New Developments in Lung Cancer Therapeutics

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Disclosures

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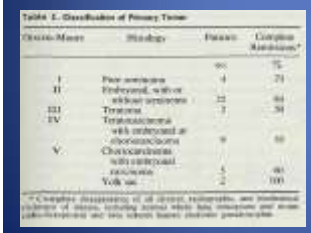
Cis-Diamminedichloroplatinum, Vinblastine, and Bleomycin Combination Chemotherapy in Disseminated Testicular Cancer

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



N=47

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

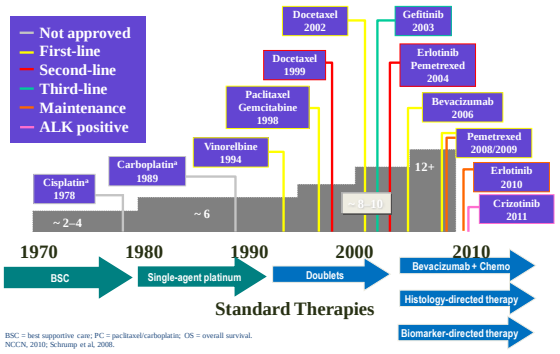
85% Disease Free Status

Annals of Internal Medicine 87:293-298, 1977





History of Therapy in Advanced NSCLC: FDA Approval Dates



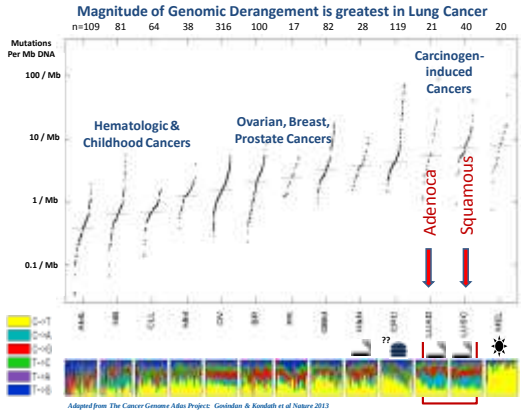
BSC = best supportive care; PC = paclitaxel/carboplatin; OS = overall survival.
NCCN, 2010; Schrump et al, 2008.

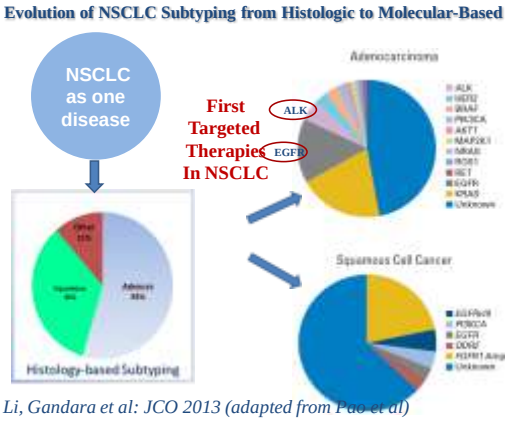
Two New Agents that Improve Overall Survival

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

ASCO Recommendations for Meaningful Outcomes: The Need to Do Better

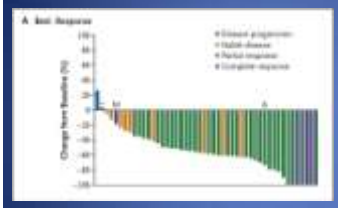
- Minimum meaningful incremental improvement is an HR of ≤0.8 and median OS improvement from 2.5 to 6 months
- New regimens that are substantially more toxic than current standards should also produce the greatest increments in OS

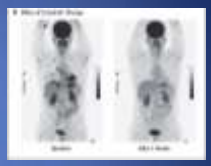




Li, Gandara et al: JCO 2013 (adapted from Pao et al)

Crizotinib in ROS1 Rearranged NSCLC: Better Than in ALK?

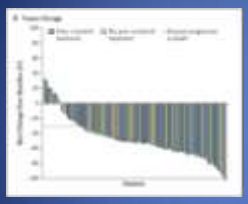


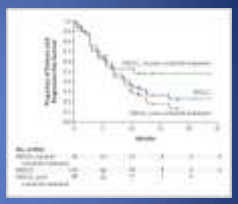


	N	ORR	PFS (months)
ROS1+ NSCLC	50	72%	19.2
ALK+ NSCLC (2nd line)	347	65% vs. 20%	7.7 vs. 3
ALK+ NSCLC (1st line)	353	75% vs. 45%	10.9 vs. 7

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

Ceritinib in ALK Rearranged NSCLC



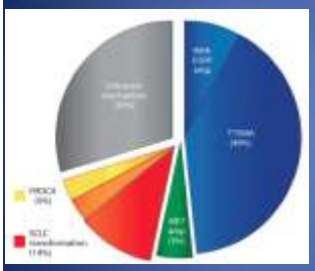


ALK+ NSCLC	ORR (All)	ORR (criz tx)	PFS (All)	PFS (criz naïve)	PFS (criz tx)
Ceritinib	58%	56%	7 mo.	10.4 mo.	6.9 mo.

Platinum based chemotherapy now 3rd Line for ALK+ NSCLC

A.T. Shaw et al. NEJM 2014

Mechanisms of Resistance to EGFR-TKIs

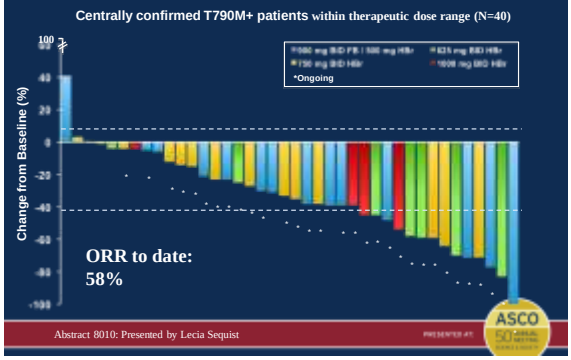


Repeat Biopsy for Mechanisms of Resistance

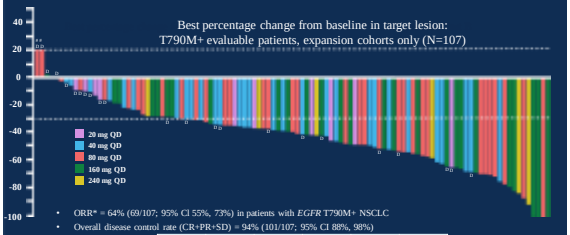
L. Sequist et al. STM 2011.

Study	N (EGFR mut +)	RR	PFS (Mo)
IPASS	261	71.2% vs 47.3	9.8 vs 6.4
WJTOG 3405	177	62.1% vs 32.2%	9.2 vs 6.3
NEJGSG 002	230	73.7% vs 30.7%	10.8 vs 5.4
OPTIMAL	154	83% vs 36%	13.1 vs 4.6
EURTAC	174	58% vs 15%	9.7 vs 5.2
LUX Lung 3	230	56% vs 23%	11.1 vs. 6.9

CO-1686: Best response in Phase 1 and early Phase 2 expansion cohort patients



Response rate* AZD9291 in central T790M+



- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with *EGFR* T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (107)	10	29	34	28	6
ORR	50%	62%	68%	64%	83%

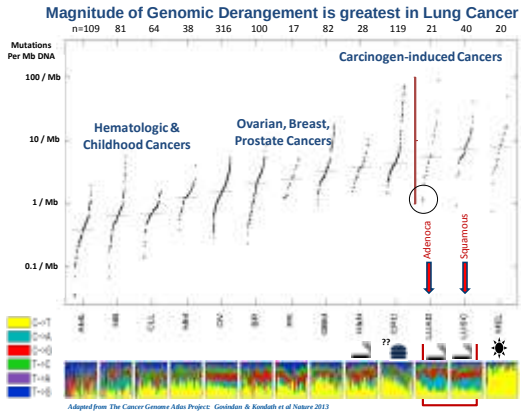
*Includes confirmed responses and responses awaiting confirmation; # represents imputed values.
Population: all dosed central T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD or PD). N=107 (from 120 T790M+ patients, 13 patients with a current non-evaluable response are not included).
QD, once daily; central T790M+, T790M positive by central laboratory testing

Presented by: Pasi A. Jänne

Afatinib/Cetuximab in EGFR+ Inhibitor Resistant NSCLC

	Overall RR	T790M+ RR	T790M- RR	Overall PFS	T790M+ PFS	T790M- PFS
AZD9291	51%	61%	21%	TBD	9.6*	2.8*
Afatinib/Cetuximab	29%	32%	25%	4.7	4.6	4.8

Magnitude of Genomic Derangement is greatest in Lung Cancer



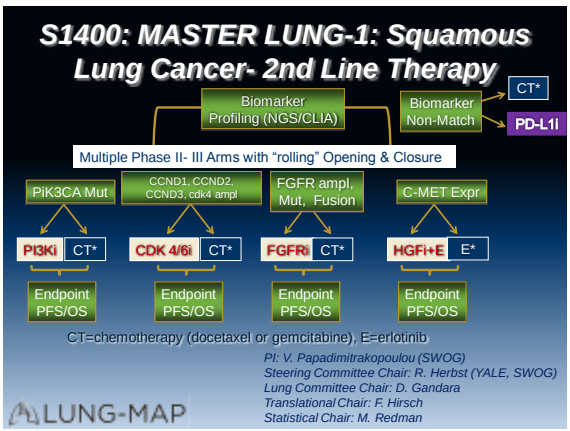
Selection of Therapeutic Targets for SCCA

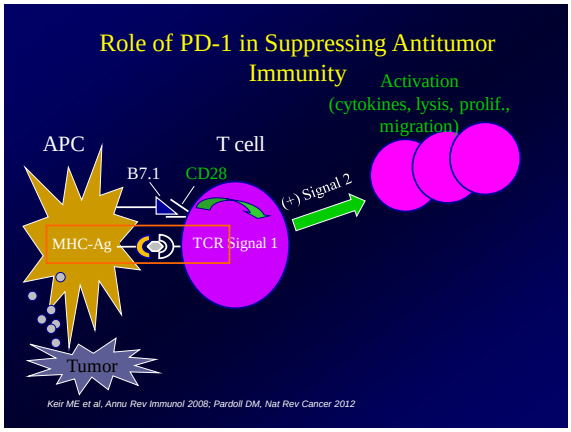
- SCCA represents an unmet need
- Candidate targets are available from results of TCGA project and other studies, identified by a biomarker
- Drugs (investigational) are now available for many of these targets
- Trials can be designed to allow testing of multiple new drug-biomarker combinations at the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

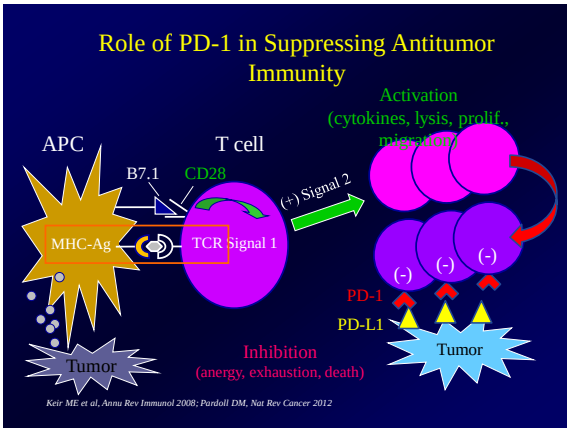
Therapeutic targets
SCCA-TCGA 2012

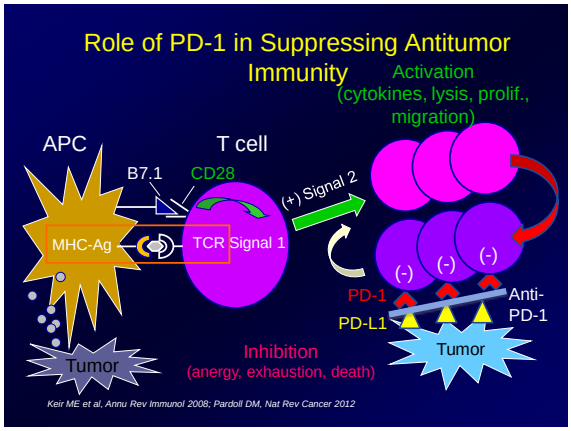
Gene	Event Type	Frequency
CDKN2A	Deletion/Mutation/Methylation	72%
PIK3CA	Mutation	16%
PTEN	Mutation/Deletion	15%
FGFR1	Amplification	15%
EGFR	Amplification	9%
PDGFRA	Amplification/Mutation	9%
CCND1	Amplification	8%
DDR2	Mutation	4%
BRAF	Mutation	4%
ERBB2	Amplification	4%
FGFR2	Mutation	3%

S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy

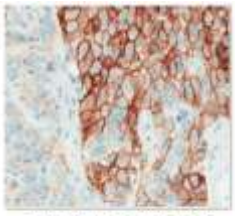








Measurement of PD-L1 in Cancer/NSCLC by IHC



Positive PD-L1 staining in NSCLC (proprietary Genentech/Roche PD-L1 IHC)

High sensitivity and specificity in FFPE samples

Tumor Type	Estimated PD-L1 Prevalence (≥ %)*
NSCLC (SCC)	50%
NSCLC (adeno)	45%
Colon	45%
Melanoma	40%
Renal	20%

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

Spigel et al: #8008 ASCO 2013.

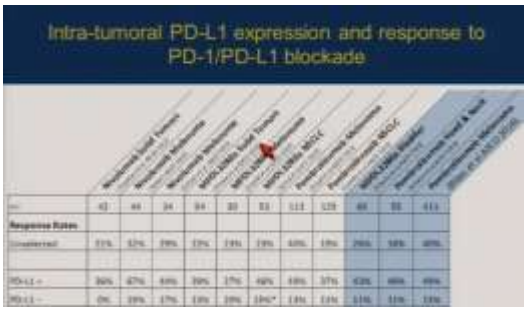
Antitumor Activity by MK-3475 Dose

MK-3475 Dose	RECIST v1.1, Central Review[a]		
		ORR[b]	DCR[b]
	n	n (%) [95% CI]	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%) [46%, 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)
[a]3 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/
[b]Includes confirmed and unconfirmed responses.
[c]From product-limit (Kaplan-Meier) method for censored data.

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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