Recent Advances in the Molecular Biology of Cancer Therapy

Gilberto Schwartsmann
How can we select a relevant molecular target for anticancer therapy?
The Long-Tail Distribution of Cancer Driver Mutations

Mutation prevalence (% of cases)

Genes:

Presented By Louis Staudt at 2016 ASCO Annual Meeting
The molecular pathology of clear cell renal cancer

**Normoxia**
- Proline hydroxylase + Oxygen → OH
- Asparagine hydroxylase + Oxygen → OH

**HIF-α**
- Normal VHL protein → HO
- Mutated VHL protein → HO

**Elongin protein**
- HIF-α ubiquitination by VHL protein complex
- HIF-α ubiquitination by Rbx1
- Proteasome → Destruction of HIF-α

**Cytoplasm**

**Hypoxia**
- No hydroxylation of HIF-α

**HIF-α**
- Translocation of HIF to nucleus

**HIF-β**

**Cytoplasm** → **Nucleus**
- HIF-mediated transcriptional activation

**p300**

**HRE**

**VEGF**
Agents Targeting the VEGF Pathway

**Anti-VEGF antibody**
- Bevacizumab*

**Soluble VEGFRs**
- Aflibercept

**VEGFR TKIs**
- Cediranib
- Nintedanib
- Sunitinib
- Sorafenib
- Pazopanib
- Axitinib
- Motesanib

**Anti-VEGFR antibody**
- Ramucirumab

* FDA-approved for treatment of advanced NSCLC.
Properties of a relevant molecular target:

a) Differentially expressed in cancer cells
b) Prevalent and biologically meaningful
   c) Clinically “dominant” biological effects
   d) Good biomarker
Targetable Oncogenic Drivers in Human Cancers

CML
- BCR-ABL

GIST
- CKIT

Melanoma
- BRAF

Breast
- HER2

Lung
- EGFR
- ALK
- ROS1
Networks 1, 2, 8 and 12 - CML signalosome

Proliferation, deregulated cell-cycle progression and defective apoptosis

Bcr-Abl

CRKL

PYK2

FAK

IRAK-1

BTK

DOCK2

Ras

Raf-1

MEK

STAT3

NLK

p90RSK

STAT5A,B

Grb2

Vav-1

PI3K

PRK2

VPS32

RPTOR

NF-κB

Networks 1 and 2

Network 8

CAMK2G

Vav1

ERK1,2

Network 12

Talin-1

CAPN1

PROK2

Grb2

Vav-1

PI3K

PRK2

VPS32

RPTOR

NF-κB

Networks 1, 2, 8 and 12 - CML signalosome

Primary CML #124

Myeloid blast crisis

PU-H71 (1 μM)
EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

Brian J. Druker, M.D., Moshe Talpaz, M.D., Debra J. Resta, R.N., Bin Peng, Ph.D., Elisabeth Buchdunger, Ph.D., John M. Ford, M.D., Nicholas B. Lydon, Ph.D., Hagop Kantarjian, M.D., Renaud Capdeville, M.D., Sayuri Ohno-Jones, B.S., and Charles L. Sawyers, M.D.

Conclusions STI571 is well tolerated and has significant antileukemic activity in patients with CML in whom treatment with interferon alfa had failed. Our results provide evidence of the essential role of BCR-ABL tyrosine kinase activity in CML and demonstrate the potential for the development of anticancer drugs based on the specific molecular abnormality present in a human cancer. (N Engl J Med 2001;344:1031-7.)

Copyright © 2001 Massachusetts Medical Society.

Table 4. Cytogenetic Responses.

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>All Patients</th>
<th>Patients with Complete or Major Responses</th>
<th>Patients with Minor Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>300–350</td>
<td>13</td>
<td>5 (38)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>400</td>
<td>6</td>
<td>3 (50)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>500</td>
<td>6</td>
<td>1 (17)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>600</td>
<td>8</td>
<td>4 (50)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>750</td>
<td>6</td>
<td>2 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>800</td>
<td>8</td>
<td>1 (12)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>1000</td>
<td>7</td>
<td>1 (14)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>17 (31)</td>
<td>12 (22)</td>
</tr>
</tbody>
</table>

Figure 2. Patients with a Major Cytogenetic Response. The percentage of cells in metaphase positive for the Ph chromosome (in bone marrow) and the number of days that the patients received STI571 are shown. Each line represents the cytogenetic response for an individual patient.
“Dominant” and “drugable” oncogenic drivers produce more robust clinical effects!
“Less dominant”, still “drugable” oncogenic drivers produce evident, though short-lasting clinical effects!
Lung Adenocarcinoma
Oncogenic Drivers

Presented By Alice Shaw at 2016 ASCO Annual Meeting
Afatinib Is the First Irreversible ErbB Family Blocker

- Afatinib covalently binds and irreversibly blocks EGFR, HER2, and ErbB4
- ErbB3 does not have a kinase domain and cannot be directly blocked by afatinib
- Afatinib prevents ligand-dependent ErbB3 phosphorylation in preclinical studies

Anti-phospho-immunoblotting has shown that afatinib prevents ligand (heregulin)-stimulated ErbB3 phosphorylation

| Heregulin | – | + | – | + | + | + | + |
| Afatinib (nM) | 0 | 0 | 300 | 1000 | 300 | 100 |

LUX-Lung 6: PFS in Mutation Subgroups by Independent Review\(^1\)

### Del19

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at Risk</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>124</td>
<td>13.7</td>
<td>0.20 (0.13-0.32), P&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Cis/Gem</td>
<td>62</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### L858R

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at Risk</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>92</td>
<td>9.6</td>
<td>0.32 (0.19-0.52), P&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Cis/Gem</td>
<td>46</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Less dominant”, “drugable” oncogenic drivers produce objective effects, but resistance is the rule!
Disease progression in CNS due to poor CNS penetration of drug

Response to TKI

Emergence of T790M-mutant clone

Indolent progression on TKI

Emergence of alternative resistance mutation (e.g. small cell transformation)

Rapid progression

Sacher, Jänne & Oxnard Cancer 2014

Presented By Pasi Janne at 2016 ASCO Annual Meeting
Mechanisms of Resistance to 1st Generation EGFR Inhibitors


Presented By Alice Shaw at 2016 ASCO Annual Meeting
### The 3rd Generation Inhibitor AZD9291 (Osimertinib) Is A T790M Mutant-Selective EGFR Inhibitor

<table>
<thead>
<tr>
<th></th>
<th>H1975 (T790M/L858R)</th>
<th>PC-9 VanR (ex19del/T790M)</th>
<th>PC-9 (ex19del)</th>
<th>Calu 3 (WT)</th>
<th>NCI-H2073 (WT)</th>
</tr>
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<tbody>
<tr>
<td>3rd</td>
<td>AZD9291</td>
<td>11 (6, 19)</td>
<td>40 (30, 54)</td>
<td>8 (7, 9)</td>
<td>650 (457, 924)</td>
</tr>
<tr>
<td></td>
<td>Dacomitinib</td>
<td>335 (265, 424)</td>
<td>531 (465, 607)</td>
<td>0.4 (0.3, 1)</td>
<td>65 (37, 116)</td>
</tr>
<tr>
<td></td>
<td>Afatinib</td>
<td>483 (403, 579)</td>
<td>679 (532, 868)</td>
<td>0.8 (0.7, 0.9)</td>
<td>71 (35, 144)</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td>6962 (6304, 7688)</td>
<td>4232 (1998, 8965)</td>
<td>23 (20, 25)</td>
<td>1933 (1299, 2876)</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>6165 (5392, 7050)</td>
<td>5778 (4766, 7029)</td>
<td>28 (22, 36)</td>
<td>4101 (2732, 6156)</td>
</tr>
<tr>
<td>2nd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cross et al., Canc Discovery 4: 1046-61, 2014
Osimertinib Binds to EGFR T790M Via Cys797

Cross et al., Canc Discovery 4: 1046-61, 2014

Presented By Alice Shaw at 2016 ASCO Annual Meeting
Plasma genotyping is faster than tissue based genotyping

- Plasma ddPCR Turn around time (TAT): 3 days (range 1-7)
- Tissue genotyping TAT:
  - Newly diagnosed: 12 days (range 1 - 54)
  - EGFR acquired resistance: 27 days (range 1- 146)

Sacher et al JAMA Oncology 2016

Presented By Pasi Janne at 2016 ASCO Annual Meeting
Clinical Activity of Osimertinib in Advanced EGFR Mutant T790M+ NSCLC

Objective response rate (N=127): 61% (95% CI, 52-70)


Presented By Alice Shaw at 2016 ASCO Annual Meeting
Can We Use Plasma and Urine to Detect T790M Acquired Resistance Mutations in Advanced NSCLC?

- TIGER-X trial with rociletinib, 3rd generation EGFR TKI w/specificity vs. T790M acquired resistance mutation (50-60% of cases)

**Plasma**

- BEAMing (Sysmex Inostics) is digital PCR followed by flow cytometry\(^1\-^3\)
- EGFR test identifies L858R, Ex19del, rare activating mutations, and T790M (0.02% level)

**Urine**

- Trovagene quantitative NGS assay for urine
- EGFR Ex19del, L858R and T790M tests with sensitivity ≥0.006\(^% \)\(^4\)

Investigator-assessed Confirmed Response Rate is Similar for T790M-positive Patients Identified by Plasma, Tissue, and Urine

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>n</th>
<th>ORR* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>443</td>
<td>33.9 (29.5–38.5)</td>
</tr>
<tr>
<td>Plasma</td>
<td>374</td>
<td>32.1 (27.4–37.1)</td>
</tr>
<tr>
<td>Urine</td>
<td>169</td>
<td>36.7 (29.4–44.4)</td>
</tr>
</tbody>
</table>

- Comparable duration of response and PFS whether positive by tissue, plasma, or urine
- Early drop in T790M in urine (21d) predicted for better radiographic/clinical response (N = 9 with serial testing)
- Overall, results show tissue, plasma, & urine each detect T790M at comparable rates, no clear “gold standard”
- Plasma & urine viable option, especially when tissue is harder to obtain

*Investigator-assessed confirmed objective response rate (RECIST v1.1)
Pharmacological resistance, such as “sanctuary sites”, can be a reason for failure!
Time on Treatment with Osimertinib in Patients with Leptomeningeal Carcinomatosis

15 patients are ongoing treatment at time of data cut-off - March 10, 2016 - 7 of which have been on treatment for >9 months

These findings are superior to currently available strategies to treat patients with leptomeningeal carcinomatosis

Presented By Pasi Janne at 2016 ASCO Annual Meeting
## Properties of Brain Penetrating EGFR Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib</th>
<th>AZD3759</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Pyrimidine</td>
<td>Quinazoline</td>
</tr>
<tr>
<td>Inhibit T790M ?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dose</td>
<td>80 mg approved</td>
<td>50 - 500 mg</td>
</tr>
<tr>
<td></td>
<td>20 - 240 mg tested</td>
<td></td>
</tr>
<tr>
<td>Brain penetration -</td>
<td>$K_{puu,\text{brain}} = 0.39$\textsuperscript{1}</td>
<td>$K_{puu,\text{brain}} = 1.3$\textsuperscript{3}</td>
</tr>
<tr>
<td>preclinical models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain penetration -</td>
<td>$K_{puu,\text{CSF}} = 0.5$\textsuperscript{2}</td>
<td>$K_{puu,\text{CSF}} = 1.0$\textsuperscript{4}</td>
</tr>
<tr>
<td>humans</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gefitinib $K_{puu,\text{brain}} = 0.021$

$K_{puu} =$ the ratio of the unbound tissue (brain) concentration over the unbound plasma concentration

\textsuperscript{1}Ballard et al. *CCR, in press*; \textsuperscript{2}Ballard et al. Personal Communication; \textsuperscript{3}Zeng et al. *J Med Chem* 2015; \textsuperscript{4}Ahn et al. *ASCO* 2016
Phase I study (BLOOM) of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM)

Myung-Ju AHN¹, Dong-Wan KIM², Tae Min KIM², Chia-Chi LIN⁵, Jayantha RATNAYAKE⁵, David J CARLILE³, Xiaolu YIN⁴, Zhenfan YANG⁴, Haiyi JIANG⁵, James Chih-Hsin YANG⁶

1. Samsung Medical Center, South Korea; 2. Seoul National University Hospital, South Korea; 3. Early Clinical Development, AstraZeneca; 4. Asia & Emerging Markets iMed, AstraZeneca; 5. Global Medicine Development, AstraZeneca; 6. National Taiwan University Hospital, Taiwan
Case study 1 – BM

Fifty-year-old Korean male, diagnosed with advanced NSCLC (Exon19Del) in Aug 2014 with most recent progression with multiple BM in Aug 2015.

- Prior therapies included gefitinib and pemetrexed
- Presented with insomnia, itching, gait disturbance

AZD3759 500mg BID started Sep 2015. Then reduced to 300mg BID within cycle 1.

- CNS disease PR since week 6 until withdrawal.
- Withdraw due to extracranial disease progression at week 18.
- Neurological function remains normal until withdrawal.
- No CNS symptoms until withdrawal.
Case study 2 – LM

Sixty-two-year-old Korean female, diagnosed with advanced NSCLC (L858R) in 2009 with most recent progression with LM in July 2015.
- Prior therapies included erlotinib, IT methotrexate and WBRT
- Presented with headache, dizziness, visual disturbance

AZD3759 300mg BID started Aug 2015; from week 6
- Improved neurological function
- Improved CNS symptoms
- CSF tumor cell clearance
- Improved LM MRI imaging

Patient still on AZD3759 treatment at 25 weeks

Baseline
CSF cytology (+)
Headache, dizziness, visual disturbance

Week 6
CSF cytology (-)
Improved headache, improved visual disturbance

Week 18
CSF cytology (-)
Normal neurological function
Necitumumab Targets EGFR

- IgG1 anti-EGFR human monoclonal antibody
- Different from the chimeric human/mouse EGFR mAb cetuximab
- Binds with high affinity and specificity to EGFR
- Blocks activation and inhibits downstream signaling pathways relevant to NSCLC
SQUIRE: Study Design

**Population**
First-Line Stage IV squamous NSCLC
ECOG PS 0-2

**NECI + Gem-Cis q3w (N=545)**
- Necitumumab (800 mg D1, D8)
- Gemcitabine (1250 mg/m², D1, D8)
- Cisplatin (75 mg/m², D1)

**Gem-Cis q3w (N=548)**
- Gemcitabine (1250 mg/m², D1, D8)
- Cisplatin (75 mg/m², D1)

Maximum of 6 cycles

**Randomization (R) stratified by:** ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia vs. South America, South Africa and India vs. Eastern Asia)

- Patient selection not based on EGFR protein expression
- Tissue collection was eligibility criterion
Overall Survival in EGFR FISH Positive* Patients

Tumor samples were available with valid FISH results obtained for 51% of ITT population


Unstratified HR (95% CI)  
GC+N 0.70 (0.52, 0.96)
GC N=97

Median, months (95% CI)  
12.6 (11.5, 15.9) 9.2 (7.2, 12.1)

Presented By Fred Hirsch at 2016 ASCO Annual Meeting
FDA approved as of November 2015

• … indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous non-small cell lung cancer
• … not indicated for treatment of nonsquamous non-small cell lung cancer
“Dominant”, “not yet drugable” oncogenic drivers may impact on the natural history of the disease and/or drug sensitivity!
Advancing discoveries

Bim expression/ Germ-line Bim polymorphisms- intrinsic resistance

Concurrent p53 alterations impacting treatment success

Faber et al, Cancer Discov, 2011

Clonal heterogeneity as a determinant of long-term cancer behavior

Ng et al, Nature Med, 2012


Presented By Balazs Halmos at 2016 ASCO Annual Meeting
ALK-ROS1 Pathway
Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer

Manabu Soda¹,2, Young Lim Choi¹, Munehiro Enomoto¹,2, Shuji Takada¹, Yoshihiro Yamashita¹, Shunpei Ishikawa³, Shin-ichiro Fujiiwa¹, Hideki Watanabe¹, Kentaro Kurashina¹, Hisashi Hatanaka¹, Masashi Bando², Shoji Ohno², Yuichi Ishikawa³, Hiroyuki Aburatani³, Toshiro Niki¹, Yasunori Sohara¹, Yukihiko Sugiyama² & Hiroyuki Mano¹,²

Inversion

Translocation

or


ALK-positive patients:
Never or minimal smokers
Young (average age 50 years)
Adenocarcinoma type
Responsive to ALK inhibitors

Presented By Alice Shaw at 2016 ASCO Annual Meeting
**Crizotinib is a Standard Therapy for Patients with Metastatic ALK+ NSCLC**

<table>
<thead>
<tr>
<th>Phase</th>
<th>PROFILE 1001&lt;sup&gt;1&lt;/sup&gt; (N=143)</th>
<th>PROFILE 1005&lt;sup&gt;2&lt;/sup&gt; (N=259)</th>
<th>PROFILE 1007&lt;sup&gt;3&lt;/sup&gt; (N=172)</th>
<th>PROFILE 1014&lt;sup&gt;4&lt;/sup&gt; (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line of therapy</td>
<td>Any line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line and beyond</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
</tr>
<tr>
<td>Response rate</td>
<td>61%</td>
<td>60%</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td>PFS, median (mos)</td>
<td>9.7</td>
<td>8.1</td>
<td>7.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Survival probability at 12 mos</td>
<td>75%</td>
<td>NA</td>
<td>70%</td>
<td>84%</td>
</tr>
</tbody>
</table>

<sup>1</sup>Camidge et al., Lancet Onc 13(10): 1011-9, 2012
<sup>2</sup>Kim et al., ASCO 2012
<sup>3</sup>Shaw et al., NEJM 368(25): 2385-94, 2013
<sup>4</sup>Solomon et al., NEJM 371(23): 2167-77, 2014

Presented By Alice Shaw at 2016 ASCO Annual Meeting
Alectinib is a Highly Selective and Potent ALK Inhibitor

Sakamoto et al., Cancer Cell 19: 679-690, 2011

Presented By Alice Shaw at 2016 ASCO Annual Meeting
Clinical Activity of Alectinib in Crizotinib-Resistant, ALK+ NSCLC

Global Phase 2 Study

Systemic BOR:  
- PD (n=22)  
- SD (n=35)  
- PR (n=61)

Sum of longest diameter, maximum decrease from baseline (%)

ORR 50% (RE population)  
Median DOR 11.2 mos

Ou et al., JCO 34: 661-8, 2016

Presented By Alice Shaw at 2016 ASCO Annual Meeting
Alectinib is Highly Active in the CNS (Pooled Analysis of Phase 2 Studies)

Best Intracranial Response

Prior CNS Radiation  
- Yes (n=34)  
- No (n=16)

Sum of longest diameter, max. decrease from baseline (%)

Data cut-off for both studies = 27 April 2015

Patients

Gadgeel et al., WCLC 2015

Presented By Alice Shaw at 2016 ASCO Annual Meeting
# Alectinib - Summary

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>small molecule tyrosine kinase inhibitor of ALK</th>
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<tbody>
<tr>
<td>Indication</td>
<td>metastatic ALK-rearranged NSCLC, previously treated with crizotinib</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>None</td>
</tr>
<tr>
<td>Dosing</td>
<td>600 mg PO twice daily, with food</td>
</tr>
<tr>
<td>Side effects</td>
<td>fatigue (41%), constipation (34%), edema (30%), myalgia (29%), cough (19%), rash (18%), nausea (18%)</td>
</tr>
<tr>
<td>CNS</td>
<td>ORR 61%, median DOR 9.1</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Alectinib vs crizotinib (1L)</td>
</tr>
</tbody>
</table>

Presented By Alice Shaw at 2016 ASCO Annual Meeting
J-ALEX: Study Design

Key Entry Criteria
- Stage IIIIB/IV or recurrent ALK-positive NSCLC
- ALK centralized testing (IHC and FISH or RT-PCR)
- ECOG PS 0-2
- Measurable target lesion
- Treated/asymptomatic brain metastases allowed
- ≤1 prior chemotherapy

Endpoints
- Primary
  - PFS assessed by IRF*
- Secondary
  - OS
  - ORR
  - PK
  - QOL
  - CNS PFS
  - Safety

Stratification factors:
Clinical stage (IIIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

N = 103
Alectinib 300 mg BID PO, 28-day cycle

N = 104
Crizotinib 250 mg BID PO, 28-day cycle

R 1:1

*IRF Independent Review Facility
Primary Endpoint: PFS by IRF (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>NR (20.3 - NR)</td>
<td>10.2 (8.2 - 12.0)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
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</table>

HR (99.6826% CI) 0.34 (0.17 - 0.71)

Time (months)

Presented By Howard West at 2016 ASCO Annual Meeting
Cell-Cycle Pathways:
CDK Inhibitors in Breast Cancer
Background: CDK 4/6

- Cyclin dependent kinases (CDKs) - family of serine-threonine kinases partner with cyclins to regulate cell cycle progression\(^1\)

- Altered expression and activation of various regulators of the cyclin D:CDK-4/6:Rb pathway have been implicated in numerous cancers

- Palbociclib is an oral, highly selective inhibitor of CDK-4/6 that inhibits cell proliferation by prohibiting cell cycle progression from G1 to S phase\(^2\)

- Alterations in the cyclin D:CDK-4/6:Rb pathway have been associated with prognosis, endocrine sensitivity, and growth factor signaling in breast cancer

Palbociclib Preferentially Inhibits Proliferation of Luminal ER+ Human Breast Cancer Cell Lines

EMT = epithelial mesenchymal transition; IC_{50} = half maximal inhibitory concentration.

Reprinted from Finn, ... Slamon et al. Breast Cancer Res. 2009.

Presented By Richard Finn at 2016 ASCO Annual Meeting
Properties of a relevant molecular target:

a) Differentially expressed in cancer cells!
b) Prevalent and biologically meaningful!
c) Clinically “dominant” biological effects!
d) Good biomarker!
Who leads this project?
Dennis Slamon
Breast Cancer

HER-2 Oncogene Amplification

HER-2 Oncoprotein Overexpression

Shortened Survival

Median Survival from First Diagnosis

- HER-2 overexpressing: 3 yrs
- HER-2 normal: 6 - 7 yrs

Slamon et al, 1987
Human Breast Cancer Cells

MCF-7

Transfect
HER-2/neu

MCF-7*

Single copy Low Expressor

Multiple copy High Expressor

Human Ovarian Cancer Cells

CaOv-3

Transfect
HER-2/neu

CaOv-3*

Single copy Low Expressor

Multiple copy High Expressor

*Consistent results in 9 additional Breast & Ovarian Cancer Cell Lines
Immunohistochemistry

MCF 7

CaOV 3
Engineered HER-2 Over-expression in MCF-7 cells
Increased Proliferation and Decreased Contact Inhibition

Anchorage-Independent Growth

Growth on Plastic

MCF-7 CN
MCF-7 H2

Number of cells x 10^3

2  4  6  8  9
days
Preclinical Impact of Trastuzumab on Tumor Growth

Effect of Trastuzumab Treatment on HER2+ Breast Cancer Xenografts

BACK TO PALBOCICLIB
PALOMA-2: Study Design (1008)\(^1\)

- Postmenopausal
- ER+, HER2– advanced breast cancer
- No prior treatment for advanced disease
- AI-resistant patients excluded

N=666\(^a\)

**RANDOMIZATION**

- 2:1

**Primary endpoint**
Investigator-assessed PFS

**Secondary endpoints**
Response, OS, safety, biomarkers, patient-reported outcomes

**Stratification factors**
- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic; ≤12 mo, >12 mo)
- Prior (neo)adjuvant hormonal therapy (yes, no)

**Palbociclib (125 mg QD, 3/1 schedule)**
+ letrozole (2.5 mg QD)

**Placebo (3/1 schedule)**
+ letrozole (2.5 mg QD)

- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events - 90% power with 1-sided \(\alpha=0.025\)

Assumptions: Median PFS of placebo plus letrozole = 9 mos vs. palbociclib plus letrozole = 13 mos

- Blinded independent central review of efficacy endpoints performed as supportive analysis

\(^a\)Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

1.clinicaltrials.gov
NCT01740427

Presented By Richard Finn at 2016 ASCO Annual Meeting
PFS: Blinded Independent Central Review
Confirmed PFS Advantage Seen Using Investigator Assessment

Number of Events, n (%)
- PAL+LET (N=444): 152 (34)
- PCB+LET (N=222): 96 (43)

Median (95% CI) PFS
- PAL+LET: 30.5 (27.4–NR)
- PCB+LET: 19.3 (16.4–30.6)

HR (95% CI); 1-sided P value
- PAL+LET: 0.65 (0.51–0.84); P=0.0005

Number of patients at risk
- PAL+LET: 444 384 344 319 281 252 228 149 68 31 9 2
- PCB+LET: 222 167 144 131 111 94 76 49 22 12 3 2

LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

Presented By Richard Finn at 2016 ASCO Annual Meeting
**Consistent Clinical Benefit Seen Across PALOMA Studies**

<table>
<thead>
<tr>
<th></th>
<th>1003¹ (PALOMA-1)</th>
<th>1008 (PALOMA-2)</th>
<th>1023² (PALOMA-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Phase 2</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Open label</td>
<td>Placebo control</td>
<td>Placebo control</td>
</tr>
<tr>
<td><strong>Endocrine partner</strong></td>
<td>Letrozole</td>
<td>Letrozole</td>
<td>Fulvestrant</td>
</tr>
<tr>
<td><strong>Patients on study, N</strong></td>
<td>n=165</td>
<td>n=666</td>
<td>n=521</td>
</tr>
<tr>
<td><strong>Efficacy (palbociclib vs control arm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary endpoint: PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.49</td>
<td>0.58</td>
<td>0.46</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>20.2 vs 10.2 (↑10.0mos)</td>
<td>24.8 vs 14.5 (↑0.3mos)</td>
<td>9.6 vs 4.6</td>
</tr>
<tr>
<td><strong>Secondary endpoints, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (ITT, measurable disease)</td>
<td>43 vs 33,</td>
<td>42 vs 35,</td>
<td>19 vs 9,</td>
</tr>
<tr>
<td></td>
<td>55 vs 39</td>
<td>55 vs 44</td>
<td>25 vs 11</td>
</tr>
<tr>
<td>CBR (ITT)</td>
<td>81 vs 58</td>
<td>85 vs 70</td>
<td>67 vs 40</td>
</tr>
</tbody>
</table>

CBR= clinical benefit response; ITT= intent-to-treat; ORR= objective response rate.


Presented By Richard Finn at 2016 ASCO Annual Meeting
Conclusions

• Palbociclib combined with letrozole significantly improved median PFS compared with placebo plus letrozole as first-line therapy in women with ER+/HER2– advanced breast cancer
  – >10 month improvement in median PFS was observed (24.8 vs 14.5 mo)
  – HR = 0.58 (95% CI, 0.46–0.72; P<0.0001)

• Clinical benefit from palbociclib was also demonstrated across all pre-specified subgroups

• Palbociclib was well tolerated with the most common AEs being neutropenia and leukopenia; however, the overall incidence of neutropenic fever was low

• These data confirm PALOMA-1 results and represent the longest front-line improvement in median PFS seen to date in women with advanced ER+ breast cancer
BRAF AS A TARGET
Vemurafenib inhibits BRAF\textsuperscript{V600E} Kinase

40-60% of melanomas

RTK

VEMURAFENIB (PLX4032, RO5185426)

Cellular Proliferation
Clinical Response and Resistance to RAF Inhibition* in Melanoma

October, 2009

January, 2010

*Vemurafenib

Wagle et al JCO 2011
Clinical Response and Resistance to RAF Inhibition in Melanoma

October, 2009  January, 2010  March, 2010

Wagle et al JCO 2011
# Targeting Mutant BRAF in Metastatic Melanoma

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Dabrafenib + Trametinib</th>
<th>Dabrafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>69%</td>
<td>53%</td>
</tr>
<tr>
<td>Median duration of response – mo</td>
<td>12.9</td>
<td>10.6</td>
</tr>
<tr>
<td>Median PFS – mo</td>
<td>11.0</td>
<td>8.8</td>
</tr>
<tr>
<td>Median OS – mo</td>
<td>25.1</td>
<td>18.7</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>51%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Long et al., Lancet 386(9992): 444-51, 2015
BRAF Mutations in Non-Small Cell Lung Cancer (NSCLC)

Presented by Alice Shaw at 2016 ASCO Annual Meeting

- NSCLC with BRAF V600E mutations has histological features suggestive of an aggressive tumor.
- Patients with BRAF V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy.

Activity of Single-Agent Dabrafenib in BRAF V600E Mutant NSCLC (Cohort A)

ORR 33%
Median PFS 5.5 mos

Maximum Percent Reduction at Time of Best Disease Assessment

- Partial response
- Stable disease
- Progressive disease

Presented by David Planchard, MD, PhD (ASCO 2014)
Targeting Mutant BRAF in Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Vemurafenib(^1) (n=21)</th>
<th>Dabrafenib + trametinib(^2) (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Median PFS – mo</td>
<td>2.1</td>
<td>3.5</td>
</tr>
<tr>
<td>Median OS – mo</td>
<td>7.7</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\(^1\)Kopetz et al., JCO 33(34): 4032-8, 2015
\(^2\)Corcoran et al., JCO 33(34): 4023-31, 2015
MET AS A TARGET
Crizotinib is a Standard Therapy for Advanced ALK- or ROS1-Rearranged NSCLC

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>ALK¹ (N=143)</th>
<th>ROS1² (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Phase 1</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Line of therapy</td>
<td>any</td>
<td>any</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>61%</td>
<td>72%</td>
</tr>
<tr>
<td>Median duration of response – mo</td>
<td>11.3</td>
<td>17.6</td>
</tr>
<tr>
<td>Median PFS – mo</td>
<td>9.7</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Crizotinib is Active in MET-Amplified Cancers

Presented By Alice Shaw at 2016 ASCO Annual Meeting
**MET** Exon 14-Altered Lung Cancers

- **Incidence**
  - 3-4% of nonsquamous NSCLCs
  - 20-30% of sarcomatoid lung carcinomas

- **Clinicopathologic Features**
  - older patients, ↓ proportion of never smokers
  - 15-20% with concurrent *MET* amplification

- **Diagnosis**
  - DNA-based next-generation sequencing
  - RNA sequencing
  - immunohistochemistry alone is insufficient
Antitumor Activity

Maximum Response to Crizotinib in Patients with MET Exon 14-Altered Lung Cancers (n=16 with measurable disease at baseline and ≥1 response assessment scan)

ORR: 44% (confirmed)

% change from baseline

- Partial response (PR), confirmed
- Stable disease (SD): includes 4 unconfirmed PRs
- * Stable disease and 0% change from baseline
MET Exon 14 Skipping Mutations Define a New Molecular Subset

CANCERS
1. Lung adenocarcinomas (3%)\(^1\)
2. Pulmonary sarcomatoid (22%)\(^2\)
3. GI cancers (5%)\(^3\)
4. Brain gliomas (0.5%)\(^1\)
5. Carcinomas of unknown primary (0.5%)\(^1\)

MET INHIBITORS
1. Crizotinib
2. Capmatinib (INC280)
3. Glesatinib (MGCD265)
4. Savolitinib (AZD6094)
5. Merestinib (LY2801653)
6. AMG 337

\(^1\)Frampton et al., Cancer Disc 5(8): 850-9, 2015; \(^2\)Liu et al., JCO 34(8): 794-802, 2016; \(^3\)Lee et al., Oncotarget 6(29): 29211-22, 2015
FGFR AS A TARGET
<table>
<thead>
<tr>
<th>FGFR</th>
<th>Alteration</th>
<th>Cancer types</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1</td>
<td>amplification</td>
<td>Lung, HNSCC, breast, ovarian, endometrial, prostate, osteosarcoma, esophageal</td>
</tr>
<tr>
<td></td>
<td>mutation</td>
<td>Melanoma, gastric, GBM</td>
</tr>
<tr>
<td>FGFR2</td>
<td>amplification</td>
<td>Gastric, breast, ovarian</td>
</tr>
<tr>
<td></td>
<td>mutation</td>
<td>Endometrial, melanoma, lung, cholangiocarcinoma</td>
</tr>
<tr>
<td></td>
<td>rearrangement</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>FGFR3</td>
<td>amplification</td>
<td>Sarcoma, bladder, GBM</td>
</tr>
<tr>
<td></td>
<td>mutation</td>
<td>Melanoma, bladder, cervical, multiple myeloma</td>
</tr>
<tr>
<td>FGFR4</td>
<td>amplification</td>
<td>Kidney, prostate, bladder</td>
</tr>
<tr>
<td></td>
<td>mutation</td>
<td>Bladder, CRC, lung, rhabdomyosarcoma</td>
</tr>
</tbody>
</table>
Clinical Activity of the Pan-FGFR Inhibitor BGJ398 in Cancers with FGFR Genetic Alterations

1. Cholangiocarcinoma
2. HNSCC
3. Cholangiocarcinoma
4. Angiosarcoma
5. Cholangiocarcinoma

Presented By Alice Shaw at 2016 ASCO Annual Meeting
# New Generation of Selective Pan-FGFR Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>ClinicalTrials.gov ID</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>BGJ398</td>
<td>Phase 2</td>
<td>NCT01975701</td>
<td>Recurrent GBM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT02706691</td>
<td>Advanced HNSCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT02150967</td>
<td>Advanced cholangiocarcinoma</td>
</tr>
<tr>
<td>AZD4547</td>
<td>Phase 2/3</td>
<td>NCT02154490</td>
<td>Lung-MAP (squamous cell lung CA)</td>
</tr>
<tr>
<td>LY2874455</td>
<td>Phase 1</td>
<td>NCT01212107</td>
<td>Advanced cancers</td>
</tr>
<tr>
<td>JNJ-42756493</td>
<td>Phase 1</td>
<td>NCT01703481</td>
<td>Advanced solid tumors, lymphoma</td>
</tr>
<tr>
<td></td>
<td>Phase 2</td>
<td>NCT02365597</td>
<td>Advanced urothelial cancer</td>
</tr>
<tr>
<td>TAS-120</td>
<td>Phase 1/2</td>
<td>NCT02052778</td>
<td>Advanced solid tumors, MM</td>
</tr>
<tr>
<td>Debio 1347</td>
<td>Phase 1</td>
<td>NCT01948297</td>
<td>Advanced solid tumors</td>
</tr>
</tbody>
</table>
GROWING NUMBER OF “DRUGABLE” TARGETS & NON-INVASIVE WAYS TO UNDERSTAND DRUG RESISTANCE
Tracking Resistance

Monitoring the emergence of resistant mutations in KRAS WT patients treated with EGFR blockade

Tracking Resistance

Interrogated all exons of KRAS, NRAS, BRAF, PIK3CA and EGFR

96% of cases had at least 1 mutation KRAS or NRAS

IMMUNOTHERAPY
## RECENT FDA IMMUNOTHERAPY APPROVALS

<table>
<thead>
<tr>
<th>Approved Agent</th>
<th>Target</th>
<th>Indication</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA4</td>
<td>Melanoma</td>
<td>Mar 25, 2011</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD1</td>
<td>Melanoma</td>
<td>Sep 4, 2014</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>BiTE T cell/CD19</td>
<td>B cell ALL</td>
<td>Dec 3, 2014</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>Melanoma</td>
<td>Dec 22, 2014</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>Squamous NSCLC</td>
<td>Mar 4, 2015</td>
</tr>
<tr>
<td><strong>Ipilimumab/Nivolumab</strong></td>
<td><strong>CTLA4/PD1</strong></td>
<td><strong>Untreated Melanoma</strong></td>
<td><strong>Oct 1, 2015</strong></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD1</td>
<td>NSCLC</td>
<td>Oct 2, 2015</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>Nonsquamous NSCLC</td>
<td>Oct 9, 2015</td>
</tr>
<tr>
<td>Talimogene laherparepvec</td>
<td>Oncolytic virus</td>
<td>Melanoma</td>
<td>Oct 27, 2015</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA4</td>
<td>Adjuvant Melanoma</td>
<td>Oct 28, 2015</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>Renal Cell; 1&lt;sup&gt;st&lt;/sup&gt; line Melanoma</td>
<td>Nov 23, 2015</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line Melanoma</td>
<td>Dec 18, 2015</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD1</td>
<td>Hodgkin Lymphoma</td>
<td>May 17, 2016</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PDL1</td>
<td>Urothelial Carcinoma</td>
<td>May 18, 2016</td>
</tr>
</tbody>
</table>
Tumors Somatic Mutations Landscape
The Cancer Genome Atlas (TCGA)

Lawrence et al., Nature, 2013

Presented By Ignacio Wistuba at 2016 ASCO Annual Meeting
### Table 3. Mutational Load in Mismatch Repair-Deficient Versus Mismatch Repair-Proficient Colorectal Tumors as Assessed by Next-Generation Sequencing Assay

<table>
<thead>
<tr>
<th>MMR Status</th>
<th>341-Gene Panel</th>
<th>410-Gene Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size</td>
<td>Median Mutational Load (range)</td>
</tr>
<tr>
<td>MMR-proficient; POLE wild-type</td>
<td>193</td>
<td>6 (0-17)</td>
</tr>
<tr>
<td>MMR-deficient</td>
<td>28</td>
<td>50 (20-90)</td>
</tr>
<tr>
<td>MMR, mismatch repair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stadler et al JCO 2016
1. Insufficient number of T cells are generated within the lymphoid compartment.

2. Insufficient number of T cells extravasate into the tumor.

3. T cells are inhibited in the tumor microenvironment.

AGONIST ANTIBODIES ON THE ACTIVATING T CELL RECEPTORS

Presented By Howard Burris at 2016 ASCO Annual Meeting
Genetic and Tumor Microenvironment Heterogeneity Pose Challenges

Metastasis 1 vs Metastasis 2

- **Treatment-Naïve**
  - Metastasis 1: 459 Mutations
  - Metastasis 2: 530 Mutations
  - Percentages:
    - Metastasis 1: 28% (5%), 431% (77%), 99% (18%)
    - Metastasis 2: 522% (36%), 422% (29%), 521% (35%)

- **Post-anti-PD-1**

Reuben et al, Wargo Lab, AACR Poster #2392, AACR 2016

Presented by: Alexandra Snyder, M.D.

Presented By Alexandra Snyder Charen at 2016 ASCO Annual Meeting
NEWS IN BILIARY TRACT
Slide 4

Presented By Mary Mulcahy at 2016 ASCO Annual Meeting

Nakamura, Nature Genetics, vol 47, No 9, Sept 2015
NEWS IN GYNAECOLOGY
Genotype-Matched Trials

All received an inhibitor targeting the RAF-MEK or PIK3CA-mTOR-AKT network
- PR in 8 of 27 evaluable (30%):
  - all 8 were KRAS or PIK3CA mut
  - 5 of 8 (63%) received combination PIK3i/AKTi

Combination targeted therapy: PR in 4 of 8 (50%)

Reduction in tumour volume (n=21 out of 27 evaluable):
- 11 of 21 (53%) received combination therapy

Low grade cancers – 13 cases
- PR in 4 of 13 (31%), 8 SD, 0 PD
  - of 4 PR, 2 MEKi, 2 combination PIK3i/AKTi

Non-low grade cancers – 14 cases
- Reduction – all KRAS or NRAS mu, 1 BRAF mu,
- PR in 4 of 14 (29%), 4 SD, 6 PD
TARGETED VERSUS NON-TARGETED?
Tissue Biopsies and Genomic Testing in Cancer: Clinical Trials Experience

MD Anderson Phase I: retrospective, non-randomized
- 1,144 patients with any tumor type
- 460 (40%) had 1 or more aberration (multiplex panel of gene mutations)
- 175 (7%) with at least 1 alteration compared 116 without alterations

SHIVA: open-label, proof-of-concept, randomised, controlled, phase 2
- 741 patients with any tumor type
- 193 (40%) had at least one molecular alteration (NGS panel, IHC/FISH)
- 195 (26%) randomly assigned: 99 experimental (10 regimens) and 92 control groups

\[ P = 0.41 \]
Molecularly targeted

\[ P = 0.017 \]
Matched

Nonmatched


Christophe Le Tourneau et al, Lancet Oncol. 2015 Oct;16(13):1324-34

Presented By Ignacio Wistuba at 2016 ASCO Annual Meeting
Lung Cancer Mutation Consortium-1 (LCMC-1)

1,000 Adenocarcinomas
13 US Institutions

Mutations (8 genes/115 Assays)
Sequenom™ and Snap Shot™
- AKT1
- BRAF
- EGFR
- HER2
- KRAS
- MEK1
- NRAS
- PIK3CA

FISH (2 genes)
- MET amplification
- EML4-LK fusion

P < 0.0001

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Median Survival Yrs. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driver, no targeted therapy (A)</td>
<td>318</td>
<td>2.4 (1.9-2.9)</td>
</tr>
<tr>
<td>Driver, targeted therapy (B)</td>
<td>260</td>
<td>3.6 (3.1-4.5)</td>
</tr>
<tr>
<td>No driver (C)</td>
<td>360</td>
<td>2.2 (1.8-2.5)</td>
</tr>
</tbody>
</table>

M Kris et al., JAMA, 2014

Presented By Ignacio Wistuba at 2016 ASCO Annual Meeting
A BIT OF PHYLOSOPHERICAL THINKING...
Combination Chemotherapy

1 cm³ Tumor = 10⁹ Cells

Tumor Burden in Most Cancer Patients = 10¹⁰-10¹² Cells

Assume 1/1,000,000 Cells Resistant to Any One Drug

Then:

Chance of Cure with Single Agent is Approximately ZERO

However:

Probability of Any One Cell Being Resistant to 3 Non-Cross Resistant Drugs is 10⁻⁶ x 10⁻⁶ x 10⁻⁶ = 10⁻¹⁸
Curative therapies against ALL, AML, Hodgkin’s lymphoma, NHL and germ-cell tumours relied on drug combinations!
Wouldn’t be naive to expect high efficacy in advanced cancers with monotherapy?