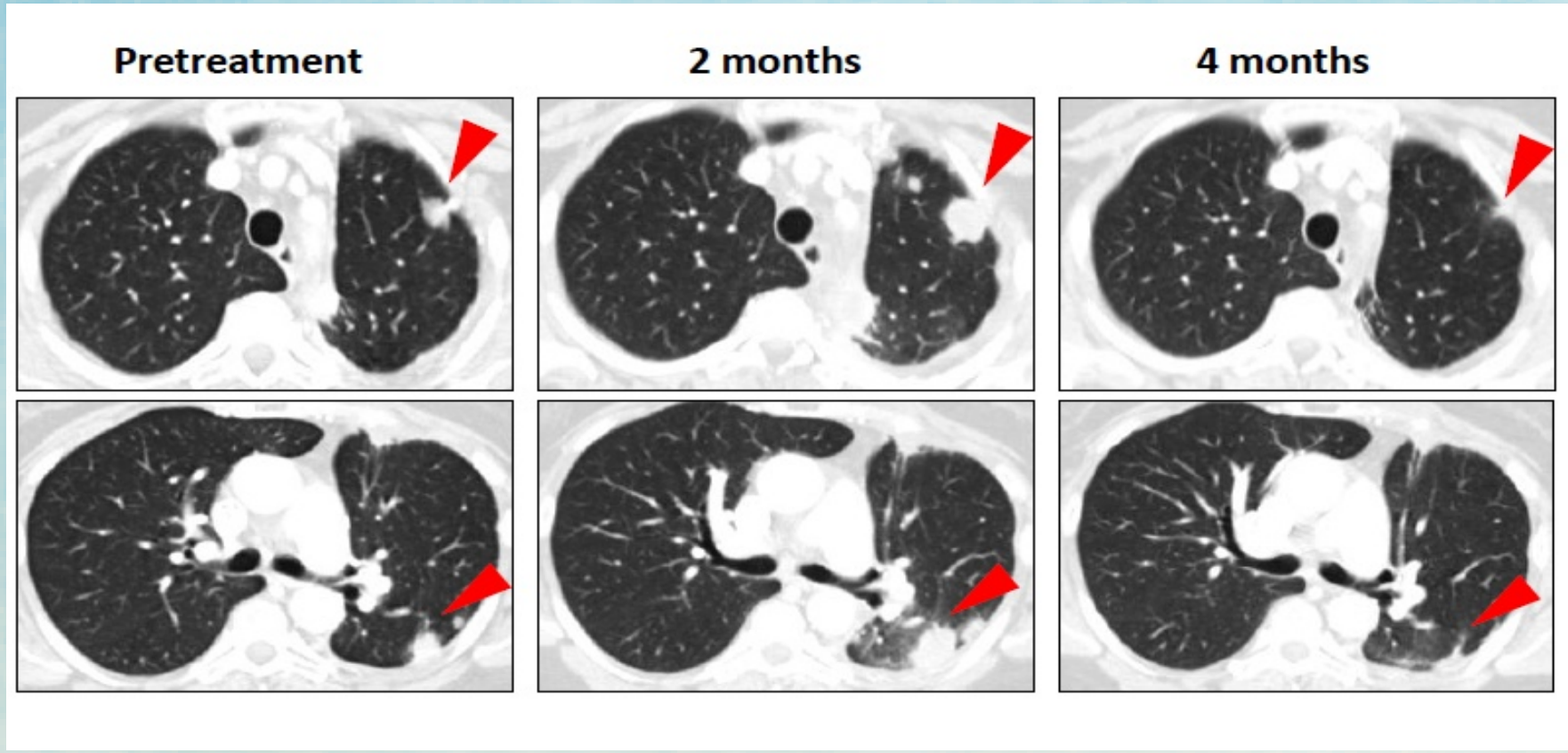


Brahmer J et al, ASCO 2012 Abst 7509

Keir ME et al, Annu Rev Immunol 2008;
Pardoll DM, Nat Rev Cancer 2012

Response of Metastatic NSCLC (Nivolumab, 10mg/kg)



- Initial progression in pulmonary lesions of a NSCLC patient with non-squamous histology was followed by regression
- Dx '04, EGFR mutation +; Rx Gem/carbo, erlotinib, erlotinib + LBH589 (trial for T790 mutation), and lastly pemetrexed

Brahmer J et al, ASCO 2012 Abst 7509

Conclusions

- For the majority of advanced NSCLC patients, platinum-based chemotherapy remains the standard of care. Treatment goals are prolongation of survival and improvement in tumor-related symptoms and quality of life.
- Molecular testing is now a standard of care for adenocarcinomas. For patients with targetable mutations, oral cancer drugs (erlotinib, gefitinib, afatinib, crizotinib) are more effective than chemotherapy.
- Clinical trials will help to define appropriate treatment options for patients who develop resistance to targeted therapies.
- Therapies targeting RAS-mutant NSCLC and anti-tumor immunity pathways represent exciting areas of clinical research.