

New Developments in Lung Cancer Therapeutics

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Disclosures

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Cis-Diamminedichloroplatinum, Vinblastine, and Bleomycin Combination Chemotherapy in Disseminated Testicular Cancer

LAWRENCE H. EINHORN, M.D., F.A.C.P., and JOHN DEBONO, M.D., Indianapolis, Indiana

Table 1. Classification of Primary Tumor

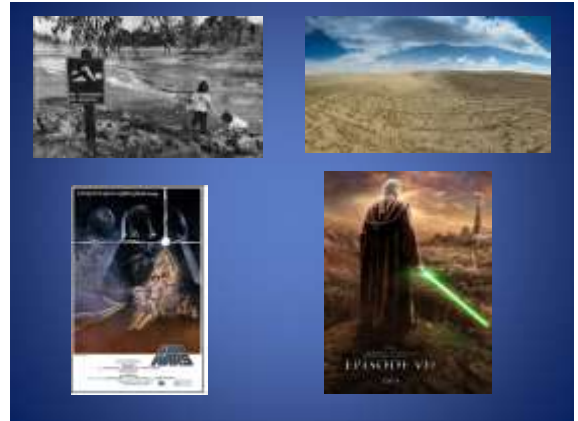
Organ-Metastasis	Staging	Patients	Complete Response*
I	Non-embryonal	40	75
II	Embryonal, without epididymal spread	22	64
III	Embryonal	7	34
IV	Teratomatous with embryonal or embryonal/chorion	9	60
V	Choriocarcinoma with embryonal metastasis	5	60
	Yolk sac	2	100

N=47

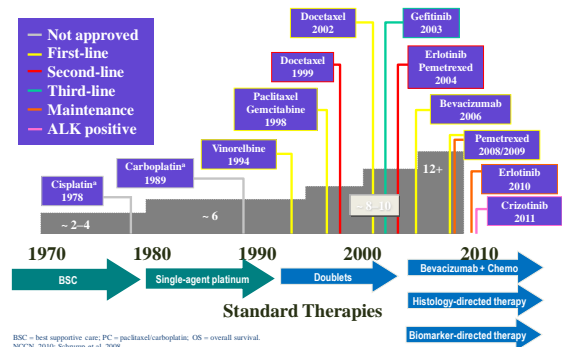
74% Complete Response
 26% Partial Response
 100% Overall Response Rate

85% Disease Free Status

Annals of Internal Medicine 87:293-298, 1977



History of Therapy in Advanced NSCLC: FDA Approval Dates

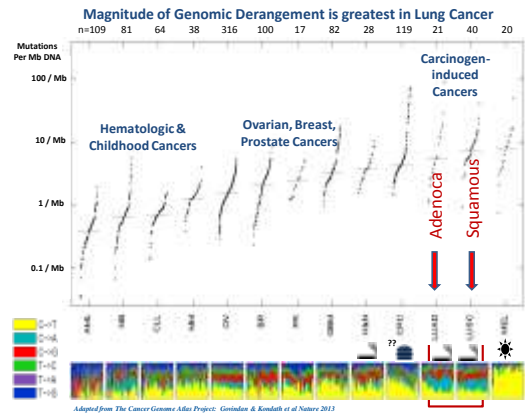


Two New Agents that Improve Overall Survival

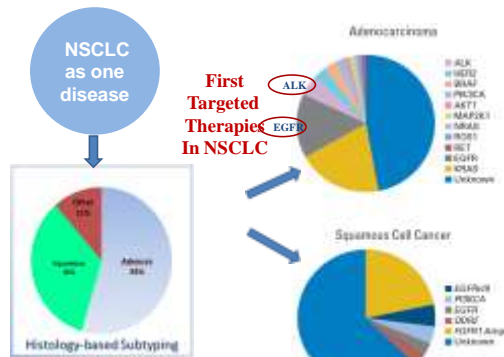
Trial	Drug	Class	Line	N	Backbone	OS (months)	p-value
		VEGFR2					
REVEL	Ramircirumab	mAb	2nd Line	1253	Docetaxel	10.5 vs 9.1	0.02
		EGFR	1st Line		cisplatin/ge	11.5 vs.	
SQUIRE	Nectinumab	mAb	Squamous	1093	mcltatine	9.9	0.012

ASCO Recommendations for Meaningful Outcomes: The Need to Do Better

- Minimum meaningful incremental improvement is an HR of ≤ 0.8 and median OS improvement from 2.5 to 6 months
- New regimens that are substantially more toxic than current standards should also produce the greatest increments in OS

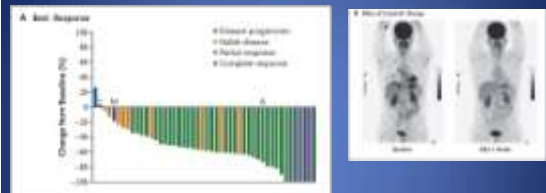


Evolution of NSCLC Subtyping from Histologic to Molecular-Based



Li, Gandara et al: JCO 2013 (adapted from Fao et al)

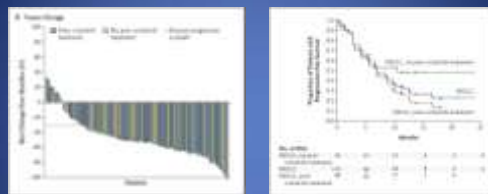
Crizotinib in ROS1 Rearranged NSCLC: Better Than in ALK?



	N	ORR	PFS (months)
ROS1+ NSCLC	50	72%	19.2
ALK+ NSCLC (2 nd line)	347	65% vs. 20%	7.7 vs. 3
ALK+ NSCLC (1 st line)	353	75% vs. 45%	10.9 vs. 7

A.T. Shaw et al. NEJM 2013, 2014; T. Mok ASCO 2014

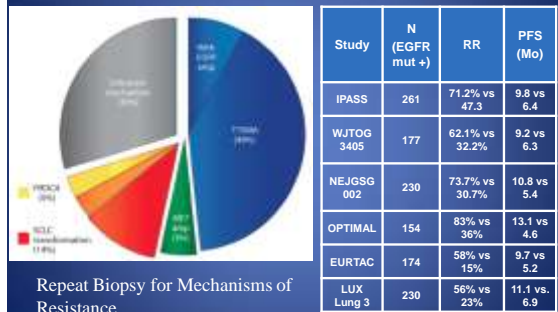
Ceritinib in ALK Rearranged NSCLC

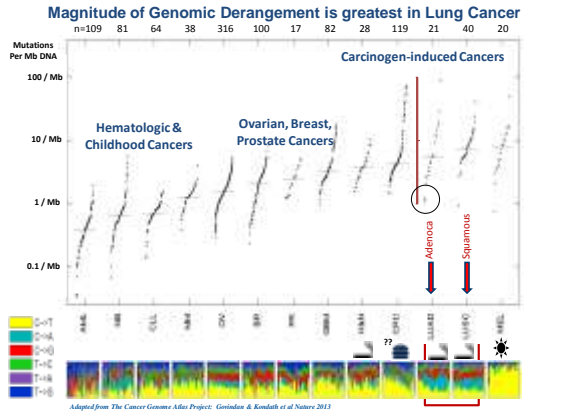
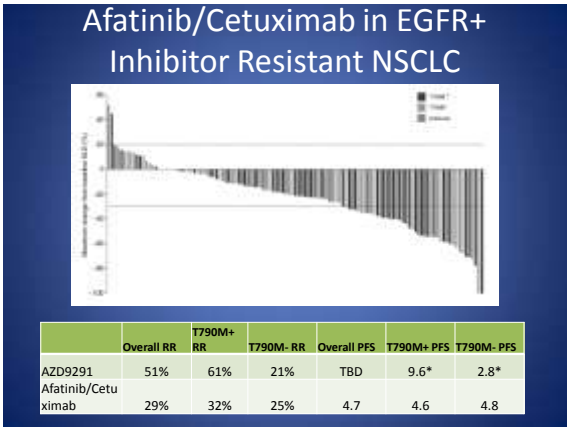
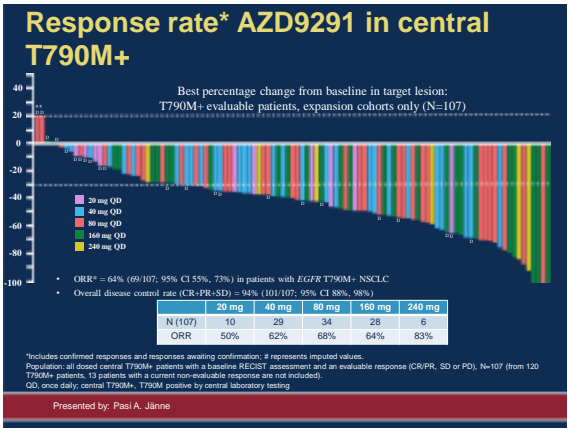
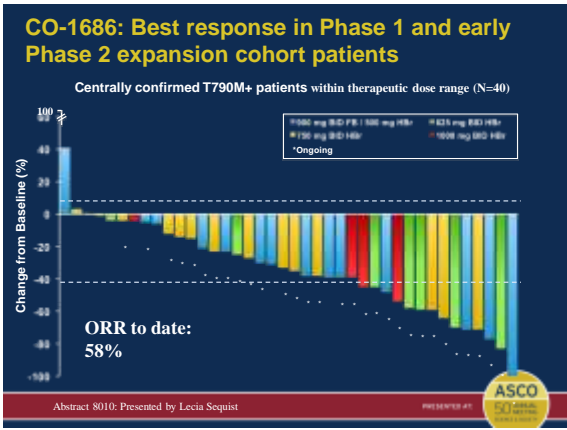


ALK+ NSCLC	ORR (All tx)	ORR (criz tx)	PFS (All)	PFS (criz naïve)	PFS (criz tx)
Ceritinib	58%	56%	7 mo.	10.4 mo.	6.9 mo.

Platinum based chemotherapy now 3rd Line for ALK+ NSCLC
A.T. Shaw et al. NEJM 2014

Mechanisms of Resistance to EGFR-TKIs

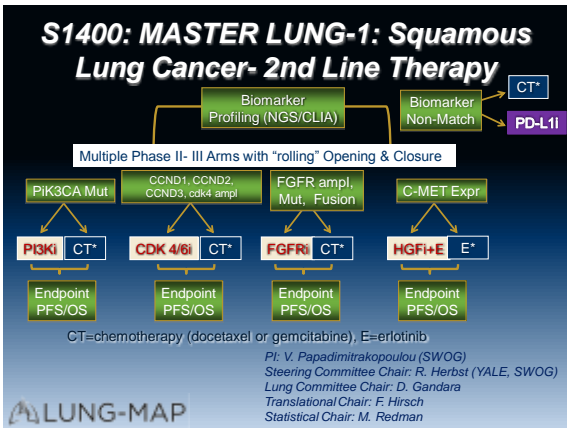


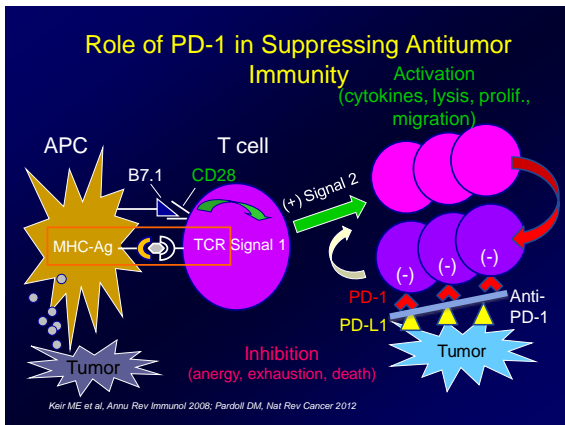
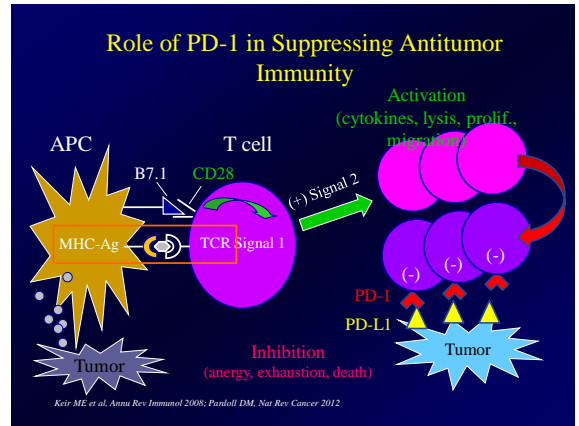
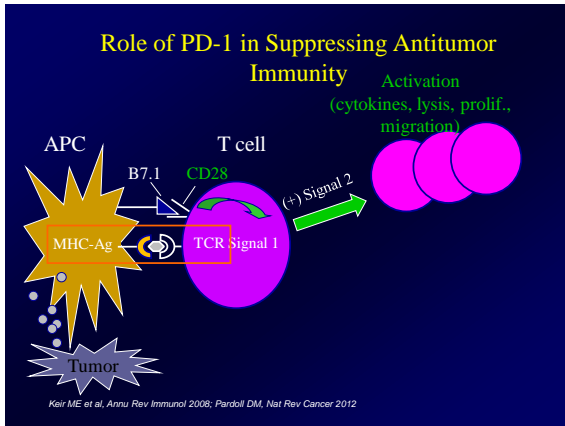


Selection of Therapeutic Targets for SCCA

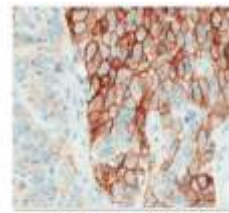
- SCCA represents an unmet need
- Candidate targets are available from results of TCGA project and other studies, identified by a biomarker
- Drugs (investigational) are now available for many of these targets
- Trials can be designed to allow testing of multiple new drug-biomarker combinations at the same time ("MASTER PROTOCOL" concept)

Gene	Event Type	Frequency
CDKN2A	Deletion/Mutation/Methylation	72%
PIK3CA	Mutation	16%
PTEN	Mutation/Deletion	15%
FGFR1	Amplification	15%
EGFR	Amplification	9%
PDX1A	Amplification/Mutation	9%
CCND1	Amplification	8%
DNAH2	Mutation	4%
BRAF	Mutation	4%
ERBB2	Amplification	4%
FGFR2	Mutation	3%





Measurement of PD-L1 in Cancer/NSCLC by IHC



Positive PD-L1 staining in NSCLC (proprietary Genentech/Roche PD-L1 IHC)
High sensitivity and specificity in FFPE samples

Tumor Type	Estimated PD-L1 Prevalance (± %)
NSCLC (SCC)	50%
NSCLC (adeno)	45%
Colon	45%
Melanoma	40%
Renal	30%

Nearly all human tumors include a subset that expresses PD-L1

Spigel et al; #8008 ASCO 2013.

Antitumor Activity by MK-3475 Dose

MK-3475 Dose	RECIST v1.1, Central Review*		
	n	ORR ^b n (%) [95% CI]	DCR ^b n (%) [95% CI]
2 mg/kg Q 3W	6	2 (33) [4 - 78]	3 (50%) [12%, 88%]
10 mg/kg Q 3W	20	4 (20) [6 - 44]	14 (70%) [48%, 88%]
10 mg/kg Q 2W	16	5 (31) [11 - 59]	10 (63) [35 - 85]
Total	42	11 (26) [14 - 42]	27 (64) [48 - 78]

- Interim median PFS^c:
 - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review
 - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

Analysis cut-off date: March 3, 2014. DCR = Disease Control Rate (complete response + partial response + stable disease)
*patients did not have measurable disease by RECIST v1.1 per independent central review at baseline and were not evaluated for response by RECIST v1.1
^bincludes confirmed and unconfirmed responses.
^cFrom product-label (Kaplan-Meier) method for censored data.

ASCO
Abstract 8007: Presented by Naiyer A. Rizvi



UC Davis Lung Cancer Trials

- Immunotherapy
 - Ph II/III MK3475 (PD1)
(Frontline and second line)
 - Ph III Roche MPDL1 (PDL1)
- EGFR-Mutation
 - CO-1686 (Tiger X and Tiger 2)
 - Erlotinib + INC280 (Met inhibitor)
 - Afatinib/Cetuximab Frontline (SWOG)
 - ALCHEMIST
- Targeted Therapies
 - Novartis Signature Trial
 - SWOG-MAP (Squamous)



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