Precision Clinical Trials
Lessons from Oncology

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Disclosures

- Advisory Board / Consultant:
  AstraZeneca, Bristol-Myers Squibb, Catalyst, Daiichi Sankyo, Eisai, Elevation Oncology, Genentech/Roche, Gilead, Guardant Health, Janssen, Jazz Pharmaceuticals, Merck/MSD, Merus, Novartis, Regeneron, Sanofi, Takeda, Turning Point Therapeutics
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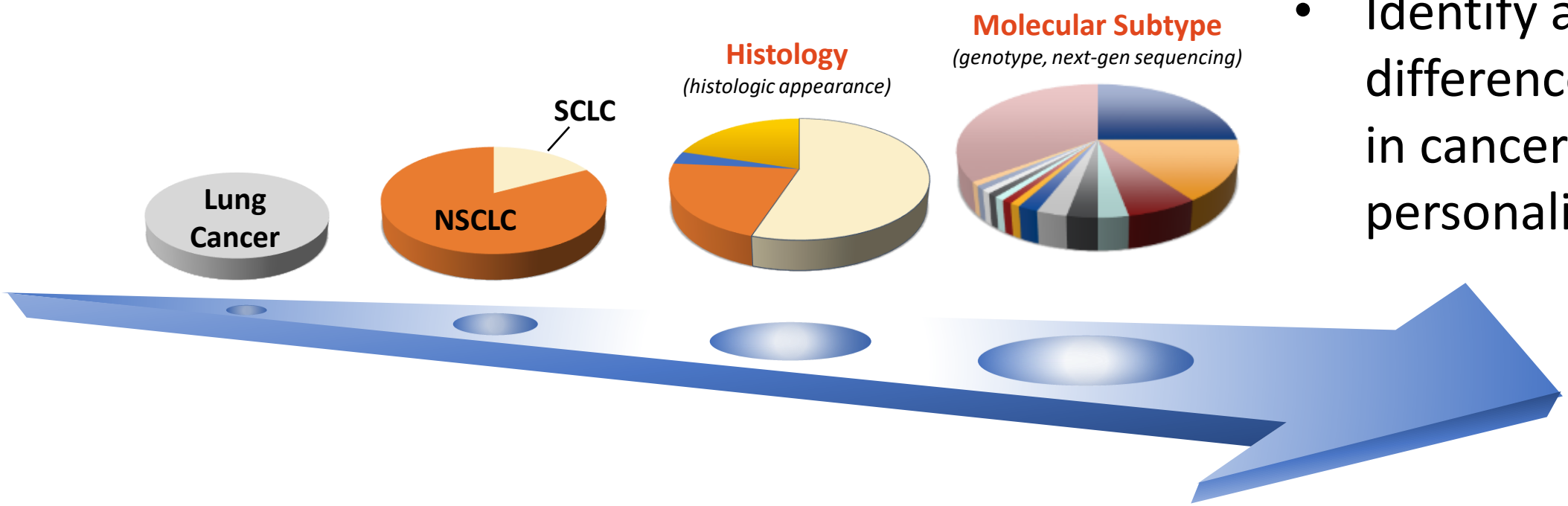
- Data Safety Monitoring Board
  Candel Therapeutics

Progress in Lung Cancer

- Lung cancer is the leading cause of cancer death for men and women
  - Few advances until the past two decades; remarkable progress recently

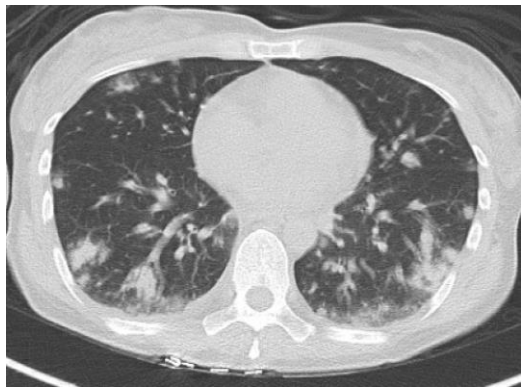


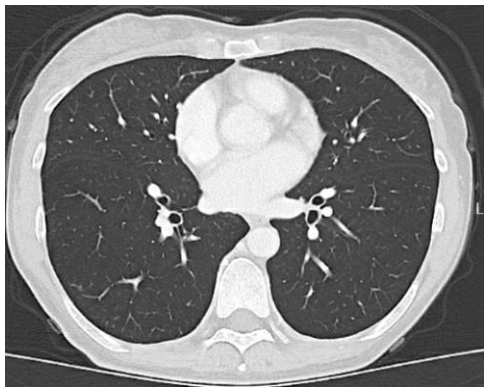
- Identify and leverage differences present in cancers to personalize care

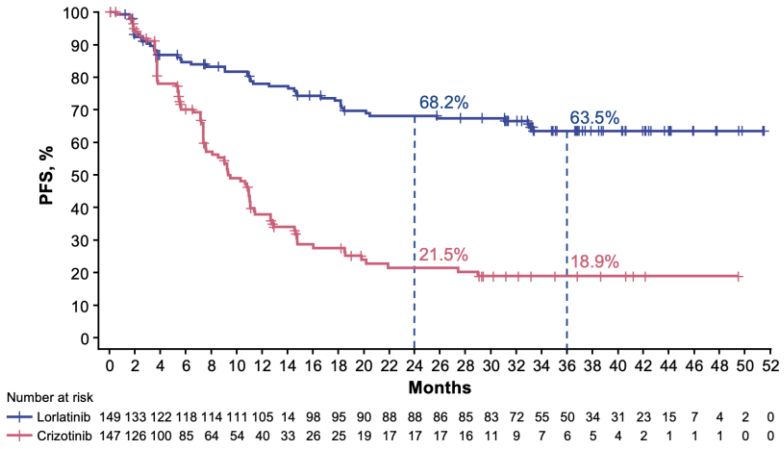
Jordan, Cancer Disc 2017

Progress in Lung Cancer

- Improvement in outcomes results from adopting precision therapy
  - Do not ignore the differences between patients' diseases
  - Embrace those differences
- Chromosomal rearrangements in ALK seen in ~5% of NSCLC
  - Oral kinase inhibitors effective
  - Immunotherapy not effective







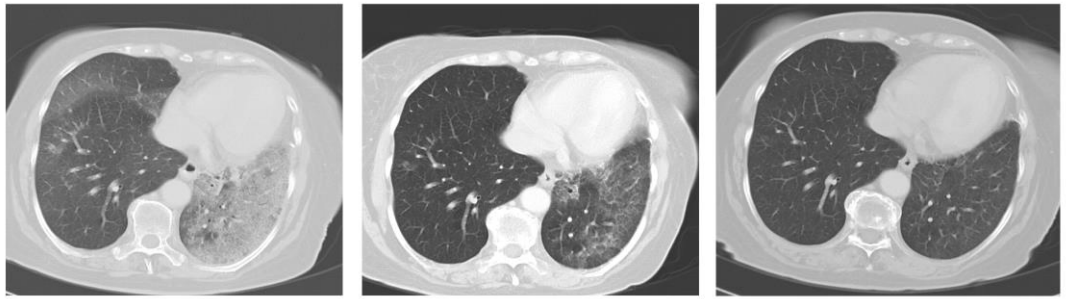
Solomon, AACR 2022

Lesson: Understand the Target Population

- Epidermal Growth Factor Receptor (EGFR) – commonly expressed protein
- EGFR kinase inhibitors studied in NSCLC (high protein expression)
  - Most patients had no response and their cancer worsened quickly
  - ~10% had a dramatic response

Table 3. Response to Erlotinib

Response	Investigator Best Response (WHO criteria)		Sponsor Best Response (RECIST criteria)	
	No. of Patients	%	No. of Patients	%
CR	2	3.5	2	3.5
PR	5	8.8	5	8.8
Stable disease	20	35.1	22	38.6
Progressive disease	28	49.1	28	49.1
Not assessable	2	3.5	—	—
Overall response rate, CR + PR	7	12.3	7	12.3
95% CI, %	5.1 to 23.7		5.1 to 23.7	

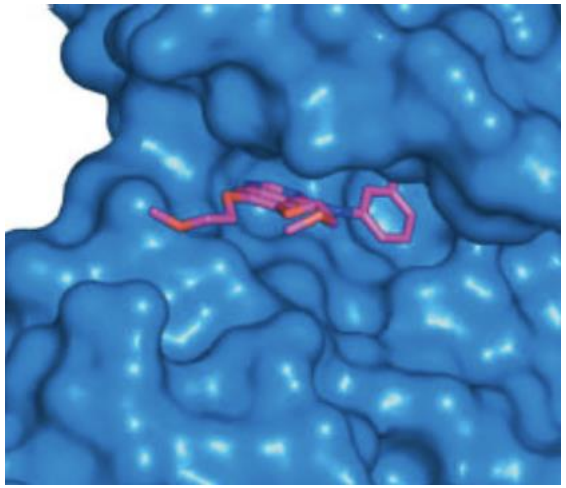


Baseline 3 months 2 years

Perez-Soler, JCO 2004

Lesson: Understand the Target Population

- Investigation at Mass General of 275 patients treated with gefitinib (first-generation EGFR inhibitor) for NSCLC
  - 25 had a major response; 9 of those had tumor tissue for analysis
  - 8 had a specific genetic mutation (EGFR kinase domain mutation)



Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
EGFR	Seq	DNA-Tumor	Pathogenic Variant	p.E746 _A750del	19	c.2236 _2250del15	31
TP53	Seq	DNA-Tumor	Pathogenic Variant	p.P60fs	4	c.177delT	48

- Invest in biomarker development
- Major advances may stem from study of small groups
- Be willing to adapt your biomarker

Lynch, NEJM 2004

Lesson: Details matter

- Different EGFR mutations and co-mutations impact outcomes

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
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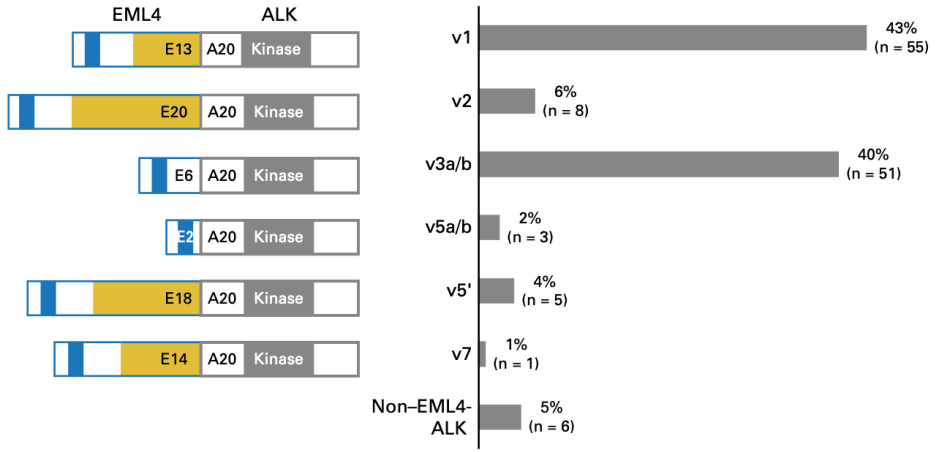
Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
EGFR	Seq	DNA-Tumor	Pathogenic Variant	p.E746 _A750del	19	c.2235 _2249del15	21
MYC	CNA-Seq	DNA-Tumor	Amplified	-	-	-	-
PIK3CA	Seq	DNA-Tumor	Likely Pathogenic Variant	p.E970K	20	c.2908G>A	18
PTEN	Seq	DNA-Tumor	Pathogenic Variant	c.254-19 _275del41	5	c.254-19 _275del41	38
RB1	Seq	DNA-Tumor	Pathogenic Variant	c.264+1G>T	2	c.264+1G>T	61
TP53	Seq	DNA-Tumor	Pathogenic Variant	p.L43*	4	c.128T>A	72

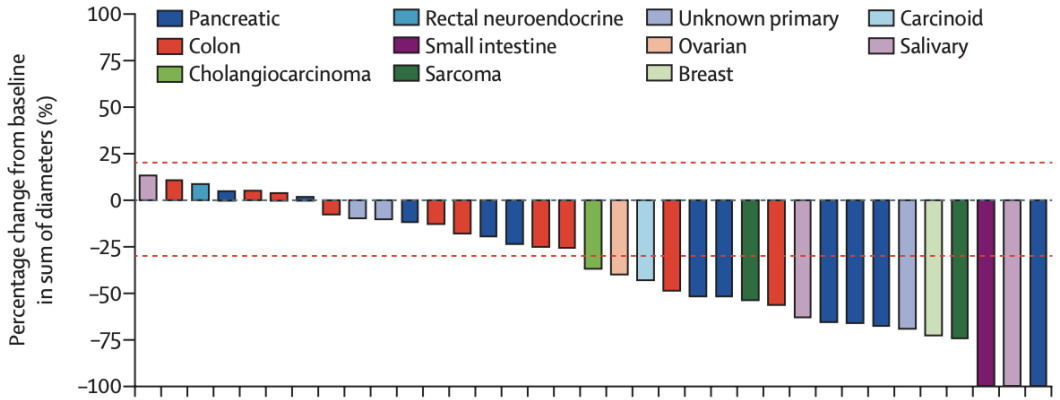
Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ARID1A	Seq	DNA-Tumor	Pathogenic Variant	p.R1335*	16	c.4003C>T	16
EGFR	Seq	DNA-Tumor	Pathogenic Variant	p.S768 _D770dup	20	c.2303 _2311dup9	40

- ALK inhibitors effective in lung cancer with an EML4-ALK fusion
  - Fusion variants (breakpoints) have very different prognoses



Lesson: Genotype can override phenotype

- Selpercatinib – selective RET inhibitor
  - Approved for medullary thyroid cancer and for RET fusion-positive NSCLC and thyroid cancer
  - September 21, 2022 – approved for any cancer with a RET fusion
- Other pan-tumor indications
  - Entrectinib (NTRK fusion)
  - Larotrectinib (NTRK fusion)
  - Pembrolizumab (MSI-high)
  - Pembrolizumab (TMB-high)
  - Dabrafenib + trametinib (BRAF V600E)

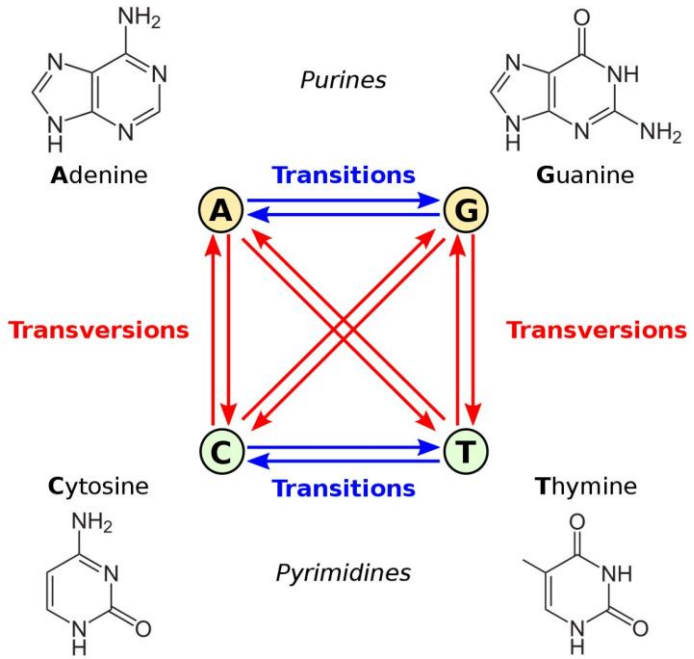


Subbiah, Lancet Oncol 2022

Lesson: Genotype may not override phenotype

- KRAS mutations among the most common oncogenic alterations
  - KRAS G12C mutations are now actionable
  - Sotorasib in KRAS G12C NSCLC
    - RR 37.1%, FDA approved
  - Sotorasib in KRAS G12C colorectal cancer
    - RR 9.7%

- Context is important, never assume
- Challenges with rare genomic subsets
  - When are large studies needed?



Skoulidis, NEJM 2021; Farikh, Lancet Oncol 2022

Lesson: Innovative Trial Design

- Basket trials – one drug/gene, many tumor types (analyzed separately)
  - NTRK inhibitor for NTRK fusion cancers
  - Baskets / cohorts for NSCLC, GI tumors, sarcomas, first-line, salvage
- Umbrella trial – one tumor type, many drugs/genes
  - BATTLE trial (2L NSCLC treatment based on profile)
  - I-SPY trial (neoadjuvant treatment for breast cancer)
- Octopus trial – one main agent with multiple combination “arms”
  - CodeBreaK 100 (sotorasib + other agents in KRAS G12C cancers)

Precision Clinical Trials

- Empiric ”one-size-fits-all” trials
  - Easy to design and complete
  - Lead to broad indications
  - Over time, offer incremental benefit
- Precision biomarker-driven trials
  - Require thoughtful design and implementation
  - Rely on biomarker discovery and development
  - Lead to focused, smaller indications
  - Potential for transformative benefit

Precision Clinical Trials: Successes and Pitfalls

- Lessons Learned
  - Do not ignore the differences – embrace them
  - When a treatment works well for a small portion of patients, invest in biomarkers to help define that patient population
  - Be willing to adapt based on emerging understanding, technology
  - Details always matter (even if we do not understand *how* they matter)
  - Genotype may or may not override phenotype
  - Trial design is critical to efficient drug development
  - Keep an open mind, borrow from other disciplines