International Academy of Pathology Hong Kong Division 2022 Scientific Congress

Novartis Sponsored Lecture: Precision Medicine in Breast Cancer: Where are we now?

Sunday December 11th

NOVARTIS | Reimagining Medicine

Agenda

Sunday December 11th 13:15-14:15 HKT

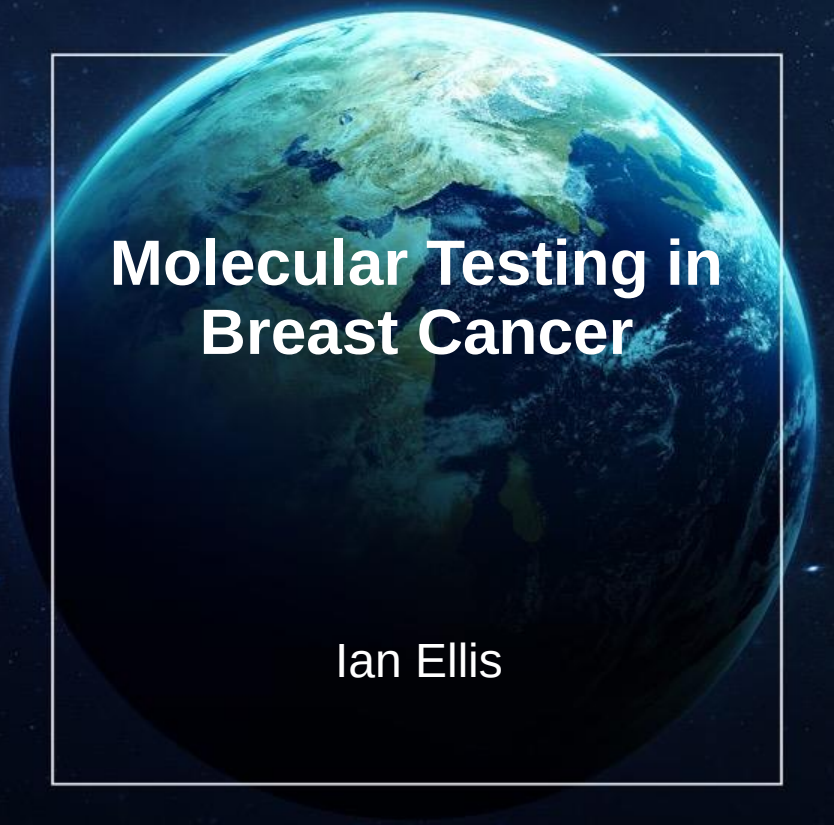
	Topic	Speaker
13:15 - 13:20	**Opening**	**Dr. Polly Cheung** Founder of Hong Kong Breast Cancer Foundation, HK
13:20 - 13:35	**Pathologist's Perspective:** Implications of Mutation Testing in Breast Cancer	**Prof. Ian Ellis** University of Nottingham, UK
13:35 - 13:50	**Clinician's Perspective:** Importance of Genetic Testing and Targeted Therapy in BreastCancer	**Dr. Roland Leung** Queen Mary Hospital, HK
13:50 - 14:10	**Precision Medicine in Breast Cancer:** Future Directions	Moderator: **Dr. Polly Cheung** Founder of Hong Kong Breast Cancer Foundation, HK Panelists: **Prof. Ian Ellis** University of Nottingham, UK **Dr. Roland Leung** Queen Mary Hospital, HK
14:10 - 14:15	**Closing**	**Dr. Polly Cheung** Founder of Hong Kong Breast Cancer Foundation, HK

ining Medicine

Prof Ian O. Ellis, Professor of Cancer Pathology, Faculty of Medicine & Health Sciences, University of Nottingham UK

- Named among the world's top 20 most influential experts on breast cancer
- Involved in the practice of pathology for over thirty years and has an international reputation in clinical and translational research in breast disease, particularly classification of breast cancer and evaluation of prognostic factors
- Author of over 600 peer reviewed scientific publications, chapters in medical textbooks and specialist textbooks in pathology and an experienced lecturer
- Founding member of the Faculty of the Nottingham International Breast Education Centre
- Fellow and Past Specialty Advisor of The Royal College of Pathologists, Past President of the Pathological Society of Great Britain and Ireland, Past Chairman of the UK National Co-ordinating Committee for Breast Pathology, Past President of the International Society of Breast Pathology, Past Councilor of The European Society of Mastology, Steering Committee Member of The European Group for Breast Screening Pathology and Past Chairman of the Breast Pathology Working Group of the European Society of Pathology
- Acted as advisor to the DoH, UICC, WHO and IARC
- Founder of PathLore and Medical Director of Source Bioscience

University of Nottingham
UK | CHINA | MALAYSIA



Molecular Testing in Breast Cancer

Ian Ellis

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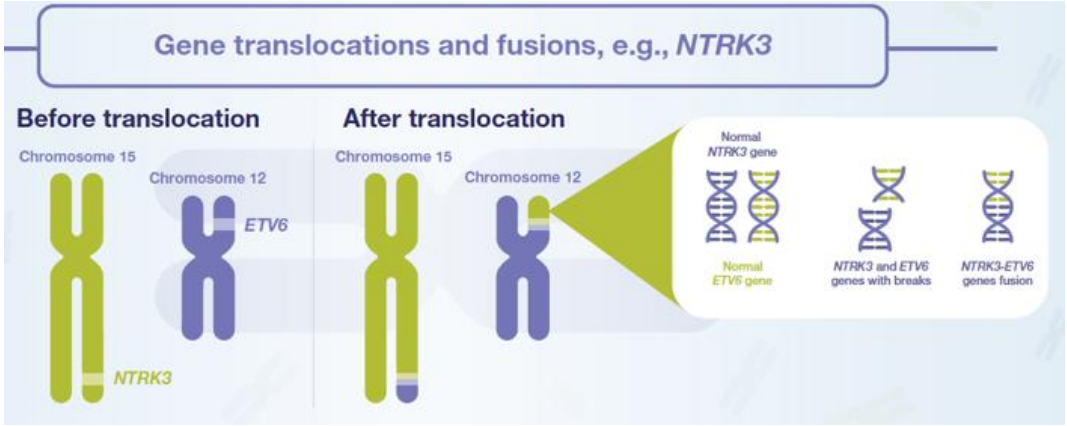
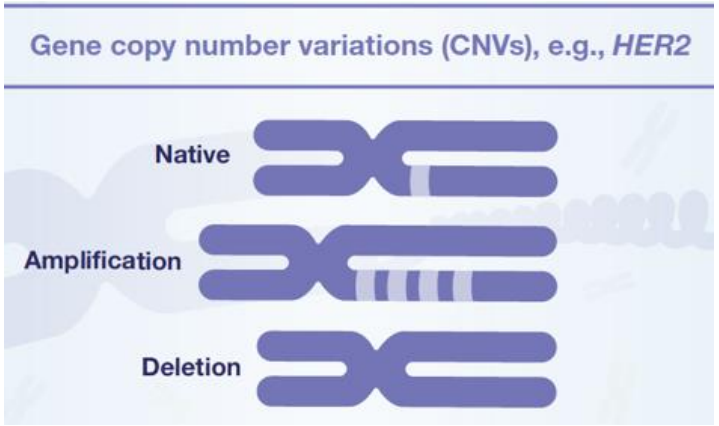
Molecular Testing in Breast Cancer

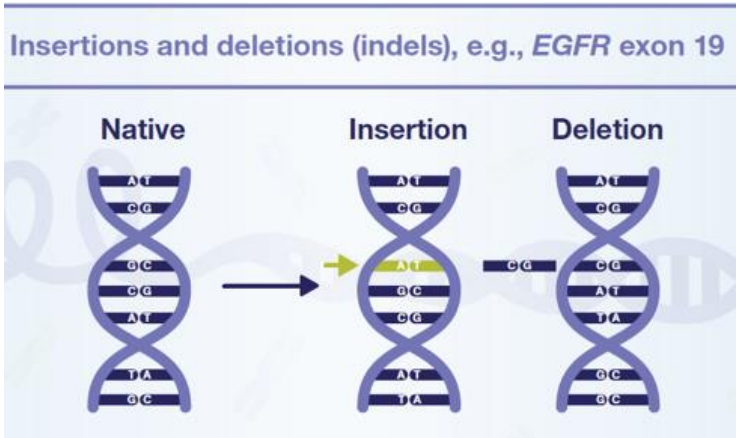
Cancer is a Disease of the Genome Caused by its Alterations

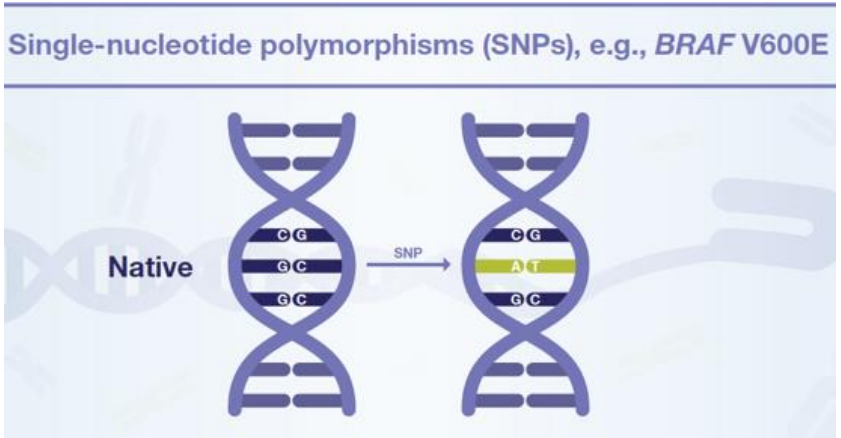
An effective and efficient tool is required to interrogate the alterations that cause cancer

Molecular Alterations in Cancer

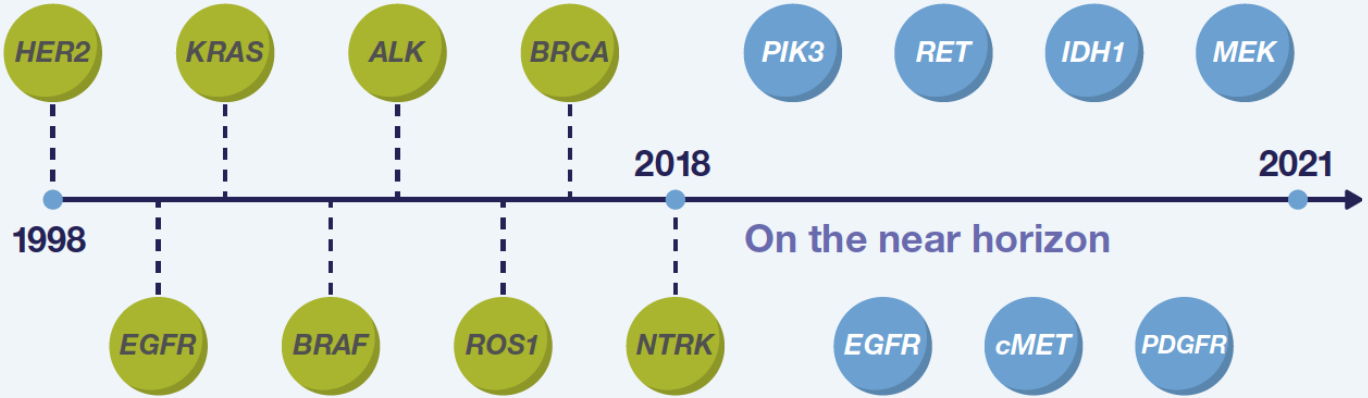


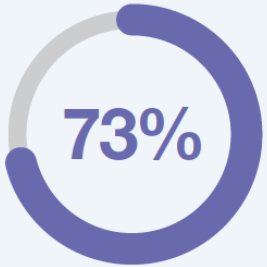






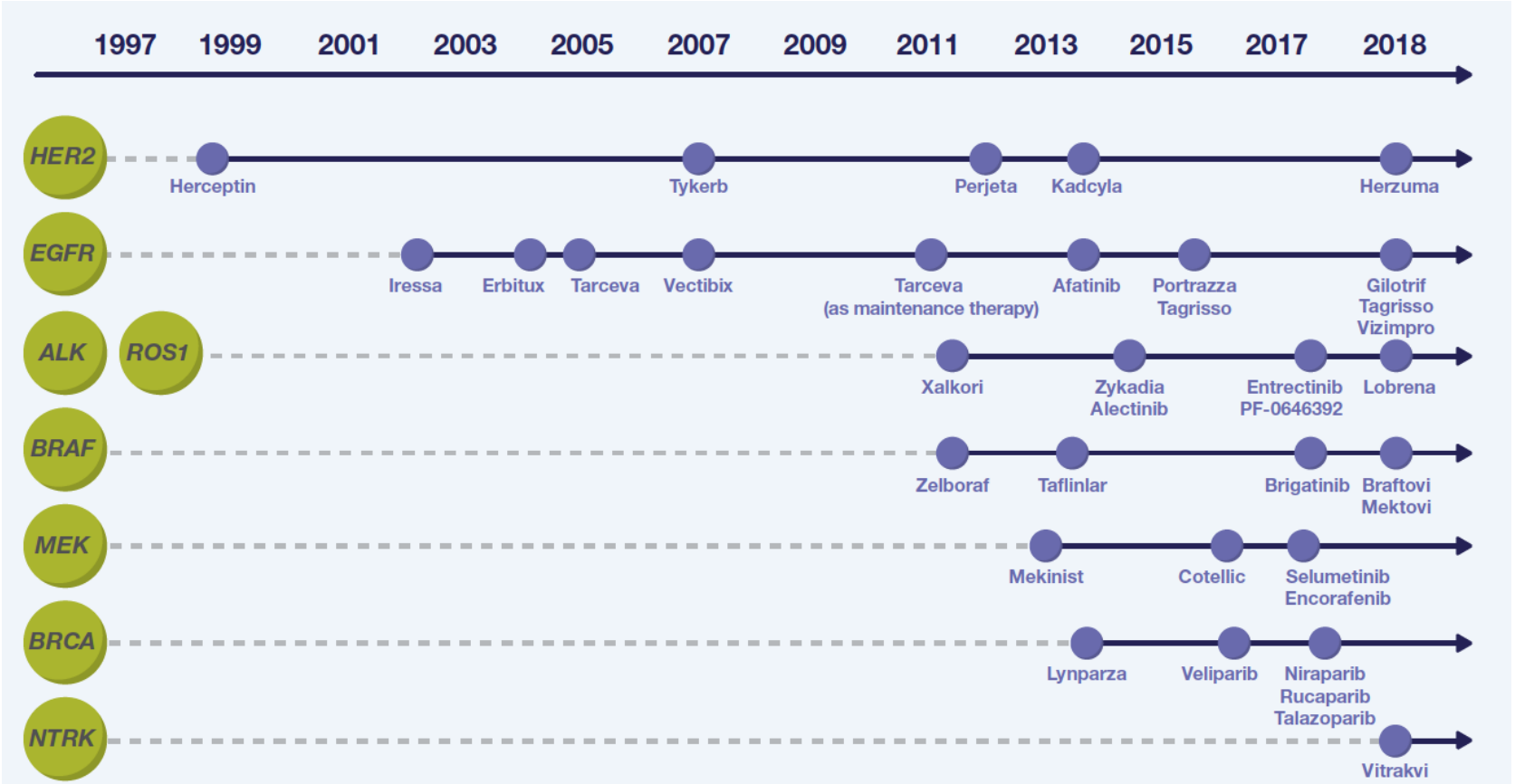
Biomarker development is accelerating



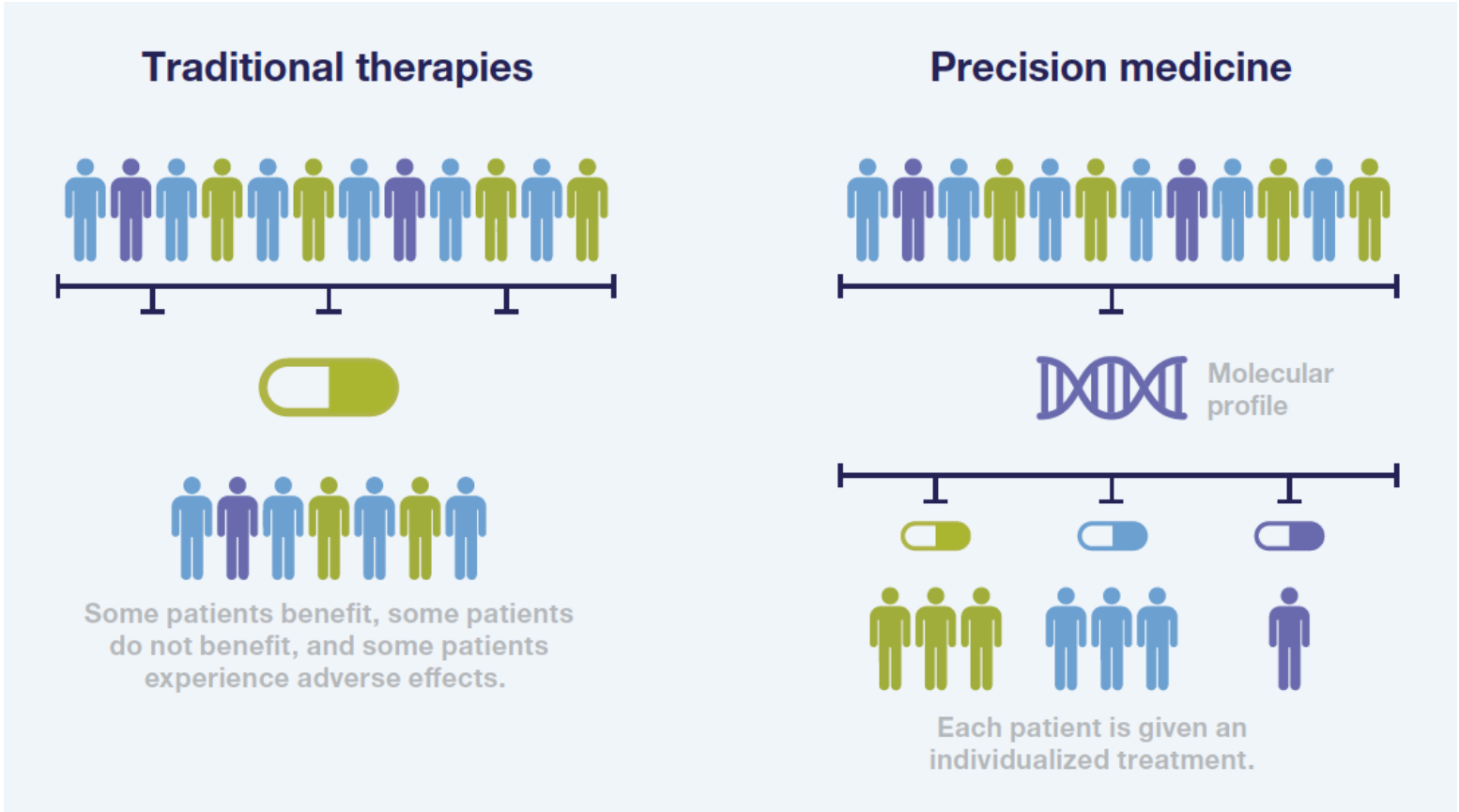


73% of medicines in oncology pipelines have associated biomarkers

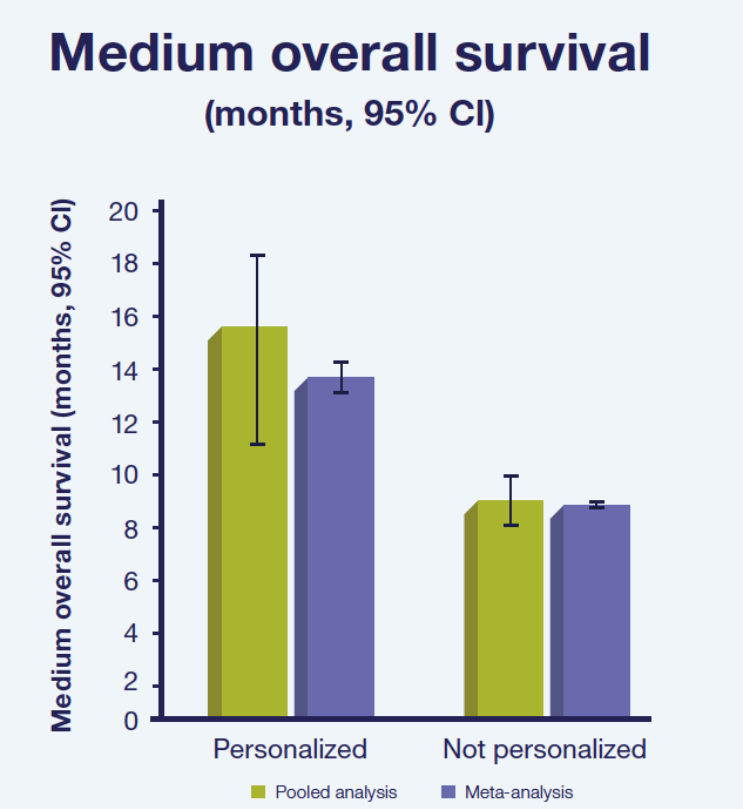
Available targeted medicines – Solid tumours



Precision medicine is enabled by molecular profiling



Precision oncology helps improve patient outcomes

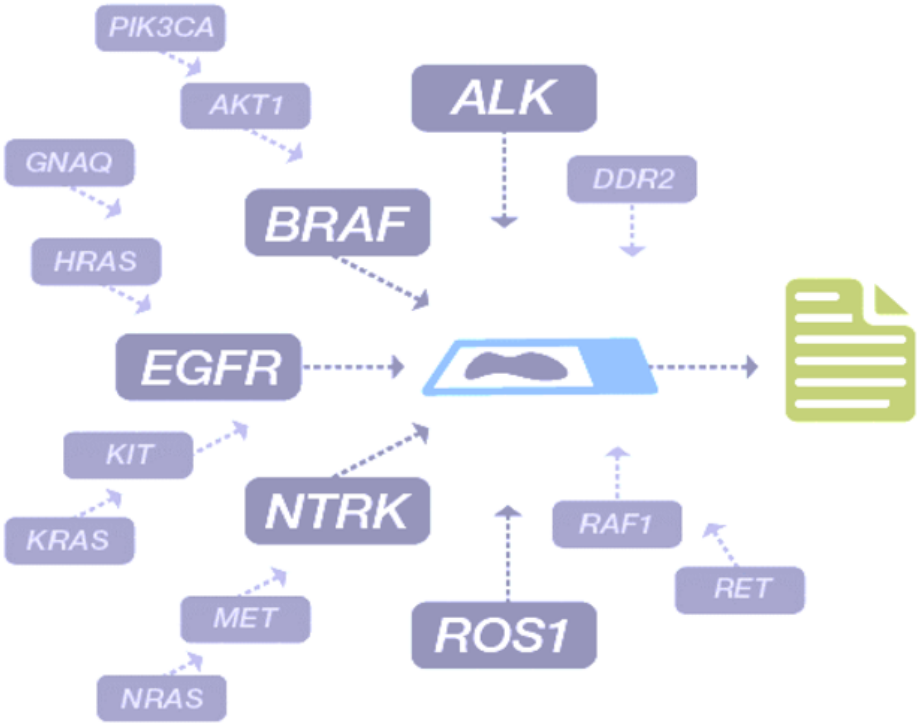


Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials *J Clin Oncol*. 2015 Nov 10; 33(32): 3817–3825. 24. doi: 10.1200/JCO.2015.61.5997.

Molecular Testing in Cancer

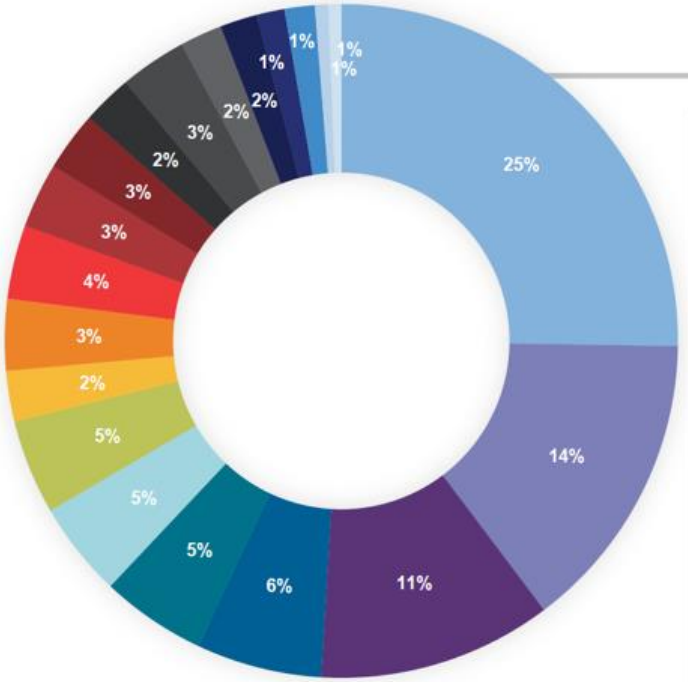
NGS is a Foundation of Precision Oncology Clinical Research

NGS can detect many different types of biomarkers simultaneously from a single sample



Molecular Testing in Breast Cancer

Pan-Cancer Clinical Research Application of OPA



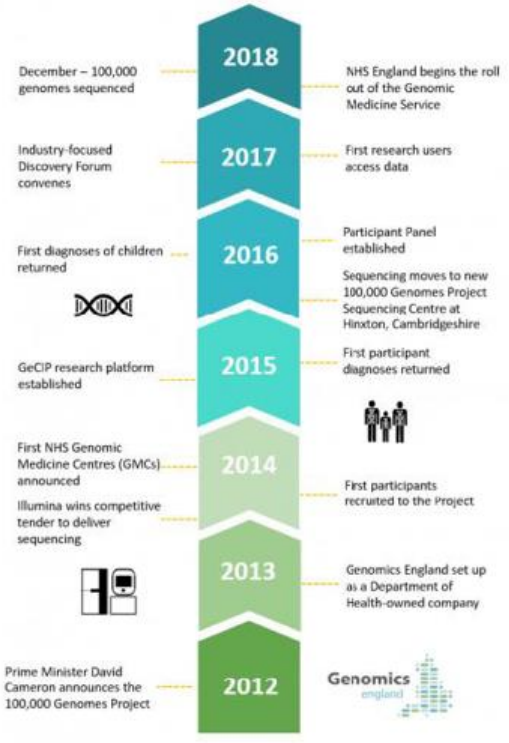
- Non-Small Cell Lung Cancer
- Breast Cancer
- Melanoma
- Gastric Cancer
- Bladder Cancer
- Head and Neck Cancer
- Pancreatic Cancer
- Thyroid Cancer
- Soft Tissue Sarcoma
- Small Cell Lung Cancer
- Unspecified Solid Tumor
- Colorectal Cancer
- Kidney Cancer
- Ovarian Cancer
- Esophageal Cancer
- Endometrial Cancer
- Liver Cancer
- Glioblastoma
- Gastrointestinal Stromal Tumor
- Cervical Cancer

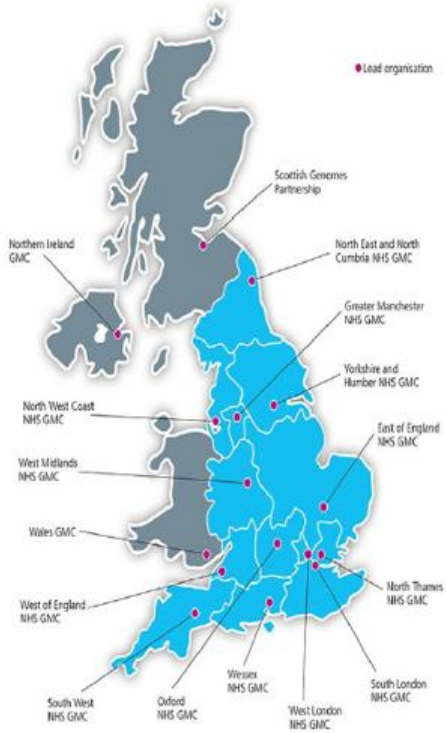
As expected, NSCLC continues to be the most “biomarker-rich” indication

HKBCF x Novartis:
Gene Testing Financial Assistance Program

ACT Genomics	Hong Kong Molecular Pathology Diagnostic Centre	Hong Kong Sanatorium & Hospital	Lucence Diagnostics	Roche	University Pathology Service, CUHK
• ACTDrug® + • ACTMonitor® Breast • ACTOnco® +	• Cancer Hotspot NGS Panel • PIK3CA Hotspot Mutation Test (Blood) • PIK3CA Hotspot Mutation Test (Tissue)	• **PIK3CA by Sanger sequencing** • **PIK3CA by NGS** • Somatic Breast Cancer Panel by NGS	• Liquid HALLMARK • Liquid MARK Breast • **Liquid MARK single PIK3CA gene** • Tissue 500 • Tissue HALLMARK • Tissue MARK Breast • **Tissue MARK single PIK3CA gene**	• FoundationOne CDx • FoundationOne Liquid CDx	• cfDNA PIK3CA test • CUHK Somatic Mutation v3 Test for Solid Cancers (Tissue) • Focused Mutation Panel for solid cancers (Tissue) • PIK3CA gene hotspot mutation detection (Exon 7, 9 and 20) • Roche Avenio surveillance mutation panel for solid cancers on peripheral blood (197 genes) • small RNA fusion panel (15 genes)

UK 100,000 Genomes Project





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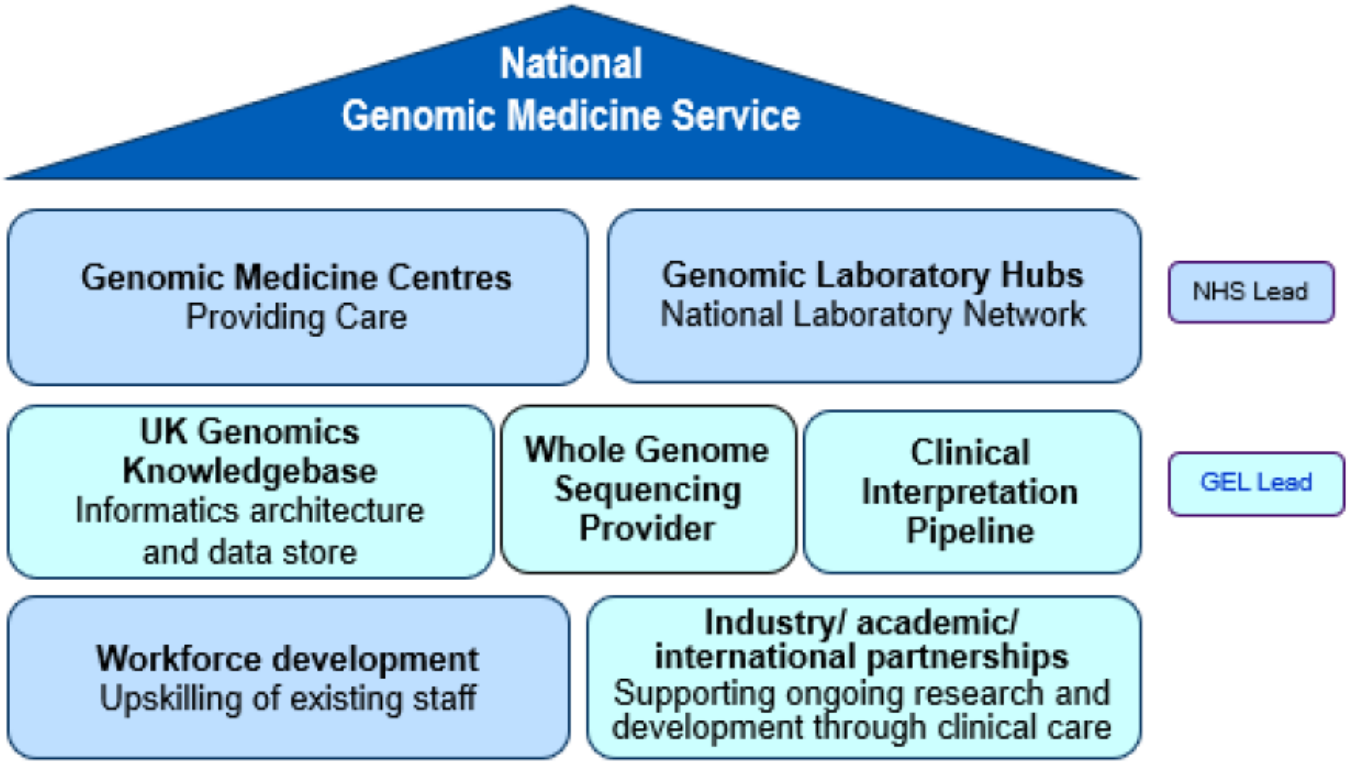
UK Genomic Medicine Service



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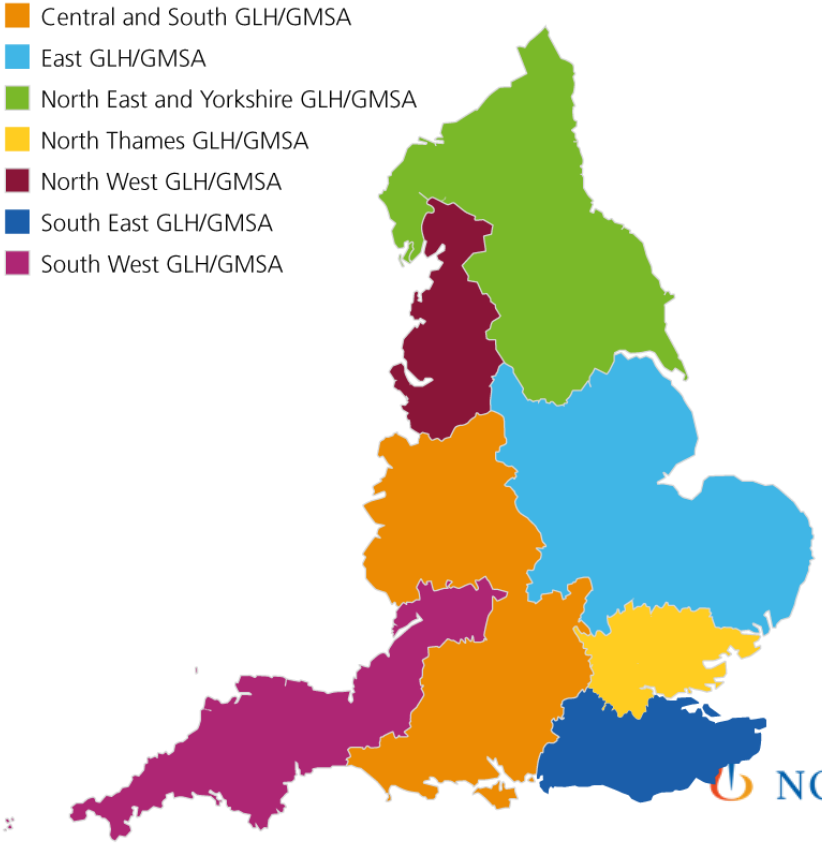
UK NHS Genomic Medicine Service Regions



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Molecular Testing in Cancer

SOLID CANCER GENOMIC TEST ORDER FORM

NHS East Genomics

PATIENT DETAILS		REFERENCE INFORMATION	
NHS NO.		SUBMITTER HOSPITAL	
HOSPITAL NO.		CLINICIAN NAME	
SURNAME		DEPARTMENT	
FORENAME		CONTACT EMAIL	Secure NHS.net
ETHNICITY		CONTACT PHONE	
SEX	MALE ☐ FEMALE ☐ OTHER ☐	REQUEST DATE	

SPECIMEN INFORMATION			
SPECIMEN NO		SPECIMEN TYPE	
BLOCK NO.		TISSUE SITE	
DIAGNOSIS		COLLECTION DATE	
REASON FOR REFFERAL			

% TUMOUR CELLS: ☐ CIRCLED ☐ DOTTED ☐ WHOLE SLIDE	☐ <10% ☐ 10-30% ☐ 30-50% ☐ 50-70% ☐ >70

Molecular Testing in Cancer

NGS SEQUENCING (tick required box)			
CLINICAL INDICATION	**TEST CODE**	**GENES SCREENED (Bold:** TSO500 large gene panel only)	**ASSAY**
☐ Colorectal Cancer	M1.1	BRAF, KRAS, NRAS, **MLH1**, **MSH2**, **MSH6 PMS2**, **POLE**, **POLD1**	DNA (SNV)
☐ Colorectal Cancer	M1.6	NTRK1/2/3	RNA (FUSION)
☐ Non Small Cell Lung Cancer	M4.1	ALK, BRAF, EGFR, KRAS, MET	DNA (SNV)
☐ Non Small Cell Lung Cancer	M4.2	ALK, ROS1, RET, MET (Ex14 skipping), NTRK1/2/3,	RNA (FUSION)
☐ Melanoma	M7.1	BRAF, KIT, NRAS	DNA (SNV)
☐ Melanoma	M7.3	NTRK1/2/3	RNA (FUSION)
☐ Gastrointestinal Stromal Tumour	M8.1	KIT, PDGFRA, BRAF	DNA (SNV)
☐ Gastrointestinal Stromal Tumour	M8.2	NTRK1/2/3	RNA (FUSION)
☐ Glioma	Specify	IDH1/2, BRAF, CDKN2A, EGFR, TP53, **ATRX, TERT, VHL, YAP1**	DNA (SNV, CNA)
☐ Glioma	Specify	BRAF, MYC, EGFRvIII, NTRK1/2/3	RNA (FUSION)
☐ Thyroid Cancer	Specify	BRAF, KRAS, NRAS, HRAS, RET	DNA (SNV)
☐ Thyroid Cancer	Specify	RET	RNA (FUSION)
☐ Other DNA Indication	Specify	Specify if known	DNA (SNV)
☐ Other RNA Indication	Specify	Specify if known	RNA (FUSION)

Molecular Testing in Cancer

FISH (tick required box)			
CLINICAL INDICATION	GENES	CLINICAL INDICATION	GENES
☐ Neuroblastoma	MYCN, TOP2A, 11q22,3 (ATM), 1p36	☐ Inflammatory Myofibroblastic Tumour	ALK
☐ Ewing's Sarcoma	EWSR1	☐ Angiosarcoma	MYC
☐ Rhabdomyosarcoma	FOX01, PAX3, PAX7	☐ Oligodendroglioma	1p36, 19q13
☐ Dermatofibrosarcoma Protuberans	PDGFB	☐ Medulloblastoma	MYC, MYCN
☐ Synovial Sarcoma	SS18	☐ Gender Identification	CEP X/Y
☐ Infantile Fibrosarcoma	ETV6	☐ Non Small Cell Lung Cancer	ALK, ROS1
☐ Liposarcoma / Osteosarcoma	MDM2	☐ Renal Cell Carcinoma	TFE3
☐ Alveolar Soft Part Sarcoma	TFE3	☐ Mammary Analogue Secretory Carcinoma of Salivary	ETV6

OTHER ASSAYS (tick required box)	
ASSAY	CLINICAL INDICATION
☐ Microsatellite Instability	Specify if known
☐ MGMT Promoter Methylation	Specify if known
☐ MLH1 Promoter Methylation	Specify if known
☐ Tissue Identity Testing (STR Genotyping)	Specify if known

Molecular Testing in Breast Cancer

INSTRUCTION FOR SENDING SAMPLES

Please send the following to the address below:

- Completed request form
- Copy of pathology report
- Appropriate tissue specimens (see below)

Address:

Cambridge Genomics Laboratory
East Genomics Laboratory Hub, BOX 143
Cambridge University Hospitals Foundation Trust
Cambridge, CB2 0QQ
TEL: (01223) 348 866
EMAIL: cuh.eastglh-cancer@nhs.net

Molecular Testing in Breast Cancer

INSTRUCTION FOR PATHOLOGISTS (Please refer to page 3 for guidance and tumour assessment)

1) Please mark tumour area on H&E slide

2) Please assess tumour percentage

- Number of tumour cells / total number of nucleated cells—**NOT AREA ASSESSMENT**
- Please provide % tumour cells in entire section **or** % tumour cells in marked area

Notes:

a. *If there are small groups of non-confluent / dispersed cells, dot or circle tumour groups/cells but do not assess % of tumour cells in the marked area.*

b. *NGS analyses: >30% tumour required in marked area / entire section*

c. *Methylation Analyses: MGMT >50%, MLH1 >30% tumour required in the marked area / entire section*

d. *MSI analysis requires area of normal in addition to tumour for non-colorectal cancer referrals. This can be normal tissue on the same slide, or normal tissue from a different block from the same case*

Molecular Testing in Breast Cancer

SPECIMEN REQUIREMENTS

Please send slides only (tissue blocks will be rejected):

FISH

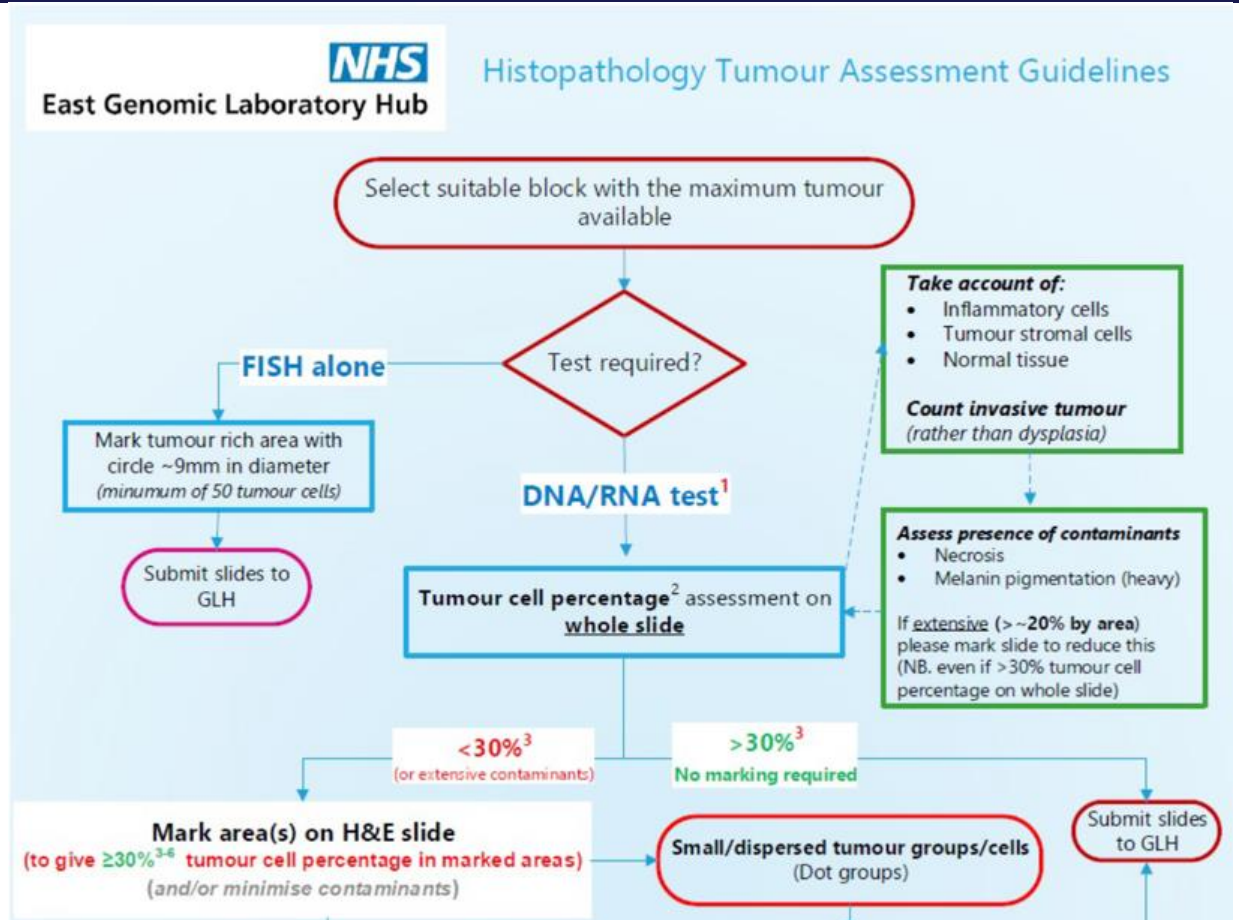
- Please send two 2uM sections on individual charged slides for each probe requested plus one H&E stained slide.

NGS | Methylation | MSI | Tissue Identity*

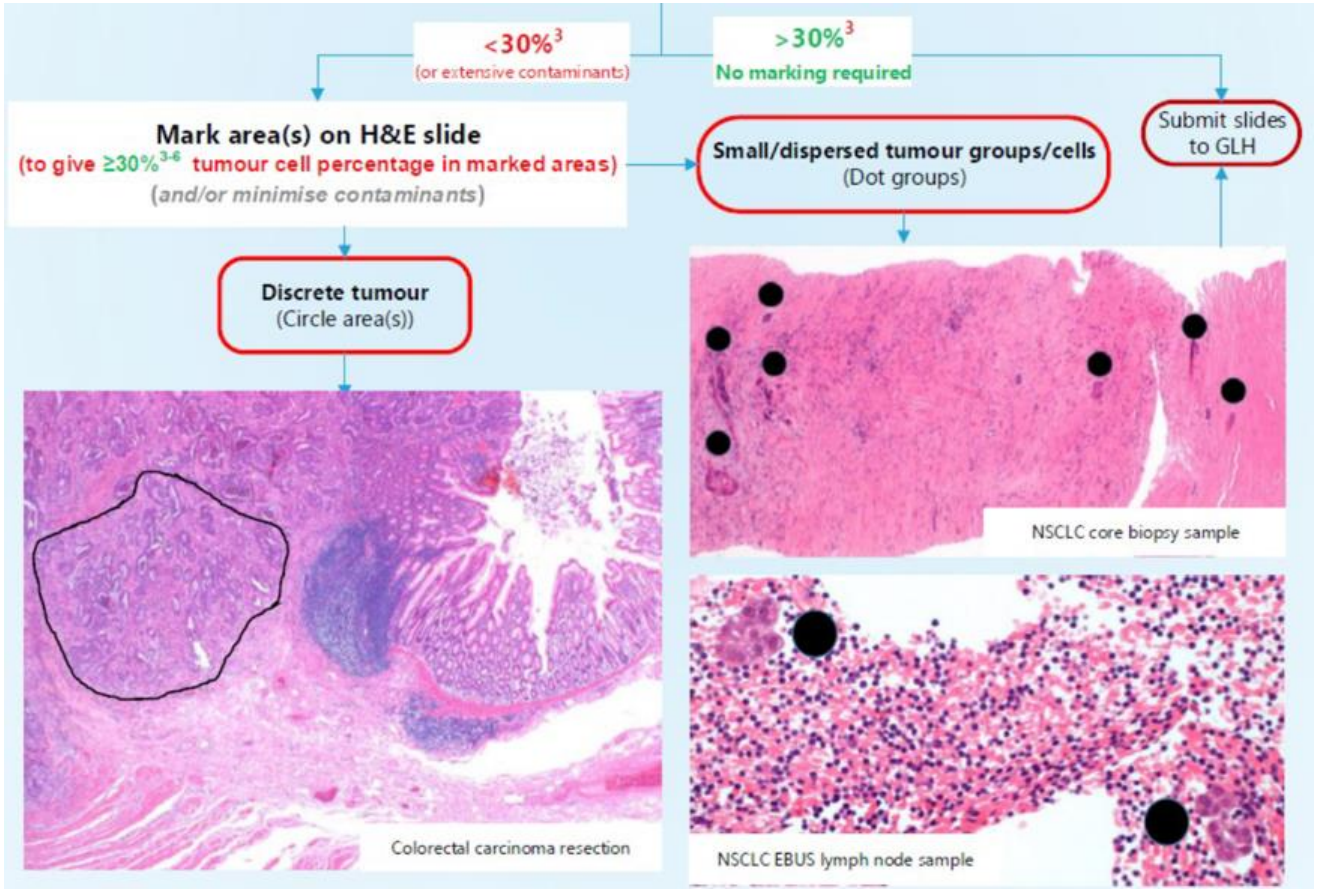
- Please send eight 4uM sections plus two H&E stained (first and last slide).

**A reference sample, preferably peripheral blood, is required for comparison*

Molecular Testing in Breast Cancer



Molecular Testing in Breast Cancer



Molecular Testing in Breast Cancer

Todays Challenges and Barriers for NGS Implementation in a Broader Lab Spectrum

Too slow

Requires days and often weeks to get the results

Too complex

High level of user expertise required to run NGS

Modular workflows requiring multiple instruments and touchpoints

Too costly

Cost of hiring and training staff

Cost penalty for running small sample batches

Too limited

Tissue requirements / QNS (quantity not sufficient) related failures

Molecular Testing in Breast Cancer

Oncomine Precision Assay on Ion Torrent Genexus System

A new generation solution for genomic profiling

Fast

Single day sample-to-report.

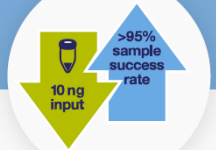
Hands free

2 touch points and only 10 min of hands-on time.

Cost saving

No more need to batch samples across multiple sequencing runs.

Tissue saving



Minimum sample requirement

Maximum results obtained.

Molecular Testing in Breast Cancer

Genexus System—Tomorrow's Specimen-to-Report NGS Workflow

- FFPE tissue
- Frozen tissue
- Bone marrow
- Whole blood
- PBL
- Urine
- Saliva

Genexus Software

Nucleic acid purification and quantitation*	Library preparation to variant interpretation	Report*

Ion Torrent™ Genexus™
Purification System (Available 2020)

2 hour turnaround time
12 FFPE (DNA and RNA)
6 Plasma

Ion Torrent™ Genexus™
Integrated Sequencer (Available November 2019)

Ion Torrent™ GX5™ Chip:
12–15M reads/lane

14 hours for a single-lane run
(approx. 24 to 30 hours for full chip)
Up to 32 Samples per run

Molecular Testing in Breast Cancer

Oncomine Precision Assay Gene Content

DNA hotspots

AKT1	ESR1	MAP2K2
AKT2	FGFR1	MET
AKT3	FGFR2	MTOR
ALK	FGFR3	NRAS
AR	FGFR4	NTRK1
ARAF	FLT3	NTRK2
BRAF	GNA11	NTRK3
CDK4	GNAQ	PDGFRA
CDKN2A	GNAS	PIK3CA
CHEK2	HRAS	PTEN
CTNNB1	IDH1	RAF1
EGFR	IDH2	RET
ERBB2	KIT	ROS1
ERBB3	KRAS	SMO
ERBB4	MAP2K1	TP53

CNV

ALK
AR
CD274
CDKN2A
EGFR
ERBB2
ERBB3
FGFR1
FGFR2
FGFR3
KRAS
MET
PIK3CA
PTEN

Inter-genetic fusions

ALK	**NTRK2**
BRAF	**NTRK3**
ESR1	NUTM1
FGFR1	**RET**
FGFR2	ROS1
FGFR3	RSPO2
MET	RSPO3
NRG1	
NTRK1	

Intra-genetic fusions

AR
BRAF
EGFR
MET

Molecular Testing in Breast Cancer

SOLID CANCER REQUEST FORM V1

Molecular Diagnostics
City Campus
Nottingham University Hospitals
Hucknall Road
Nottingham
NG5 1PB

Genomics and Molecular Medicine
Nottingham University Hospital NHS Trust

SOLID CANCER GENOMIC TEST ORDER FORM

Tel: 0115 969 1169 x77711
E-mail:
nuhnt.molecular.diagnostics@nhs.net
Website:
https://www.nuh.nhs.uk/molecular-diagnostics

PATIENT DETAILS		REFERRER INFORMATION	
SURNAME		REFERRING HOSPITAL	
FORENAME		REFERRER NAME	
DOB		DEPARTMENT	
NHS NO.		CONTACT E-MAIL	
HOSPITAL NO.		CONTACT PHONE	
SEX	☐ MALE ☐ FEMALE ☐ OTHER	REQUEST DATE	

SPECIMEN INFORMATION			
SPECIMEN NO		SPECIMEN TYPE	
BLOCK NO		TISSUE SITE	
DIAGNOSIS		COLLECTION DATE	
TISSUE TYPE	☐ PRIMARY ☐ METASTASIS	☐ BIOPSY ☐ RESECTION ☐ CYTOLOGY	
REFERRAL TYPE	☐ DIAGNOSTIC ☐ TREATMENT-REFLEX ☐ TREATMENT-OTHER		
% TUMOUR CELLS	☐ <20% ☐ 20-30% ☐ 30-50% ☐ 50-70% ☐ >70%		
CELLULARITY	☐ VERY LOW ☐ LOW ☐ INTERMEDIATE ☐ HIGH		

Molecular Testing in Breast Cancer

NGS PANEL TESTING (tick required box)			
CLINICAL INDICATION	TEST CODE[Δ]	GENES SCREENED	ASSAY
☐ Colorectal Cancer	M1.1*	BRAF, KRAS, NRAS	DNA (SNV)
☐ Colorectal Cancer	M1.6	NTRK1/2/3	RNA (FUSION)
☐ Non Small Cell Lung Cancer	M4.1	ALK, BRAF, EGFR, KRAS, MET	DNA (SNV)
☐ Non Small Cell Lung Cancer	M4.2	ALK, ROS1, RET, MET (Ex14 skipping), NTRK1/2/3	RNA (FUSION)
☐ Melanoma	M7.1	BRAF, KIT, NRAS	DNA (SNV)
☐ Melanoma	M7.3	NTRK1/2/3	RNA (FUSION)
☐ Gastrointestinal Stromal Tumour	M8.1	KIT, PDGFRA	DNA (SNV)
☐ Gastrointestinal Stromal Tumour	M8.2	NTRK1/2/3	RNA (FUSION)
☐ Breast Cancer	M3.6	PIK3CA	DNA (SNV)
☐ Breast Cancer	M3.5	NTRK1/2/3	RNA (FUSION)
☐ Glioma	Specify*	IDH1/2, BRAF, CDKN2A, EGFR, TP53	DNA (SNV)
☐ Glioma	Specify*	BRAF, EGFRvIII, NTRK1/2/3	RNA (FUSION)
☐ Thyroid Cancer	Specify*	BRAF, KRAS, NRAS, HRAS, RET, TP53	DNA (SNV)
☐ Thyroid Cancer	Specify*	NTRK1/2/3, RET, ALK	RNA (FUSION)
☐ Other DNA Indication	Specify*	Specify from Genexus OPA Panel	DNA (SNV)
☐ Other RNA Indication	Specify*	Specify from Genexus OPA Panel	RNA (FUSION)

Example NGS Report

Sample Cancer Type: Non-Small Cell Lung Cancer

Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	Not detected	NRAS	Not detected
BRAF	Not detected	NTRK1	Not detected
EGFR	Not detected	NTRK2	Not detected
ERBB2	Not detected	NTRK3	Not detected
KRAS	Not detected	RET	***KIF5B-RET fusion***
MET	Not detected	ROS1	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Annotations
IA	*KIF5B-RET fusion* kinesin family member 5B - ret proto-oncogene Locus: chr10:32317356 - chr10:43612032	
IIC	*PIK3CA G1049R* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Locus: chr3:178952090 Transcript: NM_006218.4	


University of
Nottingham
UK | CHINA | MALAYSIA
Thank You


ThermoFisher
SCIENTIFIC
Oncomine Precision Assay on Ion Torrent Genexus System

Dr Roland Leung, MB ChB (Edin), MRCP (London), DABIM (Onc)

- Consultant in the Department of Medicine, Queen Mary Hospital and Honorary Assistant Professor in Department of Medicine, The University of Hong Kong
- Medical oncologist trained in the US at New York University Medical Center and Memorial Sloan Kettering Cancer Center
- Main interests include the exploration of predictive bio-markers in the clinical treatment of cancer.
  - “With the explosion of molecular targeted therapies with specific target of action, it is imperative that we as oncologists have access to technology which can predict which patients will benefit most from these treatment and not expose patients to empirical treatment”
- Primarily focusing on breast cancer, adenocarcinoma of lung, neuroendocrine tumors and tumors with targetable genetic aberrations

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Precision Medicine:

Clinicians' perspective
Importance of genomic testing in targeted therapy and personalized therapy

DR ROLAND LEUNG MRCP (UK), DIP ABIM (MED ONC)

CONSULTANT, DEPARTMENT OF MEDICINE,

QUEEN MARY HOSPITAL

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All drugs are developed with a specific target in mind

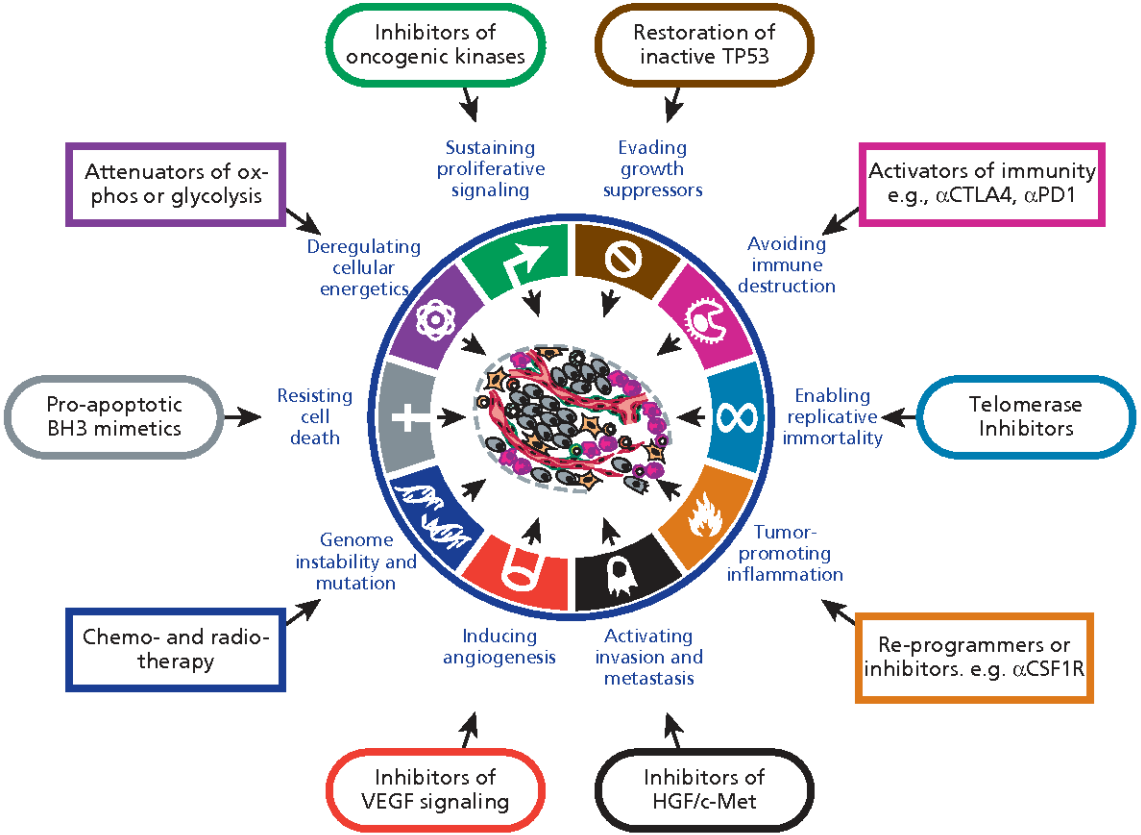
With advances in molecular science, drugs can be designed with high specificity

Targeted therapy is not new

Breast cancer had the earliest forms of targeted therapy

1) Endocrine therapy
2) HER2 directed therapy

Emerging targets in breast cancer



Modified from Hanahan & Weinberg. Hallmarks of Cancer: The Next Generation, Cell 144, 4 March 2011 Elsevier Inc. 2011,144(5), 646-674 (215).

Oncogenic kinase is a good target to design rational drugs

Differential expression between normal and tumor

Most of these are gain of function mutations

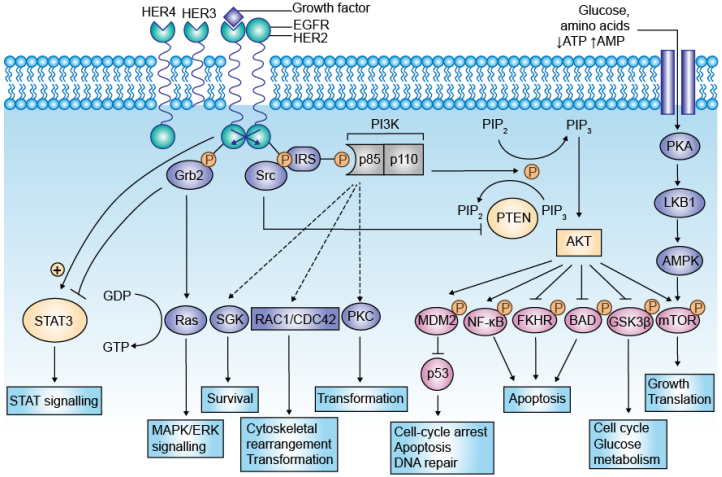
Relatively easy to test with a variety of techniques

Robust wide applicability worldwide, using EGFR mutation in lung cancer as a successful example

~40% of Patients With HR+, HER2– ABC Harbor a Mutation in PIK3CA in Their Tumors and Face a Poor Prognosis

- *PIK3CA* is the gene that encodes the α-isoform of the catalytic subunit (p110α) of PI3K[3]

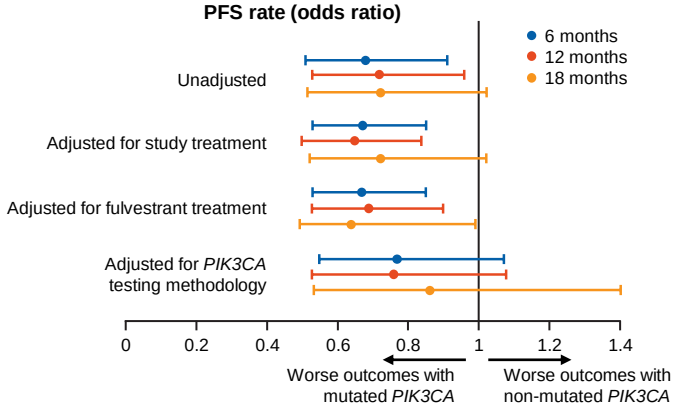
The PI3K Pathway[6]



PI3K signaling regulates diverse cellular functions including cell proliferation, survival, glucose metabolism, cell migration, and angiogenesis, and is often deregulated in cancers[6,7]

PIK3CA Mutations Are Associated With Shorter PFS and OS[4,5]

The presence of a *PIK3CA* mutation is a negative prognostic factor, associated with shorter PFS rate at 6, 12, and 18 months[4,a]

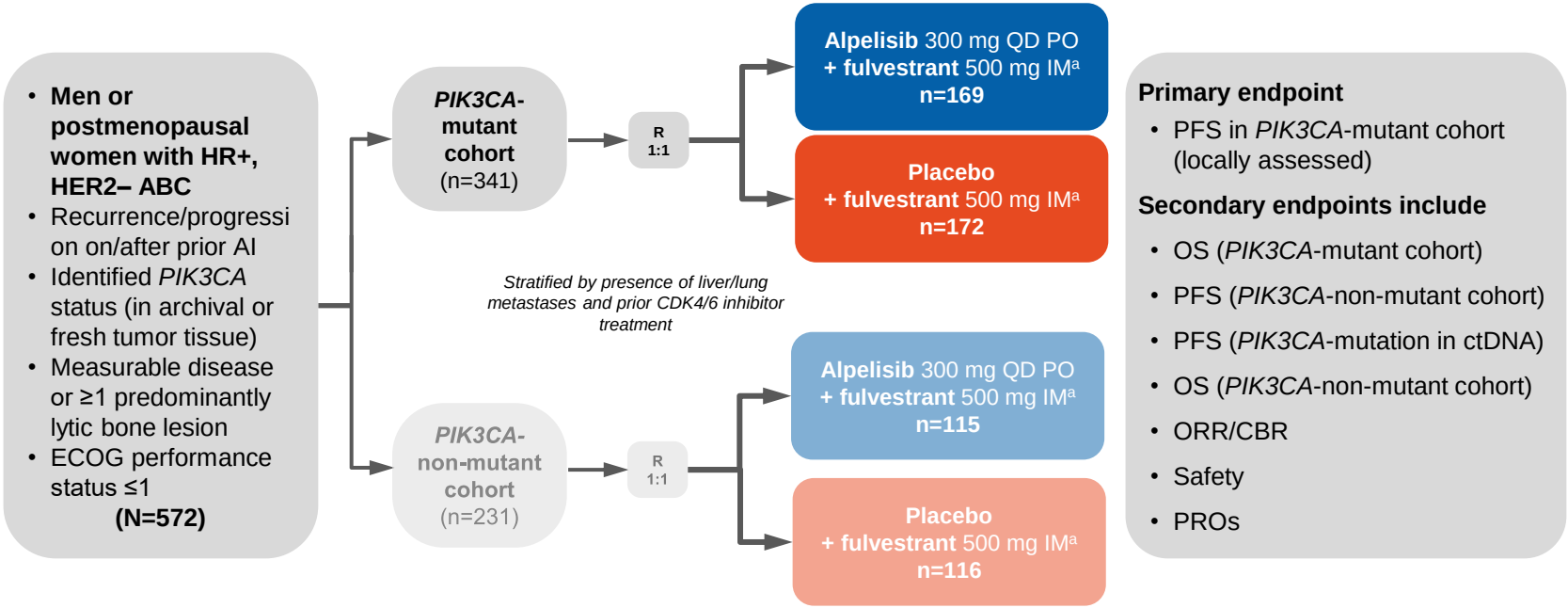


Patients from the SAFIR-02 study with *PIK3CA*-mutated ABC had 44% higher risk of death than patients without the mutation when treated with chemotherapy (HR multivariate: 1.44; 95% CI, 1.02-2.03; *P*=0.04)[5]

[a]In this systematic literature review, patients treated with PI3K-targeted therapies were excluded; allowed treatment included endocrine therapy, non-PI3K targeted therapy, and other treatment.

1. Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70; 2. Fritsch C, et al. AACR 2018. Abstract 3934 (poster); 3. Rajadurai P, et al. SABCS 2021. Abstract P5-13-25 (poster); 4. Fillbrunn M, et al. ASCO 2020. Poster 154; 5. Mosele F, et al. *Ann Oncol.* 2020;31(3):377-386; 6. Hennessy BT, et al. *Nat Rev Drug Discov*. 2005;4(12):988-1004; 7. Samuels Y. *Cell Cycle*. 2004;3(10):1221-1224.

SOLAR-1: A Pivotal Phase III Trial Evaluating Alpelisib + Fulvestrant in Patients With *PIK3CA*-mutated HR+, HER2– ABC[1,2]



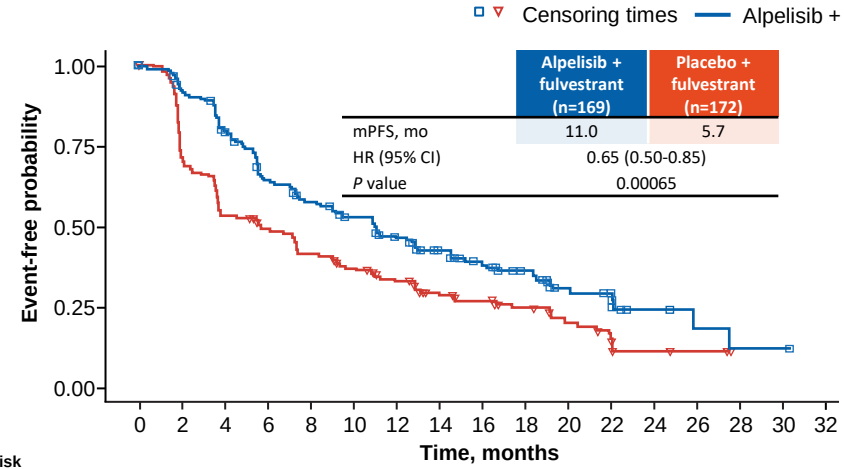
[a]Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940; 2. André F, et al. ESMO 2018. Abstract LBA3 (oral).

SOLAR-1: Alpelisib Significantly Prolonged PFS for Patients in the *PIK3CA*-mutant Cohort[1-3]

- SOLAR-1 met its primary endpoint; a statistically significant and clinically meaningful prolongation of PFS was observed with the addition of alpelisib to fulvestrant in patients with *PIK3CA*-mutant disease, but was not observed in those without *PIK3CA* mutations[1,2]

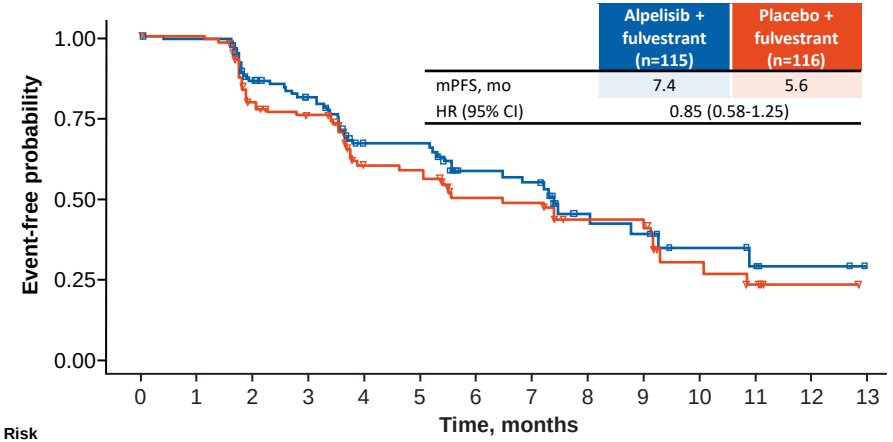
PFS in the *PIK3CA*-Mutant Cohort[1]



No. at Risk

Alpelisib + fulvestrant	169	145	123	97	85	75	62	50	39	30	17	14	5	3	1	1	0
Placebo + fulvestrant	172	120	89	80	67	58	48	37	29	20	14	9	3	2	0	0	0

PFS in the *PIK3CA*-Non-Mutant Cohort[1]



No. at Risk

Alpelisib + fulvestrant	115	110	86	76	48	48	31	29	14	12	7	5	3	0
Placebo + fulvestrant	116	110	79	72	43	42	31	30	20	20	8	5	1	0

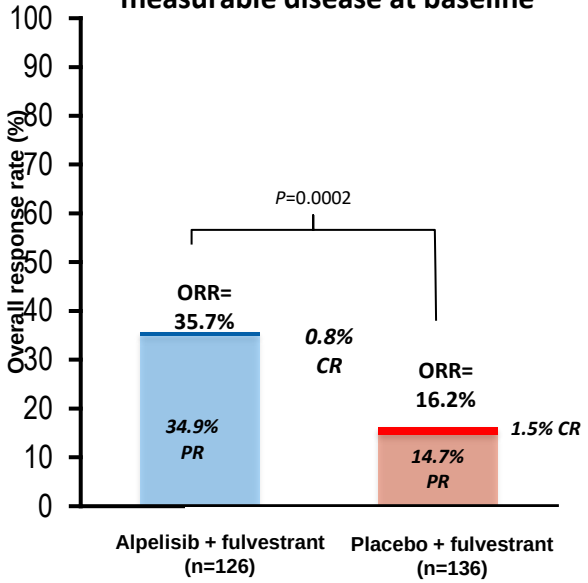
1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940. Figures reprinted from André F, et al. Alpelisib for *PIK3CA*-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. Copyright © 2019 Massachusetts Medical Society. Reproduced with permission from the Massachusetts Medical Society; 2. André F, et al. ESMO 2018. Abstract LBA3 (oral); 3. André F, et al. *Ann Oncol* 2021;32(2):208-217.

SOLAR-1: Overall Response Rate and Clinical Benefit Rate in *PIK3CA*-mutant Cohort[1,2]

Responses in patients with measurable disease at baseline

	Alpelisib + fulvestrant (n=169)	Placebo + fulvestrant (n=172)
No. of patients with measurable disease	126	136
Confirmed best overall response, n (%)		
Complete response	1 (0.8)	2 (1.5)
Partial response	44 (34.9)	20 (14.7)
Stable disease	58 (46.0)	63 (46.3)
Progressive disease	13 (10.3)	45 (33.1)
Unknown status	10 (7.9)	6 (4.4)
Overall response[b]		
No. of patients	45	22
Percentage of patients (95% CI)	35.7 (27.4-44.7)	16.2 (10.4-23.5)
Clinical benefit[c]		
No. of patients	72	60
Percentage of patients (95%CI)	57.1 (48.0-65.9)	44.1 (35.6-52.9)

ORR in patients with measurable disease at baseline[2]



In the overall patient population,

- ORR was 26.6% (95%CI, 20.1-34.0) in the alpelisib group versus 12.8% (95%CI, 8.2-18.7) in the placebo group
- CBR was 61.5% in the alpelisib group (95%CI, 53.8-68.9) versus 45.3% in the placebo group (95%CI, 37.8-53.1)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ORR, overall response rate; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a]Measurable disease defined as having ≥1 measurable lesion as per RECIST 1.1 criteria.

[b]Overall response was defined as a complete or partial response.

[c]Clinical benefit in patients with measurable disease at baseline was defined as a CR or PR or as SD lasting at least 24 weeks.

1. André F, et al. *N Engl J Med*. 2019;380:1929-1940; 2. Reprinted from André F, et al. ESMO 2018. Abstract LBA3 (oral).

Alpelisib Is the First α-Selective PI3K Inhibitor and Degrader Approved in HR+, HER2–, *PIK3CA*-mutated ABC Based on SOLAR-1[1-4]

***PIK3CA*-mutant**	▪ Alpelisib + fulvestrant is a preferred second-line treatment option by international guidelines for patients with HR+, HER2–, *PIK3CA*-mutated ABC[5-8]
	▪ Study met its primary objective; mPFS was 11.0 mo vs 5.7 mo in patients treated with alpelisib + fulvestrant vs placebo + fulvestrant (HR 0.65; 95% CI, 0.50-0.85; *P*=0.00065), respectively[2]
	▪ Overall response and clinical benefit were also improved in the alpelisib vs placebo arms of the *PIK3CA*-mutant cohort[2] – ORR: 26.6% vs 12.8%; CBR: 61.5% vs 45.3% – ORR: 35.7% vs 16.2%; CBR: 57.1% vs 44.1% (with measurable disease at baseline)
***PIK3CA*-non-mutant**	▪ The secondary endpoint and proof-of-concept criteria for PFS in the *PIK3CA*-non-mutant cohort were not met (mPFS 7.4 mo for alpelisib arm vs 5.6 mo for placebo arm, HR 0.85; *P*=0.21)[2,9]

1. Drullinsky PR, et al. *Breast Cancer Res Treat*. 2020;181(2):233-248; 2. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940; 3. Fritsch C, et al. AACR 2018. Abstract 3934 (poster); 4. FDA approves alpelisib for metastatic breast cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer. Accessed August 11, 2021; 5. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649; 6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V8.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 17, 2021; 7. Burstein HJ, et al. *J Clin Oncol*. 2021;JCO2101392; 8. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; 9. André F, et al. ESMO 2018. Abstract LBA3 (oral).

PIK3CA Mutation Testing Can Identify Patients Who Are Likely to Benefit From Alpelisib[1]

- International expert guidelines encourage biopsy at first metastasis and, when feasible, at the time of disease recurrence[2-4]

ABC5[2]	▪ Biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis, particularly when metastasis is diagnosed for the first time ▪ Biologic markers (especially HR and HER2) should be reassessed at least once in the metastatic setting if clinically feasible
NCCN[3]	▪ First recurrence of disease should be biopsied ▪ Assess for *PIK3CA* mutation if HR+, HER2– and if considering therapy with alpelisib for stage IV recurrent or initially metastatic disease
ASCO[4]	▪ A biopsy is recommended to determine or confirm whether a suspicious lesion represents metastatic disease ▪ Markers should be obtained ▪ Every attempt should be made to test the most recent tumor tissue sample for *PIK3CA* mutation
ESMO[1,5,6]	▪ Patients with newly diagnosed or recurrent MBC should have a biopsy, if technically feasible, to confirm histology and to re-assess ER, PgR, and HER2 status ▪ Other therapeutically relevant biomarkers to be assessed as part of routine clinical practice include *PIK3CA* in ER/PgR-positive, HER2-negative MBC ▪ *PIK3CA* mutations are a clinically validated biomarker that predict efficacy of alpelisib (ESCAT level IA)

1. Mosele F, et al. *Ann Oncol.* 2020;31(11):1491-1505; 2. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649; 3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V8.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 17, 2021; 4. Rugo HS, et al. *J Clin Oncol*. 2016;34(25):3069-3103; 5. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; 6. Mateo J, et al. *Ann Oncol*. 2018;29(9):1895-1902.

BYLieve: Study Design

Phase II, open-label, 3-cohort, noncomparative study to assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated, HR+, HER2– ABC whose disease progressed on/after prior treatments

- **Men or pre/postmenopausal[a] women with HR+, HER2–, *PIK3CA*-mutated ABC**
- *PIK3CA* mutation in tumor tissue or blood[b]
- Last line of prior therapy: CDK4/6i + ET, systemic chemotherapy, or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

(N=336)[c]

COHORT A (n=112)[c]
Patients who received **CDK4/6i + AI as immediate prior treatment**

Alpelisib 300 mg PO QD + **fulvestrant** 500 mg[d]

COHORT B (n=112)[c]
Patients who received **CDK4/6i + fulvestrant as immediate prior treatment**

Alpelisib 300 mg PO QD + **letrozole** 2.5 mg PO QD

COHORT C (n=112)[c]
Patients whose disease has **progressed on/after AI** and received **chemotherapy or ET as immediate prior treatment**

Alpelisib 300 mg PO QD + **fulvestrant** 500 mg[d]

Treatment crossover between cohorts not permitted

Primary endpoint
- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort

Secondary endpoints
- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

Exploratory endpoint
- Biomarker analyses

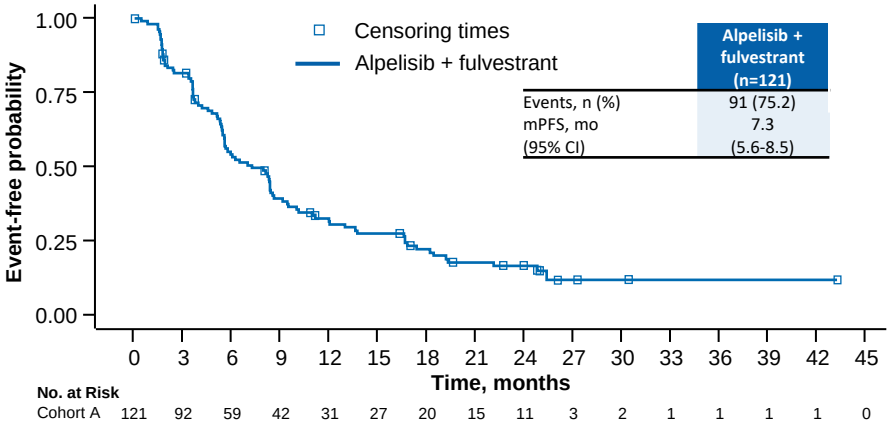
[a]Men (Cohort B only) and premenopausal women were allowed goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression; [b]Patients were enrolled and could stay on study based on confirmed *PIK3CA* mutation status from either tissue or blood by a certified local laboratory. Only patients with centrally confirmed *PIK3CA* mutation by a Novartis-designated laboratory were included in the mFAS; [c]Enrollment continued until 336 patients with a centrally confirmed *PIK3CA* mutation was reached (at least 112 patients in each cohort); [d]IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter.

Rugo HS, et al. *Lancet Oncol.* 2021;22(4):489-498.

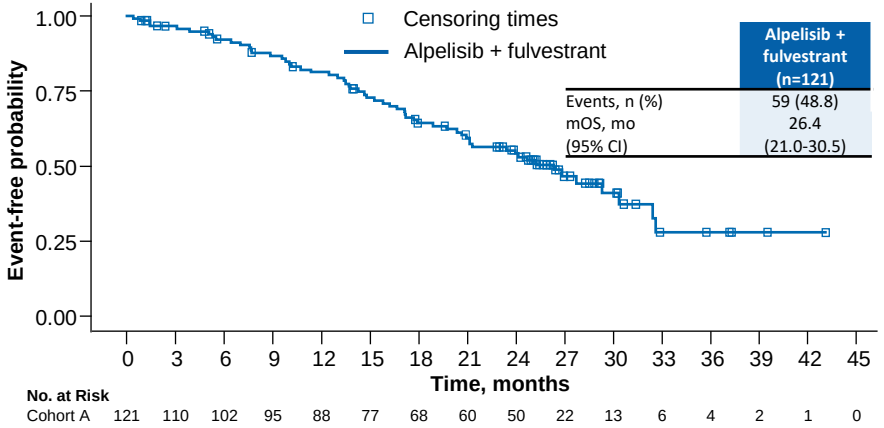
BYLieve Cohort A: Next-Line Alpelisib + Fulvestrant Demonstrated Efficacy at the 18-month Follow-up in Patients With Prior CDK4/6i + AI[1]

- Cohort A comprised patients who received alpelisib + fulvestrant after a CDK4/6i with AI as immediate prior treatment; the primary analysis for this cohort was completed at 6 months, at which efficacy was demonstrated[2]

PFS in Cohort A at 18-mo Follow-up[1]

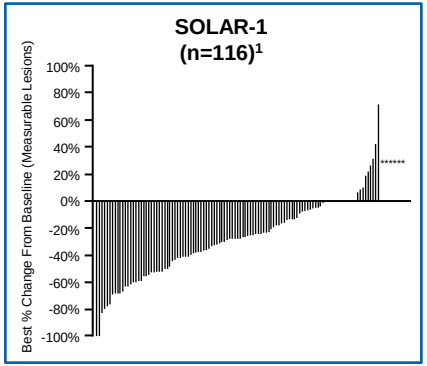


OS in Cohort A at 18-mo Follow-up[1]

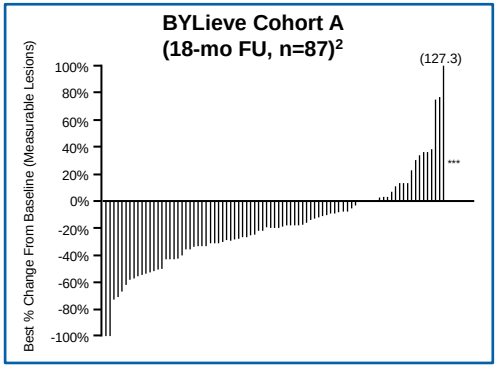


1. Ciruelos EM, et al. SABCS 2021. Abstract P1-18-03 (poster); 2. Rugo HS, et al. *Lancet Oncol*. 2021;22(4):489-498.

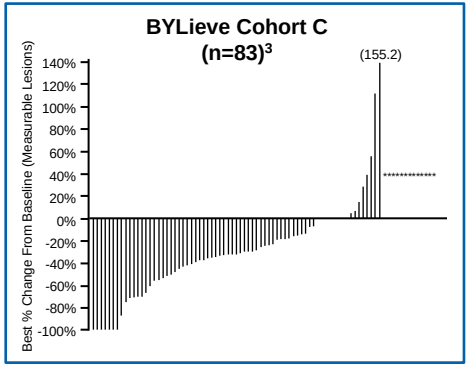
SOLAR-1 and BYLieve: Alpelisib Treatment Resulted in Tumor Shrinkage Regardless of ET Partner or Prior Therapy[1-4,a]



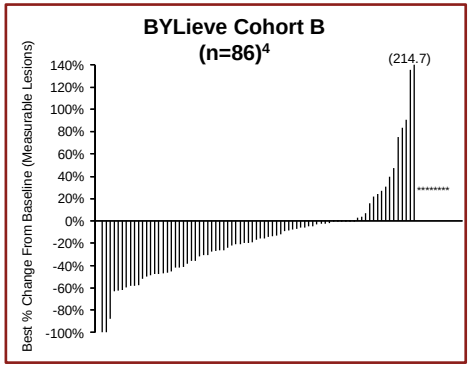
Alpelisib + fulvestrant
(prior AI)



Alpelisib + fulvestrant
(prior CDK4/6i + AI)



Alpelisib + fulvestrant
(prior CT or ET)



Alpelisib + letrozole
(prior CDK4/6i + fulvestrant)

	SOLAR-1	Cohort A (18-mo FU)	Cohort C	Cohort B
Decrease in best % change from baseline	**75.9%**	**71.3%**	**65.1%**	**66.3%**
Increase/zero change in best % change from baseline	**18.1%**	**25.3%**	**19.3%**	**24.4%**

[a]Per local radiology review. Patients for whom the best percentage change in target lesions was not available and patients for whom the best percentage change in target lesion was contradicted by overall lesion response = unknown were excluded from the analysis. Percentage above used n as denominator. Only patients with measurable disease at baseline were presented.

1. Rugo HS, et al. ASCO 2020. Abstract 1006 (oral); 2. Ciruelos EM, et al. SABCS 2021. Abstract P1-18-03 (poster); 3. Rugo HS, et al. SABCS 2021. Abstract PD13-05 (poster); 4. Rugo HS, et al. SABCS 2020. Abstract PD2-07 (poster).

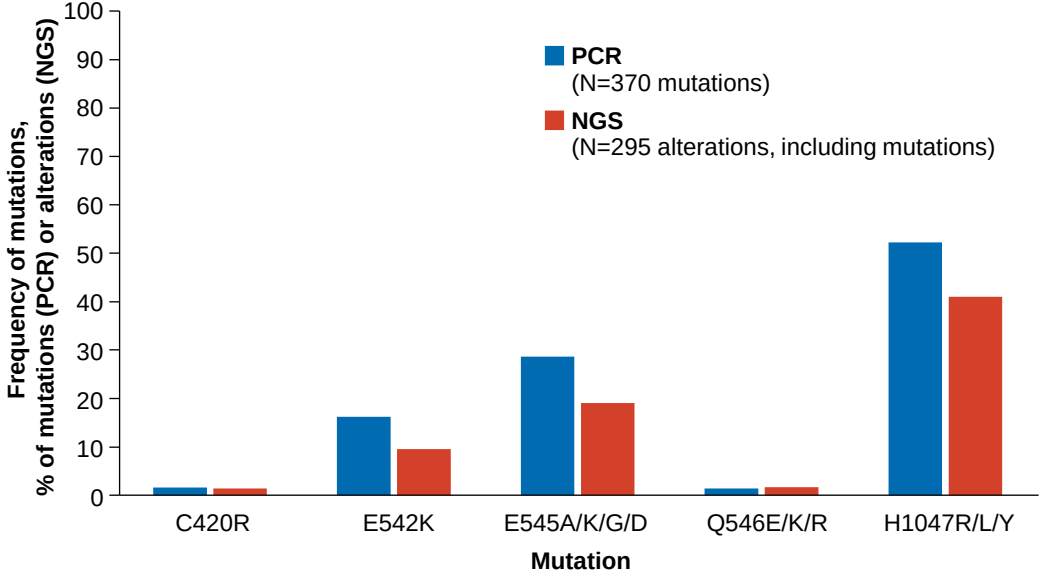
With the approval of alpelisib in PIK3CA mutated ABC

1) What to test

PIK3CA Mutation Testing Can Be Performed by PCR or NGS

- Both PCR-based testing and NGS can detect mutations in *PIK3CA*[1]
- NGS can detect any DNA alteration within a target region, whereas PCR is limited to detecting specific mutations by design[2]
- The majority of all *PIK3CA* mutations observed in HR+, HER2– ABC occur in exons 9 (helical domain) and 20 (kinase domain)[3]
- 11 hotspot mutations in exons 7, 9, and 20 detected by PCR were used to assess *PIK3CA* mutation status in SOLAR-1 and retrospective NGS analyses were consistent with PCR findings[4,a]

Frequency of *PIK3CA* Mutations in SOLAR-1 Detected in FFPE Tumor Specimens by PCR or NGS[4,b-d]



[a]*PIK3CA* mutations detectable by PCR-based assay: C420R in exon 7; E524K, E545A/D/G/K, Q546E/R in exon 9; H1047L/R/on 20.[4] The clinical significance of rarer *PIK3CA* mutations, including those in exons 1, 4, 5, 7, 10, and 18, is not yet known.[5]

[b]Figure derived from PCR and NGS data and calculated as [sum of specific mutation(s) / all mutations (for PCR) or alterations (for NGS)] × 100. [c]The Novartis clinical trial assay did not differentiate all mutations and reported E545X for E545A/D/G/K mutations, Q546X for Q546E/K/R mutations, and H1047X for H1047L/R/Y mutations. [d]Of the 295 alterations detected by retrospective NGS testing, 83 (28.1%) alterations were not detectable by PCR-based testing.

1. Arsenic R, et al. *BMC Clin Pathol*. 2015;15:20; 2. My Cancer Genome. https://www.mycancergenome.org/content/molecular-medicine/types-of-molecular-tumor-testing/. Accessed July 21, 2019; 3. Ishida N, et al. *Oncotarget*. 2018;9(25):17711-17724; 4. Rugo HS, et al. AACR 2019. Abstract CT142 (poster); 5. Gymnopoulos M, et al. *Proc Natl Acad Sci U S A*. 2007;104(13):5569-5574.

Planned Exploratory Biomarker Analysis With SOLAR-1 Baseline Tumor Samples

Primary Analysis[1]

- Baseline tissue samples from 572 SOLAR-1 randomized patients

Real-time PCR with QIAGEN *therascreen*® *PIK3CA* RGQ PCR kit

- *PIK3CA* Wild-type by PCR N=231
- *PIK3CA* Altered[a] by PCR N=341

Intention-to-Treat (ITT) *PIK3CA*-Altered Cohort

Retrospective Analysis

- Baseline FFPE tissue samples from SOLAR-1 patients with samples available
- 70% (n/N=398/572) of SOLAR-1 samples included
- 80% (n=319) primary tumor samples and 20% (n=79) metastatic samples

NGS with FoundationOne CDx 324-gene panel

- *PIK3CA* Wild-type by NGS N=161
- *PIK3CA* Altered[a] by NGS N=237

Biomarker *PIK3CA*-Altered Cohort

- Clinical benefit was assessed using progression-free survival (PFS) and hazard ratio (HR)
- HR (95% CI) was estimated using a multivariate Cox PH model by adjusting multiple clinical covariates including age, ECOG PS, bone lesion, lung/liver metastases, and prior CDK4/6 inhibitor treatment
- No multiple testing adjustments were made in this subgroup analysis

[a]Altered includes both *PIK3CA* mutations and amplifications.

CDK4/6, cyclin-dependent kinase4/6; CDx, companion diagnostic; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed, paraffin-embedded; HR, hazard ratio; ITT, intention-to-treat; NGS, next-generation sequencing; PCR, polymerase chain reaction; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RGQ, Rotor-Gene Q.

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940.

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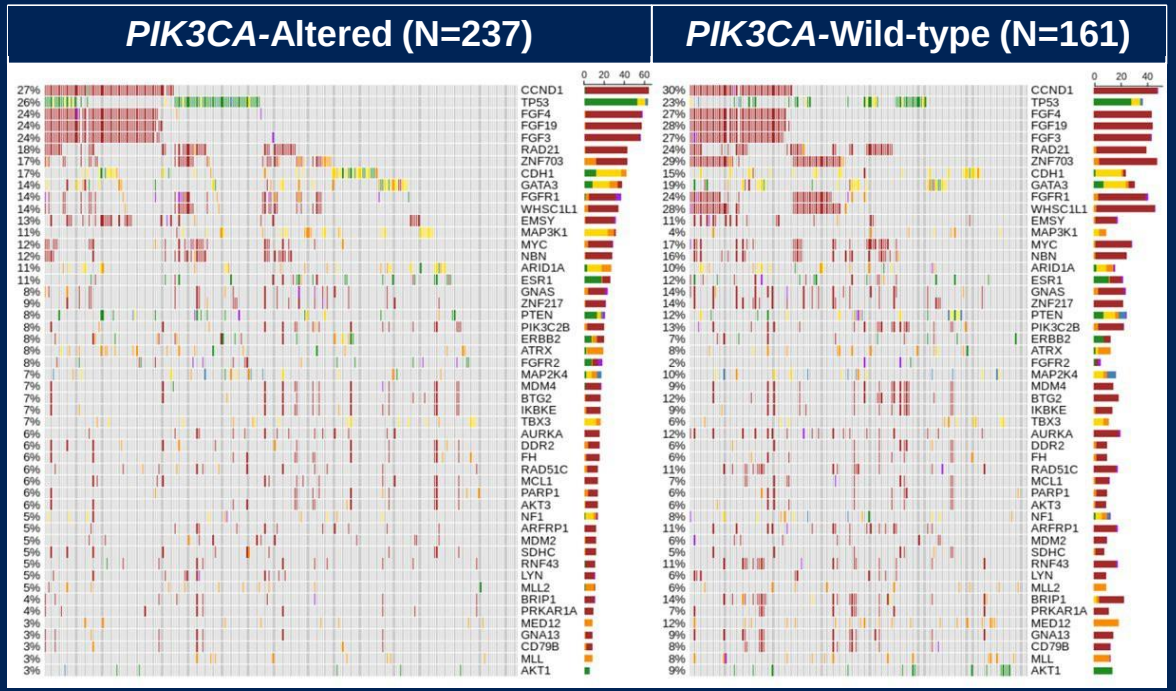
Genes Are Differentially Altered in *PIK3CA*-Altered and *PIK3CA*-Wild-type Biomarker Cohorts



- NGS sequencing of baseline tumor samples from patients randomized in SOLAR-1 including both the *PIK3CA*-altered and *PIK3CA*-wild-type cohorts

FUL, fulvestrant; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SV, sequence variant.

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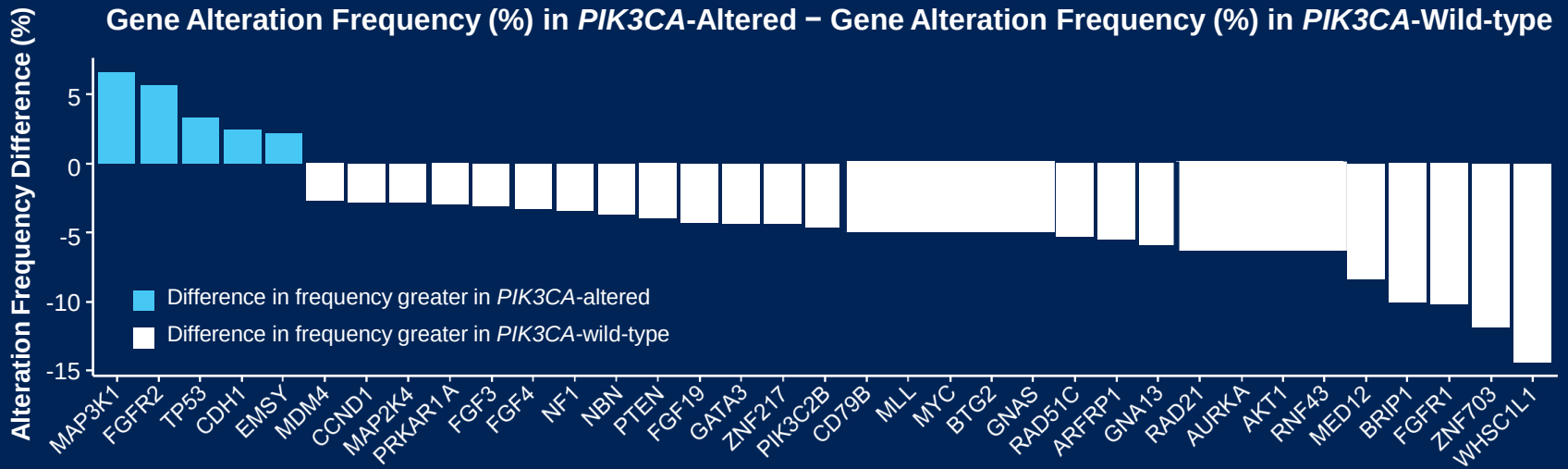
Differences in Alteration Frequency Between *PIK3CA*-Altered and *PIK3CA*-Wild-type Biomarker Cohorts



- Includes 35 genes with >2% gene alteration change between *PIK3CA*-altered and *PIK3CA*-wild-type cohorts

PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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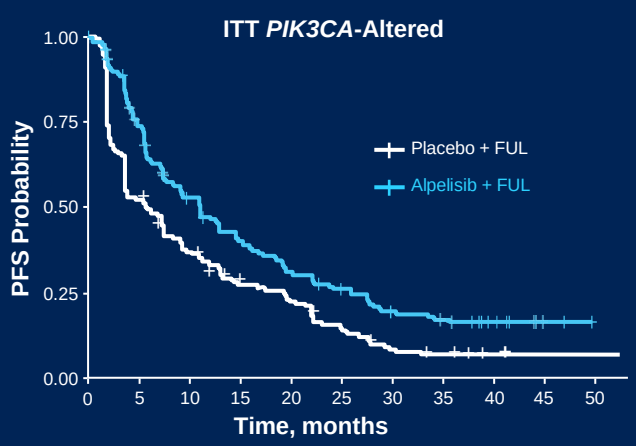
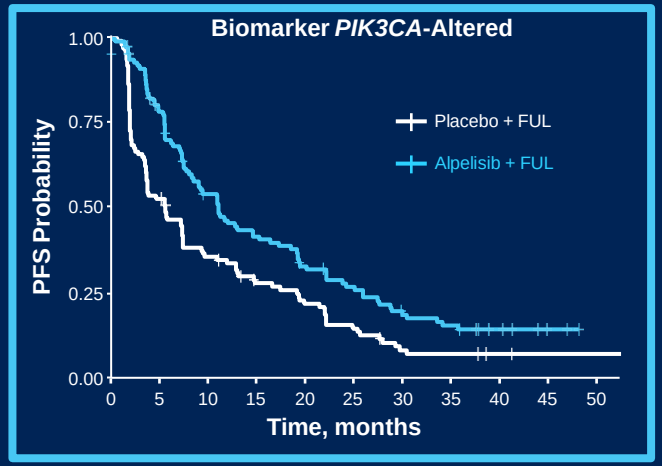
Efficacy of Alpelisib + FUL in Patients With Altered *PIK3CA* Is Consistent in SOLAR-1 ITT and Biomarker Cohorts





- Biomarker *PIK3CA*-altered cohort includes 70% of the ITT *PIK3CA*-cohort
- *PIK3CA* alterations were detected by PCR in the ITT cohort and NGS in the Biomarker cohort

	Placebo + FUL		Alpelisib + FUL		
Cohort	**n/N**	**mPFS, mo (95% CI)**	**n/N**	**mPFS, mo (95% CI)**	**HR (95% CI)**
ITT *PIK3CA*-Altered	149/172	**5.7** (3.7-7.4)	124/169	**11.0** (7.5-14.5)	0.59 (0.43-0.81)
Biomarker *PIK3CA*-Altered	101/117	**5.6** (3.6-7.4)	90/120	**11.0** (8.3-15.2)	0.56 (0.42-0.76)

FUL, fulvestrant; HR, hazard ratio; ITT, intention-to-treat; mPFS, median progression-free survival; n, number of events; N, number of patients; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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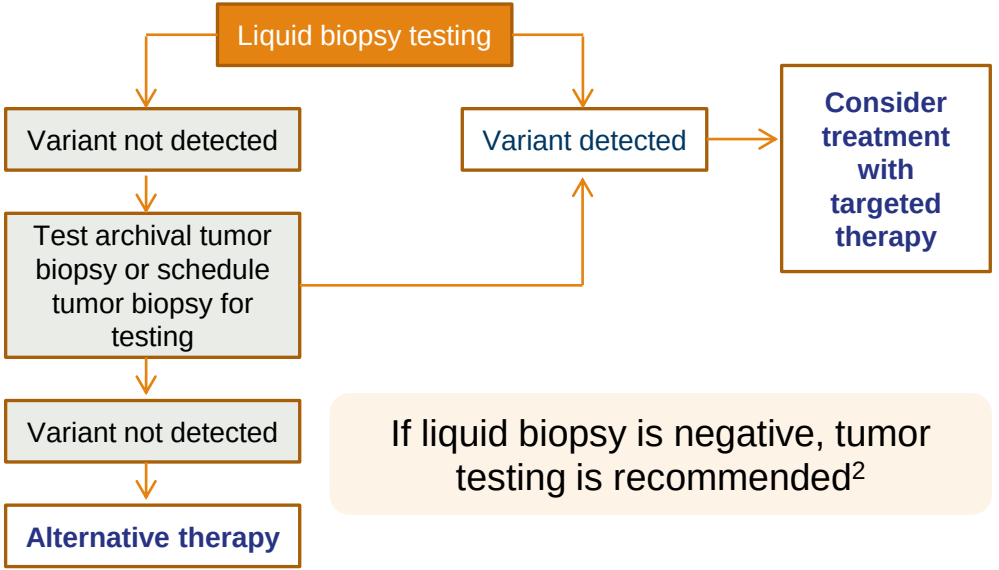
KNOWLEDGE CONQUERS CANCER

What to test?
Tumor Tissue or ctDNA Can Be Used to Test for *PIK3CA* Mutations

- Treatment guidelines recommend testing for *PIK3CA* mutations in tissue (metastasis or primary) and/or ctDNA in blood for the selection of patients with HR+, HER2– ABC who are eligible for alpelisib[1-3]



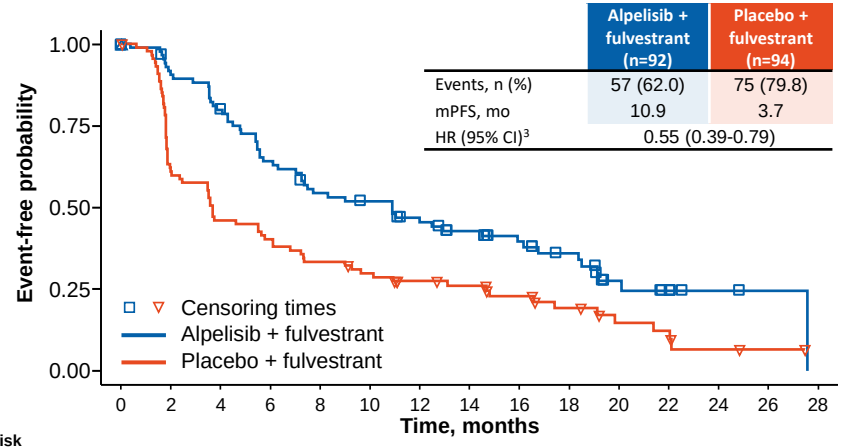
Based on Merker JD, et al. *Arch Pathol Lab Med*. 2018;142(10):1242-1253.

1. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649; 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V8.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 17, 2021; 3. Burstein HJ, et al. *J Clin Oncol*. 2021;JCO2101392.

SOLAR-1: Alpelisib Demonstrated Clinical Benefit in Patients With *PIK3CA* Mutations Detected in Plasma ctDNA[1,2]

Patients with high levels of *PIK3CA* mutation detectable in plasma ctDNA have worse prognosis and poor survival compared with patients with low or no detectable *PIK3CA* mutation[3,4]

Progression-Free Survival[1]



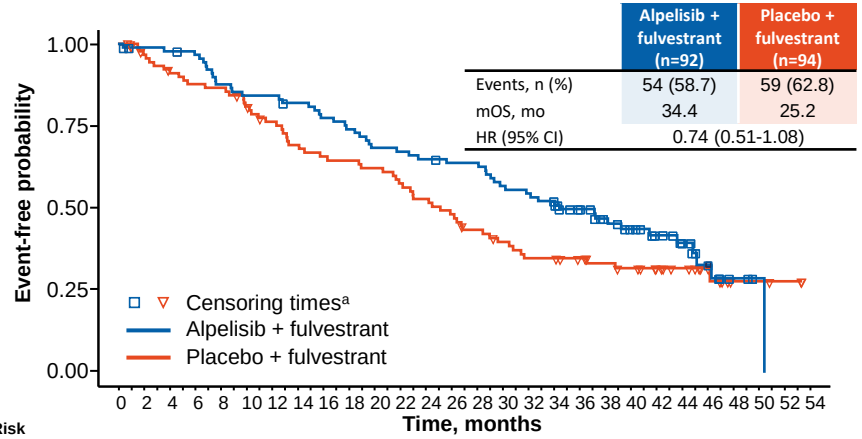
	Alpelisib + fulvestrant (n=92)	Placebo + fulvestrant (n=94)
Events, n (%)	57 (62.0)	75 (79.8)
mPFS, mo	10.9	3.7
HR (95% CI)[3]	0.55 (0.39-0.79)	

No. at Risk

Alpelisib + fulvestrant	92	87	80	77	68	61	54	52	44	43	41	38	34	31	29	24	23	19	18	16	9	8	6	2	2	1	1	1	0
Placebo + fulvestrant	94	90	58	53	42	41	37	34	30	30	26	22	20	19	18	14	14	11	10	9	6	6	5	2	2	1	1	1	0

A **7.2-mo improvement in mPFS** was observed in the alpelisib vs placebo arms

Overall Survival[2]



	Alpelisib + fulvestrant (n=92)	Placebo + fulvestrant (n=94)
Events, n (%)	54 (58.7)	59 (62.8)
mOS, mo	34.4	25.2
HR (95% CI)	0.74 (0.51-1.08)	

No. at Risk

Alpelisib + fulvestrant	92	89	88	86	78	75	75	72	68	65	60	59	57	55	55	49	47	45	37	30	25	20	15	9	3	1	0	0
Placebo + fulvestrant	94	87	82	78	77	71	65	59	56	55	53	49	45	41	36	32	28	28	25	22	20	16	13	8	3	3	2	0

A **9.2-mo improvement in mOS** was observed in the alpelisib vs placebo arms

[a]Date of censoring is defined as the last contact date for OS.

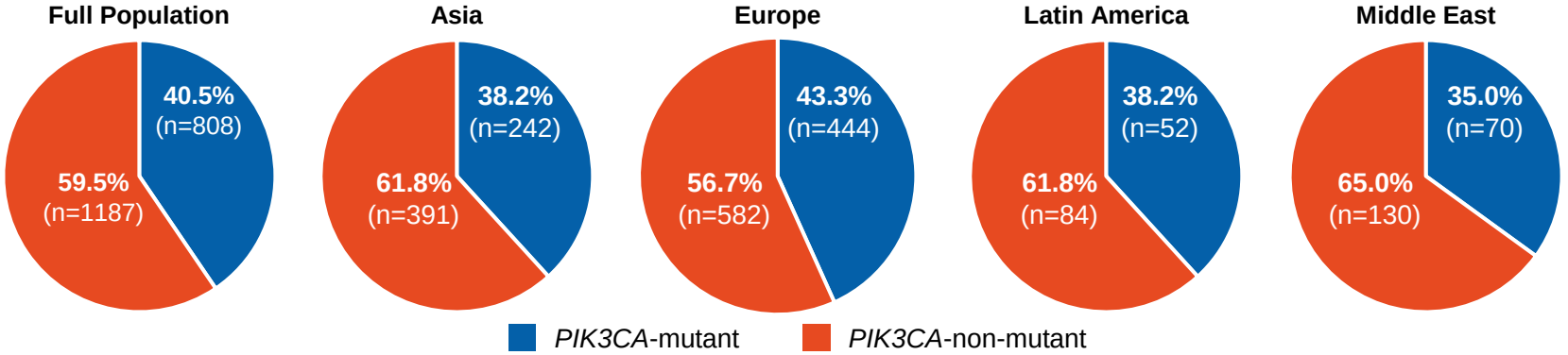
1. Juric D, et al. SABCS 2018. Abstract GS3-08 (oral); 2. André F, et al. ESMO 2020. Abstract LBA18 (oral); 3. Dumbrava EE, et al. *ESMO Open.* 2021;6(5):100230; 4. Cullinane C, et al. *JAMA Netw Open*. 2020;3(11):e2026921.

The *PIK3CA* Registry Confirms *PIK3CA* Mutation[a] Prevalence in a Real-World HR+, HER2− ABC Population Across Several Geographical Regions[1]

Expert guidelines recommend testing for *PIK3CA* mutations at advanced diagnosis; however, data on *PIK3CA* mutation prevalence in a broader population outside of clinical trials are limited

This noninterventional, retrospective cohort study enrolled approximately 2000 adult patients in 29 countries across 4 regions, with histologically and/or cytologically confirmed diagnosis of HR+, HER2− breast cancer by a local laboratory

PIK3CA Mutation Frequency Overall and by Geographic Region[1]



PIK3CA mutation rates were consistent across regions and similar in range whether tested on primary or metastatic tumors[1]

[a]For this study, *PIK3CA* mutations include the 11 hoptspot mutations as studied in SOLAR-1: C420R, E542K, E545A/D/G/K, Q546E/R, H1047L/R/Y.[2]

1.Rajadurai P, et al. SABCS 2021, Abstract P5-13-25 (poster); 2. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940.

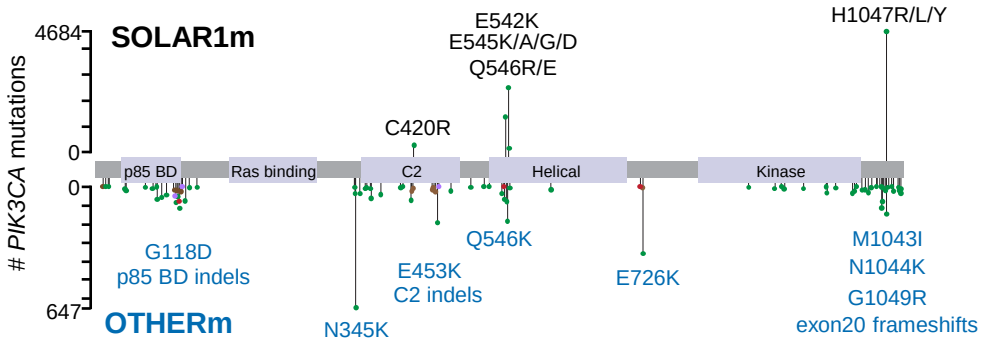
PIK3CA-activating Mutations Were Detected in 35% of Patients With HR+, HER2− ABC in a US Real-World Study[1]

Among the 31,768 BC tissue biopsies:

- 11,204 (35%) had a ***PIK3CA* mutation**
- 8750 (28%) had mutations that were observed in SOLAR-1 (**SOLAR1m**), 1146 of which also had ≥1 other additional *PIK3CA* mutation (**OTHERm**)
- In addition, 2119 (6.7%) patients had ≥1 **OTHERm** without any SOLAR1m

Prevalence of SOLAR1m and OTHERm in breast cancer[1]

PIK3CA variants detected among 31,758 (11,204 *PIK3CA*-altered) BC tissue biopsies:



	SOLAR1m					OTHERm																
	H1047R/L/Y	E545K/A/D/G	E542K	C420R	Q546R/E	N345K	E726K	p85 BD indel	C2 indels	G1049R	Q546K	E453K	G118D	M1043I	N1044K	E81K	E365K	E418K	E545Q	R88Q	exon 20 fs	K111E	Others
% Tissue N=31,758	14.7	7.9	4.3	0.8	0.4	1.9	1.1	1.0	0.5	0.4	0.4	0.4	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	3.6
% Liquid N=1,346	12.9	7.8	3.5	0.7	0.3	1.7	1.2	1.2	0.7	0.5	0.2	0.8	0.1	0.4	0.1	0.3	0.4	0.3	0	0.1	0.3	0.1	4.2

1. Rugo HS, et al. ASCO 2021. Abstract 1068 (poster).

With the approval of alpelisib in PIK3CA mutated ABC

1) What to test

2) Who to treat

Patients Whose Tumors Had Mutations in 11 Hotspots Were Included in the SOLAR-1 Mutant Cohort[1,2]

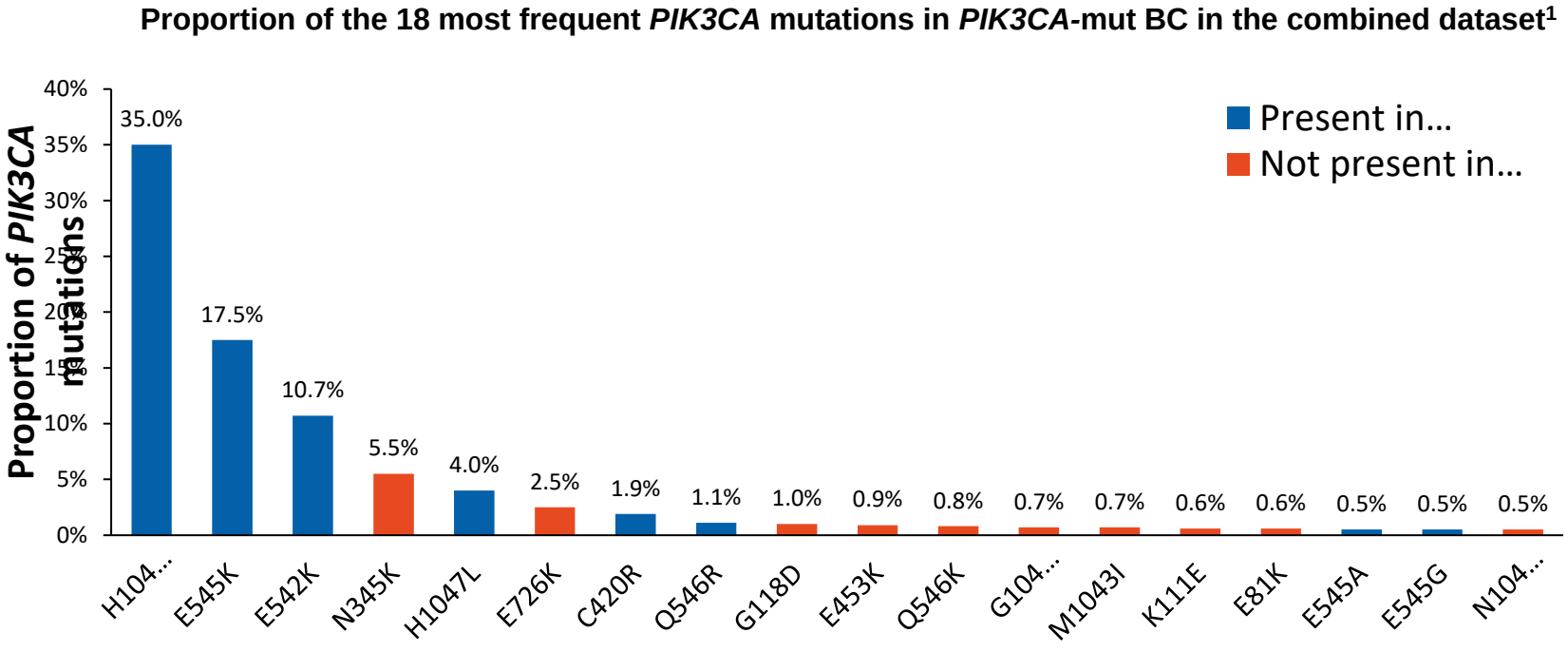
- The 11 hotspots included in SOLAR-1, **C420R, E542K, E545A/D/G/K, Q546E/R, H1047L/R/Y**, shown in white in the table, detected by the therascreen *PIK3CA* 11-mutation assay in tumor tissue,[1,2] represent >80% of all patients with a known *PIK3CA* mutation[3,4]
- *PIK3CA* mutations outside the hotspots detected by the Qiagen therascreen *PIK3CA* PCR kit are shown in light blue

The 20 Most Frequent *PIK3CA* Mutations in BC[4]

Type of PIK3CA mutation	Exon	Oncogenic by OncoKB[5]	Level of evidence to predict alpelisib benefit	Detected by therascreen	Number of mutations found in the combined dataset	Mutation frequency, %
H1047R	20	Yes	1	Yes	895	35.0
E545K	9	Yes	1	Yes	447	17.5
E542K	9	Yes	1	Yes	274	10.7
N345K	4	Yes	Yes (preclinical only)	No	142	5.5
H1047L	20	Yes	1	Yes	103	4.0
E726K	13	Inconclusive. Probably oncogenic	Unknown	No	65	2.5
C420R	7	Yes	1	Yes	48	1.9
Q546R	9	Yes	1	Yes	27	1.1
G118D	1	Yes	Unknown	No	26	1.0
E453K	7	Yes	Unknown	No	22	0.9
Q546K	1	Yes	Yes (preclinical only)	No	21	0.8
G1049R	20	Yes	Yes (preclinical only)	No	19	0.7
M1043I	20	Yes	Unknown	No	19	0.7
K111E	1	Yes	Unknown	No	16	0.6
E81K	1	Inconclusive. Probably oncogenic	Unknown	No	15	0.6
E545A	9	Yes	1	Yes	13	0.5
E545G	9	Yes	1	Yes	13	0.5
N1044K	20	Yes	Unknown	No	12	0.5
E110del	1	Yes	Unknown	No	11	0.4
Q546P	9	Yes	Unknown	No	10	0.4

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940; 2. Rugo HS, et al. AACR 2019. Abstract CT142 (poster);
3. Vorkas PA, et al. *J Mol Diagn*. 2010;12(5):697-704; 4. Martínez-Sáez O, et al.. *Breast Cancer Res.* 2020;22(1):45; 5. Dogruluk T, et al. *Cancer Res*. 2015;75(24):5341-5354.

There Are 5 *PIK3CA* Mutations With a Prevalence ≥4% in Patients With Breast Cancer



1. Martínez-Sáez O, et al.. *Breast Cancer Res*. 2020;22(1):45.

With the approval of alpelisib in PIK3CA mutated ABC

1) What to test
2) Who to treat
3) When to test

PIK3CA Mutation Testing Can Identify Patients Who Are Likely to Benefit From Alpelisib[1]

- International expert guidelines encourage biopsy at first metastasis and, when feasible, at the time of disease recurrence[2-4]

ABC5[2]	▪ Biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis, particularly when metastasis is diagnosed for the first time ▪ Biologic markers (especially HR and HER2) should be reassessed at least once in the metastatic setting if clinically feasible
NCCN[3]	▪ First recurrence of disease should be biopsied ▪ Assess for *PIK3CA* mutation if HR+, HER2– and if considering therapy with alpelisib for stage IV recurrent or initially metastatic disease
ASCO[4]	▪ A biopsy is recommended to determine or confirm whether a suspicious lesion represents metastatic disease ▪ Markers should be obtained ▪ Every attempt should be made to test the most recent tumor tissue sample for *PIK3CA* mutation
ESMO[1,5,6]	▪ Patients with newly diagnosed or recurrent MBC should have a biopsy, if technically feasible, to confirm histology and to re-assess ER, PgR, and HER2 status ▪ Other therapeutically relevant biomarkers to be assessed as part of routine clinical practice include *PIK3CA* in ER/PgR-positive, HER2-negative MBC ▪ *PIK3CA* mutations are a clinically validated biomarker that predict efficacy of alpelisib (ESCAT level IA)

1. Mosele F, et al. *Ann Oncol.* 2020;31(11):1491-1505; 2. Cardoso F, et al. *Ann Oncol*. 2020;31(12):1623-1649; 3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V8.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed September 17, 2021; 4. Rugo HS, et al. *J Clin Oncol*. 2016;34(25):3069-3103; 5. Gennari A, et al. *Ann Oncol*. 2021;32(12):1475-1495; 6. Mateo J, et al. *Ann Oncol*. 2018;29(9):1895-1902.

Thank you

Q&A

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Panel Discussion
Clinical Case Consideration

- 51-year-old woman underwent a left modified radical mastectomy
  - The mass was LN 7/41, pT2 (4.5 cm), N2aM0
  - **ER positive** (70%); **PgR** (5-10%); **HER2 IHC** (2+), **FISH negative**
- A biopsy of the mass was performed, revealing a grade 3 invasive ductal carcinoma
- She received anthracycline and taxane adjuvant chemotherapy followed by adjuvant radiotherapy
- She then received tamoxifen (5 years' duration) followed by letrozole
- One year later she experiences persistent cough and exertional dyspnea
- She is diagnosed with metastatic carcinoma

Which biomarkers should be tested for and when?

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Panel Discussion

- Considering the prognostic value of PIK3CA mutation for patients in breast cancer, should we be testing for it upon initial diagnosis rather than just for treatment decision in advanced setting?

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Panel Discussion

- Breast cancer is highly heterogeneous, how can we better characterize the genomic profile or incorporate genetic testing into routine clinical practice for better patient outcomes?

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Panel Discussion

- How can oncologists and pathologists work together to improve patient outcomes?

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Thank you

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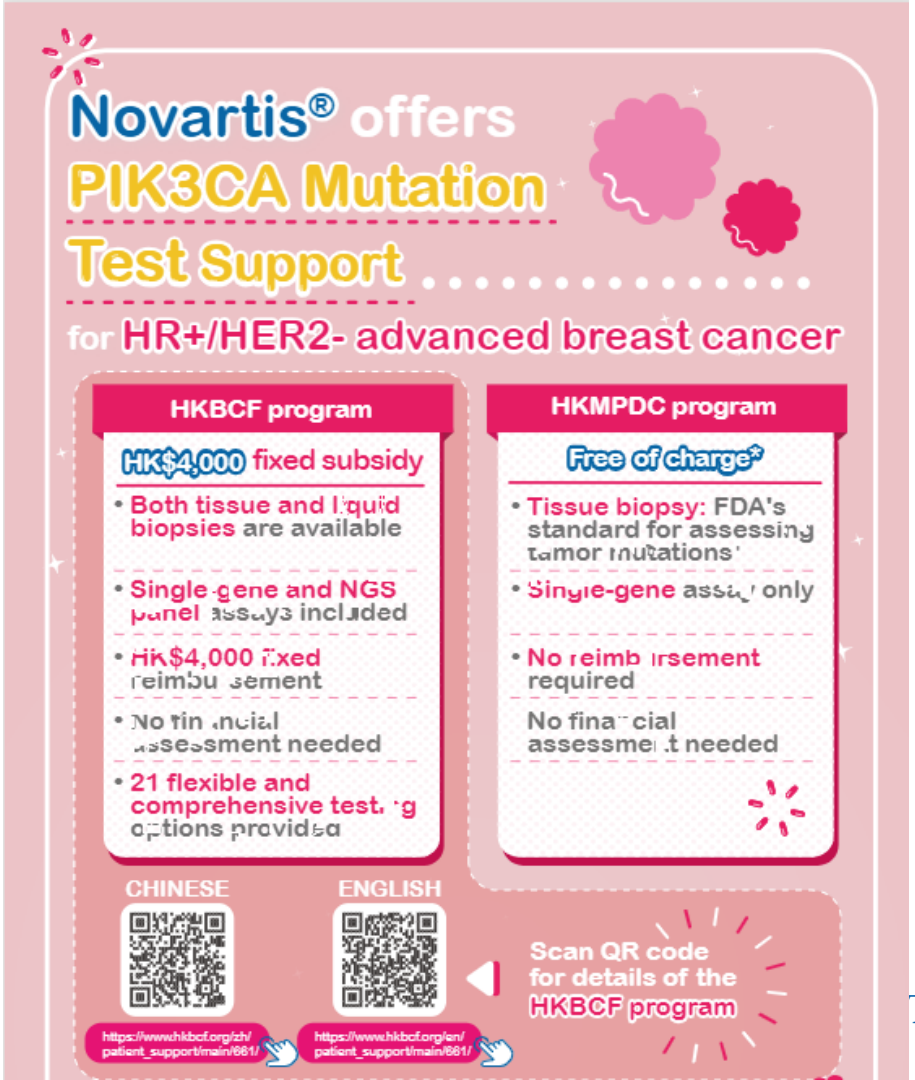
Novartis® offers
PIK3CA Mutation Test Support
for HR+/HER2- advanced breast cancer
HKBCF program
HK$4,000 fixed subsidy
• Both tissue and liquid biopsies are available
• Single-gene and NGS panel assays included
• HK$4,000 fixed reimbursement
• No financial assessment needed
• 21 flexible and comprehensive testing options provided
HKMPDC program
Free of charge*
• Tissue biopsy: FDA's standard for assessing tumor mutations
• Single-gene assay only
• No reimbursement required
No financial assessment needed
CHINESE
ENGLISH
Scan QR code for details of the HKBCF program
https://www.hkbcf.org/zh/patient_support/main/661/
https://www.hkbcf.org/en/patient_support/main/661/

HKBCF x Novartis:
Gene Testing Financial Assistance Program

ACT Genomics	Hong Kong Molecular Pathology Diagnostic Centre	Hong Kong Sanatorium & Hospital	Lucence Diagnostics	Roche	University Pathology Service, CUHK
• ACTDrug® + • ACTMonitor® Breast • ACTOnco® +	• Cancer Hotspot NGS Panel • PIK3CA Hotspot Mutation Test (Blood) • PIK3CA Hotspot Mutation Test (Tissue)	• **PIK3CA by Sanger sequencing** • **PIK3CA by NGS** • Somatic Breast Cancer Panel by NGS	• Liquid HALLMARK • Liquid MARK Breast • **Liquid MARK single PIK3CA gene** • Tissue 500 • Tissue HALLMARK • Tissue MARK Breast • **Tissue MARK single PIK3CA gene**	• FoundationOne CDx • FoundationOne Liquid CDx	• cfDNA PIK3CA test • CUHK Somatic Mutation v3 Test for Solid Cancers (Tissue) • Focused Mutation Panel for solid cancers (Tissue) • PIK3CA gene hotspot mutation detection (Exon 7, 9 and 20) • Roche Avenio surveillance mutation panel for solid cancers on peripheral blood (197 genes) • small RNA fusion panel (15 genes)