Lung Cancer Heterogeneity and Its Clinical Applications

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Disclosures

- None relevant to this presentation

Cancer Evolution

- 1890 – Von Hansemann – Hypothesized that abnormal mitoses noted in cancer cells gives rise to asymmetric chromosome distribution

- 1958 – Huxley – "Genetic Inhomogeneity of Cancer"
  - "…it will be of great interest to discover the extent of such new variance and rate at which it occurs…"

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Cancer Evolution

- Cancer – Genetically unstable
  - Increased chance of daughter cell creation capable of initiating their own cell lines
  - Leads to intra- and inter-tumor cellular heterogeneity
  - "Optimal range" of instability
- Tumor growth = tumor evolution = increasing heterogeneity
- 1.6 to 9 mutations per cell division
  - Leads to millions of mutations per tumor
  - Selection pressures

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Sources of heterogeneity within the tumor

- Tumor intrinsic factors
- Genetic
  - » Mismatch repair and Microsatellite Instability
  - » Nucleotide excision repair
  - » Base excision repair
- Epigenetic
  - » DNA methylation
  - » Histone modification
- Transcription errors
- Proteomic instability
  - » Heat shock proteins

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Sources of heterogeneity within the tumor

- Extrinsic factors/microenvironment
  - » pH
  - » Hypoxia
    - Angiogenesis
    - Selects for hypoxia "resistance" in tumor cell populations
    - Tumor cell migration
    - Anti-tumor immune response
  - » Paracrine signaling with stroma/surrounding cells
    - Active involvement with the extra-cellular matrix

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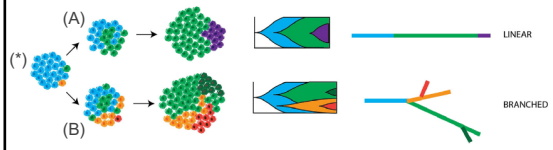
Linear vs. Branched Cancer Evolution



- (*) Intercellular heterogeneity → Clonal selection → outgrowth of subclones
- (A) Linear Evolution: subclones arise sequentially.
- (B) Branched Evolution: divergent subclones emerge independently.

Burrell and Swanton 2014 Molecular Oncology

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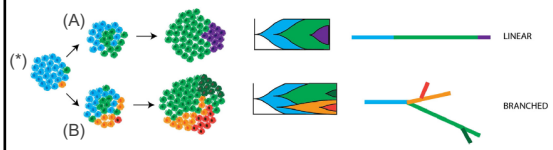
Linear vs. Branched Cancer Evolution



- Clonal Sweep: One emerging subclone outcompetes the rest of the tumor population.
- Incomplete clonal sweeps → results in clonal heterogeneity.
- Subclonal genotypes allow monitoring of tumor evolution over time.

Burrell and Swanton 2014 Molecular Oncology

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Heterogeneity is a major factor leading to therapeutic resistance

- Tumor Heterogeneity:
  - Histological
  - Genetic
  - Phenotypic
- Advances in tumor deep sequencing have resulted in the identification of extensive intra-tumor heterogeneity (ITH).

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Heterogeneity is a major factor leading to therapeutic resistance

- Tumors are constantly evolving – genetically and epigenetically – results in increased ITH.
- Cancer therapies produce a selection pressure in the evolution of the tumor.
  - Molecular mechanisms of drug resistance will vary based on the therapy used.
  - For any given therapy, there may be multiple mechanisms of resistance.
    - Within the same site of disease.
    - In parallel between different sites of disease.

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Factors which influence clonal heterogeneity

- Genetic drift
  - » Tumor cell loss of precise DNA replication
  - » Ability to undergo sequential progressive genomic changes
    - Mutation
    - Gene rearrangement
    - Gene deletion
  - » Selective effect of a mutation (clonal competition)
  - » Random drift will fix a mutation if U/s > 1
    - U = total # of mutations per genome
    - S = selection pressure against individual mutations

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Naugler et al. Theoretical Biology and Medical Modelling 2010, 7:42
Ruddon. Cancer Biology 4th edition 2007

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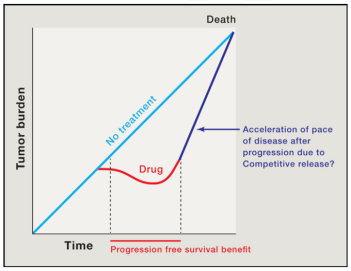
Factors which influence tumor heterogeneity

- Drug treatment
- Schedule of administration of the drug



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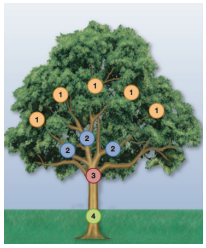
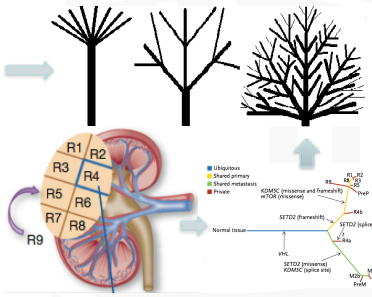
McGranahan. Cell 168, 2017

ITH and its potential clinical implications





Potential Clinical Implications

- Tumor sampling bias
- Defining actionable mutations
- Development of drug resistance
- ITH as a biomarker

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Swanton, Cancer Research, 2012
Gerlinger, NEJM, 2012

Therapeutic Resistance and Cancer Evolution

- Multiple different routes through which drug resistance may be achieved.
- Important question for cancer evolution during treatment – *are the drug resistant cells which lead to disease progression*:
  - Present prior to treatment?
  - Generated directly by treatment?
  - Generated during (but independent of) treatment?
- Are resistant cells clonal within individual patients?

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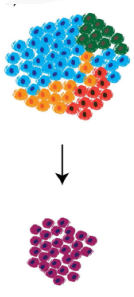
Clonal Expansions and Drug Resistance

- Acquisition of new driver mutations
- De Novo: Development of resistance in a previously sensitive clone.



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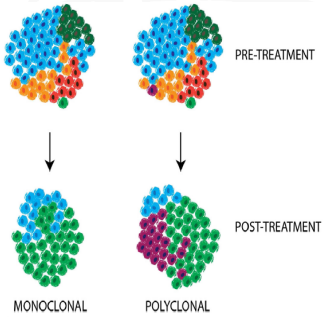
Clonal Expansion and Drug Resistance

- Acquisition of new driver mutations
- Selective pressures exerted by therapeutic agents
- Monoclonal: Pre-existing resistant subclone outgrows (the clone was initially a minor subclone).
- Polyclonal: Multiple de novo or pre-existing resistant subclones, which may be present across multiple sites of disease.



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Examples from lung cancer studies of drug resistance

EGFR

- T790M mutations have been detected in untreated samples; associated with reduced PFS to first generation EGFR TKIs.
- MET amplification detected in minor subpopulations of EGFR mutant lung cancer prior to EGFR TKI therapy; resistance develops through outgrowth of the clone harboring amplified MET.

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Examples from lung cancer studies of drug resistance

ALK

- Multiple different ALK kinase domain mutations may be identified within the same patient
  - ex: L1196M and C1156Y both detected in a patient with crizotinib resistance.
- ALK kinase domain mutations detected simultaneously with bypass signaling pathways.
  - ex: L1196M mutation detected simultaneously with increased EGFR within the same tumor site.

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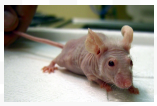
How can we study ITH?

- Techniques
  - » Single cell next generation sequencing studies
    - Need for sophisticated bioinformatics for assessing the complex data sets.
  - » Proteomic assessments
- Model systems
  - » Cell lines
  - » Patient derived xenografts (these mice lack a immune system)
  - » Genetically engineered mouse models



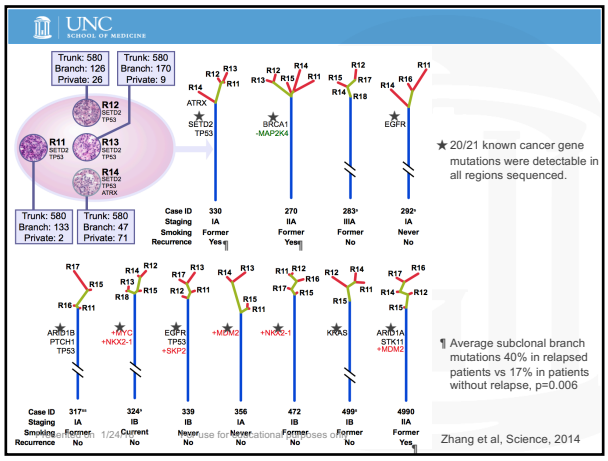
How can we study ITH?

- Access to patient tumor biopsy samples
  - » Feasibility of sampling multiple sites of disease?
  - » Can circulating tumor cells (CTCs) and circulating free tumor DNA (cfDNA) be used to track and monitor heterogeneity?
  - » Are CTC and cfDNA representative of the disease?
  - » Ability to acquire 'warm-biopsies' of patients to monitor multiple disease sites simultaneously.

ITH and mutation burden

- Tumors are heterogeneous
  - » Populations of cells with distinct molecular and phenotypic features
- A single biopsy may not represent the extent of driver mutation involvement
- Recently, group at MDACC evaluated 48 samples from 11 resected NSCLC

Zhang et al, Science, 2014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Trunk: 580 Branch: 126 Private: 26
Trunk: 580 Branch: 170 Private: 9
Trunk: 580 Branch: 133 Private: 2
Trunk: 580 Branch: 47 Private: 71
★ 20/21 known cancer gene mutations were detectable in all regions sequenced.
¶ Average subclonal branch mutations 40% in relapsed patients vs 17% in patients without relapse, p=0.006
Zhang et al, Science, 2014
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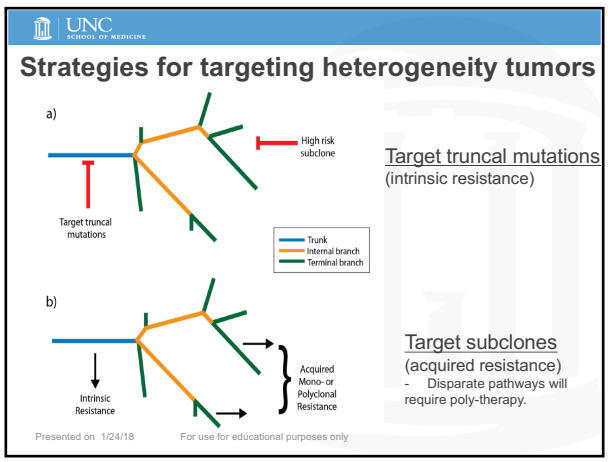
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Strategies for targeting heterogeneity tumors
a)
High risk subclone
Target truncal mutations
Trunk
Internal branch
Terminal branch
b)
Intrinsic Resistance
Acquired Mono- or Polyclonal Resistance
Target truncal mutations
(intrinsic resistance)
Target subclones
(acquired resistance)
- Disparate pathways will require poly-therapy.
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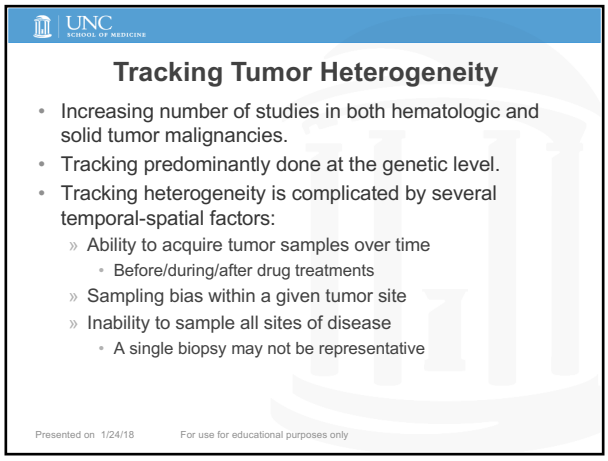
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Tracking Tumor Heterogeneity
• Increasing number of studies in both hematologic and solid tumor malignancies.
• Tracking predominantly done at the genetic level.
• Tracking heterogeneity is complicated by several temporal-spatial factors:
» Ability to acquire tumor samples over time
• Before/during/after drug treatments
» Sampling bias within a given tumor site
» Inability to sample all sites of disease
• A single biopsy may not be representative
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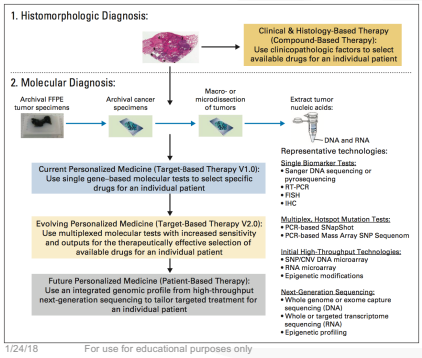
Clinical Applications to Tumor Heterogeneity



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Li et al. JCO. 2013. Vol 8(3)

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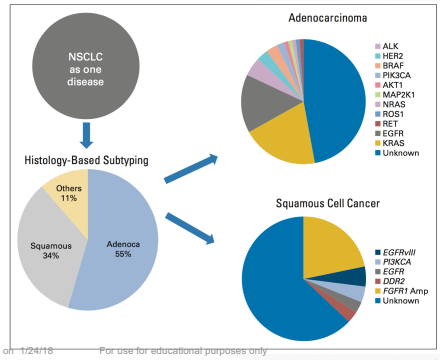
Clinical Applications to Tumor Heterogeneity



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Li et al. JCO. 2013. Vol 8(3)

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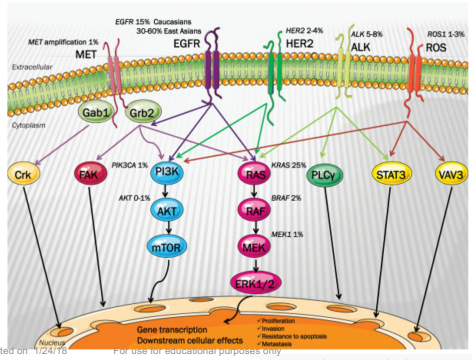
Clinical Applications to Tumor Heterogeneity



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Villaruz et al. Semin Respir Crit Care Med 2013;34:822–836

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Clinical Applications to Tumor Heterogeneity

- Endothelial Growth Factor Receptor (EGFR)
- Transmembrane protein, activation leads to tyrosine autophosphorylation and cell proliferation.
- Mutant over-expression has been found to be targetable.
- Highly prevalent in Asian patients and/or non-smokers with adenocarcinoma NSCLC
- Targeted using TKI

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Li et al. JCO. 2013. Vol 8(3)

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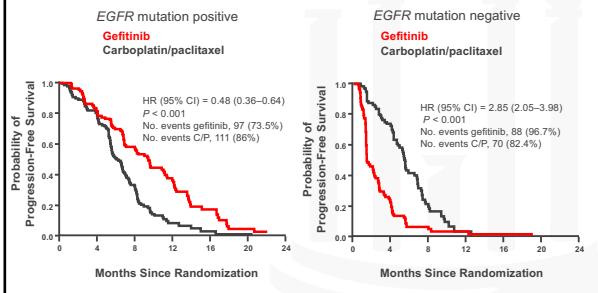
IPASS trial - Progression-free Survival by *EGFR* Mutation Status and Treatment



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Mok TS, et al. N Engl J Med. 2009;361(10):947-957

Slide Courtesy of ACCP/GAIN

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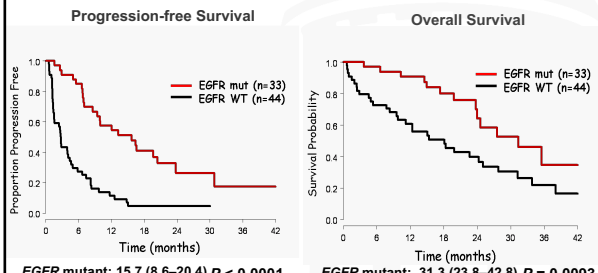
CALGB 30406 (US data): Erlotinib Improves RR and PFS in Patients with *EGFR* Mutation



***EGFR* mutant: 15.7 (8.6–20.4) *P* < 0.0001**
***EGFR* WT: 2.7 (1.4–4.4)**

***EGFR* mutant: 31.3 (23.8–42.8) *P* = 0.0093**
***EGFR* WT: 18.1 (9.5–25.0)**

RR: *EGFR* mutant: 67% (*P* < 0.0001) *EGFR* WT: 9%

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Janne PA, et al. *J Clin Oncol*. 2010;28:15S.

Slide Courtesy of ACCP/GAIN

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Phase III clinical trials of EGFR TKI vs. platinum-doublet chemotherapy in EGFR-mutated NSCLC

Trial	No. patients	Treatment	Response rate (*p*)	PFS (months)	HR for PFS (*p*)	OS (months)	HR for OS (*p*)
IPASS	437	Gefitinib Carboplatin paclitaxel	71% (<0.001) 47%	9.5 6.3	0.48 (<0.001)	21.6 21.9	1 (0.99)
WJTOG	177	Gefitinib Cisplatin docetaxel	62% (<0.001) 32%	9.2 6.3	0.49 (<0.001)	30.9 NRea	1.64 (0.21)
NEJ 002	230	Gefitinib Carboplatin paclitaxel	74% (<0.001) 31%	10.8 5.4	0.30 (<0.001)	30.5 23.6	NR
OPTIMAL	154	Erlotinib Carboplatin gemcitabine	83%(<0.001) 36%	13.1 4.6	0.16 (<0.001)	22.6 28.8	1.06 (0.68)
EURTAC	173	Erlotinib Platinum doublet	58% (<0.001) 15%	9.7 5.2	0.37 (<0.001)	19.3 19.5	1.04 (0.87)
LUX-Lung3	345	Afatinib Cisplatin pemetrexed	69% 44%	11.1 6.9	0.58 (<0.001)	28.2 28.2	1.12 (0.60)
LUX-Lung6	364	Afatinib Cisplatin gemcitabine	74% 31%	11.0 5.6	0.28 (<0.001)	23.1 23.5	0.95 (0.76)

In the trials above, starting doses were gefitinib 250 mg daily, erlotinib 150 mg daily or afatinib 40 mg daily.
EGFR epidermal growth factor receptor; EURTAC, European tarceva *versus* chemotherapy; IPASS, Iressa Pan-Asia Study; NSCLC, non-small cell lung cancer; NEJ, North East Japan; NR, not reported; NRea, not reached; OS, overall survival; PFS, progression-free survival; WJTOG, West Japan Thoracic Oncology Group.

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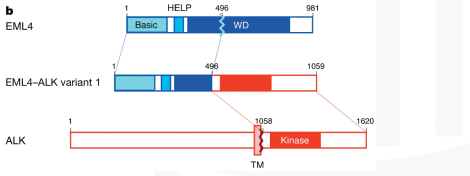
EML4-ALK Fusion Product in NSCLC

- A receptor tyrosine kinase (anaplastic lymphoma kinase [ALK]) fuses to the echinoderm microtubule-associated protein-like 4 (EML-4)
- Multiple variants of the translocation have been identified
- Oncogenic (transforms cell lines and transgenic mice develop lung cancer)
- *EML4-ALK* fusion transcript was detected in 6.7% (5 out of 75) of NSCLC patients examined



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Soda M, et al. Nature. 2007;448(7153):561-566.
Slide courtesy of ACCP/GAIN

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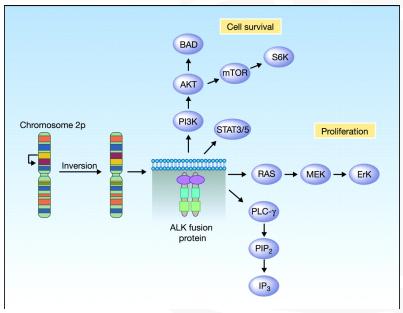
Schematic of ALK Fusion Oncogenes and Important Downstream Signalling Pathways



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Shaw AT, Solomon B. *Clin Cancer Res*. 2011;17:2081-2086.
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Results with Crizotinib

- Small-molecule tyrosine kinase inhibitor
  - » ALK, MET, and ROS1 kinases – "Dirty TKI"
- In phase 1 and 2 studies
  - » objective tumor responses in approximately 60% of patients with ALK-positive NSCLC
  - » progression-free survival of 7 to 10 months
- Randomized phase 3 trial
  - » Patients with advanced ALK-positive NSCLC
  - » Second-line – Crizotinib vs single-agent second-line chemotherapy with either pemetrexed or docetaxel – Crizotinib superior.

Solomon et al. N Engl J Med 2014; 371:2167-2177

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Results with Crizotinib

- EML4-ALK fusion gene found to be targetable using Crizotinib
- Early abstract
  - » Median PFS 10.0 months (95% CI; 8.2–14.7 months)
  - » Median OS has not been reached
    - 23 deaths (19%)
    - 94 patients (79%) remain in f/u for OS
    - No deaths related to study drug
  - » Adverse effects
    - Visual effects (62%)
    - GI effects, edema common (25-50%)
- Crizotinib approved by FDA August 26, 2011, for the treatment of patients with advanced NSCLC that is ALK positive

Camidge DR, et al. *J Clin Oncol.* 2011;29(suppl):Abstract 2501.
Slide courtesy of ACCP/GAIN

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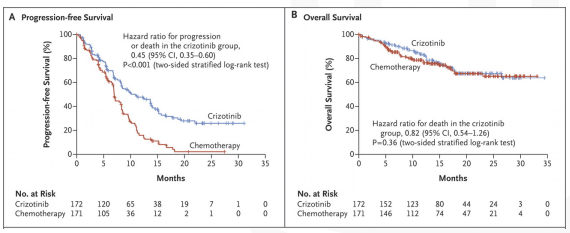
Results with Crizotinib

- First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer



Solomon et al. N Engl J Med 2014; 371:2167-2177

Results with Crizotinib

- First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Table 2. Response to Treatment in the Intention-to-Treat Population.*

Response	Crizotinib (N=172)	Chemotherapy (N=171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)
Time to response — mo§		
Median	1.4	2.8
Range	0.6–9.5	1.2–8.5
Duration of response — mo¶		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

Solomon et al. N Engl J Med 2014; 371:2167-2177

Clinical trials of crizotinib and second-generation ALK inhibitor for advanced ALK-rearranged NSCLC

Trial	No. patients	Treatment	RR (%)	PFS (months)	OS (months)
PROFILE1001	143	Crizotinib	61	9.7	NR
PROFILE1005	261	Crizotinib	53	8	NR
PROFILE1007	173	Crizotinib Pemetrexed Docetaxel	65 29 7	7.7 4.2 2.6	20.3 22.8*
PROFILE 1014	343	CrizotinibCis/carboplatin-Pemetrexed	74 45	10.9 7.0	Nrea Nrea
Seto *et al.* [2013]	46	Alectinib	93.5	NRea	NRea
Gadgeel *et al.* [2014]	47	Alectinib	59.5	NR	NR
Shaw *et al.* [2014a]	78	Ceritinib	60	8.6	NR
Camidge *et al.* [2014]	24	Brigatinib	62.5	NR	NR

ALK, anaplastic lymphoma kinase; NR, not reported; NRea, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate.
*Combined OS of docetaxel and pemetrexed arms.

Shea et al. Ther Adv Respir Dis 2016, Vol. 10(2) 113–129

ROS-1 Fusion Gene in NSCLC

- ROS-1 fusion first seen in gliobastoma
- More than 10 different fusion partners recognized
- >80% amino acid homology with ALK
- Crizotinib applied to ROS-1+ NSCLC

Available evidence of ROS1 inhibitors activity in the clinical setting.

Author [Ref.]	Inhibitor	Trial Phase or Design	N. of Patients	Setting	ORR (N. [%])	Duration of Response	Median PFS (months)
Shaw et al. *ESMO* 2016 [70]	Crizotinib	Expansion cohort (Phase I)	53	TKI-naïve	37 [70%]	Not Reached (Median)	19.3
Mazieres et al. *JCO* 2014 [59]	Crizotinib	Retrospective Study	32	TKI-naïve	24 [80%]	n.r.	9.1
Moro-Sibilot et al. *WCLC* 2016 [71]	Crizotinib	Phase II	39	TKI-naïve	25 [69%]	n.r.	9.1
Goto et al. *ASCO* 2016 [72]	Crizotinib	Phase II	127	TKI-naïve	88 [69%]	n.r.	13.4
Michels et al. *WCLC* 2016 [72]	Crizotinib	Phase II	34	TKI-naïve	23 [69%]	n.r.	n.r.
Cho et al. *WCLC* 2016 [105]	Ceritinib	Phase II	32	30 TKI-naïve, 2 post-crizotinib	20 [63%]	10 months	19.3
Solomon et al. *ASCO* 2016 [106]	Lorlatinib	Phase I/II	11	6 TKI-naïve, 5 post-crizotinib	7 [65%]	n.r.	n.r.
Drilon et al. *ACCR* 2016 [109]	Entrectinib	Phase I	13	TKI-naïve	11 [85%]	n.r	n.r.
Subbiah et al. *PNAS* 2016 [104]	Ceritinib	Case report	1	Post-crizotinib	Response	n.r.	/
Drilon et al. *CCR* 2016 [84]	Cabozantinib	Case report	1	Post-crizotinib	Response	≥8 months	/
Chong et al. *CCR* 2016 [102]	Cabozantinib	Case report	1	Post-crizotinib	Response	≈10 weeks°	/

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c-Met Amplification in NSCLC

- Met oncogenic driver via 2 mechanisms
  - » Amplification
  - » Exon 14 mutation
- Implicated in secondary resistance to EGFR and ALK
- De Novo associated with poorer outcomes in NSCLC
- High level of Met amplification (Met/CEP7 ration > 5)
- ?responses in squamous histology NSCLC

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Ignatius et al. J Thorac Oncol. 2011;6: 942–946
Schwab et al. Lung Cancer. 2014; 83(1): 109–111

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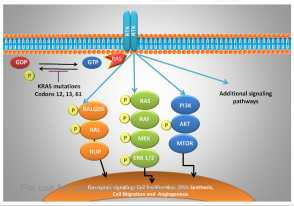
KRAS+ NSCLC

- Common oncogenic driver, mutant KRAS
- Present in approximately 25% of NSCLC
- Poor prognostic indicator (mixed result)
- Mutant KRAS constitutively bound to GTP
  - » Always on = increased cell proliferation, apoptosis suppression



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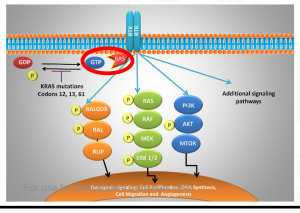
UNC SCHOOL OF MEDICINE

KRAS+ NSCLC

- Common oncogenic driver, mutant KRAS
- Present in approximately 25% of NSCLC
- Poor prognostic indicator (mixed result)
- Mutant KRAS constitutively bound to GTP
  - » Always on = increased cell proliferation, apoptosis suppression



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KRAS+ NSCLC

Agent	Mechanism of action	Number of patients	Setting	Study results
Farnesyl transferase inhibitor (R115777)	Farnesyl transferase inhibitor	44 (mutation status unknown)	Second line and beyond	No objective responses Median survival of 2.7 months
Salirasib	Prevents localization of RAS to the plasma membrane	33 (30 KRAS mutant)	All-lines	No observed responses; 11 patients with stable disease at 10 weeks (7 previously treated and 4 previously untreated) Median overall survival not reached
Sorafenib	Tyrosine Kinase Inhibitor	27 KRAS mutant	Second line and beyond	KRAS/BRAF marker group who were treated with sorafenib had a 79 % disease control rate at 8 weeks
Sorafenib	Tyrosine Kinase Inhibitor	37 (11 KRAS mutant)	Second line and beyond	Disease control rate of 65 % Median TPS of 3.4 months Median OS of 11.6 months 20 patients had stable disease and 2 had partial response
MEK inhibitor	Selumetinib and Docetaxel	87 (40 KRAS mutant)	Second line and beyond	Median OS of 9.4 months in the selumetinib group compared to 5.2 months in placebo Median PFS was 3.3 months in the selumetinib group and 2.1 months in placebo
MEK inhibitor	Trametinib	129 (40 KRAS mutant)	Second line and beyond	Median OS was 8 months in tarmetinib arm and not reached docetaxel arm Median PFS 3 months in tarmetinib group and 2.75 months in the docetaxel group 10 partial responses in tarmetinib group and 5 in docetaxel group
CDK inhibitor	LY2835219	49 (26 KRAS mutant)	Second line and beyond	Overall disease control rate of 51 %, in KRAS-mutant NSCLC, DCR of 54 % versus 37 % in KRAS wild type Median duration of SD was 16 months Median PFS was 2.1 months

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Status	Genomic event	Prevalence (%)	Therapy/drug(s)
Adenocarcinoma			
Approved			
	EGFR mutations	15–20	Gefitinib, erlotinib, afatinib
	ALK rearrangements	5	crizotinib, ceritinib
Emerging			
	EGFR-T790M (TKI resistant)	50 (resistant cases)	Osimertinib, rociletinib
	ALK (crizotinib resistant)	100 (resistant cases)	Alectinib, AP26113
	ROS1 rearrangements	1–2	Crizotinib
	BRAF mutations (V600E)	1–3	Vemurafenib, dabrafenib +trametinib
Evolving			
	MET amplification (high)	1–2	Crizotinib
	MET exon 14 skipping mutation	2–4	Crizotinib
	ERBB2 mutations	2–3	Afatinib
	RET rearrangements	1–2	Cabozantinib
Future targets			
	KRAS mutations	25–30	
	NTRK1 rearrangements	<1	
	FGFR2/3/4 mutations/ rearrangements	<1	
	MAP2K1 mutations	1	
	NRAS mutations	<0.5	
	HRAS mutations	<0.5	
	RIT1 mutations	1–2	
	NF1 mutations	5	
	PI3KCA mutations (co-occurring)	5–10	
	STK11/LKB1 mutations (co-occurring)	2	
Squamous			
Approved			
	None		
Evolving			
	DDR2 mutations	4	Dasatinib
Future targets			
	FGFR1 amplifications	15–20	
	FGFR2/3/4 mutations/ rearrangements	5–10	
	PI3KCA mutations	5–10	

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Harnessing the immune system

- Tumors resist immune attack and subsequent destruction by:
  - » Inducing tolerance among tumor-specific T-cells
  - » Expression of inhibitory ligands
- Check-point inhibition enhances anti-tumor immune response
- Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)
  - » Down modulates T-cell activation
- Programmed death 1 (PD-1) – Ligands selectively expressed on many tumors
  - » PD-L1 and PD-L2
  - » Inhibit cytokine production and cytolytic CD4 and CD8 T-cells
- 2 anti-PD-L1 drugs
  - » Pembrolizumab
  - » Nivolumab

Brahmer et al. N Engl J Med 2012; 366:2455-2465

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Harnessing the immune system

- Pembrolizumab
  - » KEYNOTE-001 – Proportion score (PS) >50% PD-L1 expression
    - OOR 45%
    - Both treated and treatment naïve patients with >44% OOR
  - » KEYNOTE-010 – Pembrolizumab vs. Docetaxel in previously treated NSCLC patients with PS >50%
    - HR 0.54 and 0.50 (2 different doses of Pembrolizumab), p<0.001
    - OS 14.9, 17.3 and 8.2 mo. for Pembrolizumab (2 doses) and Docetaxel respectively

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Garon et al. N Engl J Med 2015;372:2018–2028
Herbst A Lancet 2015 S0140-6736(15)01281-7

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Harnessing the immune system

- Pembrolizumab
  - » KEYNOTE-024 – Pembrolizumab (PS >50%) vs platinum-doublet first-line
    - PFS 10.3 vs. 6 mo.
    - RR 44.8% vs. 27.8%
  - » No survival benefit in EGFR mutated patients, even with detectable PS

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Reck et al. N Engl J Med 2016; 375:1823-1833

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Harnessing the immune system

- Nivolumab
- CheckMate-017 – Nivolumab vs. Docetaxel in patients with advanced squamous cell NSCLC, failed first-line chemotherapy.
  - » OS nivolumab 9.2 vs. docetaxel 6 months
  - » RR 20% vs. 9%
  - » Patients w/ advanced squamous cell NSCLC
    - Nivolumab – survival benefit regardless of PD-L1
- CheckMate-057 – Nivolumab vs. Docetaxel in advanced non-squamous cell NSCLC
  - » OS 12.2 months vs. 9.4 months
  - » RR 19% vs. 12%
  - » Objective response rate correlated with PD-L1 PS score, all groups superior to Docetaxel arm

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Brahmer et al. N Engl J Med 2015;373:123–135
Borghaei et al. N Engl J Med 2015;373:1627–1639

Harnessing the immune system

- Nivolumab
- CheckMate-026 – Nivolumab (PS >5%) vs. platinum-doublet as first-line therapy
  - PFS (median) 4.2 and 5.9 mo. respectively
  - HR 1.15 [95% CI: 0.91, 1.45, p=0.25])
  - OS 14.4 vs. 13.2 mo. respectively
  - 60% of patients on the chemotherapy arm received nivolumab after progression (crossover or commercial).

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Socinski et al. Ann Oncol (2016) 27 (suppl_6)

Lessons from Targeted Therapy in Lung Cancer

- Choosing the right therapy for an individual patient does matter (for tolerability and survival)
- Tailored therapy
  - EGFR mutations
  - EML-4-ALK and ROS-1 translocations
  - c-MET amplification
  - Histologic type – Adenocarcinoma
  - Immunotherapy – PD-L1
- Research will identify more predictive factors/targets

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Acknowledgements

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- Chad Pecot
- ACCP/GAIN

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