Personalised Healthcare (PHC) with Foundation Medicine (FMI)

Fatma Elçin KINIKLI,

FMI Turkey, Science Leader

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Agenda

- **PHC Approach Provides Better Patient Outcome**
- **FMI offers Comprehensive Genomic Profiling, providing patients with more and personalised therapeutic options to improve outcomes**

1. Foundation Medicine, Inc. (2017) https://www.foundationmedicine.com/ Accessed Feb 2017; 2. Schwaederle, M., et al. (2015) Mol Cancer Ther. 14(6):1488-94; 3. Wheler, J., et al. (2016) Cancer Research 76(13): 3690-701; 4. Rozenblum, A.B., et al. (2017) J Thorac Oncol. 12(2):258-68; 5. Drilon, A., et al. (2015) Clin Cancer Res. 21(16):3631-9. 6. Kris MG et al. (2014) JAMA 311(19):1998-2006. 7. Barlesi F et al. (2016) Lancet S0140-6736(16)

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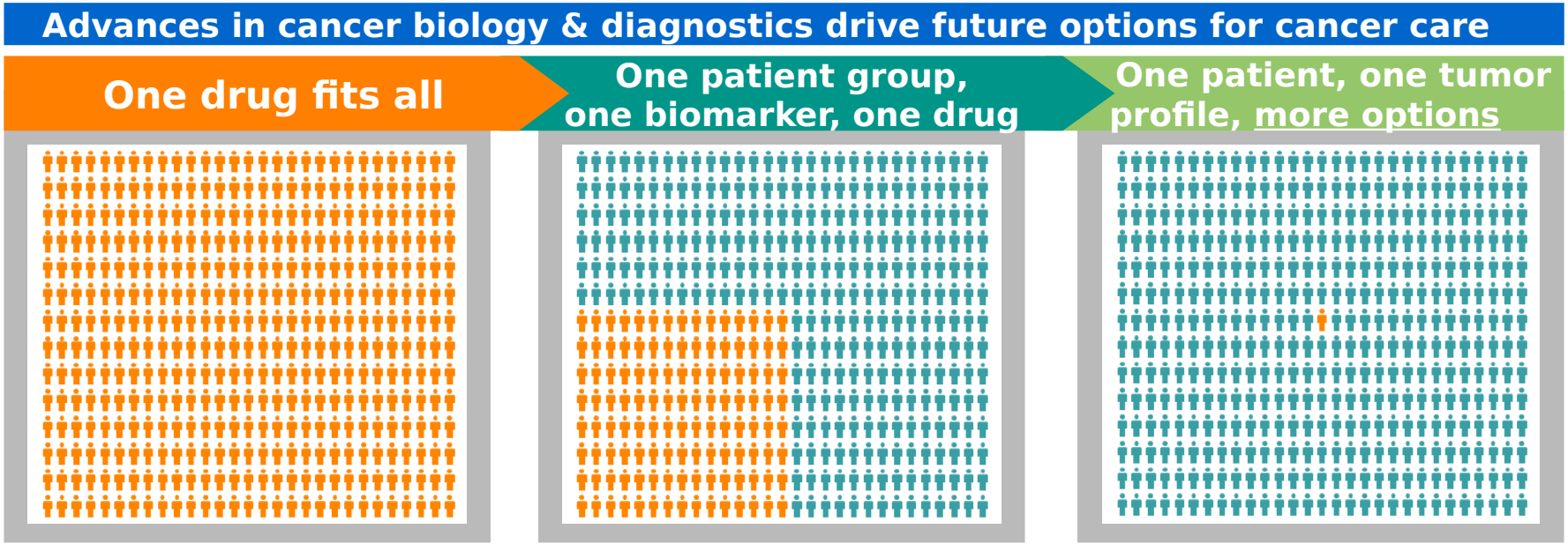
The genetic complexity of cancer

Cancer care becoming more personalised by understanding disease biology



1. Agyeman, A.A. and Ofori-Asenso, R. (2015) *J Pharm Bioallied Sci* 7(3):239–244;
2. Schwaederle, M. and Kurzrock, R. (2015) *Oncoscience* 2(10):779-80.

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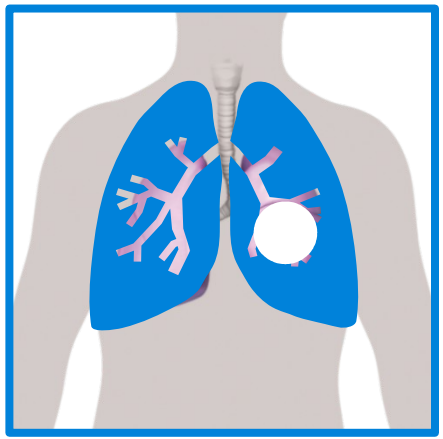
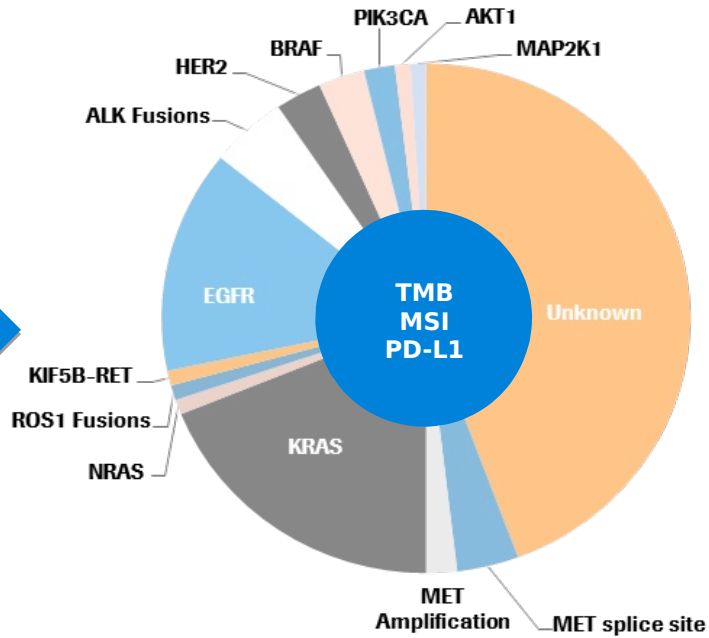
Cancer care is increasingly complex





2000 **2015**

Modified and updated from Pao W and Hutchinson KE (2012) Nat. Med. 18:349-351
NSCLC NCCN Guidelines Version 2.2017

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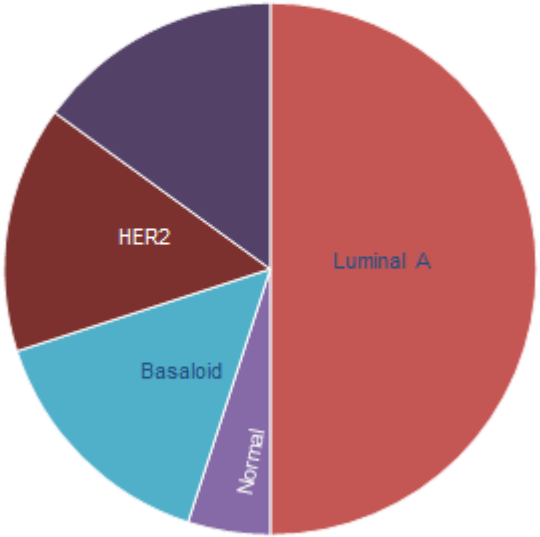
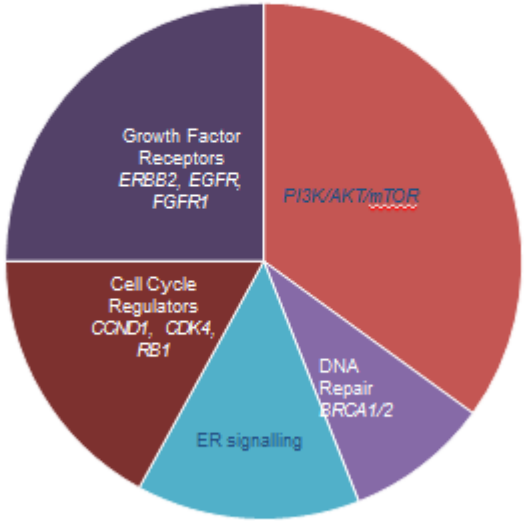
The classical approach to cancer is evolving

2000: Breast cancer subtypes



Clinical decisions based on **affected tissue, histology** and **disease stage**

2017: Genomic drivers



Clinical decisions based on the **results of comprehensive genomic profiling**

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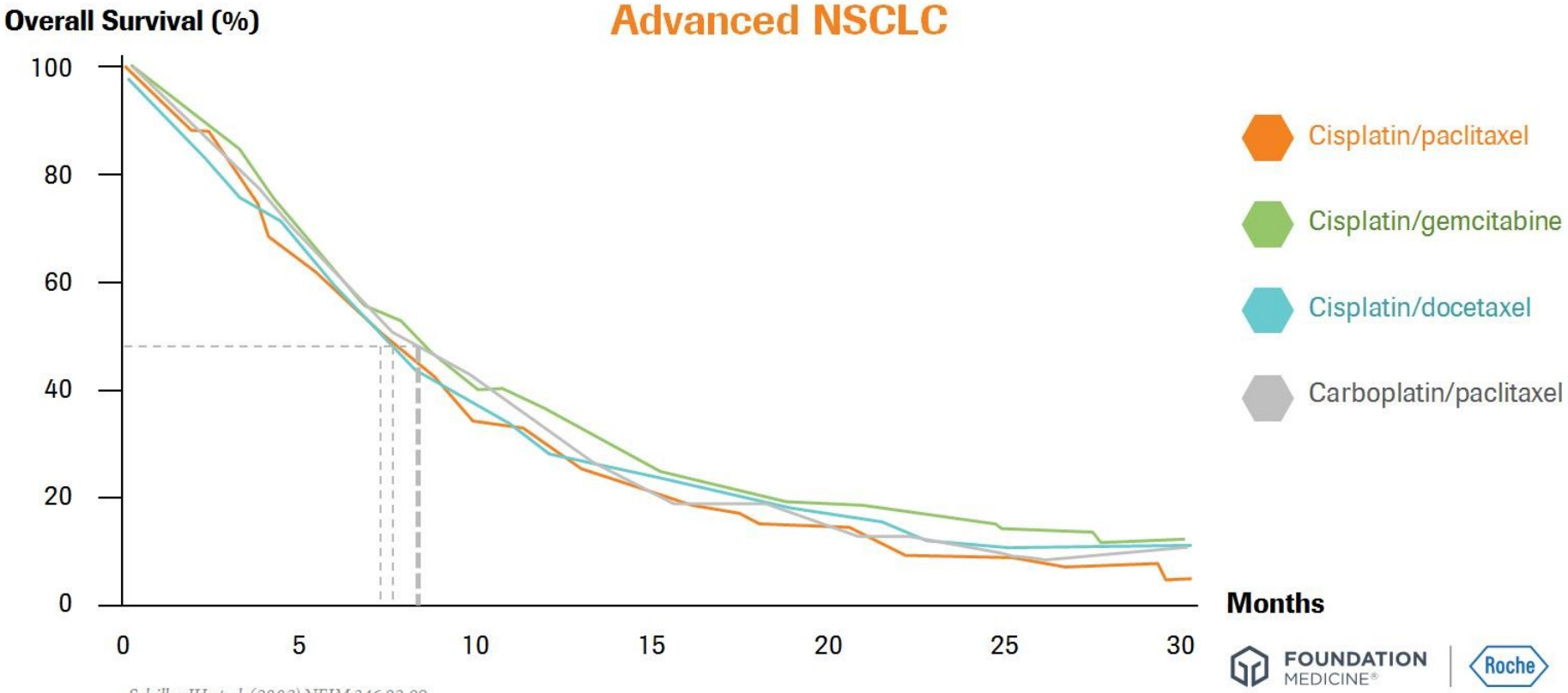
Unmet need in lung cancer

Negligible difference between chemotherapy regimens



Schiller JH et al. (2002) NEJM 346:92-98

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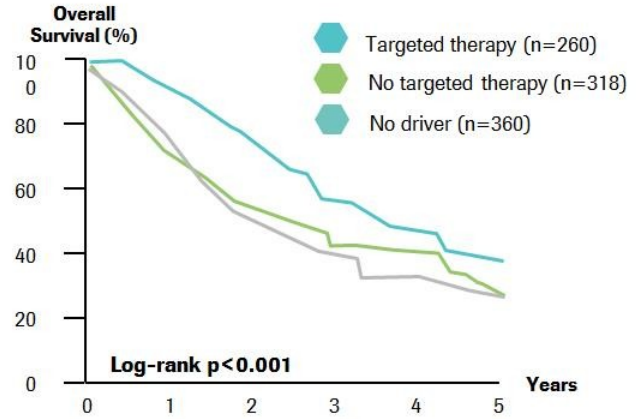
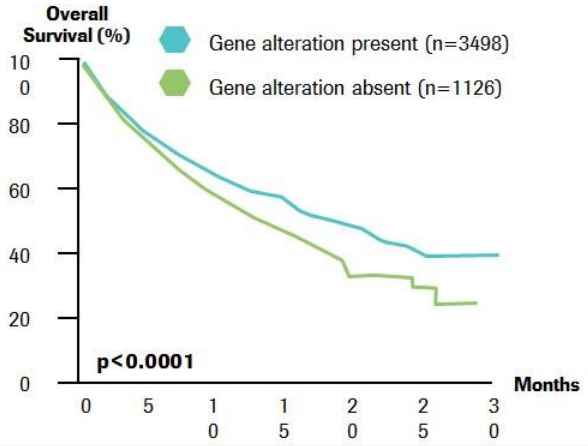
Profiling has been shown to improve outcomes in lung cancer patients

Metastatic lung adenocarcinoma patients



- **Biomarkers associated with targeted therapies in guidelines:** HER2, EGFR, ALK, BRAF, MET
- **Biomarkers not associated with targeted therapies in guidelines:** PIK3CA, MEK, AKT1, KRAS, NRAS

Advanced NSCLC patients



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- **Biomarkers not associated with targeted therapies in guidelines:** PIK3CA, KRAS

Kris MG et al. (2014) JAMA 311(19):1998-2006
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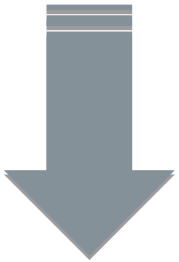
Meta analysis of ~85,000 patients in Phase I, II and III trials

Targeted therapy in of itself is not generally effective – a biomarker is needed

Worst outcome



Best outcome

	Pooled Analysis			Meta-analysis		
ARMS type	RR (%)	PFS (Mos)	OS (Mos)	RR (%)	PFS (Mos)	OS (Mos)
Non-personalized targeted	4	2.6	8.7	7.5	2.5	8.3
Cytotoxic	12	3.3	9.4	16.1	3.3	9.3
Personalized targeted	30	6.9	15.9	31.3	6.1	13.7

Schwaederle, M., et al. (2015) *J Clin Oncol.* 33(32):3817-25; Jardim, D.L., et al. (2015) *JNCI.* 107(11):djv253; Schwaederle, M., et al. (2016) *JAMA Oncol.* 2(11):1452-59.

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Roche and Foundation Medicine Inc. (FMI)

Entered into a broad strategic collaboration in 2015

The strategic collaboration aims to further advance **FMI's leading position in molecular information** and **analysis** while **providing Roche** a unique **opportunity to identify and develop novel treatment options** for **patients**

Foundation Medicine is a **molecular information company leading a transformation in cancer care**, where each patient's treatment is informed by a **deep understanding** of the **molecular changes** that contribute to their disease.

Roche media release, Basel, 12 January 2015. Access: http://www.roche.com/media/store/releases/med-cor-2015-01-12.htm

Foundation Medicine's comprehensive genomic profiling approach

Data aggregation and analysis

Scientific/clinical expert review

A report connecting patients to targeted therapies

FMI is taking patients from comprehensive identification of gene alterations to more personalised therapies and improved outcomes

FMI: Foundation Medicine, Inc.; NGS: next-generation sequencing.

Foundation Medicine, Inc. (2017) https://www.foundationmedicine.com/ Accessed Feb 2017; Foundation Medicine, Inc. Patient report.

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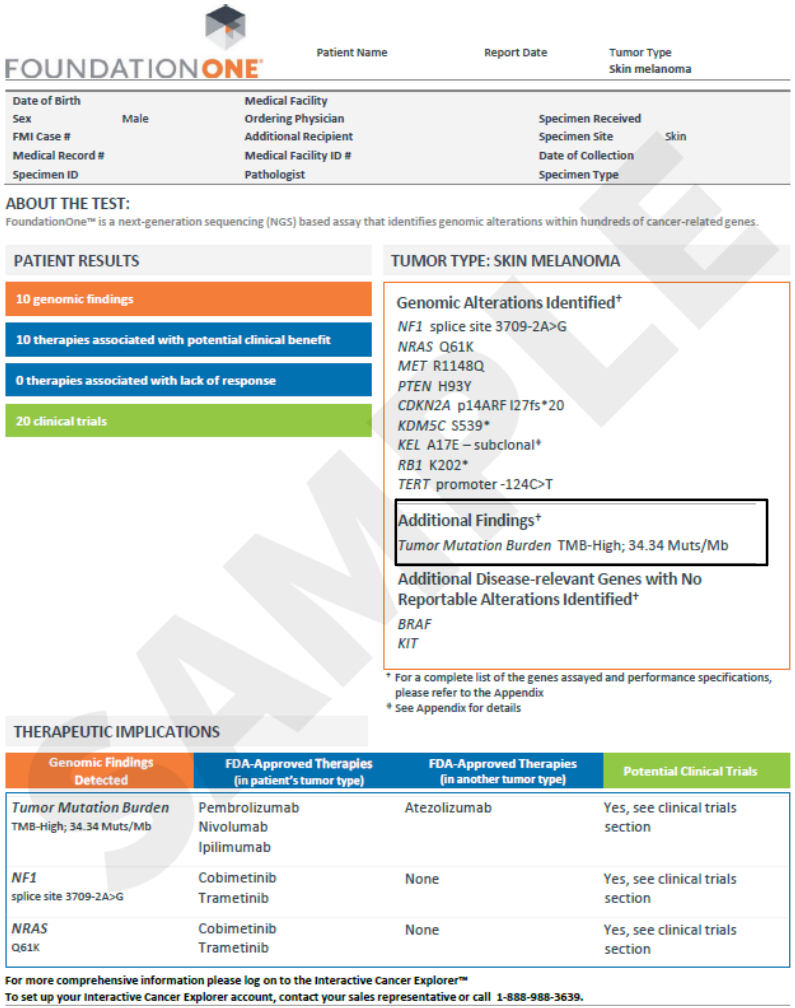
First page of the FoundationOne® Report

MSI & TMB



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Patient Name | Report Date | Tumor Type: Skin melanoma

Date of Birth		Medical Facility	
Sex	Male	Ordering Physician	Specimen Received
FMI Case #		Additional Recipient	Specimen Site: Skin
Medical Record #		Medical Facility ID #	Date of Collection
Specimen ID		Pathologist	Specimen Type

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

- 10 genomic findings
- 10 therapies associated with potential clinical benefit
- 0 therapies associated with lack of response
- 20 clinical trials

TUMOR TYPE: SKIN MELANOMA

Genomic Alterations Identified†

NF1 splice site 3709-2A>G
NRAS Q61K
MET R1148Q
PTEN H93Y
CDKN2A p14ARF I27fs*20
KDM5C S539*
KEL A17E – subclonal*
RB1 K202*
TERT promoter -124C>T

Additional Findings†

Tumor Mutation Burden TMB-High; 34.34 Muts/Mb

Additional Disease-relevant Genes with No Reportable Alterations Identified†

BRAF
KIT

* For a complete list of the genes assayed and performance specifications, please refer to the Appendix
† See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
Tumor Mutation Burden TMB-High; 34.34 Muts/Mb	Pembrolizumab Nivolumab Ipilimumab	Atezolizumab	Yes, see clinical trials section
NF1 splice site 3709-2A>G	Cobimetinib Trametinib	None	Yes, see clinical trials section
NRAS Q61K	Cobimetinib Trametinib	None	Yes, see clinical trials section

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SAMPLE

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Foundation Medicine, Inc. (2017) https://www.foundationmedicine.com/ Accessed Feb 2017; Foundation Medicine, Inc. Patient report.

Section on identified genomic alterations

The GENOMIC ALTERATIONS section contains a detailed interpretive statement that references:

- Each **gene** and its alteration(s)
- **Frequency** of each genomic alteration(s) identified in patient cohorts with similar tumor type
- **Prognosis** and biological implication of each genomic alteration(s)
- Potential **treatment strategies** specific for each genomic alteration

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Patient Name	Report Date	Tumor Type
Not Given	30 August 2014	Lung adenocarcinoma

GENOMIC ALTERATIONS

GENE ALTERATION	INTERPRETATION
MET exon 14 splice site (3028+2T>A)	**Gene and Alteration:** MET, also known as hepatocyte growth factor receptor (HGFR) or c-MET, encodes a receptor tyrosine kinase that is activated by the ligand HGF; MET activation results in signaling mediated in part through the RAS-RAF-MEK and PI3K pathways to promote proliferation[1]. MET alterations predicted to affect exon 14 splicing, such as seen here, have been reported in 1-4% of lung tumors[2,4,4,5,6] and have been associated with skipping of exon 14[2,7,8,9]. Loss of exon 14 increases MET stability, leading to prolonged signaling upon HGF stimulation and increased oncogenic potential[7,10,11,12,13]. This mutation is therefore expected to be activating. Responses to various MET inhibitors have been reported for multiple patients with alterations in their tumors predicted to affect splicing of MET exon 14 [2,9,14,15,16]. **Frequency and Prognosis:** In one study of 4402 lung adenocarcinoma cases, MET mutations (primarily those affecting MET exon 14 splicing) have been reported in ~3% of samples[2]. In the TCGA datasets, MET mutation has been observed in 8.3% of lung adenocarcinomas and 2.1% of lung squamous cell carcinomas[3,17]. MET amplification has been reported at incidences of 14-48% in NSCLC and correlated with increased MET protein expression[18,19,20,21,22,23]. Studies into the effect of MET amplification on prognosis for patients with NSCLC have yielded conflicting results[18,22,24,25,26]. One study observed an association between MET amplification and increased long-term survival for patients with lung adenocarcinoma, although concurrent MET amplification and EGFR mutation have been correlated with reduced disease-free survival[27,28]. **Potential Treatment Strategies:** MET amplification or activating mutations may predict sensitivity to targeted therapies[29] such as the kinase inhibitors crizotinib and cabozantinib. Crizotinib is FDA approved for the treatment of ALK-positive NSCLC[30]. Cabozantinib is FDA approved for the treatment of metastatic medullary thyroid cancer[31], and a patient with a MET amplification and a mutation associated with MET exon 14 skipping has achieved a complete response to cabozantinib[9]. Crizotinib has benefited patients with MET-amplified NSCLC[32], lung squamous cell carcinoma[33], lung adenocarcinoma[34], gastroesophageal cancer[35], glioblastoma[36], and carcinoma of unknown primary[37]. In one clinical trial, treatment with AMG 337 led to a response rate of 50% (5/10), including 1 complete response, for patients with MET-amplified gastric, esophageal, or gastroesophageal junction cancer (Kwak et al., 2015; ASCO GI Abstract 01). MET-targeting antibodies onartuzumab and MetMAb have elicited responses in patients with MET-amplified NSCLC[38] and gastric cancer[39]. In addition, high MET expression has been suggested to predict patient response to therapy regimens involving rilotumumab, a monoclonal HGF-targeting antibody (Oliner et al., 2012; ASCO Abstract 4005). Furthermore, MET inhibitors crizotinib, capmatinib, PF-04217903, and foretinib have provided benefit to patients with MET-mutated papillary renal cell carcinoma[29,40,41], histiocytic sarcoma[2], lung adenocarcinoma[9,14,15], lung large cell carcinoma[2], and lung squamous cell carcinoma[2,16].
CDKN2A/B loss	**Gene and Alteration:** CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[42,43]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, maintaining the growth-suppressive activity of the RB tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin D-RB pathway and loss of cell cycle control[44,45]. The p14ARF tumor-suppressive functions

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THERAPEUTIC IMPLICATIONS

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
CCND1 amplification	None	Palbociclib Ribociclib	Yes, see clinical trials section
PIK3CB amplification	None	None	Yes, see clinical trials section
EMSY amplification	None	None	None
FGF19 amplification	None	None	
FGF3 amplification	None	None	

● ***PIK3CB*** amplification

Gene and Alteration: PIK3CB (PI3K-beta, p110-beta) encodes a member of the class IA phosphoinositide 3-kinases (PIK3CA, PIK3CB, PIK3CD, and PIK3CG), which are essential regulators of cellular proliferation, survival, metabolism and motility. Dysregulation of the PI3K signaling pathway is observed in many human cancers and occurs most frequently through loss of the tumor suppressor PTEN or activating mutations in PIK3CA (p110-alpha). Contrary to PIK3CA, which is frequently mutated within hot spots causing increased kinase activity, mutation of PIK3CB is quite rare[20,21,22]. PIK3CB amplification has been identified in various tumor types[9,23,24], and PIK3CB overexpression has been shown to be oncogenic in vitro[25]. A patient with PTEN-deficient prostate cancer and PIK3CB amplification had a partial response to the PI3K-beta-selective inhibitor GSK2636771 (de Bono et al., 2015; AACR Abstract CT328).

Frequency and Prognosis: PIK3CB mutation has been reported in up to 1% of prostate adenocarcinoma cases, while amplification has been found in up to 2% of samples analyzed[5,26]. A constitutively active form of p110-beta induces prostatic intraepithelial neoplasia in a murine prostate tumor model[27]. In addition, inactivation of p110-beta, but not p110-alpha, was shown to inhibit prostate cancer development in a mouse model drive by PTEN heterozygous deletion[28].

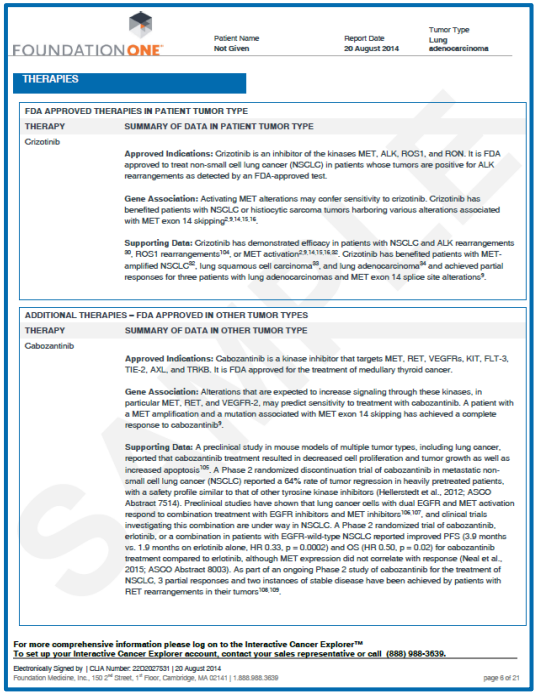
Potential Treatment Strategies: Preclinical evidence indicates that PTEN-deficient tumors depend on PI3K-beta[29,30,31], and inhibitors selective for PI3K-beta, including GSK2636771 and AZD8186, are in clinical trials for PTEN-deficient tumors (Arkenau et al., 2014; ASCO Abstract 2514, Siu et al., 2015; AACR Abstract CT329). PIK3CB activating alterations may further refine the use of PI3K-beta-selective inhibitors[22]. Whereas two patients with PTEN-deficient prostate tumors and concurrent PIK3CB L1049R mutation or PIK3CB amplification derived significant clinical benefit with GSK2636771 (de Bono et al., 2015; AACR Abstract CT328), PIK3CB D1067 mutations rendered PTEN-deficient breast cancer cells less sensitive to pan-PI3K or PI3K-beta-selective inhibitors in preclinical assays[32].

Section on possible treatments

The THERAPIES section provides further details on:

- **Approved therapies** to which the patient's tumor type may be sensitive or resistant based on genomic profile
- Approved therapies associated with benefit based on similar genomic alterations in **other tumor types***

With information on approved indications, gene association and supporting data



FOUNDATIONONE

Patient Name: Not Given
Report Date: 20 August 2014
Tumor Type: Lung adenocarcinoma

THERAPIES

FDA APPROVED THERAPIES IN PATIENT TUMOR TYPE

THERAPY	SUMMARY OF DATA IN PATIENT TUMOR TYPE
Crizotinib	**Approved Indications:** Crizotinib is an inhibitor of the kinases MET, ALK, ROS1, and RON. It is FDA approved to treat non-small cell lung cancer (NSCLC) in patients whose tumors are positive for ALK rearrangements as detected by an FDA-approved test. **Gene Association:** Activating MET alterations may confer sensitivity to crizotinib. Crizotinib has benefited patients with NSCLC or histiocytic sarcoma tumors harboring various alterations associated with MET exon 14 skipping[2,9,14,15,16]. **Supporting Data:** Crizotinib has demonstrated efficacy in patients with NSCLC and ALK rearrangements [30], ROS1 rearrangements[104], or MET activation[2,9,14,15,16,32]. Crizotinib has benefited patients with MET-amplified NSCLC[32], lung squamous cell carcinoma[33], and lung adenocarcinoma[34] and achieved partial responses for three patients with lung adenocarcinomas and MET exon 14 splice site alterations[9].

ADDITIONAL THERAPIES – FDA APPROVED IN OTHER TUMOR TYPES

THERAPY	SUMMARY OF DATA IN OTHER TUMOR TYPE
Cabozantinib	**Approved Indications:** Cabozantinib is a kinase inhibitor that targets MET, RET, VEGFRs, KIT, FLT-3, TIE-2, AXL, and TRKB. It is FDA approved for the treatment of medullary thyroid cancer. **Gene Association:** Alterations that are expected to increase signaling through these kinases, in particular MET, RET, and VEGFR-2, may predict sensitivity to treatment with cabozantinib. A patient with a MET amplification and a mutation associated with MET exon 14 skipping has achieved a complete response to cabozantinib[9]. **Supporting Data:** A preclinical study in mouse models of multiple tumor types, including lung cancer, reported that cabozantinib treatment resulted in decreased cell proliferation and tumor growth as well as increased apoptosis[105]. A Phase 2 randomized discontinuation trial of cabozantinib in metastatic non-small cell lung cancer (NSCLC) reported a 64% rate of tumor regression in heavily pretreated patients, with a safety profile similar to that of other tyrosine kinase inhibitors (Hellerstedt et al., 2012; ASCO Abstract 7514). Preclinical studies have shown that lung cancer cells with dual EGFR and MET activation respond to combination treatment with EGFR inhibitors and MET inhibitors[106,107], and clinical trials investigating this combination are under way in NSCLC. A Phase 2 randomized trial of cabozantinib, erlotinib, or a combination in patients with EGFR-wild-type NSCLC reported improved PFS (3.9 months vs. 1.9 months on erlotinib alone, HR 0.33, p = 0.0002) and OS (HR 0.50, p = 0.02) for cabozantinib treatment compared to erlotinib, although MET expression did not correlate with response (Neal et al., 2015; ASCO Abstract 8003). As part of an ongoing Phase 2 study of cabozantinib for the treatment of NSCLC, 3 partial responses and two instances of stable disease have been achieved by patients with RET rearrangements in their tumors[108,109].

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* IMPORTANT: this does **not** indicate evidence for off-label use in patient's tumor type

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Section on clinical trials to consider

The CLINICAL TRIALS TO CONSIDER section of the report provides:

- **Rationale** for potential clinical trials
- Details on **keyword terms** used for search on clinicaltrials.gov for relevant clinical trials
- Details on currently available clinical trials for which the patient **may be eligible** based on the genomic profile of patient's tumor

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Patient Name	Report Date	Tumor Type
Not Given	20 August 2014	Lung adenocarcinoma

CLINICAL TRIALS TO CONSIDER

IMPORTANT: While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continuously updated and should be investigated by the physician or research staff. This is not meant to be a complete list of available trials. In order to conduct a more thorough search, please go to www.clinicaltrials.gov and use the search terms provided below. For more information about a specific clinical trial, type the NCT ID of the trial indicated below into the search bar.

GENE	RATIONALE FOR POTENTIAL CLINICAL TRIALS
MET exon 14 splice site (3028+2T>A)	MET amplification or activating mutations may confer sensitivity to therapies targeting this kinase. Examples of clinical trials that may be appropriate for this patient are listed below. These trials were identified through a search of the trial website clinicaltrials.gov using keyword terms such as "MET", "crizotinib", "cabozantinib", "NSCLC", "lung", "solid tumor", and/or "advanced cancer".

TITLE	PHASE	TARGETS	LOCATIONS	NCT ID
Phase 1 Safety, Pharmacokinetic And Pharmacodynamic Study Of PF-02341066, A c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally To Patients With Advanced Cancer	Phase 1	MET	California, Colorado, Illinois, Massachusetts, Michigan, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Seoul (Korea, Republic of), Victoria (Australia)	NCT00585195
Phase I Study of INC280 Plus Erlotinib in Patients With C-Met Expressing Non-Small Cell Lung Cancer	Phase 1	MET, EGFR	California	NCT01911507
A Phase I Open-label Dose Escalation Study With Expansion to Assess the Safety and Tolerability of INC280 in Patients With c-MET Dependent Advanced Solid Tumors	Phase 1	MET	Arkansas, Illinois, Maryland, Michigan, New York, Tennessee, Texas, Utah, multiple ex-US locations	NCT01324479
Open-Label Dose-Escalation Trial to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Daily Oral MGCD265 Administered Without Interruption to Subjects With Advanced Malignancies	Phase 1	AXL, DDR2, EPH, FLT1, KDR, KIT, MET, PDGFRs, RET, TRK, VEGFRs	California, Illinois, Massachusetts, Missouri, New York, North Carolina, Pennsylvania, Texas, Utah, Washington, Alberta (Canada), British Columbia (Canada), Gyeonggi-do (Korea, Republic of), Quebec (Canada), Seoul (Korea, Republic of)	NCT00997632
A Phase II, Multicenter, Open-label Study of EGF816 in Combination With Nivolumab in Adult Patients With EGFR Mutated Non-small Cell Lung Cancer and of INC280 in Combination With Nivolumab in Adult Patients With cMet Positive Non-small Cell Lung Cancer	Phase 2	MET, EGFR, PD-1	Amsterdam (Netherlands), Chur (Switzerland), New South Wales (Australia), PG (Italy), PI (Italy), PN (Italy), Queensland (Australia), Singapore (Singapore), South Australia (Australia)	NCT02323126

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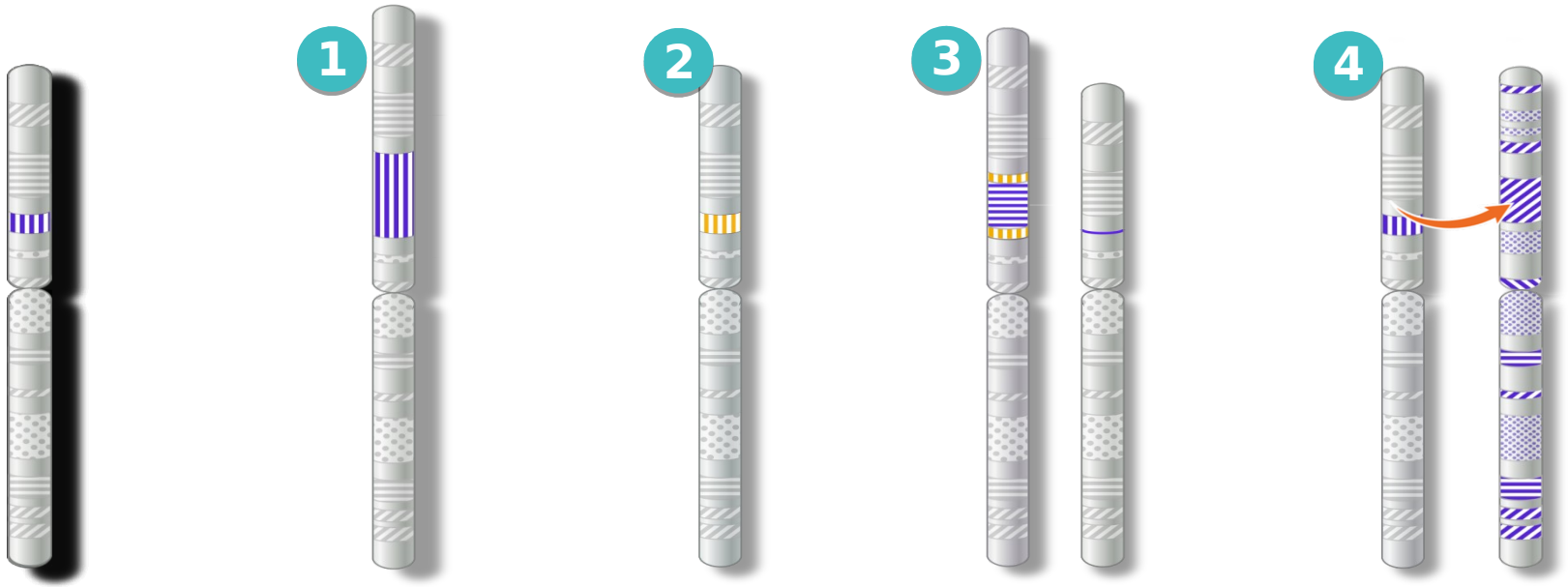
Four types of ways genes can be altered



Normal

Copy number Alterations

Substitutions

Insertions and deletions

Rearrangements

Suh J et al. (2016) Oncologist. http://dx.doi.org/10.1634/theoncologist.2016–0030.

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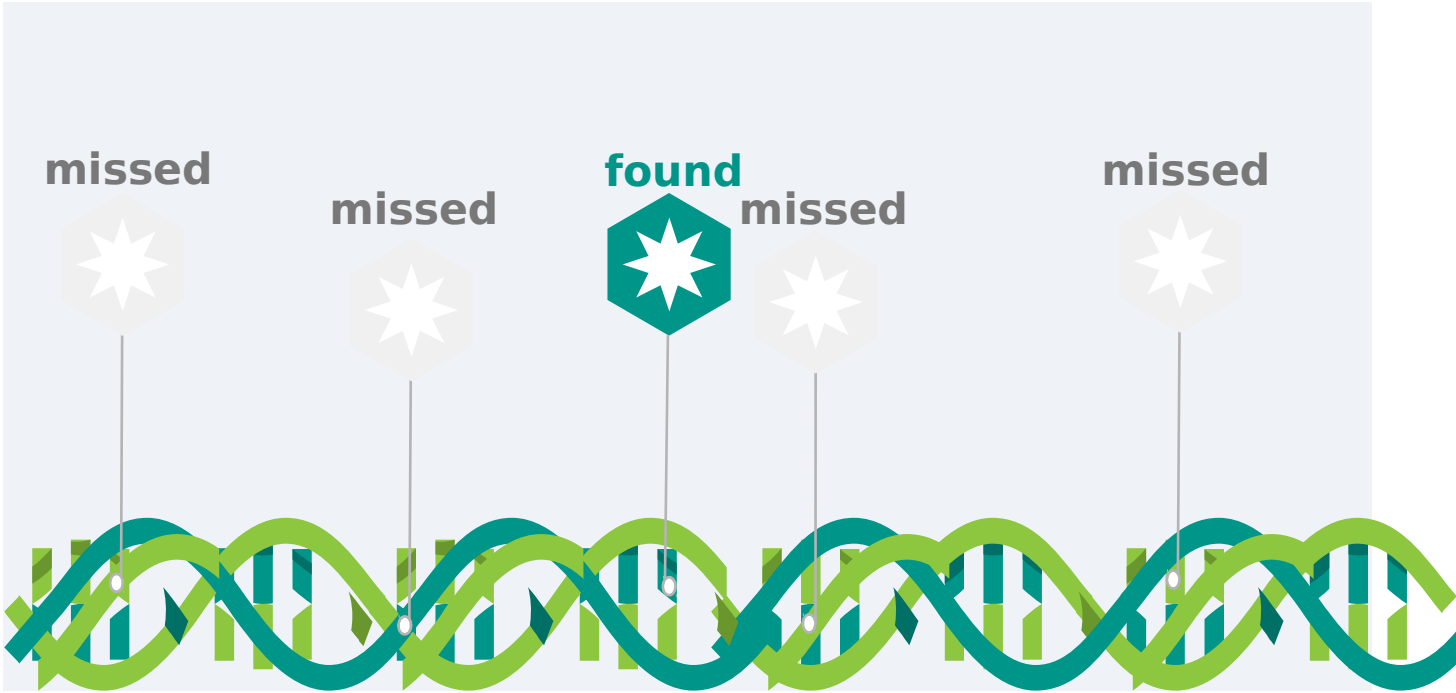
The most common type of molecular testing

CATEGORY **ONE**

Routine single marker molecular tests such as **IHC, PCR** and **FISH** that have been used for decades and will continue to play an important role in cancer diagnosis

CATEGORY **TWO**

CATEGORY **THREE**



FISH: fluorescence *in situ* hybridization; IHC: Immunohistochemistry; PCR: Polymerase chain reaction

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Frampton G et al. (2013) Nature Biotech 31, 1023-34

Multi-gene “hot spot” test

Broader testing focused on a narrow subset of genes

CATEGORY **ONE**

CATEGORY **TWO**

The **hot spot NGS** panels identify pre-specified mutations occurring in very limited areas of genes of interest and fail to detect all

CATEGORY **THREE**

NGS: Next-generation sequencing

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Frampton G et al. (2013) Nature Biotech 31, 1023-34

Foundation Medicine®

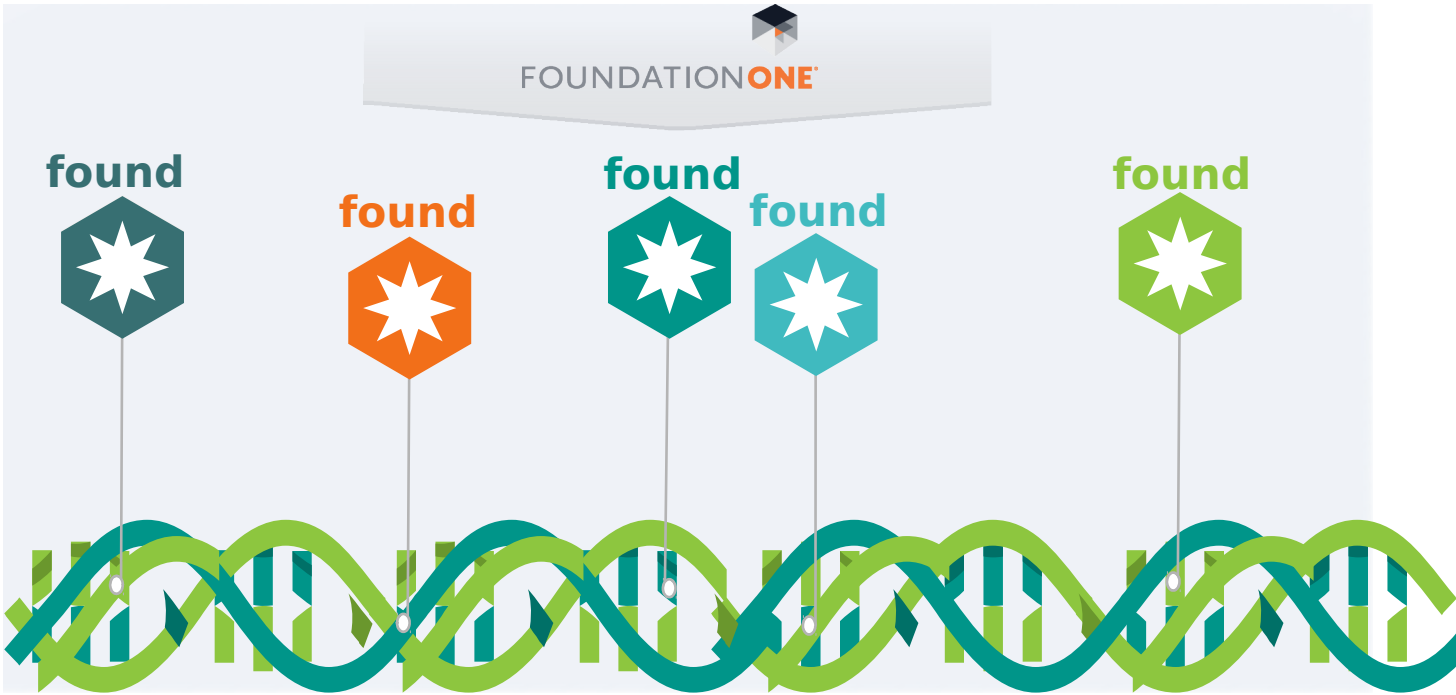
The most comprehensive genomic test available

CATEGORY **ONE**

CATEGORY **TWO**

CATEGORY **THREE**

FMI's **comprehensive genomic profiling** approach of testing all of the known clinically relevant cancer genes for **all**



FMI: Foundation Medicine, Inc.

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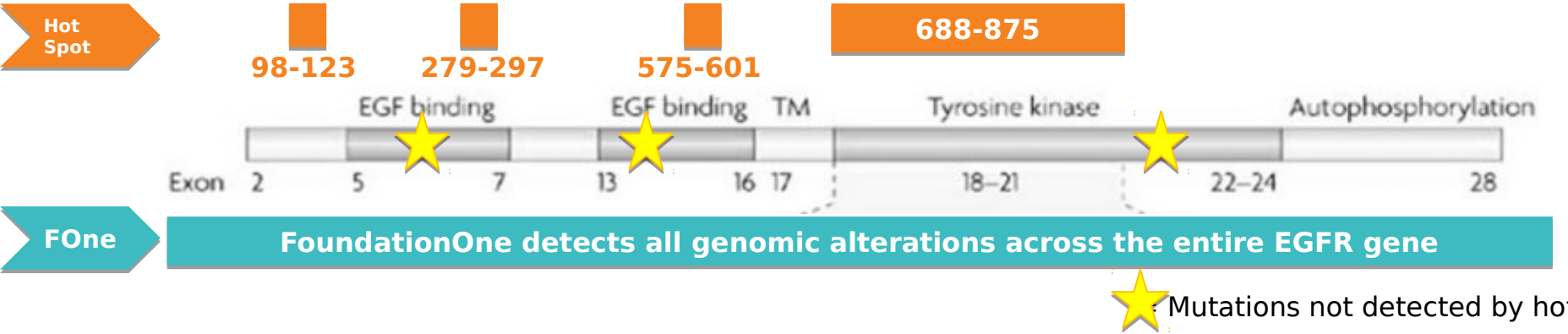
Frampton G et al. (2013) Nature Biotech 31, 1023-34

Two Different Targeted Sequencing Approaches

Comprehensive Genomic Profiling detects more than Hot Spot NGS

Example: EGFR gene

Hot spot tests detect selective alterations in selective parts of the EGFR gene*



Meric-Bernstam F et al. (2015) J Clin Oncol 33:2753-2762

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Agenda

1. Foundation Medicine, Inc. (2017) https://www.foundationmedicine.com/ Accessed Feb 2017; 2. Schwaederle, M., et al. (2015) *Mol Cancer Ther*. 14(6):1488-94; 3. Wheler, J., et al. (2016) *Cancer Research* 76(13): 3690-701; 4. Rozenblum, A.B., et al. (2017) *J Thorac Oncol.* 12(2):258-68; 5. Drilon, A., et al. (2015) *Clin Cancer Res.* 21(16):3631-9. 6. Kris MG et al. (2014) JAMA 311(19):1998-2006. 7. Barlesi F et al. (2016) Lancet S0140-6736(16)

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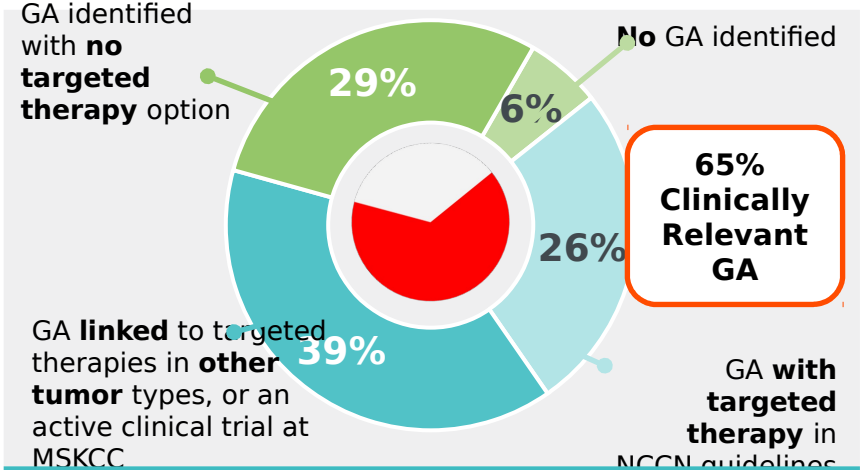
MSKCC experience with FoundationOne®
Supporting first-line use of CGP in lung cancer

Background

- **31** lung adenocarcinoma patients with available tissue specimen were identified
- Those patient's tumors harbored **no evidence of a genomic alteration** via extensive, focused non-NGS testing covering known lung cancer alterations in 11 genes (*EGFR, ERBB2, KRAS, NRAS, BRAF, MAP2K1, PIK3CA, AKT1, ALK*

Results

- FoundationOne® detected genomic alterations in **94% of patients with pan-negative lung adenocarcinoma**



These findings support the **first-line use** of CGP to detect the broadest range of genomic alterations in lung adenocarcinomas while **preserving tissue**

GA: Genomic Alteration

Drilon, A., *et al.* (2015) *Clin Cancer Res 21(16):3631-9.*

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Clinical utility of finding more alterations with FoundationOne®

NSCLC patients can benefit from targeted therapies

of EGFR exon 19 deletions missed by hotspot tests[1]

of NSCLC patients with EGFR exon 19 deletions can respond to EGFR tyrosine kinase inhibitors, with median OS > 1 year[2]

of ALK-rearranged cases missed by FISH[3]

of ALK-rearranged patients identified by FoundationOne respond to ALK inhibitor crizotinib[3]

1. Schrock AB et al. (2016) Clin Cancer Res. Mar 1.
2. Sequist LV et al. (2007) J Clin Oncol. 25:587–95.
3. Ali AM et al. (2016) The Oncologist

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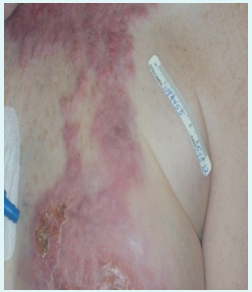
Patient Case

Patient Information

- 58-year-old female



Diagnosis

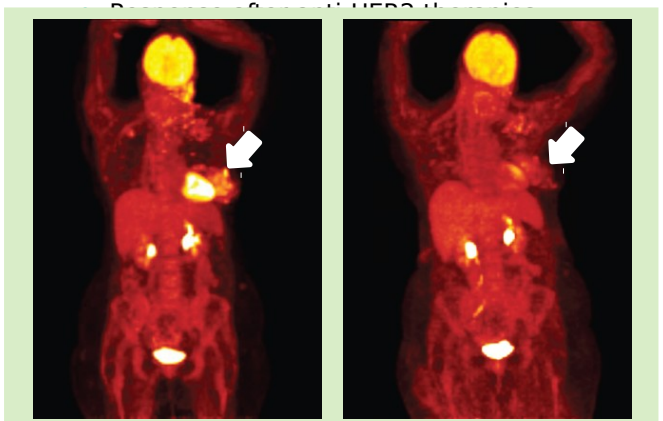
- Triple negative inflammatory breast cancer

Treatment status

- Refractory to taxanes, dasatinib, bevacizumab, ixabepilone and gemcitabine
- After progressive disease additional biomarker testing done and histology, ER/PR (by IHC) and HER2 (by FISH) confirmed as all negative

FoundationOne® analysis

- The same sample sent for CGP. HER2 was consistent with FISH, but **two distinct HER2 mutations** (V777L and S310F) found



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Ali SM et al. J Clin Oncol. 2014

Patient Case

Patient Information

- 43-year-old female

Diagnosis

- **Breast carcinoma**.
- **ER** positive, **PR** negative and **HER2 negative** by **FISH** and **IHC**.

Treatment status

After chemotheraphy peritoneal and omental metastases, a left adrenal mass and enlargement of liver metastatases are observed.

FoundationOne® analysis

The sample was found to have an ERBB2 L755S base substitution mutation and the tumors responded to neratinib

TABLE 2. Summary of Clinical Characteristics for 138 Breast Cancers With *ERBB2* Short-Variant Mutations

	NOS	IDC	ILC	MUC	
No. of cases	69	40	27	2	
Median age	61 y	60 y	58 y	58 y	
Average age	60.9 y	58.5 y	58 y	58 y	
Specimen site					Percentage of all *ERBB2* mut samples
Bone	0	1	0	0	0.7%
Breast	7	28	16	0	37%
Liver	18	5	3	0	18.8%
Lung	5	0	1	0	4.3%
Lymph node	14	2	3	1	14.5%
Other	24	5	4	1	24.6%

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Ross et al. (2016) Clin Cancer Res. Mar 1.

Patient Case

Patient Information

- 58-year-old female

Diagnosis

- **Metastasic inflamatory breast carcinoma**.
- **Triple negative** by **FISH** and **IHC**.

Treatment status

Patient was previously treated with multiple courses of cytotoxic chemotherapy. However disease remain active.

FoundationOne® analysis

2 distinct ERBB2mut, 1 each in the kinase domain (V777L) and the ECD (S310F). The patient received multiple anti-HER2 targeted therapies combined with chemotherapy and demonstrated substantial clinical response.

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Ross et al. (2016) Clin Cancer Res. Mar 1.

Patient Case

Patient Information

- 58-year-old female

Diagnosis

- **Breast carcinoma**.
- **ER** positive, **PR** positive and **HER2 negative** by **FISH** and **IHC**.
- With the treatment refractory hepatic metastasis.

FoundationOne® analysis

The sample was found to have ERBB2 S310F mutation and positive HER2.

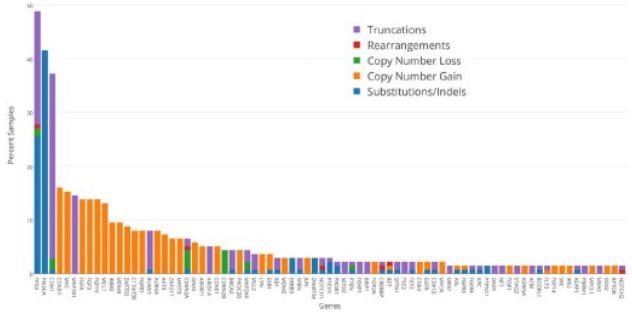

Figure 2. Long tail plot of genomic alterations in 138 cases of ERBB2-mutated recurrent metastatic breast cancer.

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Ross et al. (2016) Clin Cancer Res. Mar 1.

Agenda

1. Foundation Medicine, Inc. (2017) https://www.foundationmedicine.com/ Accessed Feb 2017; 2. Schwaederle, M., et al. (2015) *Mol Cancer Ther*. 14(6):1488-94; 3. Wheler, J., et al. (2016) *Cancer Research* 76(13): 3690-701; 4. Rozenblum, A.B., et al. (2017) *J Thorac Oncol.* 12(2):258-68; 5. Drilon, A., et al. (2015) *Clin Cancer Res.* 21(16):3631-9. 6. Kris MG et al. (2014) JAMA 311(19):1998-2006. 7. Barlesi F et al. (2016) Lancet S0140-6736(16)

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Analytic Validation

nature biotechnology

Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing

Garrett M Frampton[1,9], Alex Fichtenholtz[1,9], Geoff A Otto[1], Kai Wang[1], Sean R Downing[1], Jie He[1], Michael Schnall-Levin[1], Jared White[1], Eric M Sanford[1], Peter An[1], James Sun[1], Frank Juhn[1], Kristina Brennan[1], Kiel Iwanik[1], Ashley Maillet[1], Jamie Buell[1], Emily White[1], Mandy Zhao[1], Sohail Balasubramanian[1], Selmira Terzic[1], Tina Richards[1], Vera Banning[1], Lazaro Garcia[1], Kristen Mahoney[1], Zac Zwirko[1], Amy Donahue[1], Himisha Beltran[2,3], Juan Miguel Mosquera[3,4], Mark A Rubin[3,4], Snjezana Dogan[5], Cyrus V Hedvat[5], Michael F Berger[5], Lajos Pusztai[6], Matthias Lechner[7], Chris Boshoff[7], Mirna Jarosz[1], Christine Vietz[1], Alex Parker[1], Vincent A Miller[1], Jeffrey S Ross[1,8], John Curran[1], Maureen T Cronin[1], Philip J Stephens[1], Doron Lipson[1] & Roman Yelensky[1]

As more clinically relevant cancer genes are identified, comprehensive diagnostic approaches are needed to match patients to therapies, raising the challenge of optimization and analytical validation of assays that interrogate millions of bases of cancer genomes altered by multiple mechanisms. Here we describe a test based on massively parallel DNA sequencing to characterize base substitutions, short insertions and deletions (indels), copy number alterations and selected fusions across 287 cancer-related genes from routine formalin-fixed and paraffin-embedded (FFPE) clinical specimens. We implemented a practical validation strategy with reference samples of pooled cell lines that model key determinants of accuracy, including mutant allele frequency, indel length and amplitude of copy change. Test sensitivity achieved was 95–99% across alteration types, with high specificity (positive predictive value >99%). We confirmed accuracy using 249 FFPE cancer specimens characterized by established assays. Application of the test to 2,221 clinical cases revealed clinically actionable alterations in 76% of tumors, three times the number of actionable alterations detected by current diagnostic tests.

Base Substitutions
Sensitivity: >99.9% PPV: >99%

Insertions/Deletions
Sensitivity: 98% PPV: >99%

Copy Number Alterations
Sensitivity: >95% PPV: >99%

Gene Fusions[1]
Sensitivity: >95% PPV: >99%

(>99% for ALK fusion[2])

1. Based on analysis of coverage and re-arrangement structure in the COSMIC database for solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.
2. Yelensky et al, *Presented at AACR 2014*

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FoundationOne CDx : First Commercial Pan-tumour Comprehensive Genomic Profiling Assay Approved by FDA

- **First assay,** incorporating a broad range of **companion diagnostics**
- **17 targeted therapies** across five types of advanced cancers: non-small cell lung, melanoma, breast, colorectal and ovarian cancers
- Reports the genomic markers **MSI** and **TMB** to help inform decisions on **immunotherapy**

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Summary

Why consider profiling with Foundation Medicine?

- **Profiling has been shown to improve outcomes for patients**
- **Foundation Medicine's** profiling services are designed to **capture all four types of genomic alterations** and accurately identifies actionable targets across a spectrum of cancers
- These alterations are delivered in a **comprehensive report** which describes potential therapies, trials, and the latest clinical literature to inform physician's decisions
- Evidence has shown **FoundationOne® detects alterations in patients that are pan-negative with single gene panels,** and in some indications can improve outcomes

Profiling with FoundationOne® finds more clinically-relevant alterations and can lead to better patient outcomes

1. Kris MG et al. (2014). JAMA 311(19):1998-2006; 2. Barlesi F et al. (2016). Lancet S0140-6736(16); 3. Ganesan P et al. (2014) Mol Cancer Ther; 13(12); 3175–84; 4. Ali S et al. (2016) Oncologist. 5 Schrock AB et al. (2016) Clin Cancer Res. Mar 1. pii: clincanres.1668.2015; 6 Suh J et al. (2016) Oncologist; 7. Drilon A et al. (2015) Clin Cancer Res 21(16):3631-9; 8.

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Doing now what patients need next