„Lung Cancer“ Highlights IASLC 2013

Mauricio Lema Medina – Clínica de Oncología Astorga / Clínica SOMA, Medellín

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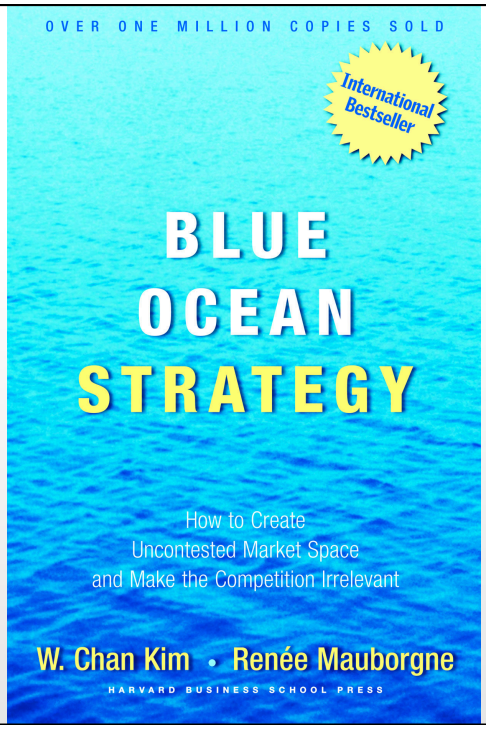
Agenda

1. **Red Ocean *vs* Blue Ocean**
2. Today's Red Ocean in mNSCLC
3. New Contestants in Red Ocean's mNSCLC
4. A Glimpse of a Blue Ocean Strategy in mNSCLC
5. Proof-of-Principle?
6. Conclusion: Ushering a New Era in mNSCLC

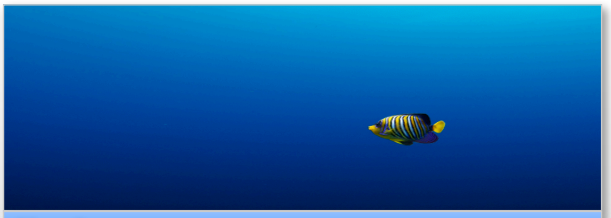


"Blue Ocean" vs. "Red Ocean"

Definition

Red Ocean

- Existing market
- Fierce fight for market segments
- Fear of customer loss



Blue Ocean

- New uncontested market
- No competitors
- Exotic pioneer in a new market

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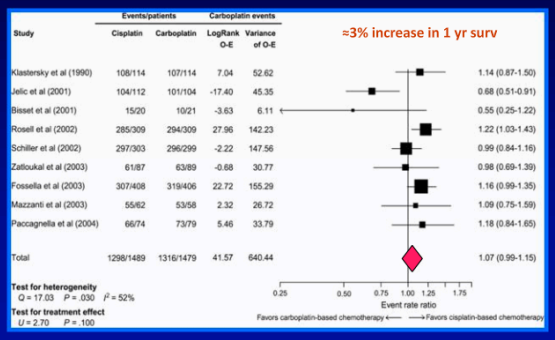
ECOG 1594 Randomized 4-Arm Study in Advanced NSCLC

Parameter	*$P_{xl}C_{is}$*	*$G_{em}C_{is}$*	*$D_{oc}C_{is}$*	*$P_{xl}C_{b}$*
Response Rate	21%	21%	17%	15%
TTP	3.5 m	4.5 m*	3.3 m	3.3 m
Median Survival	8 m	8 m	7 m	8 m
1-Yr Survival	31%	36%	31%	35%
2-Yr Survival	11%	16%	12%	11%

*P>.05 vs. PC arm

Schiller et al. NEJM 2002: 346, 92-98

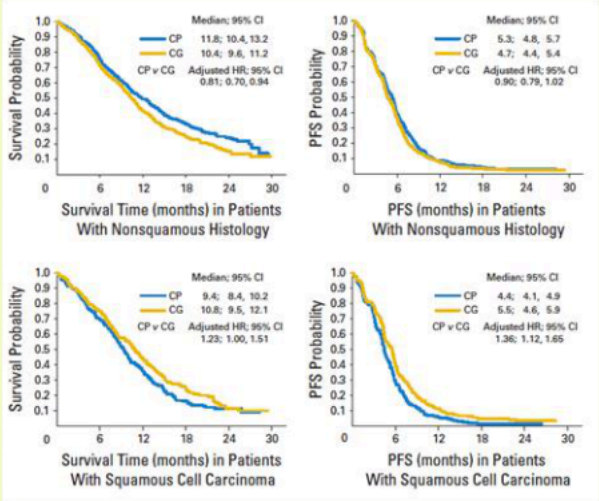
Cisplatin vs. Carboplatin as Front-line Therapy in Advanced NSCLC



Ardizzoni et al. *J. Natl. Cancer Inst.* 99(11):847, 2007

E03.1 - Maximising the Benefit of Chemotherapy for Advanced NSCLC (ID 382)
G. Giaconne – Educational Session

Pemetrexed is superior to gemcitabine in non-squamous carcinomas; gemcitabine is superior to pemetrexed in squamous cell carcinomas



Scagliotti G et al JCO JCO 2008

E03.1 - Maximising the Benefit of Chemotherapy for Advanced NSCLC (ID 382)
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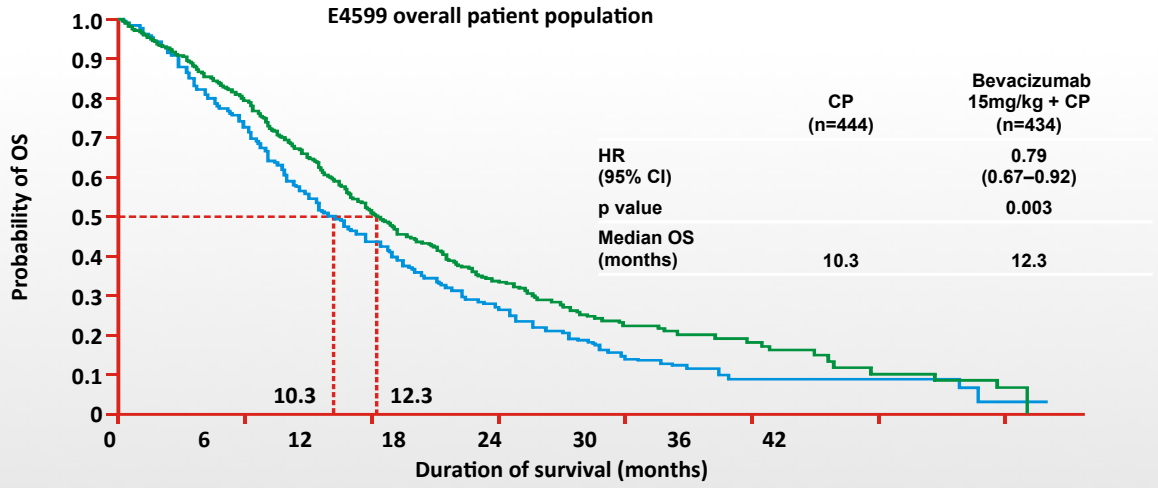
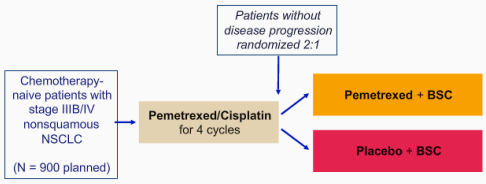
Bevacizumab extends survival beyond historical benchmark of 1 year



	CP (n=444)	Bevacizumab 15mg/kg + CP (n=434)
HR (95% CI)		0.79 (0.67–0.92)
p value		0.003
Median OS (months)	10.3	12.3

Sandler, et al. NEJM 2006

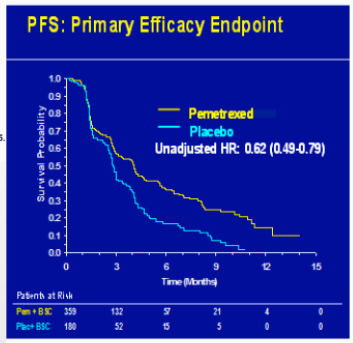
Paramount Trial
Pemetrexed Continuation Maintenance

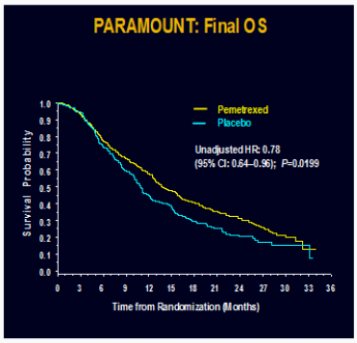


- Primary endpoint: PFS
- Other endpoints: OS, ORR, safety, patient-reported outcomes, resource utilization,

Paz-Ares LG, et al. BMC Cancer. 2010;10:85.

Paramount Trial
Pemetrexed Continuation Maintenance





Paz-Ares L et al., Lancet Oncol 2012
Paz-Ares L, et al., J Clin Oncol 2013

L. Paz.Ares – Educational Session

SATURN study design

Chemonaïve advanced NSCLC n=1,949 → 4 cycles of 1st-line platinum-based doublet* → Non-PD n=889 (1:1) → Erlotinib 150mg/day → PD; Placebo → PD

Mandatory tumour sampling

Stratification factors:
- EGFR IHC (positive vs negative vs indeterminate)
- Stage (IIIB vs IV)
- ECOG PS (0 vs 1)
- CT regimen (cis/ge
- Smoking history (c
- Region

*Cisplatin/paclitaxel; cisp carboplatin/gemcitabine; EGFR = epidermal growt

Co-primary endpoints:
- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

PFS*: all patients (ITT)

	Erlotinib	Placebo
PFS at 12 wks (%)	53	40
PFS at 24 wks (%)	31	17

HR=0.71 (0.62–0.82)
Log-rank p<0.0001

Erlotinib (n=437)
Placebo (n=447)

PFS probability; Time (weeks)

OS*: all patients (ITT)

Erlotinib (n=438)
Placebo (n=451)

HR=0.81 (0.70–0.95)
Log-rank p=0.0088

OS probability; Time (months)

*OS is measured from time of randomisation into the maintenance phase;
ITT = intent-to-treat population

PFS according to *EGFR* mutation status

EGFR mutation+: HR=0.10 (0.04–0.25), Log-rank p<0.0001; Erlotinib (n=22), Placebo (n=27)

EGFR wild-type: HR=0.78 (0.63–0.96), Log-rank p=0.0185; Erlotinib (n=199), Placebo (n=189)

PFS probability; Time (weeks)

Interaction p<0.001

Capuzzo et al. Lancet Oncol 2010

E03.1 - Maximising the Benefit of Chemotherapy for Advanced NSCLC (ID 382)
G. Giaconne – Educational Session

AVAPERL

Non-squamous NSCLC
↓
4 cycles q 3w of cisplatin 75 mg/m2, pemetrexed 500mg/m2, bevacizumab 7.5mg/kg
↓
Non-progressors
↙ ↘
pemetrexed 500mg/m2, bevacizumab 7.5mg/kg q3w | bevacizumab 7.5mg/kg q3w

Primary endpoint: PFS from randomization

Barlesi F et al. JCO 2013;31:3004-3011

(A) progression-free survival and (B) overall survival from randomization, and (C) PFS and (D) OS from first induction treatment

A: Progression-Free Survival (%); Time Since Random Assignment (months)
B: Overall Survival (%); Time Since Random Assignment (months)
C: Progression-Free Survival (%); Time Since Induction (months)
D: Overall Survival (%); Time Since Induction (months)

Barlesi F et al. JCO 2013;31:3004-3011

Should we use it just because the PFS was better?

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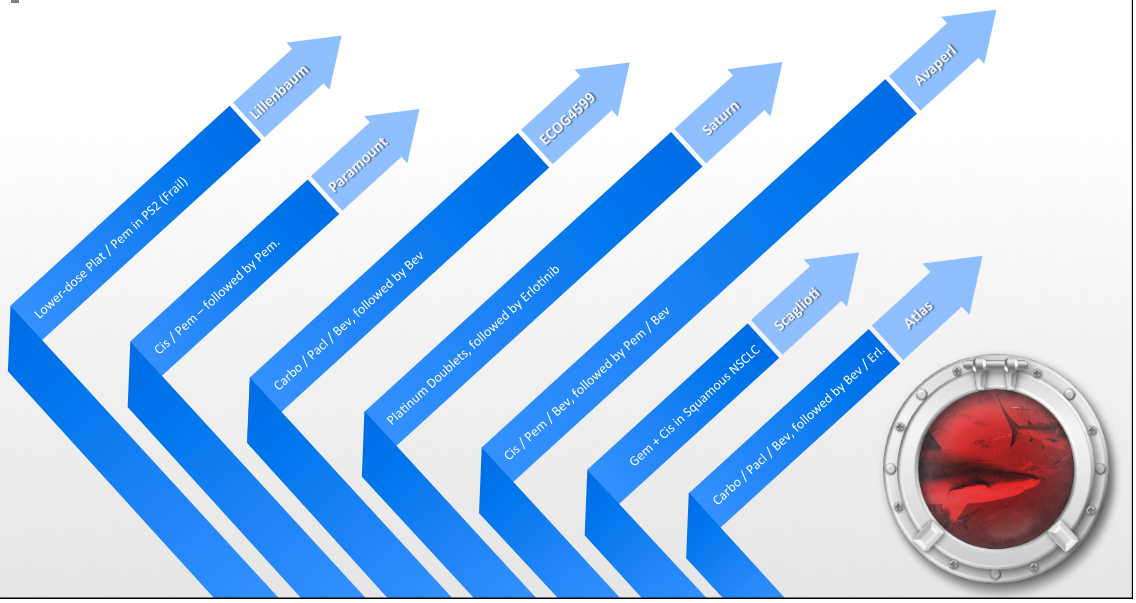
Maintenance Efficacy PFS & OS

Trial	N	Maintenance drug	PFS HR (95% CI)	OS HR (95% CI)
Switch Maintenance				
Westeel et al.	181	Vinorelbine	0.77 (0.56-1.07)	1.08 (0.79-1.47)
Fidias et al.	309	Docetaxel	0.71 (0.55-0.92)	0.84 (0.65-1.08)
Capuzzo	889	Erlotinib	0.71 (0.62–0.82)	0.81 (0.70-0.95)
Ciuleanu et al.	663	Pemetrexed	0.60 (0.49-0.73)	0.79 (0.65-0.95)
Continuation Maintenance				
Paz-Ares et al	539	Pemetrexed	0.62 (0.49-0.79)	0.78 (0.64-0.96)
Brodowicz et al.	206	Gemcitabine	0.69 (0.56-0.86)	0.84 (0.52-1.30)
Belani et al.	255	Gemcitabine	1.09 (0.81-1.45)	0.97 (0.72-1.30)
Perol et al.	309	Gemcitabine	0.56 (0.44-0.72)	0.89 (0.67-1.15)

L. Paz.Ares – Educational Session

Unselected mNSCLC

´Red Ocean´ World – Too many options



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"Blue Ocean" vs. "Red Ocean"

Definition

Red Ocean

- Compete in existing market space
- Beat the competition
- Exploit existing demand
- Make the value/cost trade-off
- Align the whole system of a company's activities with ist strategic choice of differentiation or low cost

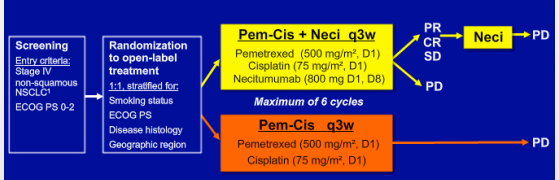
Randomized Phase 3 Trial (INSPIRE) of Necitumumab plus Cisplatin-Pemetrexed versus Cisplatin-Pemetrexed Alone as First-line Therapy in Stage IV Non-squamous NSCLC

*Luis Paz-Ares**
J. Mezger, T. Ciuleanu, J.R. Fischer, J. von Pawel, M. Provencio, A. Kazarnowicz, G. Losonczy, G. Castro Jr., A. Szczesna, L. Crino, M. Reck, R. Ramlau, E. Ulsperger, C. Schumann, J.E. Miziara, A. Lessa, H. Depenbrock, V. Soldatenkova, B. Balint, F.R. Hirsch, M.A. Socinski

On behalf of the INSPIRE Investigators

** Hospital Virgen del Rocío, Sevilla, Spain*
Presenting Author

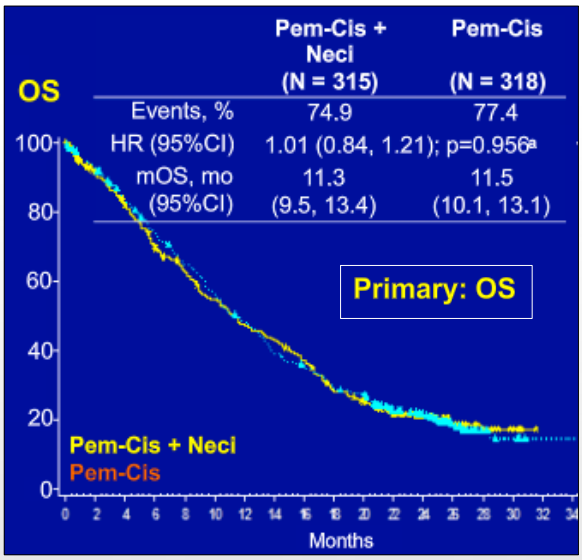
Study Design



Radiographic tumor assessments: at baseline and q6w (±3 days) until radiographic documentation of PD

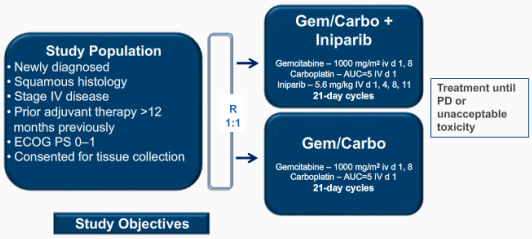
Mandatory tissue collection: minimum 4 slides of paraffin embedded tissue per patient

Necitumumab (Neci: IMC-11F8) is a human IgG1 anti-EGFR1 monoclonal antibody[2]



ECLIPSE Phase 3 Study Design

Multi-center, multi-national, randomized open-label Phase 3 (N=780)
March 2010 to May 2012



Study Objectives

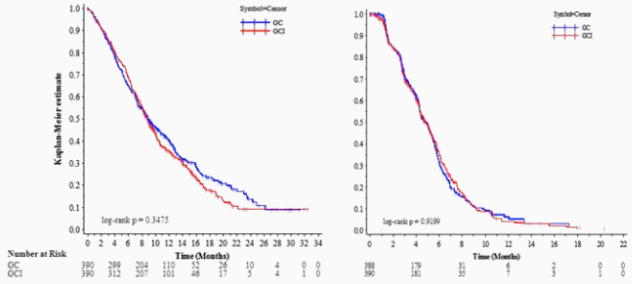
Primary endpoint: OS
Secondary endpoints: Safety, PFS, TTP, ORR (RECIST 1.1), QOL
Exploratory molecular substudy: Biomarker analysis (gene expression)

- DSMB reviewed safety 4 times plus 1 interim futility analysis recommending to continue the trial without modifications

SCRI

O15.06 ECLIPSE : Study Results

- The addition of Iniparib did not improve the efficacy of GC in the treatment of patients with advanced squamous lung cancer.



O15.06 - Randomized Phase III Trial of Gemcitabine (G)/Carboplatin (C) with or without Iniparib (I) in Patients (Pts) with Previously Untreated Stage IV Squamous Lung Cancer – Spigel D, et al

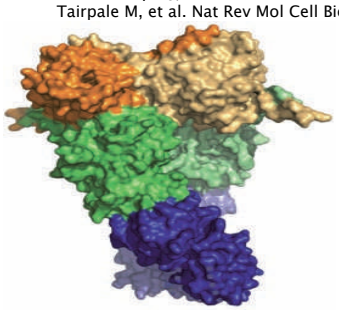
국립암센터 NATIONAL CANCER CENTER

Heat Shock Protein 90 (HSP90)

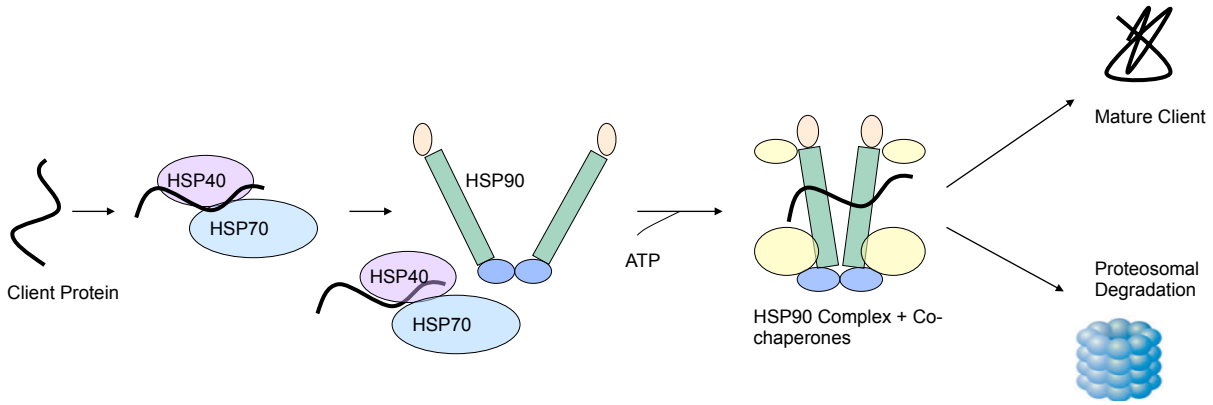
- HSP90 is a ubiquitous and highly-conserved molecular chaperone.
  - Facilitates post-translational folding and stabilization of "client proteins."
  - Although expressed in normal tissues, HSP90 is up-regulated in response to cellular stress (e.g. anoxia, acidosis, etc).
  - Without HSP90, client proteins become misfolded and subject to ubiquitin-mediated proteasomal degradation.

Banerji U. Clin Cancer Res 2009.
Trepel J, et al. Nat Rev Cancer 2010.
Tairpale M, et al. Nat Rev Mol Cell Biol 2010

Class	Examples
Steroid Receptors	Androgen receptor, estrogen receptor, progesterone receptor, glucocorticoid receptor, mineralocorticoid receptor
Transcription Factors	STAT3, p53, heat shock factor 1, HIF1α, HIF2α, HIF3α
Kinases	HER2, AKT, MET, CDK4, BCR-ABL, mutant EGFR, mutant BRAF, KIT, EML4-ALK, VEGFR
Miscellaneous	Telomerase, BCL-2, Apaf-1



HSP90 Function



Patel HJ, et al. Expert Opin Drug Discov 2011.
Taipale M, et al. Nat Rev Mol Cell Biol 2010

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CANCER CENTER

International Association for the Study of Lung Cancer

IASLC 15th World Conference on Lung Cancer
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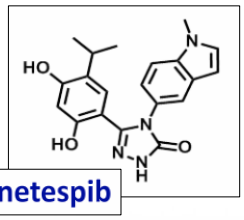
WCLC.IASLC.ORG

GALAXY-1: Randomized phase II study of docetaxel with or without ganetespib in advanced lung adenocarcinoma: Results in biomarker sub-groups and all adenocarcinoma patients.

Abstract # O03.01

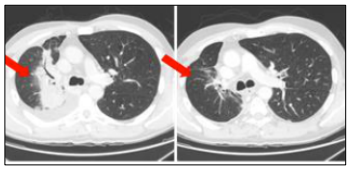
PRESENTER: Suresh S. Ramalingam
Emory University, Atlanta, USA

Geoffrey Shapiro, Vera Hirsh, Bojan Zaric, Timur Ceric, Elena Poddubskaya, Jonathan Goldman, Tudor Ciuleanu, Fadlo R. Khuri, James Spicer, Olga Skrylnik, Enriqueta Felip, Christian Manegold, Zoran Andric, Rafael Rosell, Sonja Badovinac, Thierry Pieters, Manuel R. Modiano, Vojo Vukovic, Ilker Yalcin, Florentina Teofilovici, Iman El-Hariry, Wei Guo, Safi R. Bahcall, Glenwood Goss, Dean Fennell

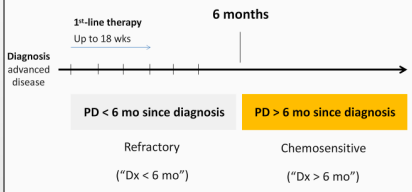


Ganetespib

Novel, second-generation Hsp90 inhibitor



Stratification for refractory vs. chemosensitive disease



6 months cutoff consistent with convention in second-line NSCLC trials (time since completion of first line treatment > 3 mo)

Rationale for key GALAXY-1 patient populations

Population	Elevated LDH	KRAS mutations	Chemosensitive (Diagnosis of advanced disease > 6 months)	ITT
Rationale	• **LDH-A is a marker** of HIF-1α activity • HIF-1α is Hsp90 client, drives invasiveness, metastasis	• **RAS** signaling kinases are Hsp90 clients • Medical need	• Key **cell cycle checkpoint/ DNA repair** kinases are Hsp90 clients • Potential cross-resistance to G in refractory patients	All

- eLDH and mKRAS: co-primary endpoints
- Dx>6m was used as a stratification factor

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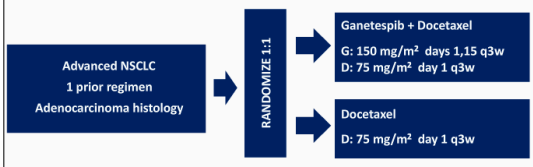
GALAXY-1 Schema



Stratification Factors
- ECOG PS (0 vs. 1)
- Time since diagnosis of advanced disease (≤6 mo vs. >6 mo)
- Baseline serum LDH (< or ≥ ULN)
- Smoking status

Endpoints
- Co-primary: PFS in elevated LDH, mKRAS groups
- Key secondary: PFS and OS in all adenocarcinoma patients

Eligibility

- Advanced NSCLC
- ECOG PS of 0 or 1
- One prior regimen for advanced NSCLC
- Presence of measureable disease per RECIST 1.1
- Documented progressive disease after first-line therapy
- Brain metastasis was allowed after treatment and documented stability
- Tumor tissue availability
- Adequate organ function

	G+D vs. D	Elevated LDH N=76	mKRAS N=63	Chemosensitive (Dx >6m) N=178	ITT N=253
PFS	Median (months)	3.4 vs. 1.9	4.1 vs. 3.0	5.3 vs. 3.4	4.3 vs. 3.2
	Events	63 (83%)	50 (79%)	138 (78%)	199 (79%)
OS	Median (months)	5.2 vs. 4.3	9.8 vs. 6.3	10.7 vs. 7.4	10.4 vs. 8.4
	(90% CI)	(3.9, 9.8) vs (3.1, 5.1)	(4.3, 12.3) vs (4.9, 14.0)	(8.5, 13.9) vs (5.8, 10.0)	(8.0, 12.6) vs (6.3, 10.9)
	Events	64 (84%)	41 (65%)	115 (65%)	166 (66%)

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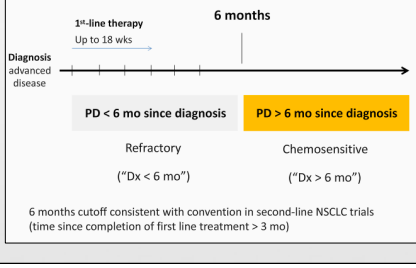
	Hazard Ratio G+D vs. D (90% CI)	Elevated LDH N=76	mKRAS N=63	Chemosensitive (Dx >6m) N=178	ITT N=253
PFS	Unadjusted	**0.94** (0.62, 1.43) p=0.409	**0.83** (0.52, 1.33) p=0.256	**0.73** (0.55, 0.96) p=0.031	**0.84** (0.67, 1.06) p=0.114
	Adjusted	**0.69** (0.43, 1.08) p=0.088	**0.95** (0.58, 1.54) p=0.427	**0.72** (0.53, 0.96) p=0.030	**0.84** (0.66, 1.06) p=0.110
OS	Unadjusted	**0.69** (0.45, 1.05) p=0.073	**1.12** (0.67, 1.88) p=0.641	**0.75** (0.56, 1.03) p=0.065	**0.90** (0.70, 1.17) p=0.217
	Adjusted	**0.52** (0.33, 0.81) p=0.009	**1.22** (0.71, 2.07) p=0.727	**0.72** (0.52, 0.98) p=0.040	**0.86** (0.66, 1.12) p=0.175

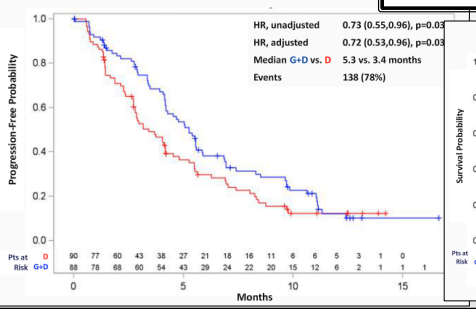
Ganetespib in combination with docetaxel improved OS and PFS compared to docetaxel alone in the > 6 m population

Stratification for refractory vs. chemosensitive disease

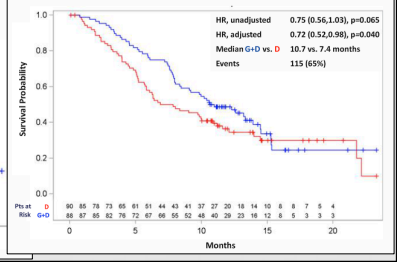


6 months cutoff consistent with convention in second-line NSCLC trials (time since completion of first line treatment > 3 mo)

PFS: Dx >6 months Population



OS: Dx >6 months Population



Chinese Thoracic Oncology Group(CTONG)

Final results of CTONG 0806: a phase II trial comparing pemetrexed with gefitinib as second-line treatment of advanced non-squamous NSCLC patients with wild-type EGFR

Qing Zhou[1], Ying Cheng[2], Ming-fang Zhao[3], Jin-ji Yang[1], Hong-hong Yan[1], Li Zhang[4], Yong Song[5], Jian-hua Chen[6], Wei-neng Feng[7], Chong-rui Xu[1], Yi-long Wu[1]*
Chinese Thoracic Oncology Group (CTONG)

Chinese Thoracic Oncology Group(CTONG)

Study Design

- A multi-center, randomized, controlled, open-label phase II trial

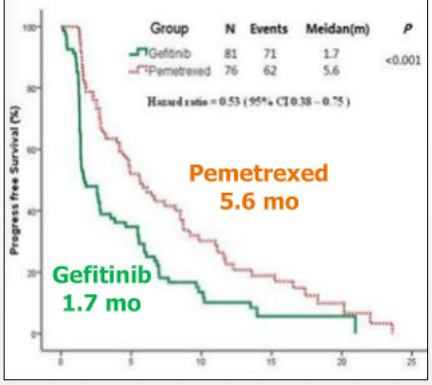
•locally advanced or metastatic, non-squamous NSCLC
• previously treated with one platinum-based chemotherapy
• no EGFR mutation in exons 18-21 tested by direct sequencing

→ Pemetrexed 500mg/m², iv, d1, with vitamin B12 and folic acid supplement, q3w → PD

→ Gefitinib 250mg qd → PD

Primary endpoint: PFS

PFS (HR 0.53, p<0.001)



CTONG0806 is the first trial to show significant improvement in PFS, DCR and a trend of improving OS with pemetrexed compared with gefitinib in second-line setting for EGFR wild-type advanced non-squamous NSCLC.

TAILOR Study Design

To test superiority of docetaxel versus erlotinib

- Advanced/recurrent
- Previous platinum based doublet
- EGFR wild-type
- KRAS determined
- ECOG PS 0-2

R 1:1

DOCETAXEL
75 mg/m2 iv on day 1,21
35 mg/m2 iv on day 1,8,15

ERLOTINIB
150 mg po, daily

CROSS OVER NOT ALLOWED

PRIMARY ENDPOINT
Overall Survival (OS)

SECONDARY ENDPOINTS
Progression Free Survival (PFS)
Response Rate (RR)
Quality of Life (QoL)
Safety

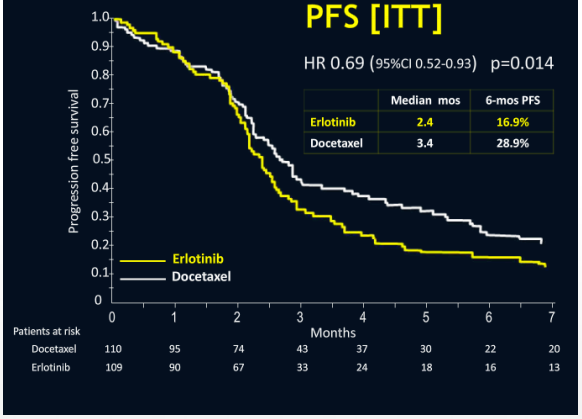
STRATIFICATION
Centre
Stage
Prior chemotherapy
ECOG-PS (0-1 vs. 2)
Quality of sample

Garassino et al. Lancet Oncol. 2013

PFS [ITT]

HR 0.69 (95%CI 0.52-0.93) p=0.014

	Median mos	6-mos PFS
Erlotinib	2.4	16.9%
Docetaxel	3.4	28.9%



Response Rate

	DOCETAXEL n=94 %	ERLOTINIB n=92 %	χ^2 test
CR	4.2	0.0	p = 0.0023
PR	9.5	2.1	
SD	27.6	20.6	
PD	58.1	77.1	
RR (CR+PR)	13.8	2.1	p = 0.0036
DCR (CR+PR+SD)	41.4	22.8	p = 0.0066

TAILOR does not support the use of an EGFR TKI (erlotinib) in advanced NSCLC patients with wild type EGFR in comparison to standard chemotherapy (docetaxel)

E03.1 - Maximising the Benefit of Chemotherapy for Advanced NSCLC (ID 382)
G. Giaconne – Educational Session

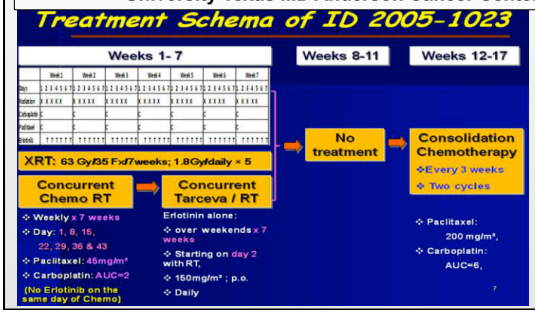
International Association for the Study of Lung Cancer
IASLC
IASLC 15th World Conference on Lung Cancer
October 27 - October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

PRESENTATION NUMBER 2436:
TITLE: Value of Adding Erlotinib to Thoracic Radiation Therapy with Chemotherapy for Stage III Non-Small Cell Lung Cancer: A Prospective Phase II Study

Presenter: Ritsuko Komaki, MD,FACR,FASTRO

Pamela K. Allen, Xiong Wei, George R. Blumenschein, Ximing Tang, J. Jack Lee, James W. Welsh, Ignacio I. Wistuba, Diane D. Liu, and Waun Ki Hong
University Texas MD Anderson Cancer Center

Treatment Schema of ID 2005-1023



Materials & Methods

- 48 Stage III NSCLC patients were prospectively enrolled from 3/2008 through 6/2010.
- Eligibility :
  - -Karnofsky's Performance Status (KPS) > 70,
  - -Weight loss ≤ 5% over past 3 months,
  - -FEV1 ≥ 1.0 L, adequate hematologic, hepatic, and renal functions.
- Primary endpoint was to determine efficacy of erlotinib/ radiotherapy after ChT/RT measured by time to progression

Results

Tumor Responses by RECIST 3.0

	CR	PR	SD or PD	Not Available*
all 46 cases	14/46 (30%)	23/46 (50%)	8/46 (18%)	1/46 (2%)
EGFR mutation (EGFR-M)	3/4 (75%)	0 (0%)	0 (0%)	1/4 (25%)
EGFR wild type	11/36 (30%)	19/36 (53%)	6/36 (17%)	0 (0%)
no data	0 (0%)	4/5 (80%)	1/5 (20%)	0 (0%)

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- **Grade 3 pneumonitis rate was 6.5%.**

Treatment Outcome for all 46 cases

	OS	PFS	LRFS	DMFS
Median Survival (mths)	34.1	13.7	Not Reached	18.2
12–Mth	82.9%	55.7%	74.6%	66.3%
24–Mth	67.7%	31.8%	59.7%	44.3%
36–Mth	48.3%	24.5%	59.7%	32.2%

Excellent 2-yr OS…
Further study warranted

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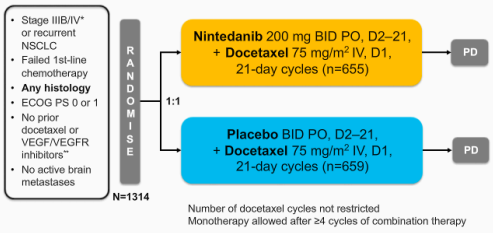
Abstract: 3284 Presentation: O16.01

Impact of tumour burden on the overall survival analysis of the LUME-Lung 1 study: a randomized, double-blind phase 3 trial of nintedanib (BIBF 1120) + docetaxel in NSCLC patients progressing after first-line chemotherapy

Presenting Author:
M Reck

Disclosure information: M Reck has served as a member of advisory boards and received honoraria for lectures for Boehringer Ingelheim

LUME-Lung 1 Study Design

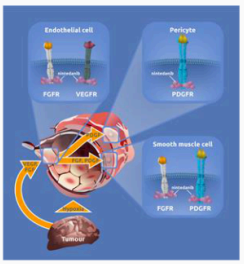


Number of docetaxel cycles not restricted
Monotherapy allowed after ≥4 cycles of combination therapy

Stratification: ECOG performance status (0 vs 1)
Prior bevacizumab (yes vs no)
Histology (squamous vs non-squamous)
Brain metastases (yes vs no)

*AJCC 6th/7th edition; **Other than bevacizumab

Characteristics of Nintedanib*



- Oral angiokinase inhibitor targeting VEGFR 1–3, FGFR 1–3, and PDGFR α/β as well as RET[1,2]
- No drug–drug interaction liability via CYP450[3]
- Manageable safety profile in combination with
  - docetaxel[4]
  - pemetrexed[5]
  - paclitaxel/carboplatin[6]
  - gemcitabine/cisplatin[7]
  - volasertib[2]
  - afatinib[8]
- Single-agent nintedanib was active in a phase II trial in recurrent NSCLC[9]

*Nintedanib is an investigational compound and is not yet approved
FGFR, fibroblast growth factor receptor
VEGFR, vascular endothelial growth factor receptor
RET, rearranged during transfection

1. Hilberg F, et al. Cancer Res 2008;68:4774–8;
2. Data on file (Boehringer Ingelheim);
3. Stopfer P, et al. Xenobiotica 2011;41:297–311;
4. Bousquet G, et al. Br J Cancer 2011;105:1640–5;
5. Ellis PM, et al. Clin Cancer Res 2010;16:2881–9;
6. Doebele RC, et al. Ann Oncol 2012;23:2094–102;
7. Clinicaltrials.gov; NCT01346540);
8. Soria J-C, et al. Ann Oncol 2012;23 (abstract 979);
9. Reck M, et al. Ann Oncol 2011;22:1374–81

1 Primary endpoint: Independently assessed PFS
- All histologies
- 90% power after 713 PFS events, HR 0.78
- Two-sided stratified log-rank test, α=0.05

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Abstract: 3284 Presentation: O16.01

Impact of tumour burden on the overall survival analysis of the LUME-Lung 1 study: a randomized, double-blind phase 3 trial of nintedanib (BIBF 1120) + docetaxel in NSCLC patients progressing after first-line chemotherapy

Presenting Author:
M Reck

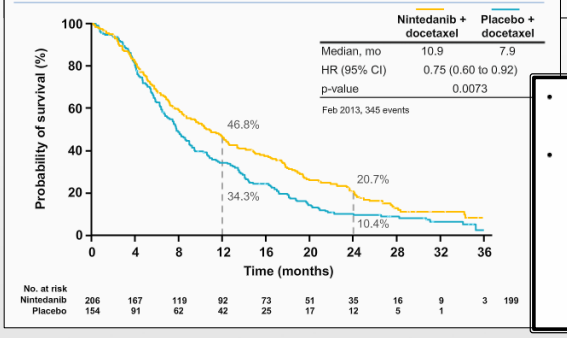
Disclosure information: M Reck has served as a member of advisory boards and received honoraria for lectures for Boehringer Ingelheim

Summary of LUME-Lung 1 clinical results

- LUME-Lung 1 met its primary endpoint: PFS (HR: 0.79 p=0.0019)
- A significant improvement in OS was demonstrated in patients with adenocarcinoma (OS; HR: 0.83 p=0.0359 median 12.6 vs 10.3 months)

Nintedanib plus docetaxel had a manageable safety profile with no unexpected safety findings

LUME Lung 1 Overall Survival: Patients with Adenocarcinoma Histology and Time Since Start of 1st Line Therapy < 9months



- A significant improvement in OS was demonstrated in patients with adenocarcinoma (OS; HR: 0.83 p=0.0359 median 12.6 vs 10.3 months)
- Patients with a poor prognosis had the highest OS benefit:
  - **adenocarcinoma histology** and time since start of 1st line therapy <9 months (HR: 0.75 p=0.0073 median OS 10.9 vs 7.9 months)
  - **adenocarcinoma histology** with PD as best response to 1st line treatment (HR: 0.62 p=0.0246 median OS 9.8 vs 6.3 months)
  - **squamous cell histology** with a high tumour burden showed a trend towards improved OS (SLD ≥7.5 cm; HR=0.82 p=0.0995 median OS 7.7 vs 6.1 months)

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Antibody	Molecule	Company	Development stage
PD-1	Nivolumab-BMS-936558	Fully human IgG4	Bristol-Myers Squibb	Phase III multiple tumors
	Pidilizumab CT-011	Humanized IgG1	CureTech	Phase II multiple tumors
	Lambrolizumab MK-3475	Humanized IgG4	Merck	Phase I-II
PD-L1	BMS-936559	Fully human IgG4	Bristol-Myers Squibb	Phase I
	MedI-4736	Engineered human IgG1	MedImmune	Phase I
	MPDL-3280A	Engineered human IgG1	Genentech	Phase I-II

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G. Giaconne – Educational Session

Efficacy of Nivolumab in NSCLC

Histology	Dose mg/kg	ORR % (n/N)	SD ≥ 24 wks % (n/N)	Median OS (95% CI)
Squamous	All doses	16.7 (9/54)	14.8 (8/54)	9.2 (7.3, 12.5)
	1	0 (0/18)	26.7 (4/15)	8.0 (2.6, 13.3)
	3	22.2 (4/18)	5.6 (1/18)	9.5 (6.7, NE)
	10	23.8 (5/21)	14.3 (3/21)	10.5 (7.8, 12.5)
Non-squamous	All doses	17.6 (13/74)	6.8 (5/74)	10.1 (7.2, 13.7)
	1	5.6 (1/18)	5.6 (1/18)	9.9 (5.6, 22.7)
	3	26.3 (5/19)	10.5 (2/19)	18.2 (10.3, 18.2)
	10	18.9 (7/37)	5.3 (2/37)	7.4 (4.6, 12.4)

Brahmer J et al. ASCO 2013

E03.1 - Maximising the Benefit of Chemotherapy for Advanced NSCLC (ID 382)
G. Giaconne – Educational Session

"Lung Cancer" Highlights IASLC 2013

Agenda

1. Red Ocean *vs* Blue Ocean
2. Today's Red Ocean in mNSCLC
3. New Contestants in Red Ocean's mNSCLC
4. **A Glimpse of a Blue Ocean Strategy in mNSCLC**
5. Proof-of-Principle?
6. Conclusion: Ushering a New Era in mNSCLC

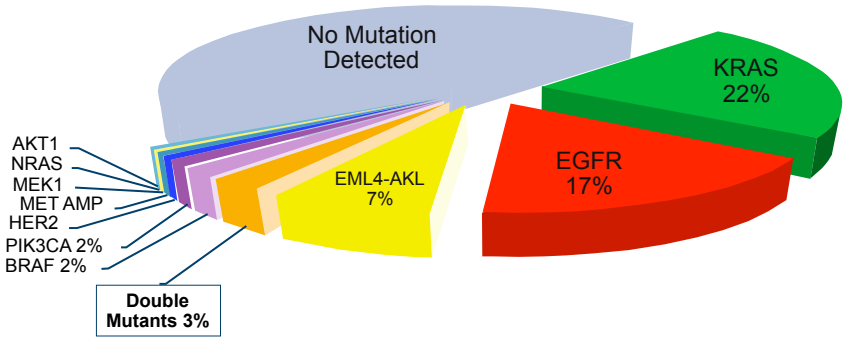
“Blue Ocean” vs. “Red Ocean”

Definition

Blue Ocean

- Create uncontested market space
- Make the competition irrelevant
- Create and capture new demand
- Break the value/cost trade-off
- Align the whole system of a company‘s activities in pursuit of differentiation and low cost

Lung Cancer Molecular Consortium Analysis in Lung Adenocarcinomas



Kris MG, et al. ASCO 2011. CRA7506. Johnson BE, et al. IASLC WCLC 2011. Abstract O16.01

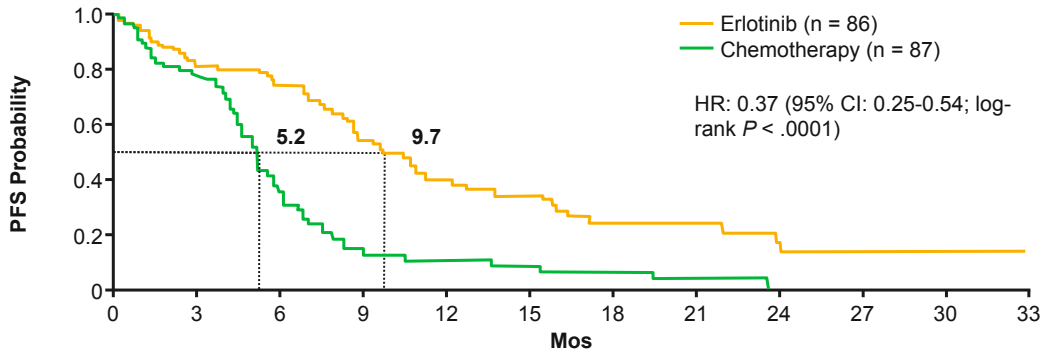
EURTAC: First-line Erlotinib vs Chemo in European Patients With EGFR Mutations

- 174 patients
- Trial run in Europe (lead by Spanish group)

Outcome	CT	Erlotinib	HR	*P* Value
Response rate, %	15	58	-	NR
Median PFS, mos	5.2	9.7	0.37	< .0001
Median OS, mos	NR	NR	0.80	.42
Most common toxicities, %	ALT elevation: 72 Anemia: 46 Neutropenia: 36	ALT elevation: 80 Rash: 80 Diarrhea: 57		

Rosell R, et al. ASCO 2011. Abstract 7503.

EURTAC: PFS in ITT Population



Patients at Risk, n

Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0
Chemo	87	49	20	8	5	4	3	1	0	0	0	0

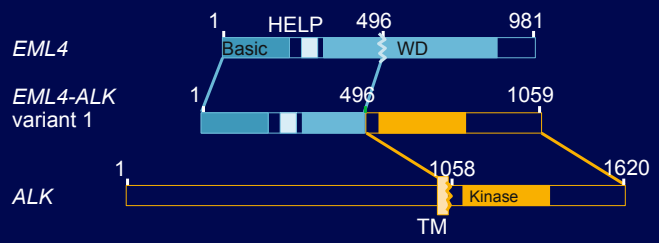
Rosell R, et al. ASCO 2011. Abstract 7503.

EML4-ALK Translocations in NSCLC

Vol 448|2 August 2007|doi:10.1038/nature05945 nature

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]



***EML4-ALK* frequency:**
~ 4% (64/1709)
Primarily in adenocarcinoma
More common in younger patients
More common in never-smokers
(~ 20%)

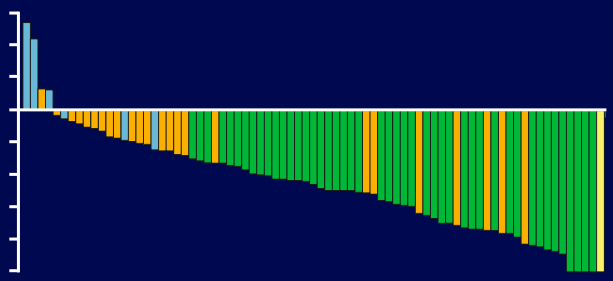
Soda M, et al. Nature. 2007;448:561-566.

ALK-Positive NSCLC and Impact of *ALK* Inhibition

ALK Rearrangement in NSCLC

- Rarely overlaps with *EGFR* and *KRAS* mutations
- Clinical testing
  - Break-apart FISH assay (FDA-approved test)
  - IHC
  - RT-PCR

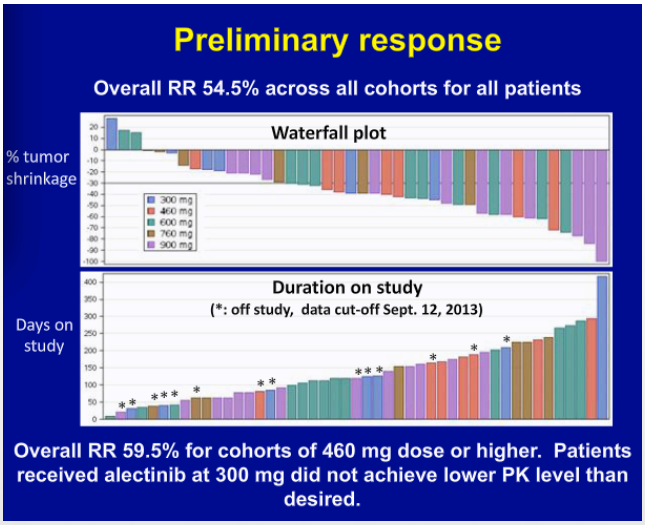
Activity of *ALK* Inhibitor in Patients With Advanced *ALK*-FISH–Positive NSCLC (N = 82)



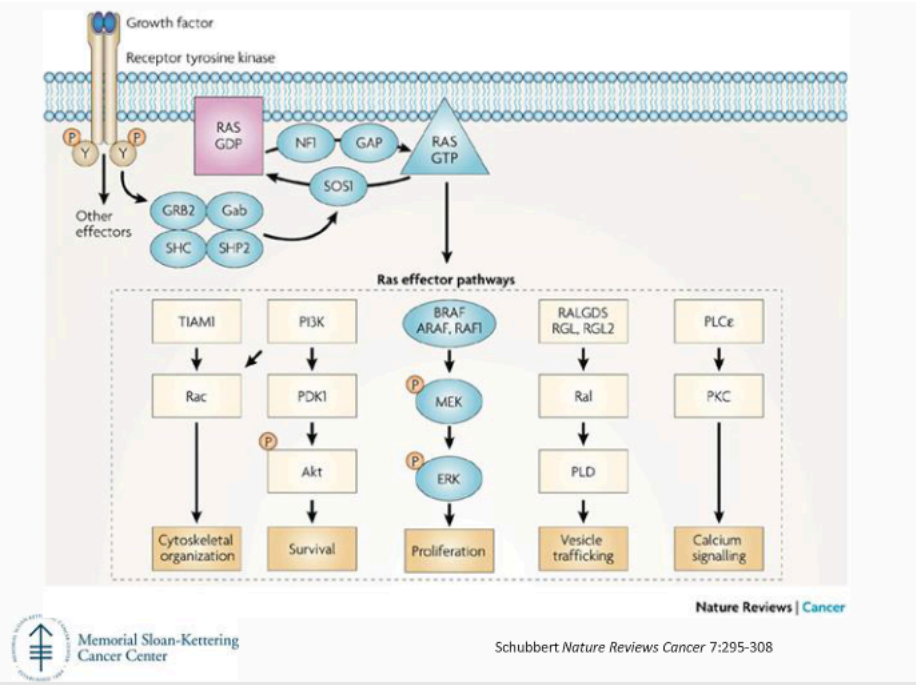
Shaw AT, et al. ASCO 2011. Abstract 7507.

Alectinib is a novel anti ALK

High activity after ALK-directed therapy in ALK+ NSCLC



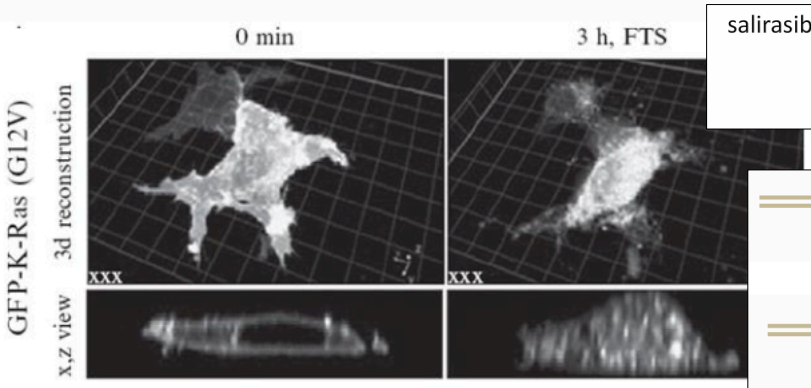
Shirish et al. IASLC 2013



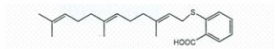
Schubbert *Nature Reviews Cancer* 7:295-308

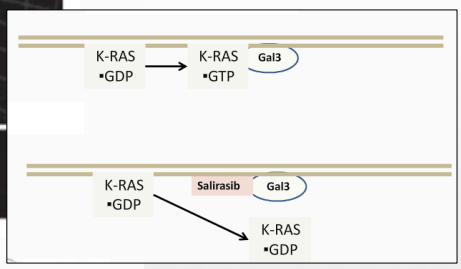
G. Riely – Educational Session

Salirasib Disrupts Membrane Localization of K-RAS



salirasib (S-*trans*, *trans*-farnesyl thiosalicylic acid, FTS)





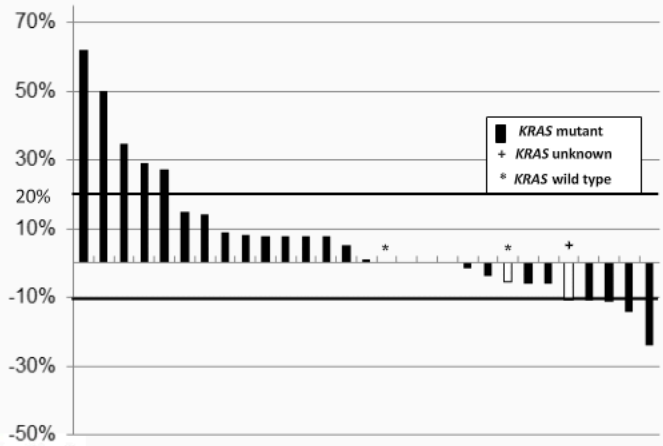
Mouse brain endothelial cells (Bend 3) transfected with GFP-K-RasG12V

Memorial Sloan-Kettering Cancer Center

Rotblat et al, Methods in Enzymology 2008

G. Riely – Educational Session

Phase 2 Study of Salirasib in Advanced NSCLC
Best Response of Indicator Lesions

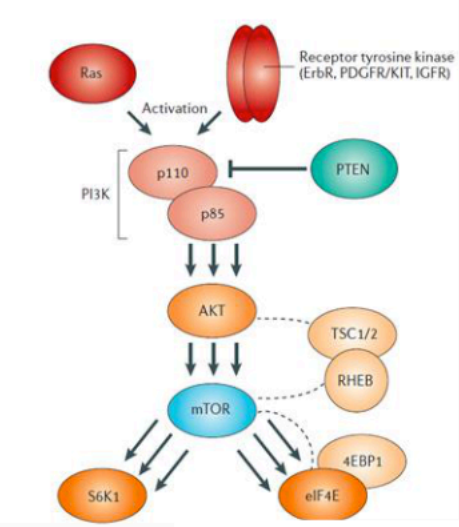


Memorial Sloan-Kettering Cancer Center

Riely et al, J Thor Onc 2011

G. Riely – Educational Session

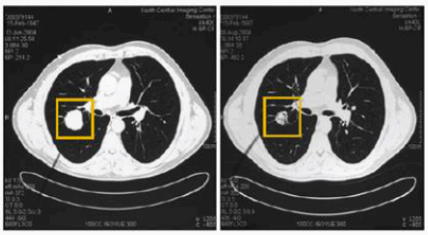
Ras Signaling



Faivre et al 2006, Nature Reviews Drug Discovery

Ridaforolimus: anecdotal activity in NSCLC

Pretreatment after 2 cycles



57 y/o with metastatic non-small cell lung cancer

Mila et al. JCO, 2008

G. Riely – Educational Session

Ridaforolimus in *KRAS* Mutant Lung Cancers

Patients with:
Stage IIIB/IV NSCLC
KRAS mutation
2 prior regimens
ECOG PS 0-2

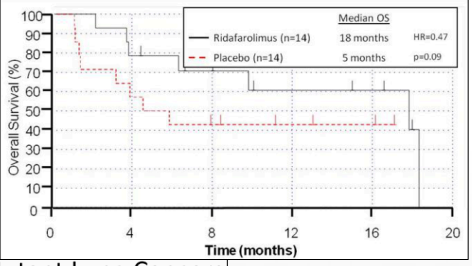
ridaforolimus → 8 weeks →
- PR → Continue ridaforolimus
- SD → ridaforolimus / placebo
- PD → Stop ridaforolimus

Primary Objective: PFS of randomized patients
Secondary Objectives: OS in the randomized population; Overall RR, PFS, survival; Safety profile

Ridaforolimus in *KRAS* Mutant Lung Cancers

Overall Survival from Randomization

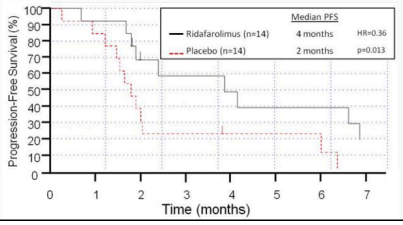
(of randomized patients, from randomization at 2 months)



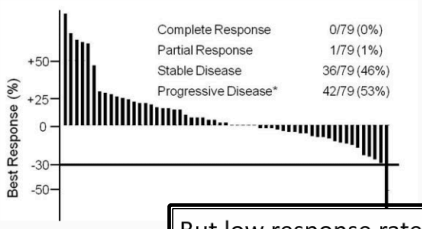
Ridaforolimus in *KRAS* Mutant Lung Cancers

Progression-Free Survival

(of randomized patients, from randomization at 2 months)



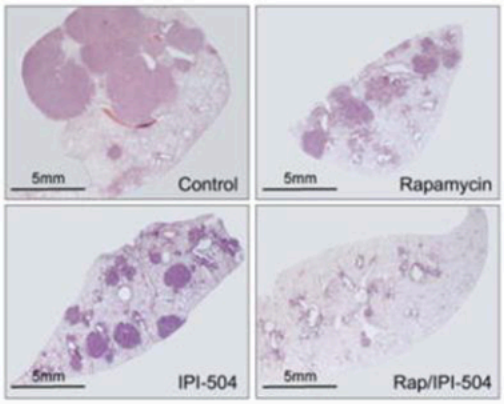
Ridaforolimus in *KRAS* Mutant Lung Cancers

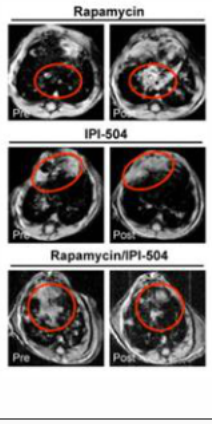


But low response rate in overall group of patients with KRAS mutant lung cancers limits enthusiasm for this approach

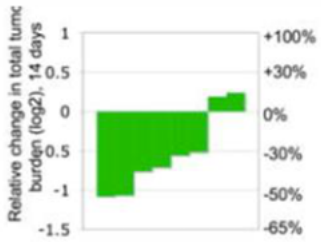
Riely et al. ASCO 2012
G. Riely – Educational Session

Rapamycin + IPI-504 (retaspamycin) leads to regression of KRAS G12D, p53 deficient tumors





Treatment	Tumor	Change in size (%)
Rapamycin	1	+ 193
	2	+ 75
IPI-504	1	+ 333
	2	+ 517
Rap/ IPI-504	1	- 82
	2	- 53

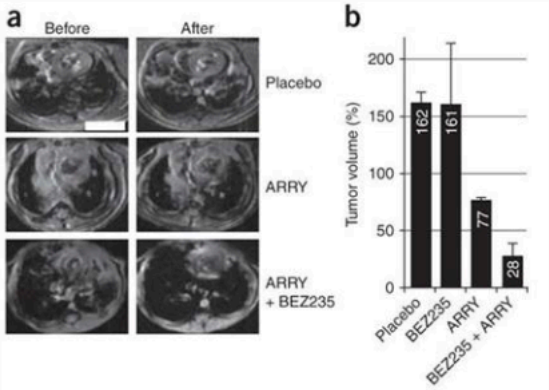


Memorial Sloan-Kettering Cancer Center

De Raedt T et al, Cancer Cell 2011

G. Riely – Educational Session

Combined PI3K and MEK inhibition shrinks *KRAS* G12D induced lung tumors



Engelman, Nature Medicine 2008
G. Riely – Educational Session

Docetaxel +/- Selumetinib in KRAS Mutant Lung Cancers

Patients
- Locally advanced or metastatic NSCLC (stage IIIB-IV)
- Progressed after first-line therapy
- Confirmed *KRAS* mutant tumor[a]
- WHO PS 0-1
- Excluding symptomatic brain metastases

Selumetinib 75 mg BID + docetaxel 75 mg/m²

Placebo BID + docetaxel 75 mg/m²

Endpoints

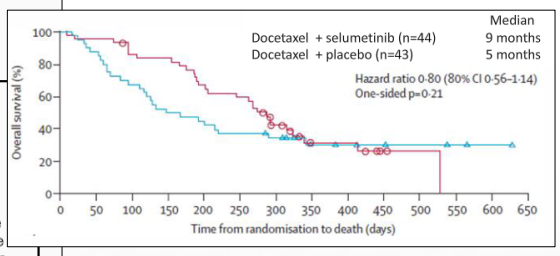
Primary
- OS

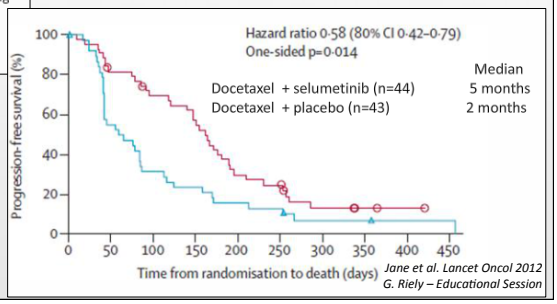
Secondary
- PFS
- ORR
- Duration of response
- Change in tumor size
- Alive and progression-free at 6 months
- Safety and tolerability

- Following completion of patient enrollment, the primary endpoint was changed from PFS to OS, without changing the sample size[§]
  - OS analysis was planned for after approximately 58 events; HR 0.57, 80% power assuming a 1-sided 10% significance level

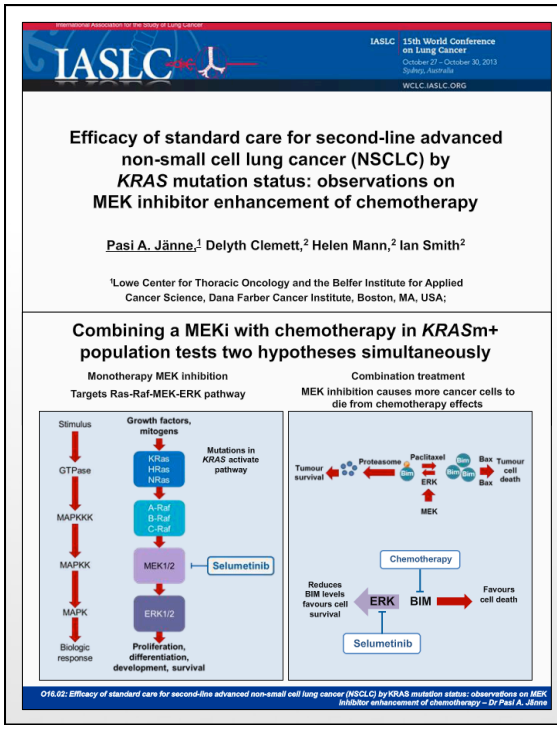
	Selumetinib plus docetaxel (n=43)	Placebo plus docetaxel (n=40)
Complete response	0	0
Partial response	16 (37%)	0†
Stable disease ≥6 weeks	19 (44%)	20 (50%)
Progressive disease	8 (19%)	18 (45%)
Not evaluable	0	2 (5%)

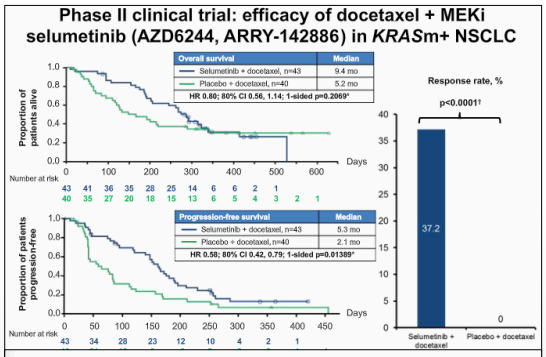
Data are n (%). *Analyses exclude four patients who had an unconfirmed *KRAS*-mutation test. †Adjusted least squares means.





Jane et al. Lancet Oncol 2012
G. Riely – Educational Session





Studies included

	Study	Phase	Treatment	Reference
AZ database of RCT in 2nd-line NSCLC	INTEREST NCT00076388	III	Docetaxel vs gefitinib	Kim et al. Lancet 2008;372:1809–1818 Douillard et al. J Clin Oncol 2011;29: 744–752
	ZODIAC NCT00312377	III	Docetaxel vs docetaxel + vandetanib	Herbst et al. Lancet Oncol 2010;11: 744–752 Johnson et al. J Clin Oncol 2010;28 (Suppl 15): Abstract 7516
	ZEAL NCT00418886	III	Pemetrexed vs pemetrexed + vandetanib	De Boer et al. J Clin Oncol 2011;29: 1067–1074
	Study 16 NCT00890825	II	Docetaxel vs docetaxel + selumetinib	Jänne et al. Lancet Oncol 2013;14: 38–47
Published data on MEKi	NCT01362296	II	Docetaxel vs trametinib	Blumenschein et al. J Clin Oncol 2013; 31:Abstract 8029
	NCT01192165	I/Ib	Docetaxel + trametinib	Gandara et al. J Clin Oncol 2013;31: Abstract 8028
	NCT01192165	I/Ib	Pemetrexed + trametinib	Kelly et al. J Clin Oncol 2013;31: Abstract 8027

International Association for the Study of Lung Cancer
IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

Efficacy of standard care for second-line advanced non-small cell lung cancer (NSCLC) by *KRAS* mutation status: observations on MEK inhibitor enhancement of chemotherapy

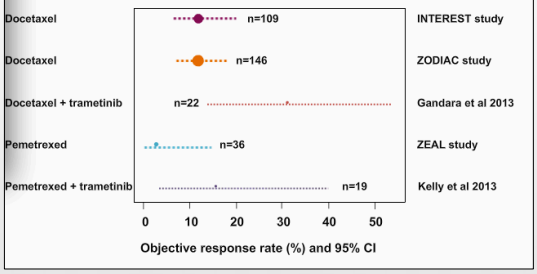
Pasi A. Jänne,[1] Delyth Clemett,[2] Helen Mann,[2] Ian Smith[2]

[1]Lowe Center for Thoracic Oncology and the Belfer Institute for Applied Cancer Science, Dana Farber Cancer Institute, Boston, MA, USA;

[2]AstraZeneca, Macclesfield, UK

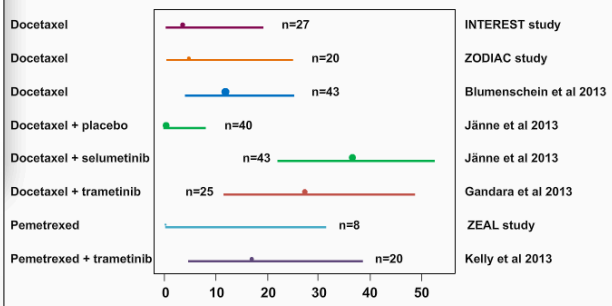
Results: chemotherapy with and without MEK inhibition

- Hypothesis – *KRAS*wt: chemo + MEK better than chemo alone



Results: chemotherapy with and without MEK inhibition

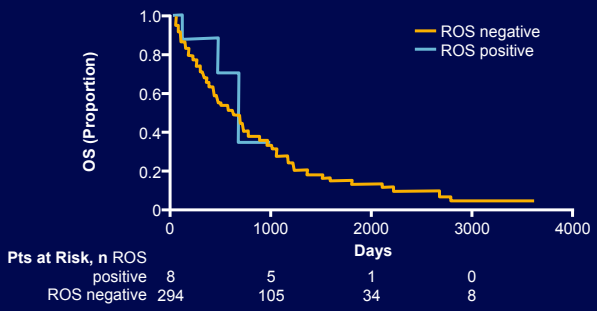
- Hypothesis – *KRAS*m+: chemo + MEK better than chemo alone



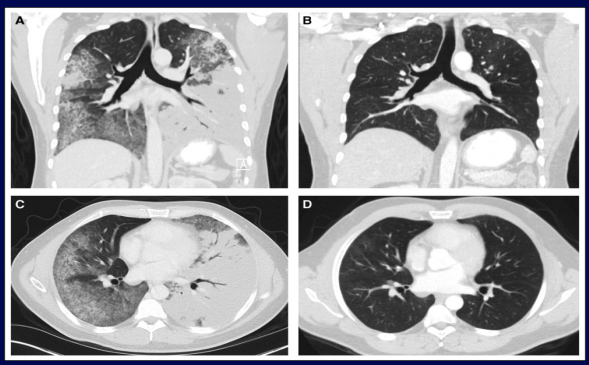
- **Retrospective comparison suggests that**
  - Singlet chemotherapy is an active second-line treatment in patients with *KRAS*m+ NSCLC and in patients with *KRAS* wild-type tumours
  - Singlet chemotherapy may be more active in *KRAS* wild-type than in *KRAS*m+ tumours
  - MEK inhibition may enhance the activity of chemotherapy in both *KRAS*m+ and *KRAS* wild-type NSCLC
- **Observations support prospective evaluation of MEK inhibitors plus chemotherapy as second-line treatment for patients with NSCLC that is *KRAS*m+ or wild-type**

ROS1 Rearrangements in NSCLC: Clinical Implications

- *ROS1* rearrangements
  - Similar phenotype to other mutations: scant or never smokers, adenocarcinoma histology, etc
  - Responsive to TKI



Bergethon K, et al. J Clin Oncol. 2012;30:863-870.



Response of an *ROS1*-positive patient with advanced NSCLC to crizotinib. CT scans of the chest were obtained (A and C) at baseline and (B and D) after 12 wks of anti ROS1 TKI. Shown are (A and B) coronal reconstructions and (C and D) axial slices

Targeted therapy vs chemotherapy

- In patients with EGFR mutations or ALK traslocations, targeted TKIs are preferred over chemotherapy, due to increased RR, PFS and improved safety profile. Overall survival however is not improved.

E03.1 - Maximising the Benefit of Chemotherapy for Advanced NSCLC (ID 382)
G. Giaconne – Educational Session

"Lung Cancer" Highlights IASLC 2013

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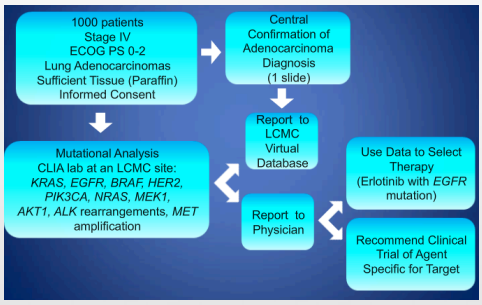
1. Red Ocean *vs* Blue Ocean
2. Today's Red Ocean in mNSCLC
3. New Contestants in Red Ocean's mNSCLC
4. A Glimpse of a Blue Ocean Strategy in mNSCLC
5. **Proof-of-Principle?**
6. Conclusion: Ushering a New Era in mNSCLC

Treatment with Therapies Matched to Oncogenic Drivers Improves Survival in Patients with Lung Cancers: Results from the Lung Cancer Mutation Consortium (LCMC)

Mark G. Kris, Bruce E. Johnson, Lynne D. Berry David J. Kwiatkowski, A. John Iafrate, Ignacio I. Wistuba, Marileila Varella-Garcia, Samuel L. Aronson, Pei-Fang Su, Yu Shyr, Lecia Sequist, Fadlo R. Khuri, Edward B. Garon, William Pao, Charles Rudin, Joan Schiller, Eric B. Haura, Mark Socinski, Keisuke Shirai, Giuseppe Giaccone, Marc Ladanyi, Kelly Kugler, John D. Minna, Paul A. Bunn

LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

Supported by
American Recovery and Relief Act
Grand Opportunity Grant – Paul Bunn PI
NCI 1 RC2 CA148394-01



Determine the frequency of ten established oncogenic drivers in tumor specimens from 1000 patients with advanced lung adenocarcinomas

Measure survival (from the time of diagnosis of metastatic or recurrent disease) for each molecularly defined cohort and for individuals receiving targeted therapy

Driver	Any Genotyping (n=1007)	Targeted Therapy (n=1007)
Any Driver	622 (63%)	279 (28%)
EGFR (sensitizing)	156 (16%)	129 (82%)
EGFR (other)	53 (5%)	40 (75%)
ALK	78 (8%)	51 (65%)
KRAS	244 (24%)	22 (9%)
HER2	19 (2%)	11 (58%)
BRAF	18 (2%) (14-V600E)	3 (17%)
PIK3CA	7 (1%)	0
MET Amplification	6 (1%)	3 (50%)
NRAS	5 (1%)	0
MEK1	2	0
Two Drivers	34 (3%)	20 (58%)

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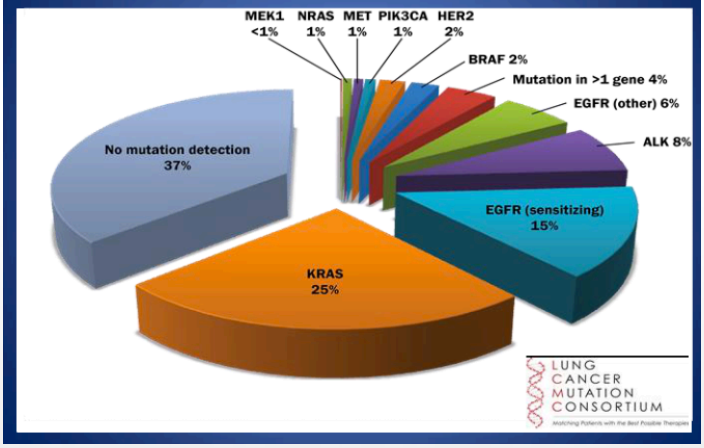
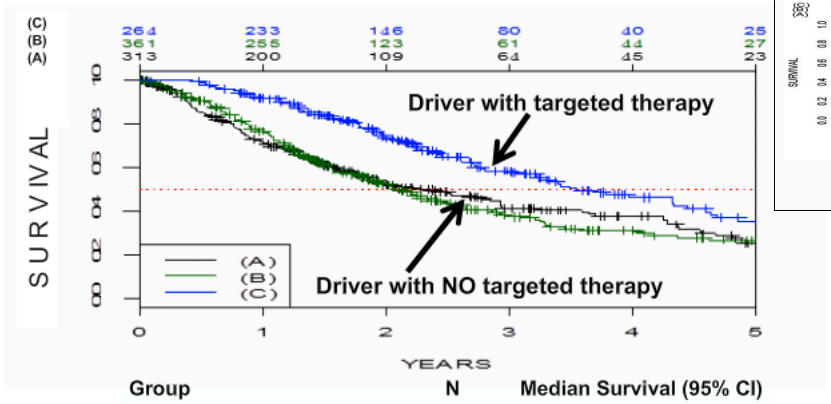
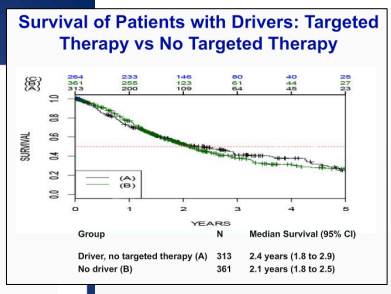
LCMC: Frequency of Oncogenic Drivers 733 Specimens with All 10 Drivers Assayed



Survival of Patients with Drivers: Targeted Therapy vs No Targeted Therapy

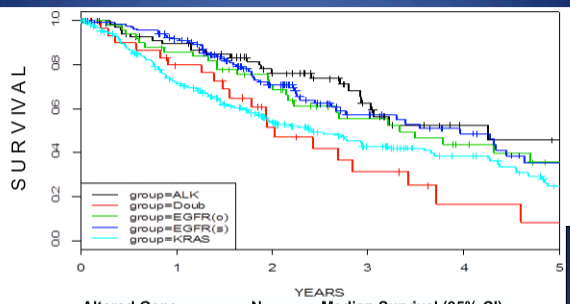


Group	N	Median Survival (95% CI)
Driver, no targeted therapy (A)	313	2.4 years (1.8 to 2.9)
No driver (B)	361	2.1 years (1.8 to 2.5)
Driver, targeted therapy (C)	264	3.5 years (3.2 to 4.6)



Kris MG et al. IASLC 2013

Survival with the five most frequent oncogenic drivers (n=526)



Altered Gene	N	Median Survival (95% CI)
EGFR (sensitizing)	140	4.0 years (2.7 to 5.4)
EGFR (other)	50	3.3 years (2.2 to 6.2)
ALK	73	4.3 years (3.0 to NA)
KRAS	231	2.4 years (1.9 to 3.6)
Two Drivers	32	2.0 years (1.6 to 4.6)

p=0.001

Retrospective analysis of prospectively collected data in a selected population.

The LCMC and related platforms are what "next generation lung cancer care" looks like.

Conclusions

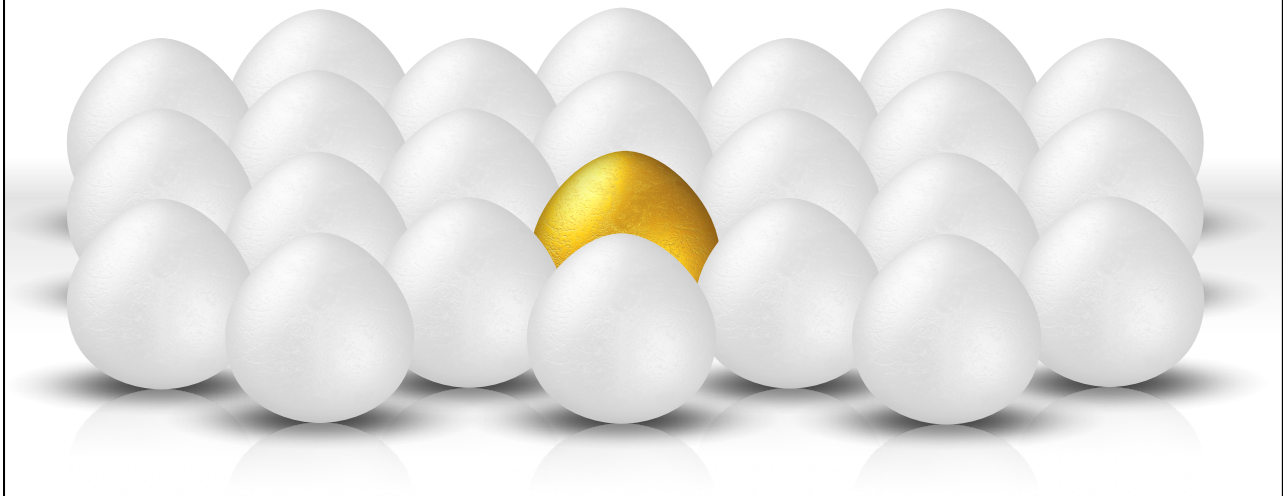
- The LCMC genotyped tumors from more than 1000 patients with lung adenocarcinomas
- An oncogenic driver was identified in 63%
- 28% of patients were treated with a targeted agent
- Patients with an oncogenic driver treated with a targeted agent lived longer than those not treated with targeted agents
- The presence of an oncogenic driver defined groups of patients with distinct clinical courses

Kris MG et al. IASLC 2013

“Blue Ocean” Strategy

Quote

Where is YOUR Golden Egg?



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Conclusion

mNSCLC

We no longer can afford to treat ALL mNSCLC as if they are ONE disease

- Diverse DRIVERS and TAILORED therapeutic strategies
  - EGFR
  - ALK/ROS, etc
- Heterogeneous patient population with widely diverse tolerance
  - Age
  - Comorbidity
  - Performance

Back-up slides

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YOUR LOGO

International Association for the Study of Lung Cancer

IASLC

IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
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PL03: Lung cancer probability in subjects with CT-detected pulmonary nodules

Nanda Horeweg

Erasmus University Medical Center
Department of Public Health / Pulmonology
Rotterdam, the Netherlands

Horeweg N*, van Rosmalen J*, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, ten Haaf K, Nackaerts K, Lammers JWJ, Groen HJM, Weenink C, Thunnissen E, van Ooijen P, de Jong PA, de Bock MD GH, Mali W, Oudkerk M*, de Koning HJ*

Results: nodule volume algorithm based on LC probability

Screening result	Nodule volume	
negative	< 100 mm³	Diameter: 5 mm
indeterminate*	≥ 100 to 300 mm³	
positive	≥ 300 mm³	Diameter: 10 mm

* Follow-up CT for VDT assessment:
- final screening result negative for VDT ≥ 600 days
- final screening result positive for VDT < 600 days

Results: performance nodule volume algorithm

Similar overall performance compared to Fleishner Criteria

Screen test parameters	Performance percentage (95%CI)
Diagnostic work-up	5.9
Follow-up CT scan	7.8
Sensitivity	90.9 (81.2-96.1)
Specificity	94.9 (94.4-95.4)
Positive predictive value	14.4 (11.3-18.1)
Negative predictive value	99.9 (99.8-100.0)

Discussion: main results

- LC risk nodules <5mm (100mm³) NS different from no nodules
- LC risk nodules 5-10mm (100-300mm³) justifies follow-up CT
- VDT useful for LC risk stratification
- LC risk nodules ≥10 mm (≥300mm³) warrants immediate work-up

GECP Grupo Español de Cáncer de Pulmón Spanish Lung Cancer Group

GFPC Groupe Français de Pneumo-Cancérologie French Lung Cancer Group

ESOGIA-GFPC 08-02

Elderly Selection on Geriatric Index Assessment

Phase III, randomized, multicenter study comparing in elderly patients (≥70 years) with stage IV NSCL a standard strategy of treatment allocation (carboplatin based bi-therapy or monotherapy with docetaxel) based on PS and age with an experimental strategy allocating the same regimen or BSC according to a comprehensive geriatric assessment

Presenting author: R. Corre

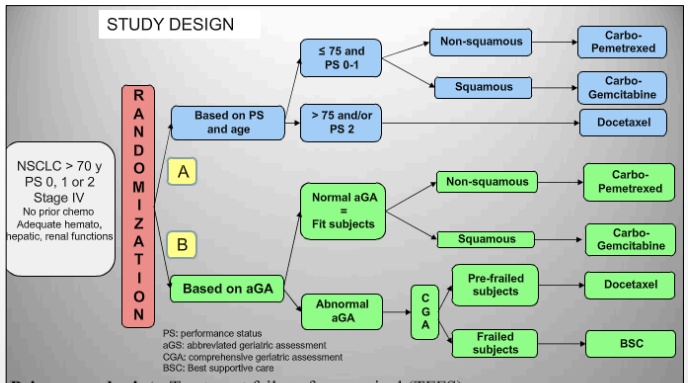
Co-authors: C. Chouaid, L. Greillier, H. Le Caer, C. Audigier-Valette, N. Baize, H. Bérard, L. Falchero, I. Monnet, E. Dansin, A. Vergnenegre, M. Marcq, C. Decroisette, S. Bota, R.Lamy, B.Massuti, C. Dujon, G. Fraboulet, J. Minguet, C. Plassot, H. Lena

Presentation 01503

GERIATRIC DEFINITIONS

GERIATRIC PARAMETERS	FIT If all criteria +	PRE-FRAILED If ≥ 1 criteria +	FRAILED If ≥ 1 criteria +
ADL	6	6	≤5
IADL	0	1	≥2
Gognition Schultz-Larsen mini-MMSE Folstein's MMSE ≤23	≥9	>23	≤23
Repeated falls	No	No	Yes
Urinary or fecal incontinence	No	No	Yes
Charlson's comorbidity index score	low	Moderate	Severe
Depression score GDS 5	0-1	2-3	4-5

STUDY DESIGN



Primary endpoint: Treatment failure-free survival (TFFS) documented progression, death of any cause, exit for toxicity considered unacceptable, or withdrawal of consent

Secondary endpoints: ORR, toxicities, OS, QoL, survival adjusted on QoL

Planned sample size: 490 patients for an expected hazard ratio of 1.30, a power of 80%, a two-sided overall type 1 error of 5%, assuming 5% of dropout patients.

ESOGIA-GFPC 08-02

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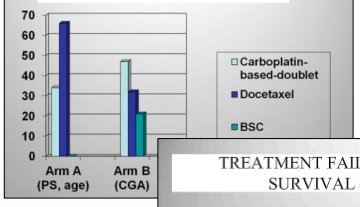
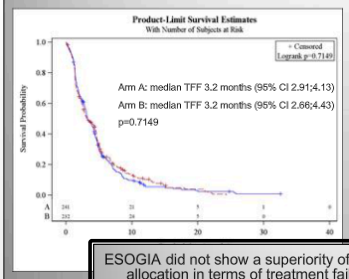
Presentation 01503

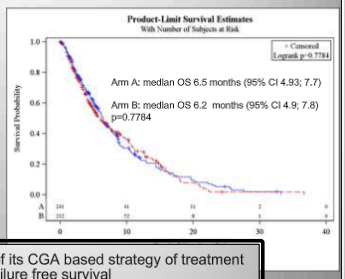
TREATMENTS ADMINISTRED



TREATMENT FAILURE FREE SURVIVAL (ITT)



OVERAL SURVIVAL (ITT)



ESOGIA did not show a superiority of its CGA based strategy of treatment allocation in terms of treatment failure free survival

	Arm A (PS,age) n=241			Arm B (CGA) n=232			
	C-pem N=62 (25%)	C-Gem N=21 (9%)	Doc N=158 (66%)	C-pem N=84 (36%)	C-Gem N=25 (11%)	Doc N=73 (32%)	BSC N=50 (21%)
mTFF (months)	4.4	4.53	3.1	4.9	4.8	2.7	1.3
mOS (months)	8.9	6.3	5.9	10.2	8.4	4.9	2.9

CGA: Comprehensive Geriatric Assessment

CAUSES OF TREATMENT FAILURE

	Arm A (PS, Age) n=241	Arm B (CGA) n=232	p
Progression	150 (66.08%)	156 (71.23%)	0,0970
Toxicity	27 (11.89%)	10 (4.57%)	**0,0053***
Withdrawal of consent	9 (3.96%)	7 (3.2%)	ns
Death	30 (13.22%)	30 (13.70%)	ns
Investigator's decision	9 (3.96%)	13 (5.94%)	ns
Intercurrent disease	2 (0.88%)	3 (1.37%)	ns
missing	14	13	ns