COR2ED

THE HEART OF MEDICAL EDUCATION

VIRTUAL EXPERTS KNOWLEDGE SHARE

PRECISION ONCOLOGY IN PRACTICE – THE JOURNEY FROM TESTING TO TREATMENT IN LUNG AND PROSTATE CANCER

Tuesday 30th April 2024

DEVELOPED BY PRECISION ONCOLOGY CONNECT

This programme is developed by PRECISION ONCOLOGY CONNECT, an international group of experts in the field of oncology.

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POWERED BY COR2ED

Acknowledgement and disclosures

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- **Prof. Fernando Lopez-Rios:** AbbVie, Astellas, AstraZeneca, Bayer. BMS, Daiichi Sankyo, Janssen, Lilly, Merck, MSD, Pfizer, Roche, Takeda and Thermo Fisher
- **Assoc. Prof. Alicia Morgans:** Astellas, AstraZeneca, AAA, Bayer, Exelixis, Janssen, Lantheus, Myovant, Novartis, Pfizer, Telix, Sanofi
- **Assoc. Prof. Herbert Loong**: AbbVie, Bayer, Boehringer-Ingelheim, Celgene, Daiichi-Sankyo, Eisai, Eli-Lilly, George Clinical, Guardant Health, Illumina, Merck Sereno, MSD, Mundipharma, Novartis, Pfizer, Takeda

IN THIS MEETING YOU WILL

- Know how to address pre-analytical phase challenges, and how to collect, store, process and prepare the samples
- Recognise the relevant biomarkers and appropriate molecular tests/assays to request for your patients
- Understand the diagnostic modalities, and the role of biomarkers in oncology
- Be able to implement or improve the leading role of the pathologist on the MDT

MDT, multidisciplinary team

AGENDA: TUESDAY 30TH APRIL 2024

PRECISION ONCOLOGY IN PRACTICE – THE JOURNEY FROM TESTING TO TREATMENT IN LUNG AND PROSTATE CANCER

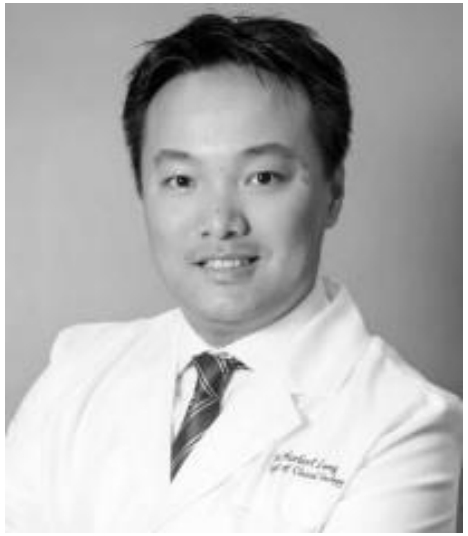
Timings	Topic	Facilitator
5 mins	Welcome and introductions	COR2ED
10 mins	Scene setting: Overview of the challenges related to biomarker testing across all tumours	Fernando López-Ríos
5 mins	Q&A	
20 mins	Addressing the challenges of biomarker testing in **lung cancer***	Herbert Loong
5 mins	Q & A	Fernando López-Ríos
20 mins	Addressing the challenges of biomarker testing in **prostate cancer***	Alicia Morgans
5 mins	Q & A	Fernando López-Ríos
15 mins	Panel discussion and audience questions	All
5 mins	Future perspectives and summary	Fernando López-Ríos

* Includes MDT discussion and best practice recommendations

INTRODUCING THE SCIENTIFIC COMMITTEE

Prof. Fernando López-Ríos

Pathologist
12 de Octubre University Hospital,
Madrid, Spain



Assoc. Prof. Herbert Loong

Medical Oncologist
The Chinese University
of Hong Kong, HK

Assoc. Prof. Alicia Morgans

GU Medical Oncologist
Dana-Farber Cancer Institute,
Boston, USA

OVERVIEW OF CHALLENGES RELATED TO BIOMARKER TESTING ACROSS ALL TUMOURS

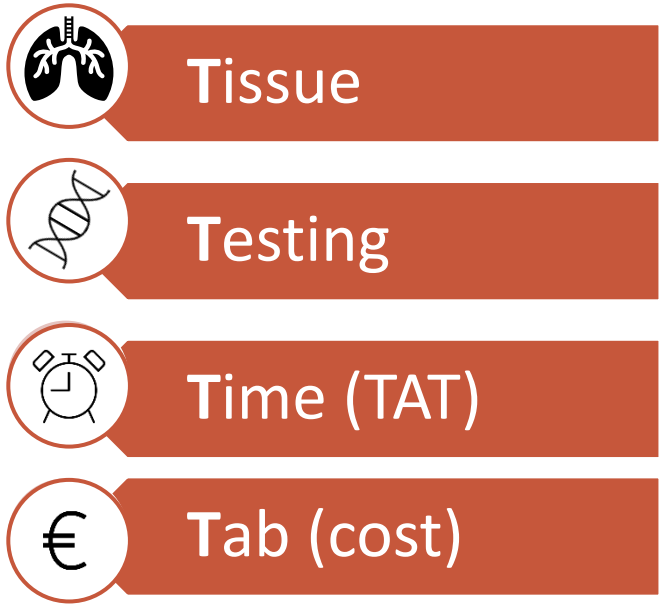
Fernando López-Ríos MD, PhD

Department of Pathology
Hospital Universitario 12 de Octubre
Madrid, Spain

WHAT ARE THE CLINICAL PRACTICE GAPS?

THE FOUR "Ts"

RESULTS: For every 1,000 patients in the study cohort, 497 (49.7%) are lost to precision oncology because of factors associated with getting biomarker test results.



Step 1: Biopsy referral: Initial solid or blood biopsy was never performed
Step 2: Biospecimen collection: Biospecimen collection challenges including insufficient tissue or tumour cell content of initial biopsy or rebiopsy inhibited biomarker testing and its accuracy
Step 3: Biospecimen evaluation/pathology: Biospecimen tumour cell content was overestimated, inhibiting biomarker testing and its accuracy
Step 4: Biomarker test ordering: Appropriate testing was not ordered, or treatment began before testing was ordered
Step 5: Biomarker testing performance: Biomarker testing provided inconclusive or false-negative (FN) results
Step 6: Test result reporting: As a result of turnaround time (TAT) delays, treatment was initiated without consideration of test results
Step 7: Treatment decision: Targeted treatment was not selected despite positive test results

Sadik H, et al. JCO Precis Oncol. 2022:Oct;6:e2200246

CONTENT

Six opportunities for improvement!

- **Tissue:**
  - Less is more
  - A molecular pathology code of conduct
- **Testing**
  - Focus on results not methods
  - The whole is greater than the sum of its parts
- **Time**
  - Remove, do not add
  - Good teams are noisy

CONTENT

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SENSIBLE USE OF DIAGNOSTIC IHC

TISSUE – LESS IS MORE

Key questions and recommendations for diagnostic immunohistochemistry in lung cancer

Key questions	Short answers
1. **What is the best combination of markers to use in daily practice?**	When IHC is needed for the subtyping of NSCC, TTF1 and p40 are the criterion standard, and these two markers are usually sufficient in clinical practice if there are no morphologic features of NE differentiation. p40 is preferable to p63 to identify squamous cell carcinoma
2. **What extent of TTF1- and p40-positive reactions should we consider to be positive?**	Focal positivity for TTF1 is considered a positive reaction indicating pulmonary adenocarcinoma in the proper clinical context, whereas for p40 the cutoff rate should be positivity in more than 50% of tumour nuclei. Focal or weak positivity for p40 is not diagnostic of squamous cell carcinoma
3. **Are there any staining differences in lung among TTF1 clones (SPT24, SP141, and 8G7G3/1)?**	The staining performance of TTF1 varies among the clones. Among the most commonly used antibodies, 8G7G3/1 is the most specific antibody to identify lung adenocarcinoma
4. **Should an NSCC that is diffusely positive for CK7 but negative for TTF1 and p40 be regarded as probably adenocarcinoma?**	CK7 is not specific for adenocarcinoma; the marker can be seen in squamous cell carcinoma. The use of CK7 is discouraged for subtyping of NSCC
5. **When should NE markers be applied to an NSCC?**	NE markers should be applied only in support of NE morphology
6. **What is the best antibody panel to differentiate NE tumours from other types of NSCC, and which one is the most reliable?**	A panel of chromogranin A, synaptophysin, and CD56 is the best combination to identify NE tumours. The staining significance of each antibody varies among the sample types, histologic subtypes, and extent and/or intensity of positive reactions
7. **When should a proliferation marker be used in diagnosis?**	The main established role of Ki-67 in lung carcinomas is to help distinguish carcinoids from high-grade NE carcinomas (large cell NE carcinoma and small cell carcinomas), especially in small or crushed biopsy or cytologic samples. The role of Ki-67 in separating typical from atypical carcinoids is not established and needs more investigation

IHC, immunohistochemistry; NE, neuroendocrine; NSCC, non-small cell carcinoma; TTF1, thyroid transcription factor-1

Yatabe Y, et al. J Thorac Oncol. 2019;14(3):377-407

DNA & RNA: QUANTITY AND QUALITY

A MOLECULAR PATHOLOGY CODE OF CONDUCT

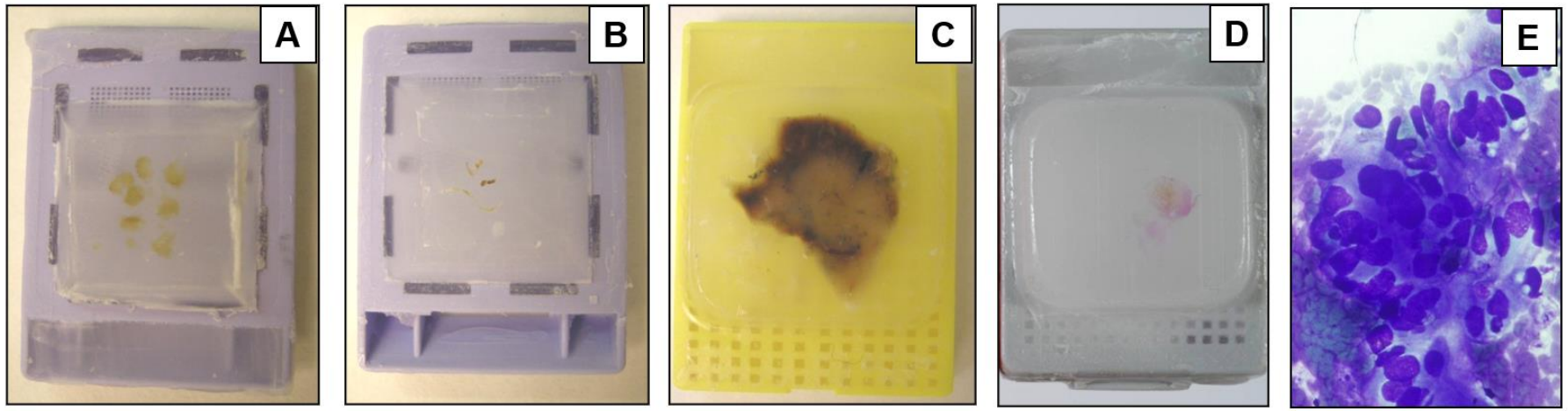
Tissue
- A. Biopsy
- B. Core needle biopsy
- C. Surgical specimen

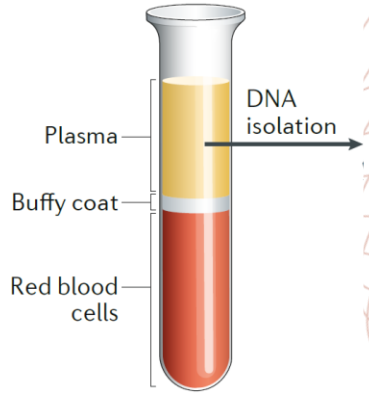
Cytology
- D. Cell block
- E. Cytological slide

Formalin fixed paraffin embedded (FFPE)

✓ Paraffin blocks preferred

E. Cytological slide ⋯⋯▸ Depends on the lab





Personal communication, López-Ríos, F

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COEXISTENCE OF MULTIPLE ASSAYS

FOCUS ON RESULTS NOT METHODS

Methods for detecting mutations

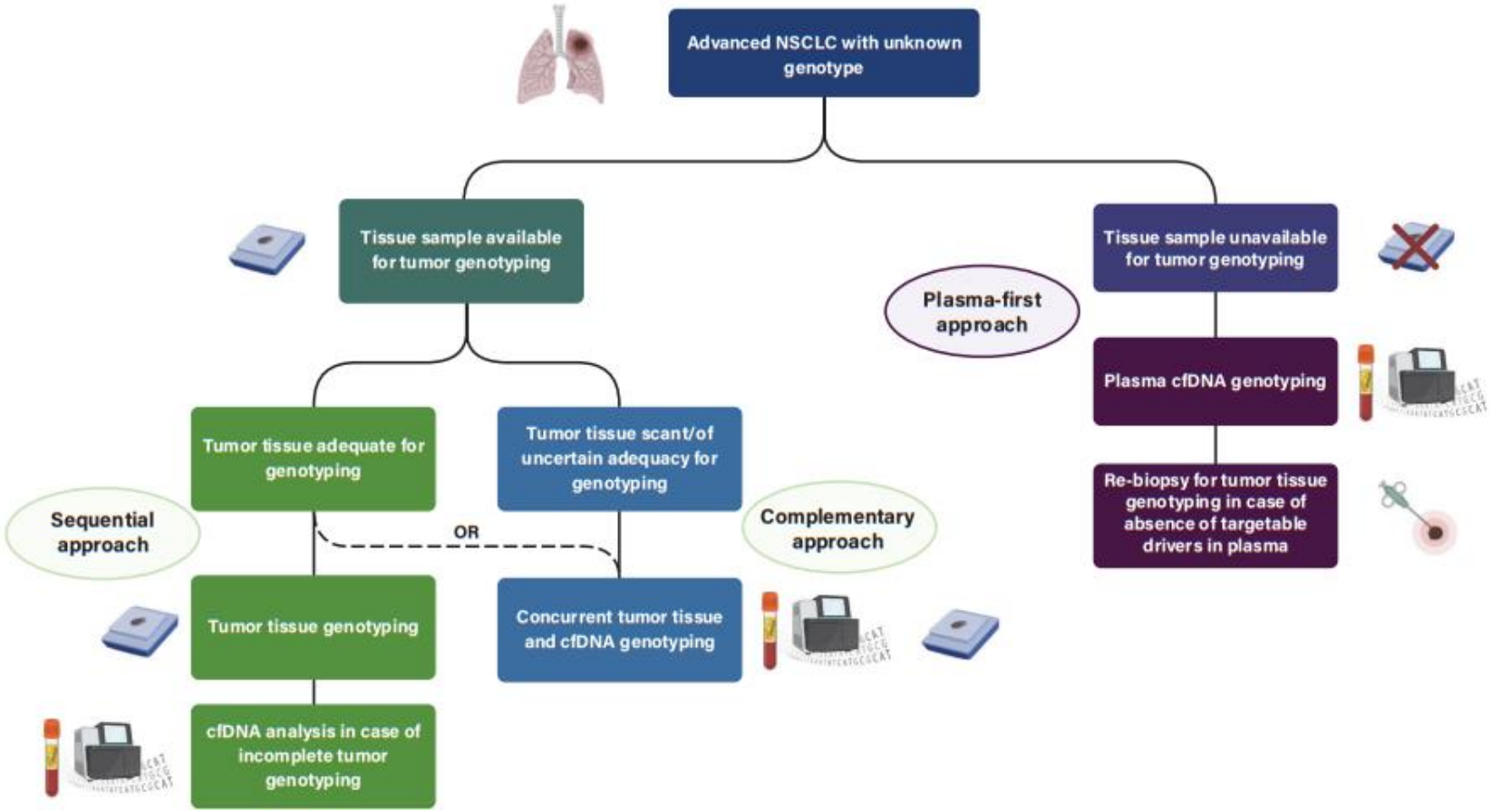
Technique	Analytical sensitivity	Diagnostic sensitivity	Precise annotation of variants	Allele frequency reported	Input DNA	Cost	Turn-around time
PCR and direct sequencing	Lowest	Excellent	Yes	No	High	Lowest	3-4 days
PCR and pyrosequencing	Variable	Intermediate	Sometimes	No	High	Low	3-4 days
Real-time PCR	High	Intermediate	Sometimes	No	Low	Low	Hours to 1-2 days
Digital PCR	Highest	Low	Yes	No	Lowest	Low	Hours to 1-2 days
NGS-targeted amplicon based	Variable (high)	Variable (high)	Yes	Yes	Low	Intermediate	1-2 to 10 days
NGS-targeted hybridisation capture	Variable (high)	Variable (high)	Yes	Yes	High	Intermediate	15-20 days
NGS-whole exome	Variable	Excellent	Yes	Yes	High	High	Weeks
NGS-whole genome	Variable	Excellent	Yes	Yes	High	Highest	Weeks

EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; PCR, polymerase chain reaction

IASLC (International Association for the Study of Lung Cancer) Atlas of Molecular Testing for Targeted Therapy in Lung Cancer 2023. Available at: https://www.iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer/. Accessed 27 February 2024

CORRELATION BETWEEN TISSUE & PLASMA

THE WHOLE IS GREATER THAN THE SUM OF ITS PARTS



cfDNA, cell-free DNA; NSCLC, non-small cell lung cancer

IASLC (International Association for the Study of Lung Cancer) Atlas of Molecular Testing for Targeted Therapy in Lung Cancer 2023. Available at: https://www.iaslc.org/iaslc-atlas-molecular-testing-targeted-therapy-lung-cancer/. Accessed 27 February 2024

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- Tissue:
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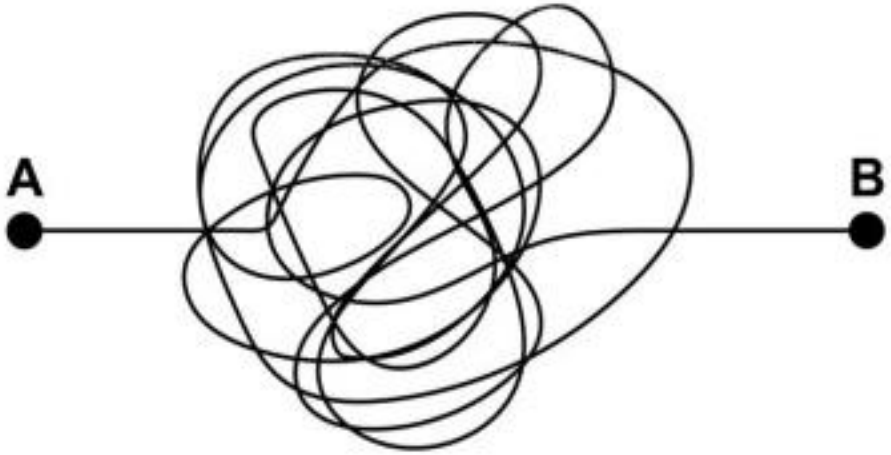
REFLEX WORKFLOW

REMOVE, DO NOT ADD

Remember Gall's Law

If you want to build
a complex system that works,
build a simpler system first,
and then improve it over time



EFFECTIVE COMMUNICATION

GOOD TEAMS ARE NOISY

Intra-laboratory molecular tumour board

- ✓ **Members:**
  - Molecular biologist
  - Pathologist
  - Technicians
- ✓ **Aims:**
  - Check NGS quality
  - Discuss NGS data
  - Request additional molecular studies
  - Integrate histology + clinical history + molecular data
- ✓ **Final result:**
  - NGS report

Pre-analytical & Analytical issues

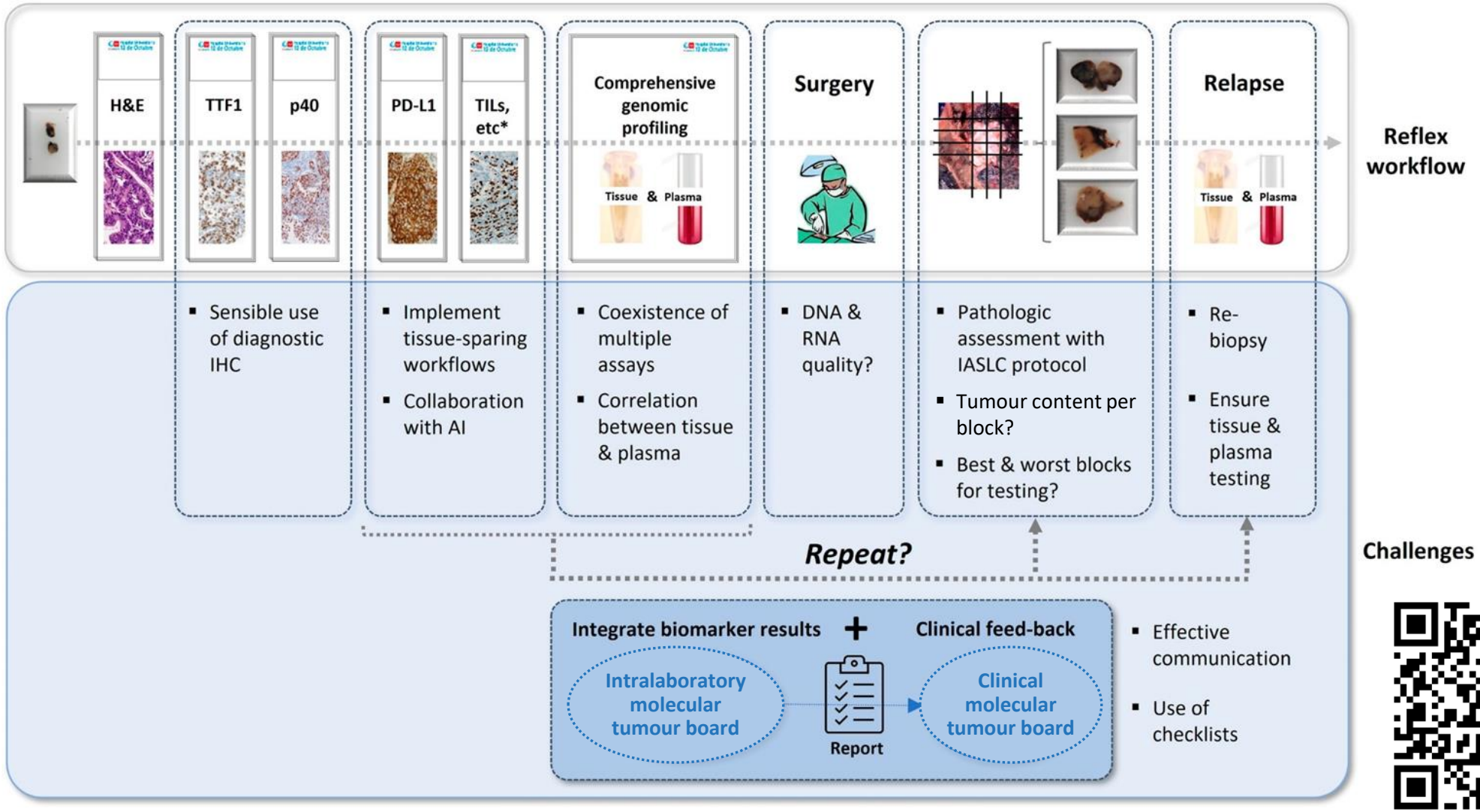
Pathogenicity & Actionability

Molecular redundancy & Pan-negative

NGS, next-generation sequencing

Personal communication, López-Ríos, F

A COMPREHENSIVE PERSPECTIVE OF CANCER BIOMARKER TESTING



AI, artificial intelligence; H&E, hematoxylin and eosin; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry; PD-L1, programmed death ligand-1; TIL, tumour infiltrating lymphocytes; TTF1, thyroid transcription factor-1

Conde E, et al. Mod Pathol. 2022;35:1754-1756

OVERVIEW OF CHALLENGES RELATED TO BIOMARKER TESTING ACROSS ALL TUMOURS

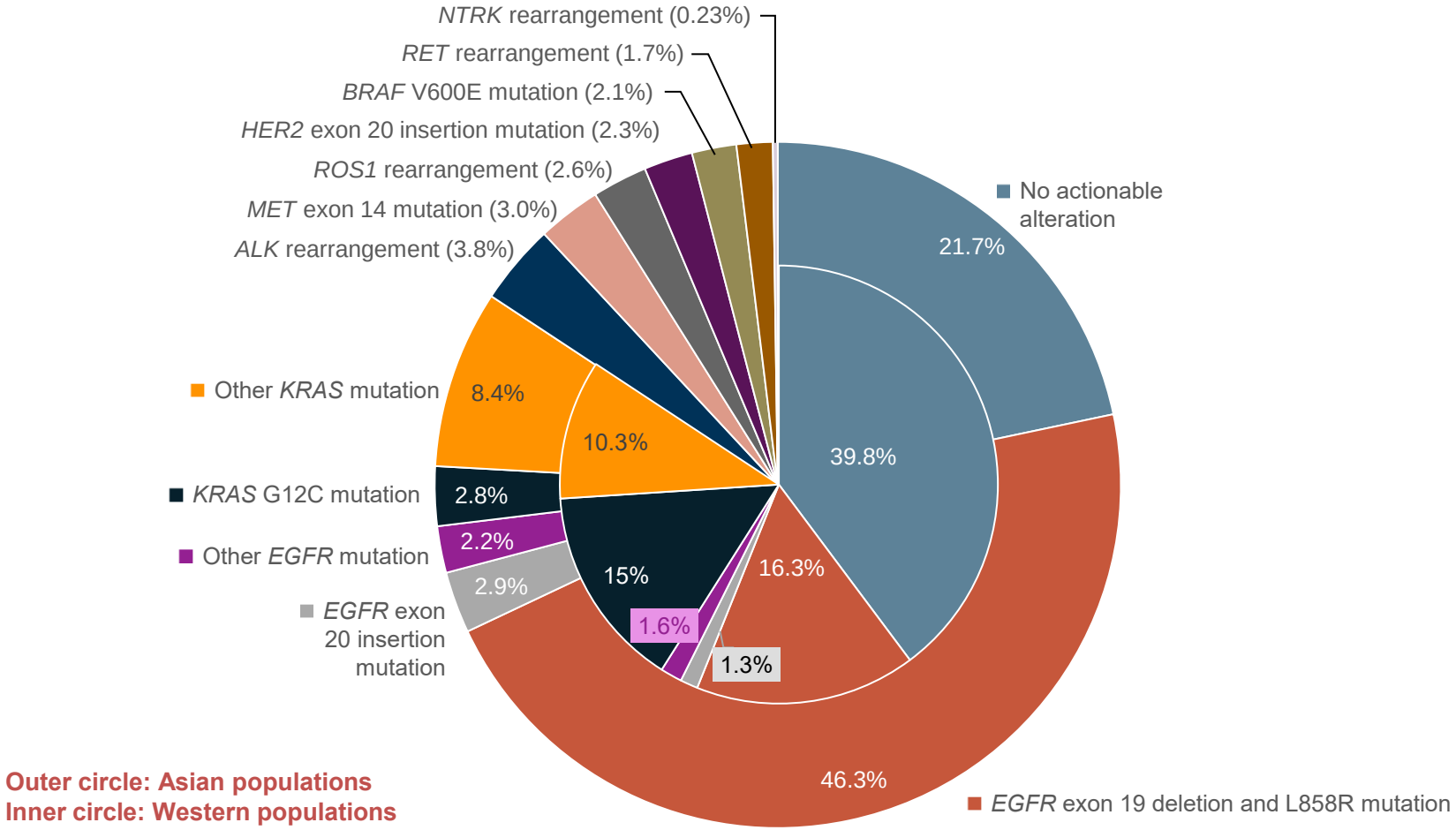
Q&A SESSION

ADDRESSING THE CHALLENGES OF BIOMARKER TESTING IN LUNG CANCER

Assoc. Prof. Herbert Loong

Medical Oncologist
The Chinese University of Hong Kong, HK

ACTIONABLE BIOMARKERS IN LUNG CARCINOMA



ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten ras oncogene; MET, MET proto-oncogene; NTRK, neurotrophic tyrosine receptor kinase; RET, RET proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase

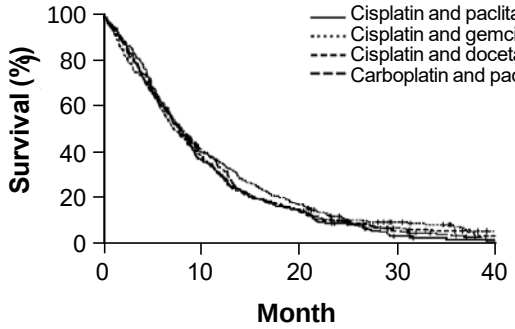
Tan AC and Tan DSW. J Clin Oncol. 2022;40:611-625

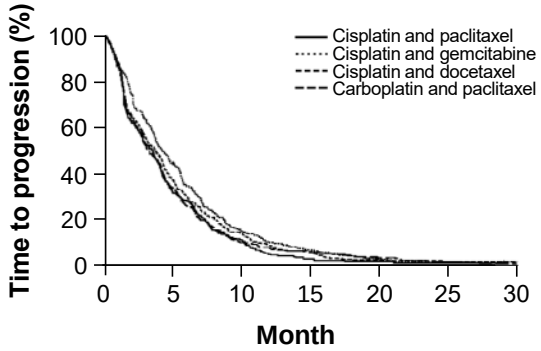
NSCLC as one disease

NSCLC circa 2020

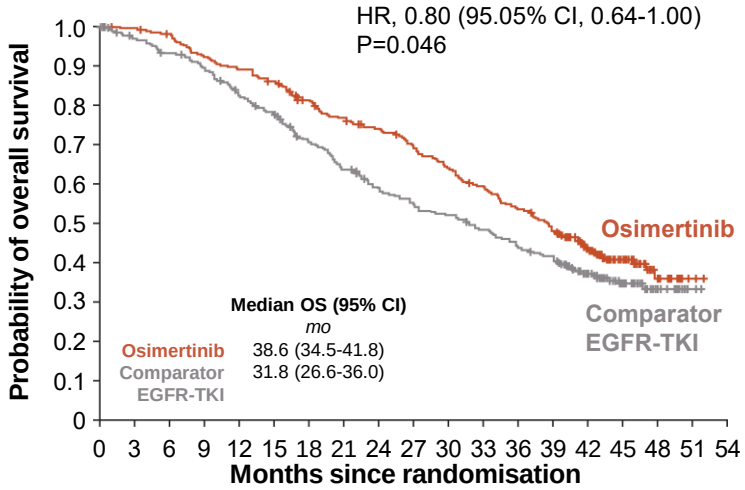
COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

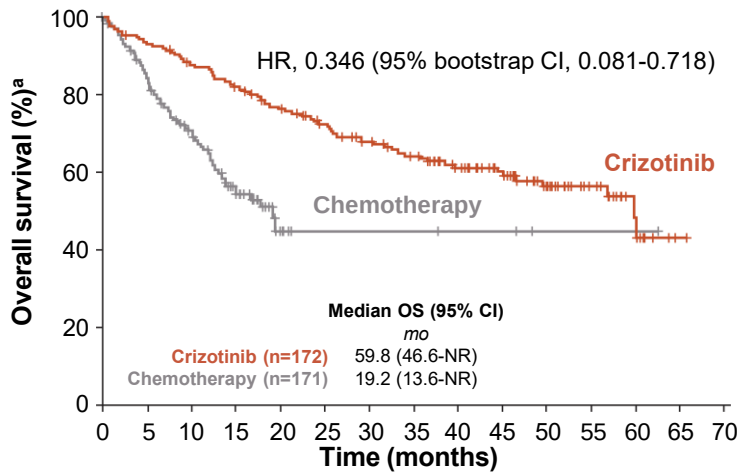




Median OS ~7-8 months
Median TTP 3.5 months
In treatment naïve patients!



EGFR+ (FLAURA – 1st line osimertinib OS = 38.6 mo, comparator [1st gen EGFR TKIs] 31.8 mo)

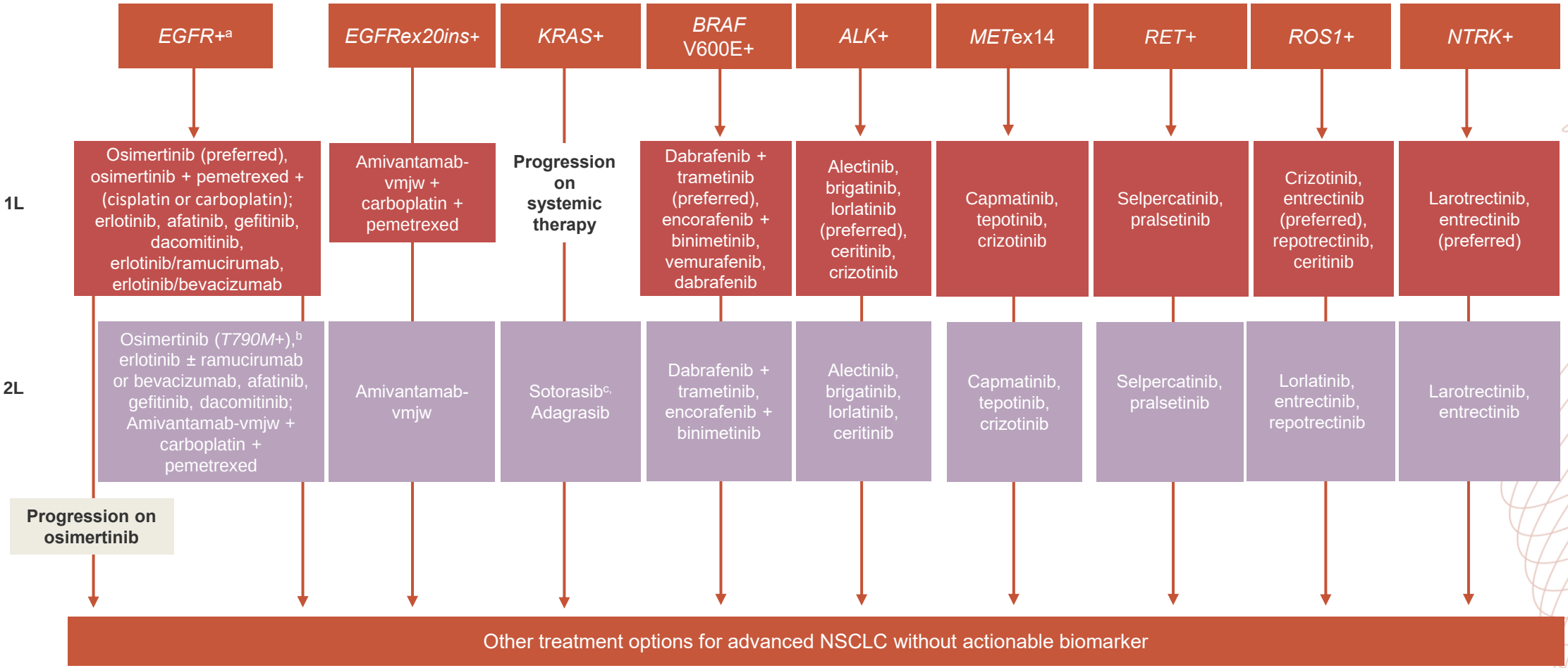


ALK+ (PROFILE 1014) – 1st line crizotinib group median OS = 59.8 mo (upper bound not reached)
[a]OS adjusted for crossover

ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; gen, generation; HR, hazard ratio; mo, months; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor; TTP, time to progression

Schiller JH, et al. N Engl J Med. 2002;346:92-98; Ramalingam SS, et al. N Engl J Med. 2020;382:41-50; Solomon BJ, et al. J. Clin Oncol. 2018;36:2251-2258

CURRENT TREATMENT PARADIGM FOR MOLECULAR BIOMARKER-POSITIVE ADVANCED NSCLC – NCCN GUIDELINES



[a] exon 19 deletion or exon 21 L858R. [b] Osimertinib is recommended as 2L and beyond for patients with *EGFR* T790M-positive metastatic NSCLC who have progressed on erlotinib, afatinib, gefitinib, or dacomitinib.

1L, first line; 2L, second line; ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; KRAS, Kirsten ras oncogene; METex14, MET proto-oncogene exon 14 mutation; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RET, RET proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase

NCCN guidelines V4.2024. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed April 2024

WHAT ARE THE FACTORS THAT CONTRIBUTE TO 'BEST PRACTICE'?

What can the clinician do to help achieve these targets?

Accurate & **Precise** pathological diagnosis

Timely initiation of **Effective** treatment

Accessibility to effective therapies

Molecular testing is now standard of care

Increasing varieties and lines of treatment deemed efficacious

Increasing costs of healthcare and associated disparities

IDENTIFYING THE RIGHT PATIENTS TO BE TREATED WITH THE RIGHT DRUGS …

IS IT COST-EFFECTIVE TO PROCEED WITH MULTIPLEX TESTING UPFRONT?

- **Upfront NGS:** At mNSCLC diagnosis, pts received a panel that tested simultaneously for all alterations with or without FDA-approved therapies
- **Sequential testing:** Received a sequence of single-gene tests for alterations of FDA approved Tx (*EGFR, ALK, ROS1, BRAF*). If all four negative, move onto single-gene or NGS testing for alterations with non-FDA approved therapies (*MET, HER2, RET, NTRK1*)
- **Exclusionary testing:** Tested KRAS first, if negative, move onto sequential testing pathway
- **Hotspot panel:** Testing of four FDA-approved Tx alterations simultaneously, if negative, move onto NGS

Total cost vs cost difference vs NGS

Testing strategy	Medicare-insured patients (n=2,066)		Commercially insured patients (n=156)	
	Total cost	Cost difference vs NGS	Total cost	Cost difference vs NGS
NGS	2,190,499	–	620,369	–
Sequential	3,721,368	1,530,869	747,771	127,402
Exclusionary	3,584,177	1,393,678	624,178	3,809
Hotspot panel	4,331,295	2,140,795	871,211	250,842

NOTE: Costs are given in 2017 US dollars

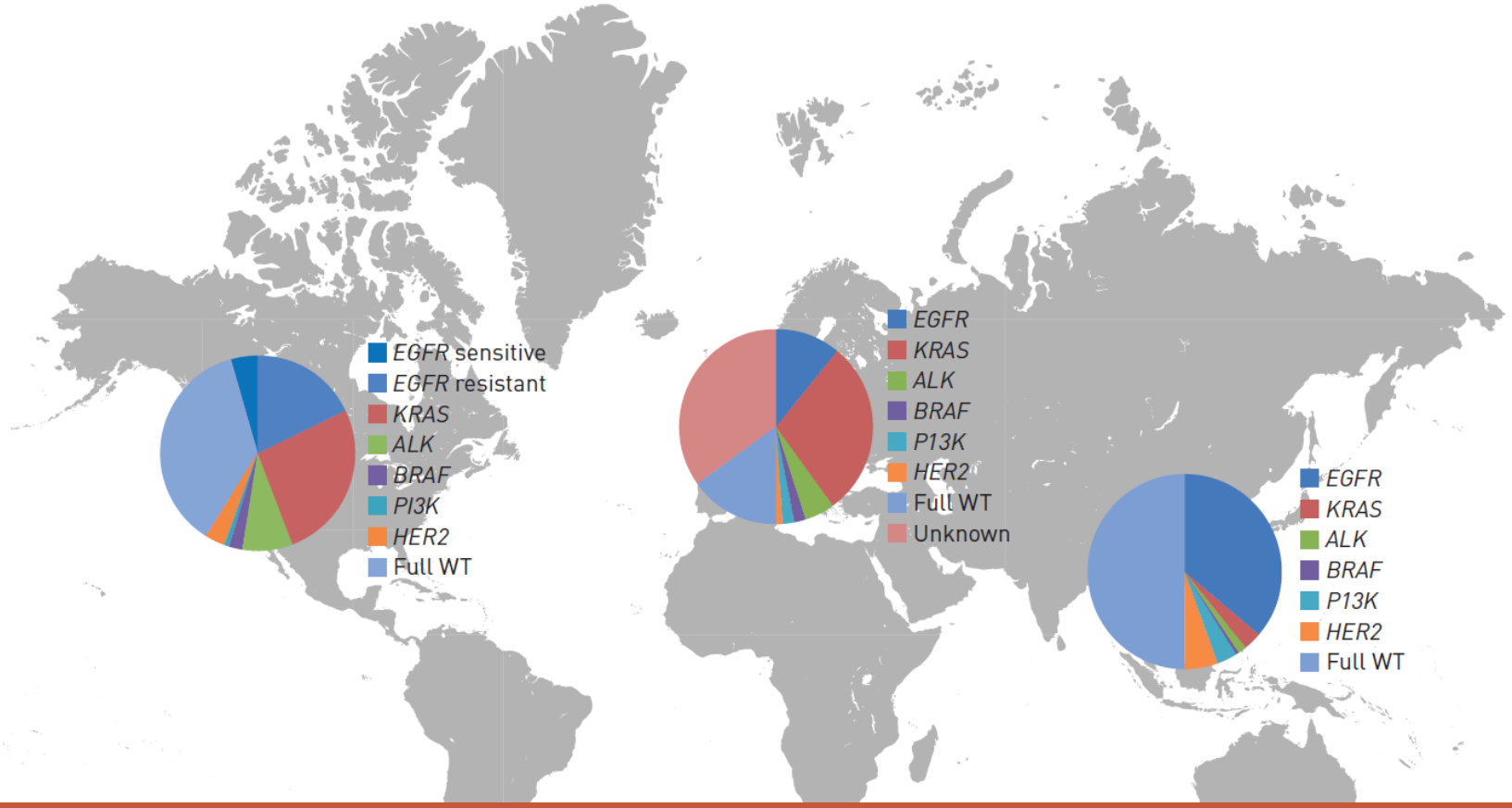
Upfront NGS testing in patients with mNSCLC was associated with:
(i) **cost savings** and
(ii) **shorter time**

to test results for both Medicare and commercial payers

ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten ras oncogene; MET, MET proto-oncogene; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; NTRK1, neurotrophic tyrosine receptor kinase1; RET, RET proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase; Tx, treatments; US, United States

Pennell NA, et al. JCO Precision Oncol. 2019;3:1-9

BUT DOES THIS NECESSARILY APPLY WORLDWIDE?

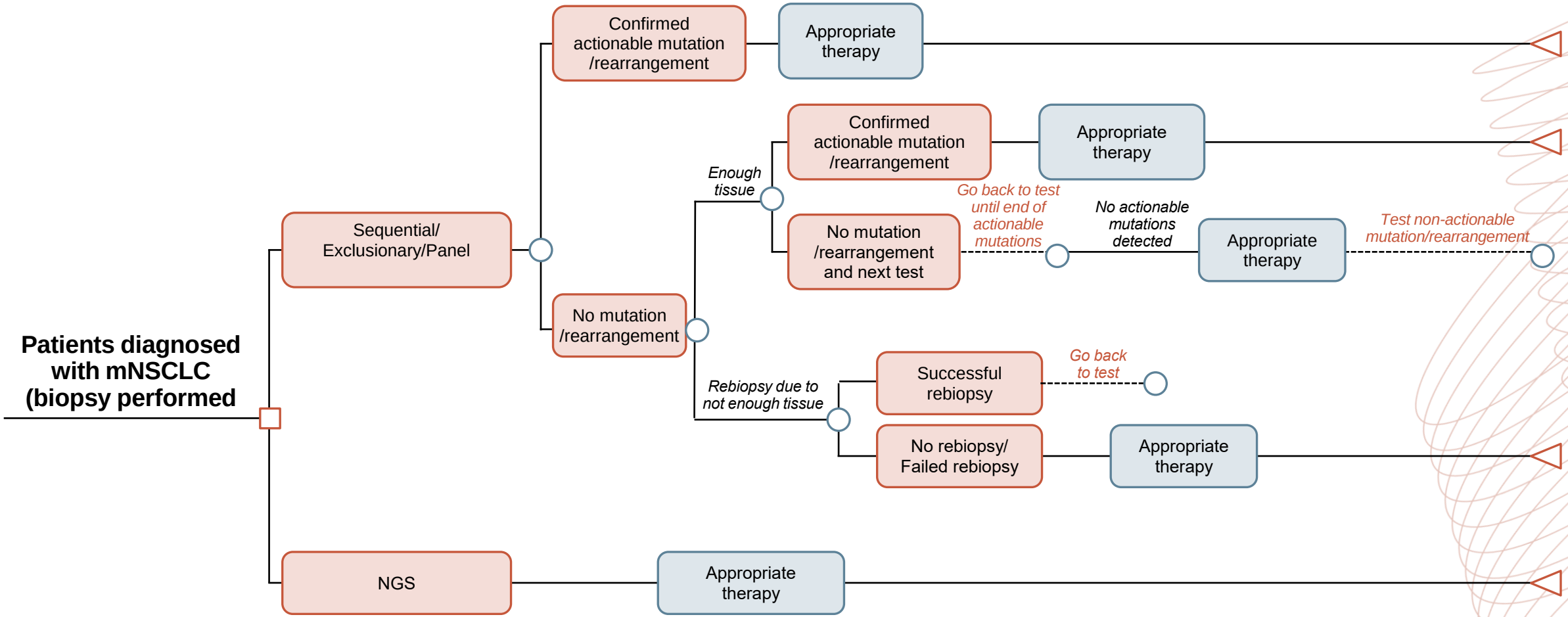


- In East Asia, predominant *EGFR*+ population is actionable!
- Thus, if we replace *KRAS* with *EGFR* and use the **exclusionary approach** → we may see these findings less significant

ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; PI3K, phosphoinositide-3-kinase; WT, wild-type

Calvayrac O, et al. Eur Respir J. 2017;49:1601734

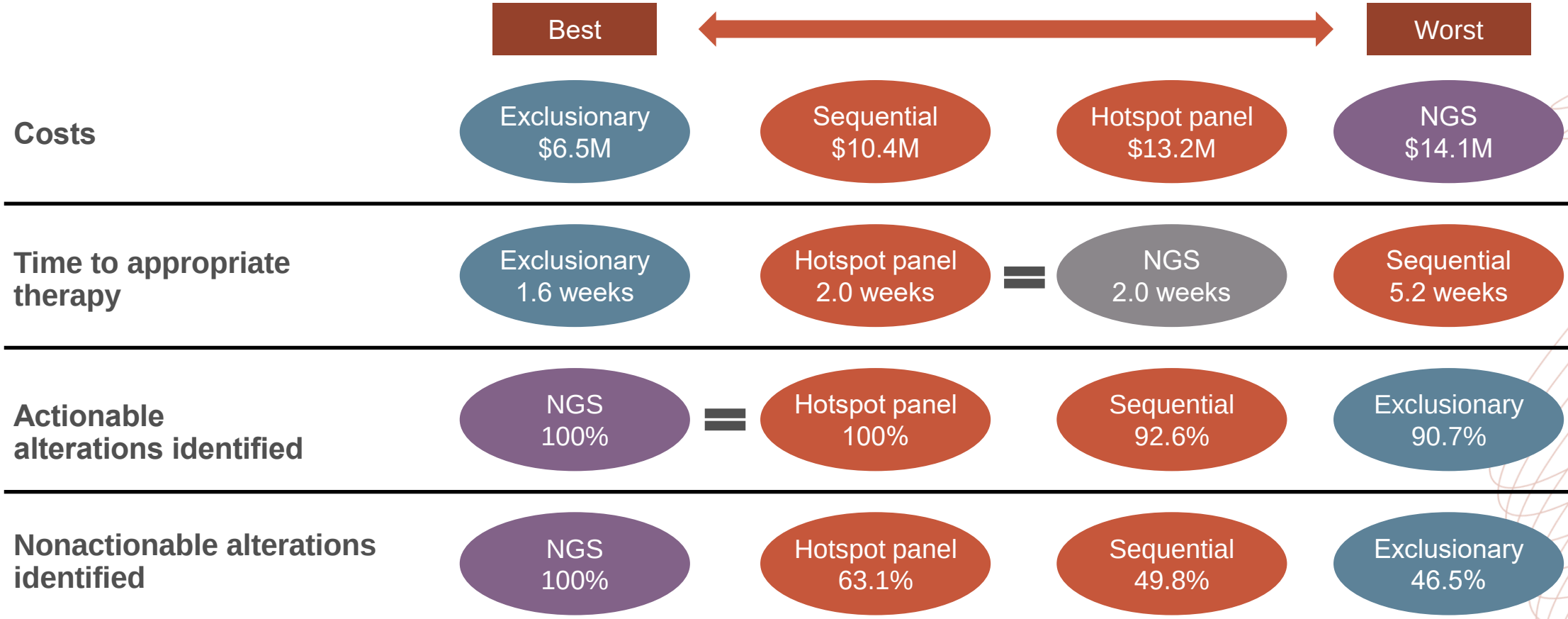
CLINICAL AND ECONOMIC IMPACT OF UPFRONT NGS FOR mNSCLC IN EAST ASIA



mNSCLC, metastatic non-small cell lung cancer; NGS, next generation sequencing

Loong HH, et al. JTO Clin Res Rep. 2022;3:100290

RESULTS – COMPARISON OF NGS VS EACH TESTING MODALITY



Values reported in 2020 US dollars.

M, million; NGS, next generation sequencing; US, United States

Loong HH, et al. JTO Clin Res Rep. 2022;3:100290

COST EFFECTIVENESS OF DIFFERENT TESTING STRATEGIES BASED ON REGIONAL MOLECULAR EPIDEMIOLOGY

- Outcome **influenced by the higher prevalence of mNSCLC patients with *EGFR* mutations in East Asian populations** versus Western populations, which can be readily detected by single-gene tests
- Exclusionary testing, however, does not capture all possible genomic alterations. As **more non-actionable genomic alterations become actionable**, and **NGS testing costs reduce**, upfront NGS may potentially be a cost saving option

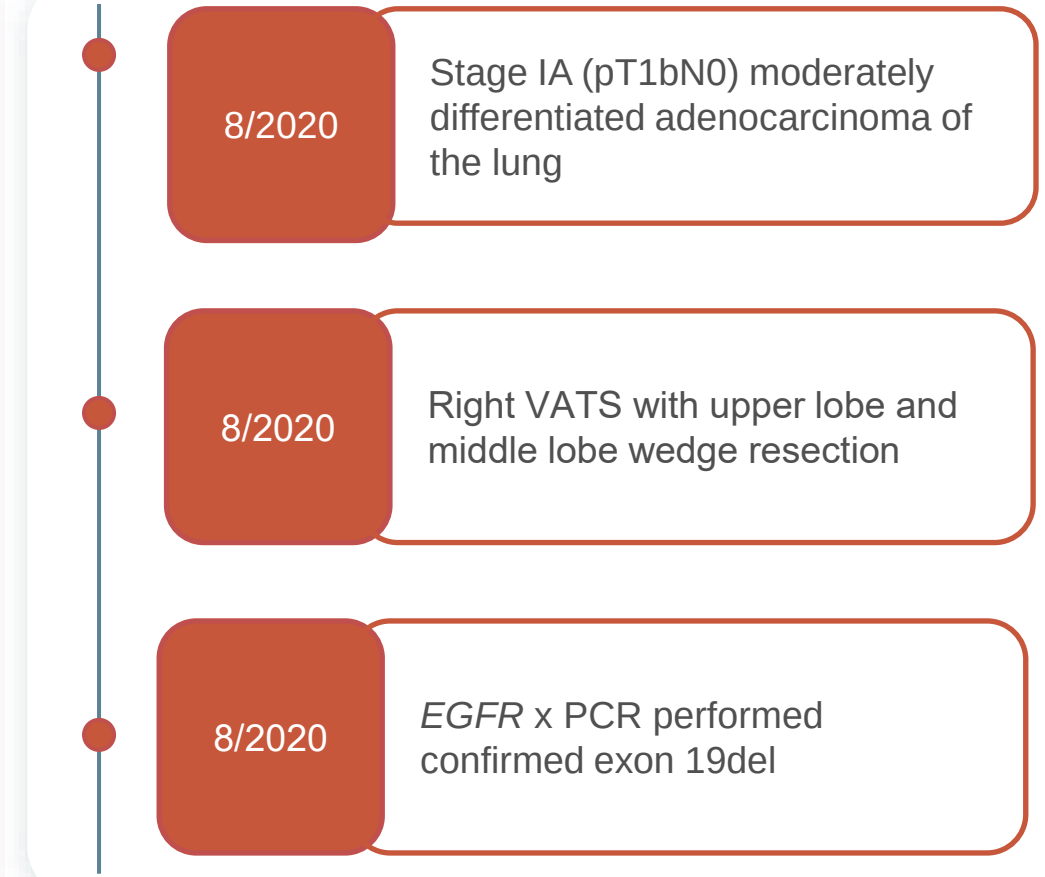
EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; NGS, next generation sequencing

Loong HH, et al. JTO Clin Res Rep. 2022;3:100290

PATIENT'S BACKGROUND

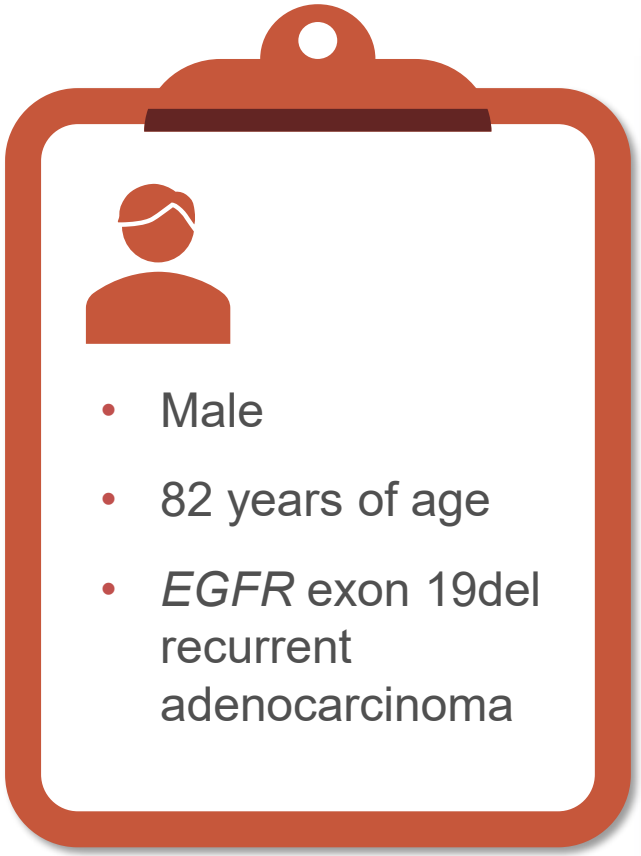
Age: 82 years
Sex: M
Race: Asian
ECOG PS: 1
Medical history:

- Hyperlipidaemia
- Ischemic heart disease
- Parkinsonism
- Benign prostatic hypertrophy
- History of pulmonary TB



del, deletion; EGFR, epidermal growth factor receptor; M, male; N, lymph nodes; p, pathology (staging); PCR, polymerase chain reaction; T, (primary) tumour; TB, tuberculosis; VATS, video-assisted thoracoscopic surgery

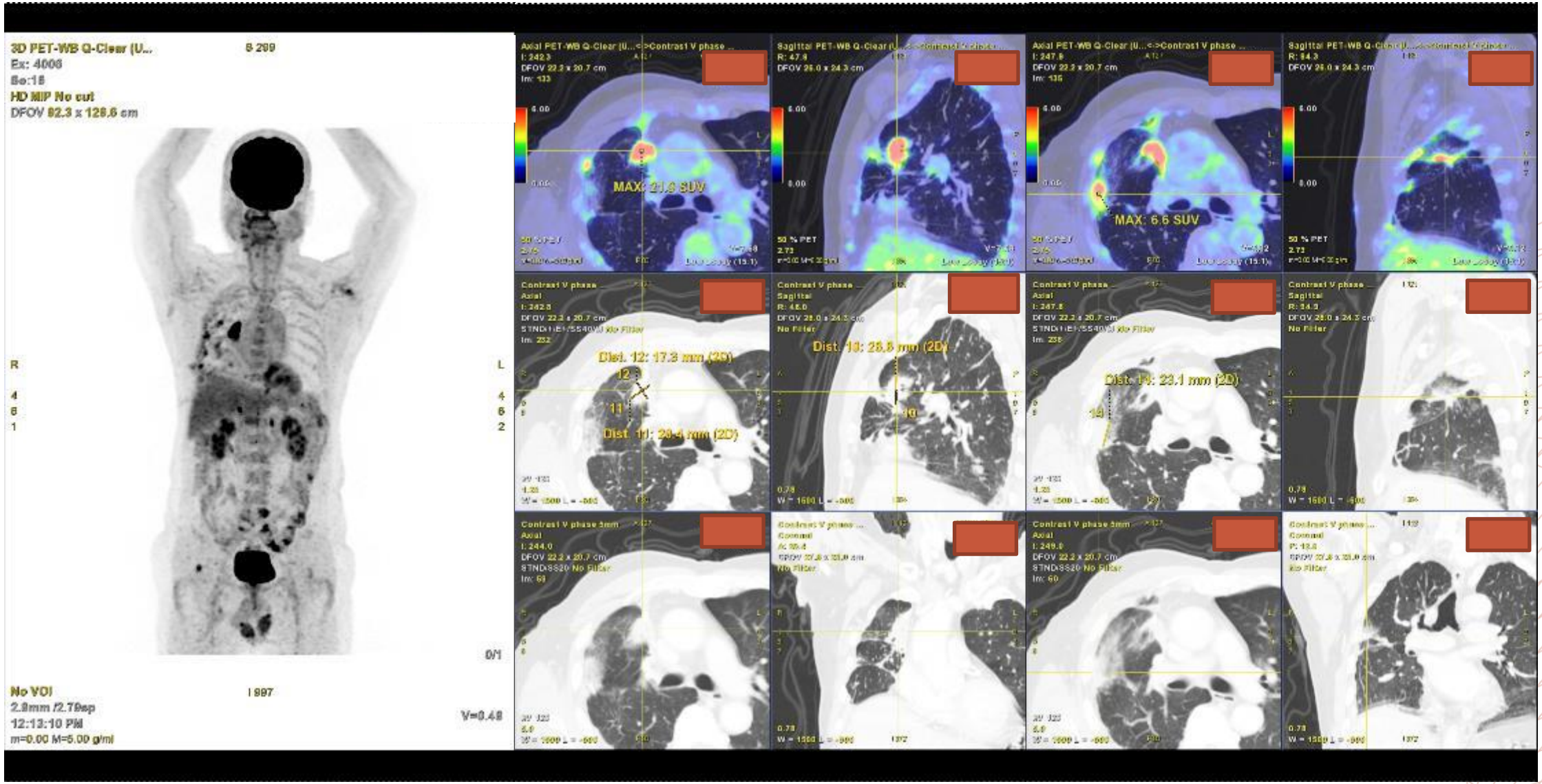
PATIENT'S PROGRESS



- Male
- 82 years of age
- *EGFR* exon 19del recurrent adenocarcinoma

- Close observation with serial CT imaging and monitoring of CEA (no adjuvant treatment was given due to early stage and advanced age)
- **10/2020:** Surveillance CT scan – Non-specific ground glass opacification in the right upper lobe
- **03/2021:** CEA elevated at 24.8 µg/L

CEA, serum carcinoembryonic antigen; CT, computed tomography; del, deletion; EGFR, epidermal growth factor receptor



PET-CT 3/2021: Local tumour recurrence in association with hypermetabolic soft tissue at lateral inferior aspect of right upper lobe → suspicious of malignancy. Irregular hypermetabolic nodular thickening along right fissure and right pleura suspicious of tumour deposits

CT, computed tomography; PET, positron emission tomography

PATIENT'S PROGRESS

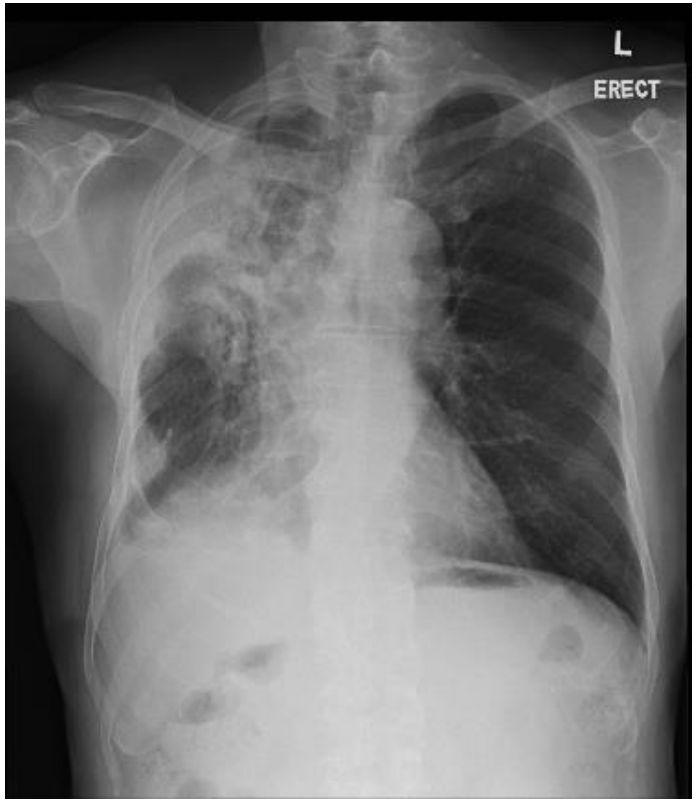
- Male
- 82 years of age
- Recurrent adenocarcinoma in lung (*EGFR* exon 19del)

03/2021:

- Began receiving 1L osimertinib
- Developed increasing symptoms whilst on osimertinib

06/2021:

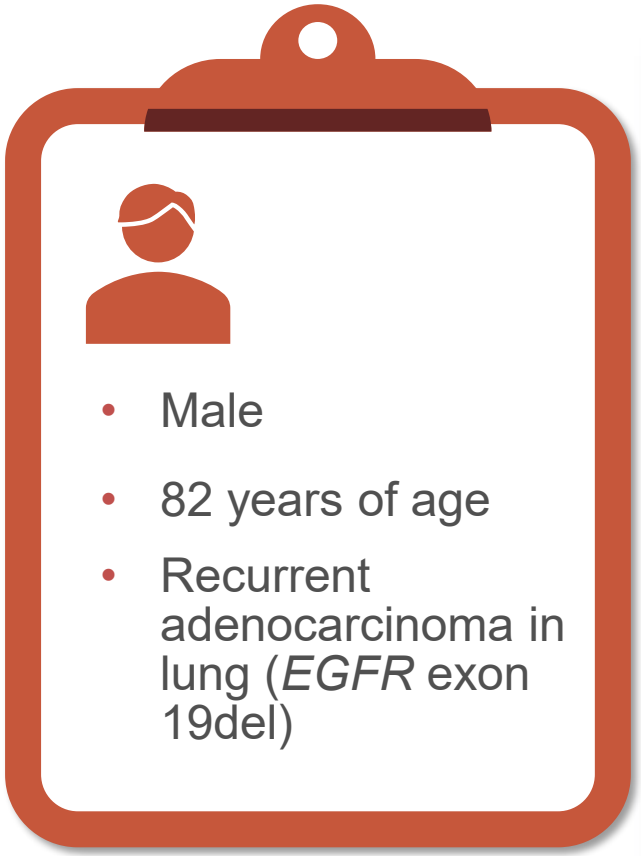
- Admitted for haemoptysis (3 months after starting osimertinib)
- Reassessment PET-CT: PD with extensive hypermetabolic lesions along the resection margin and pleural right hemithorax, associated with worsening ground glass appearance in the RUL



CXR taken 6/2021

1L, first line; CT, computed tomography; CXR, chest X-ray; del, deletion; EGFR, epidermal growth factor receptor; PD, progressive disease; PET, positron emission tomography; RUL, right upper lobe

PATIENT'S PROGRESS



- Male
- 82 years of age
- Recurrent adenocarcinoma in lung (*EGFR* exon 19del)

06/2021: Bronchoscopy:

- Blood over the whole right lung-dependent area of the right lower lobe with fresh blood in RB3 and RB4
- Adrenaline instillation was performed, and a biopsy taken

del, deletion; EGFR, epidermal growth factor receptor; RB3, right upper lobe anterior segmental bronchus; RB4, medial segmental bronchus

POLLING QUESTION

WHAT BIOMARKER TESTING WILL YOU CONSIDER IN THIS SITUATION?

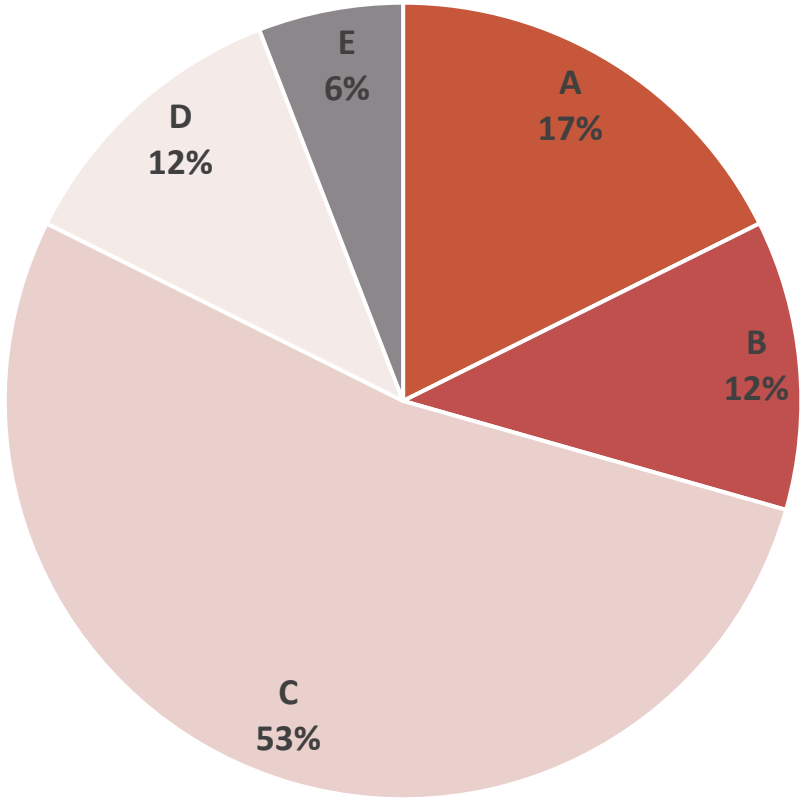
A. Repeat *EGFR* x PCR testing on bronchoscopy specimen

B. Perform PD-L1 testing on bronchoscopy specimen

C. Perform tissue-based NGS testing on bronchoscopy specimen ✅

D. Perform liquid-based NGS testing

E. No need for biomarker testing. To proceed directly with chemotherapy
+/- immunotherapy (e.g. KEYNOTE-189 regimen with pemetrexed+carboplatin
+/- pembrolizumab)



EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1

POLLING QUESTION

WHAT BIOMARKER TESTING WILL YOU CONSIDER IN THIS SITUATION?

A. Repeat *EGFR* x PCR testing on bronchoscopy specimen

B. Perform PD-L1 testing on bronchoscopy specimen

C. Perform tissue-based NGS testing on bronchoscopy specimen

D. Perform liquid-based NGS testing

E. No need for biomarker testing. To proceed directly with chemotherapy +/- immunotherapy (e.g. KEYNOTE-189 regimen with pemetrexed+carboplatin +/- pembrolizumab)

EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1

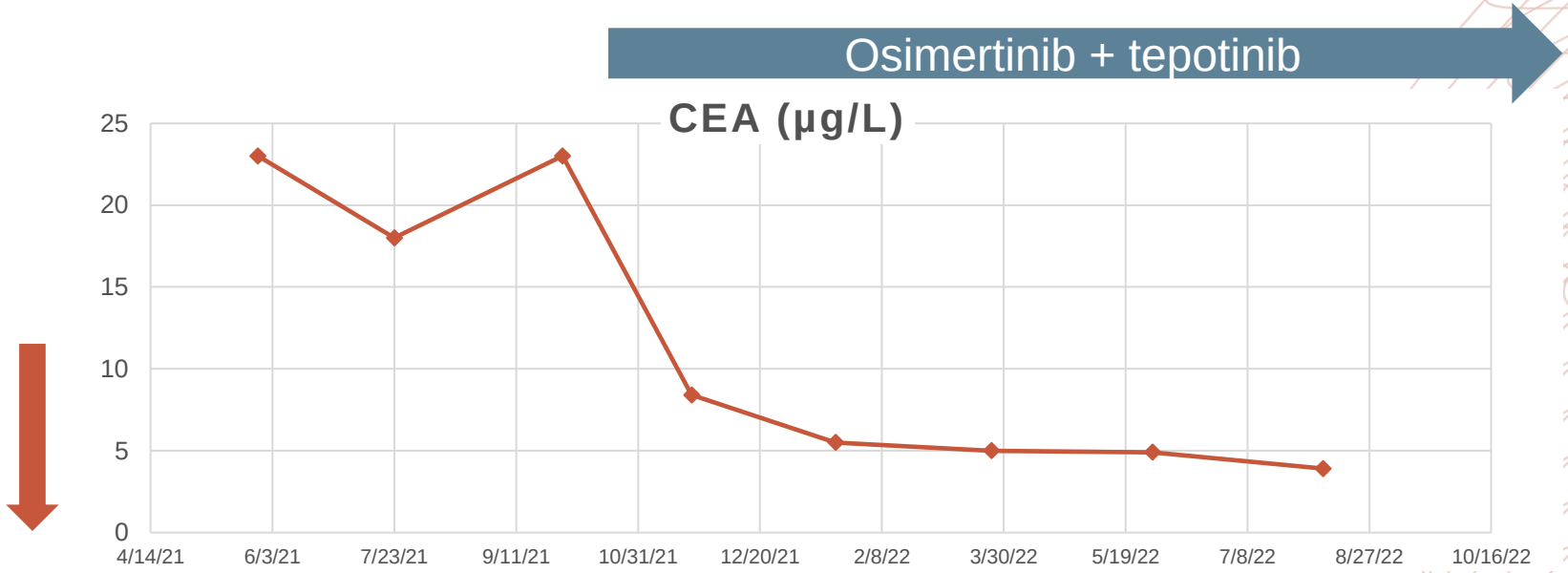
WHAT DID WE DO?

"OPTION C" – NGS TESTING ON BRONCHOSCOPY SPECIMEN

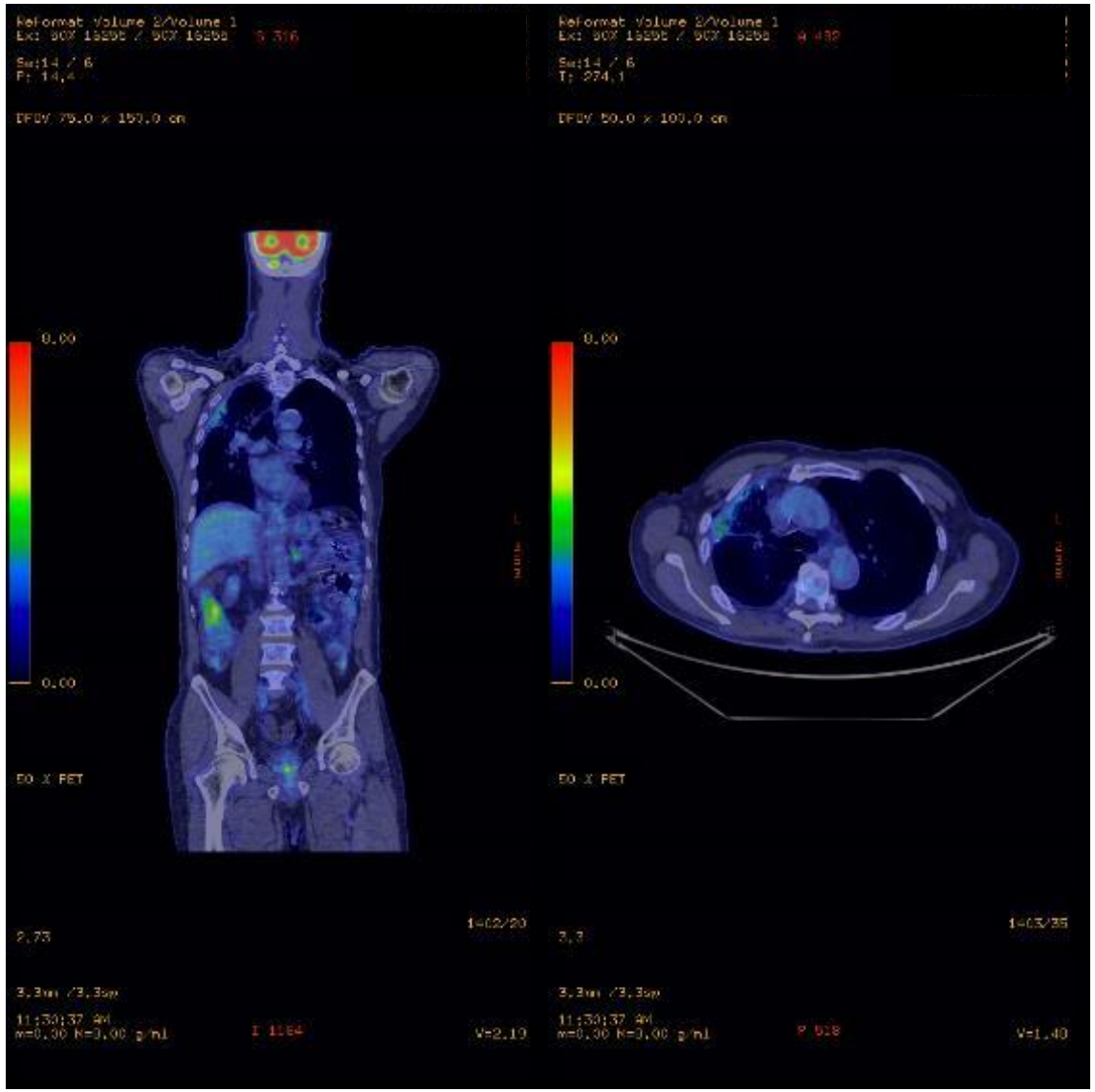
- NGS performed on bronchial biopsy specimen:
  - MET amplification +++
  - *EGFR* exon 19del

- Identification of **MET amplification** allowed for concurrent use of **osimertinib + tepotinib**

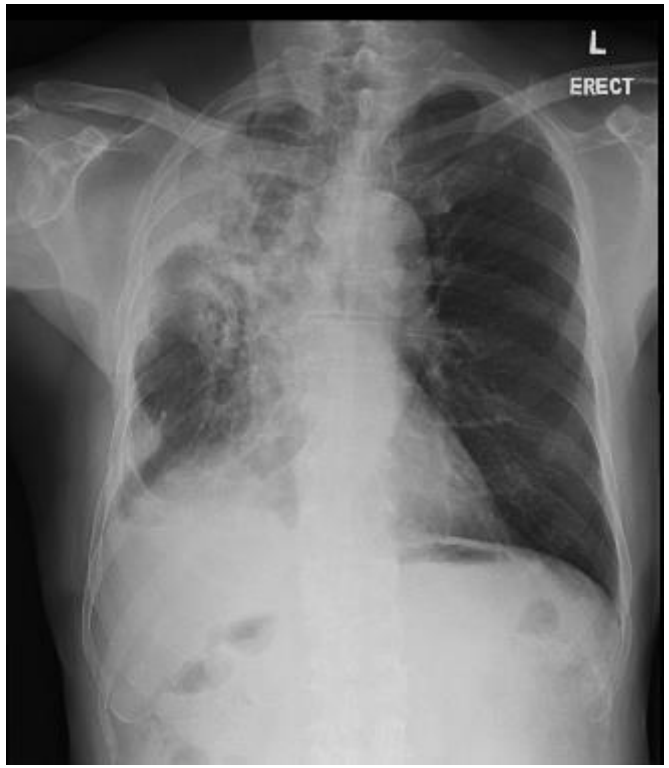
Date	CEA (µg/L)
5/28/2021	23
7/23/2021	18
9/30/2021	**23**
11/22/2021	8.4
1/20/2022	5.5
3/25/2022	5
5/30/2022	4.9
8/8/2022	3.9



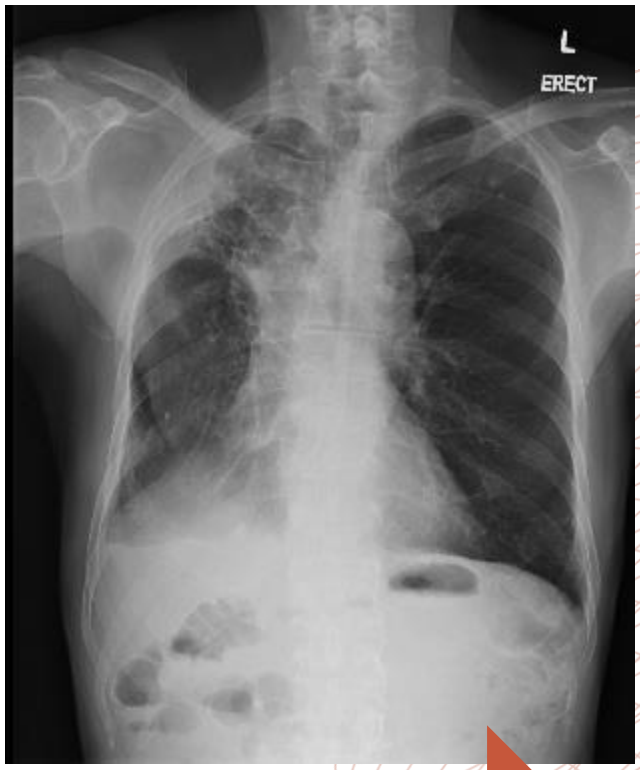
CEA, serum carcinoembryonic antigen; del, deletion; EGFR, epidermal growth factor receptor; MET proto-oncogene; NGS, next-generation sequencing



9/2021



11/2022



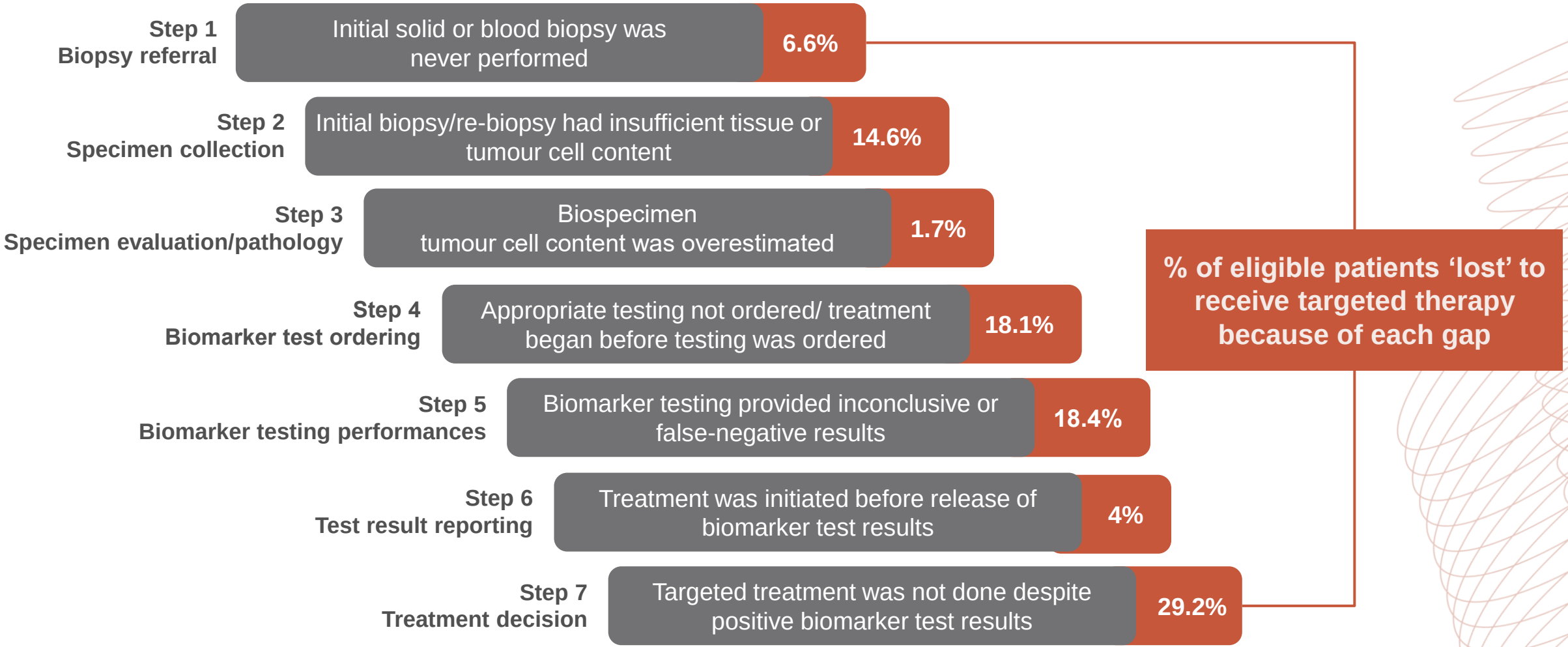
Osimertinib + tepotinib for 15 months and on-going

PET-CT 8/2022:
metabolic quiescence

PET, positron emission tomography

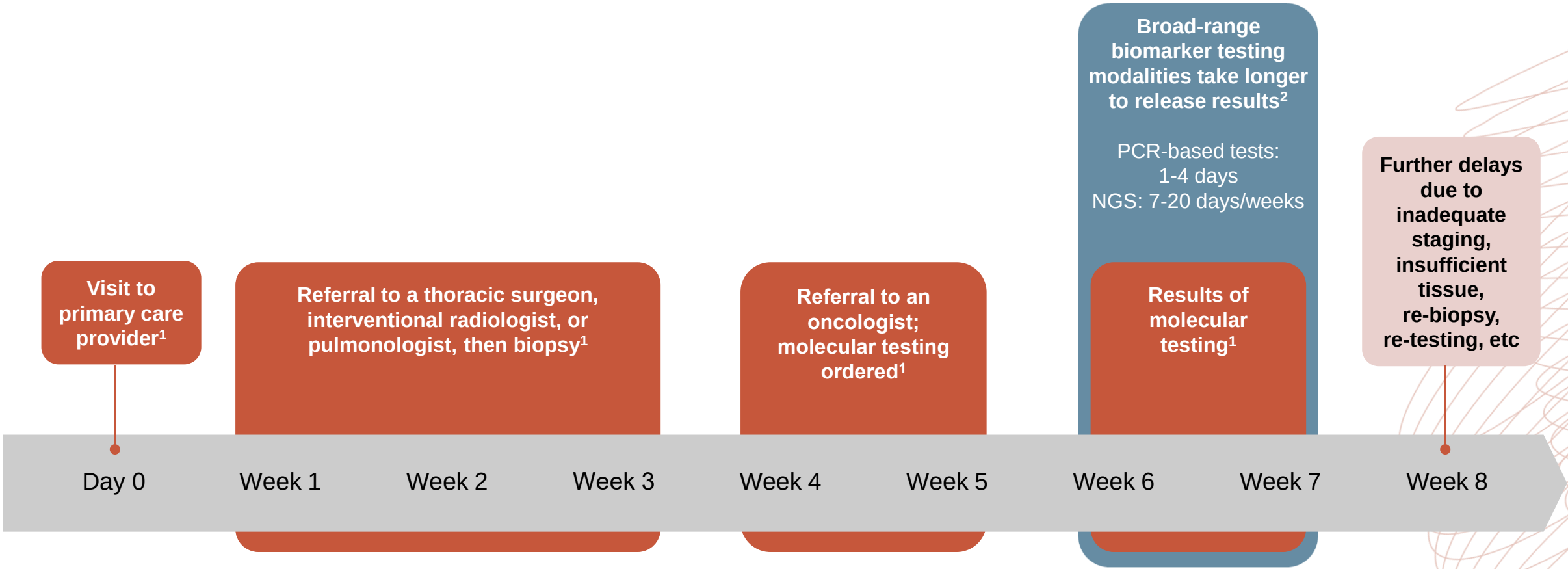
WHAT ARE SOME OF THE REMAINING CHALLENGES?

GAPS THROUGHOUT THE PATIENT JOURNEY IMPACT MOLECULAR TESTING AND CLINICAL OUTCOMES



Sadik H, et al. JCO Precis Oncol. 2022;6:e2200246

CHALLENGES IN THE REAL WORLD CONTRIBUTE TO DELAYS IN PATIENTS' DIAGNOSTIC JOURNEYS



NGS, next-generation sequencing; PCR, polymerase chain reaction

1. Gregg JP, et al. Transl Lung Cancer Res. 2019;8:286-301; 2. Pennell NA, et al. Am Soc Clin Oncol Educ Book. 2019;39:531-542; 3. Loong H, personal experience

CHALLENGES IN THE REAL WORLD CONTRIBUTE TO DELAYS IN PATIENTS' DIAGNOSTIC JOURNEYS

Visit to primary care provider

Referral to a thoracic surgeon, interventional radiologist, or pulmonologist, then biopsy

Referral to an oncologist; molecular testing ordered

Day 0 | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8

Moving this process earlier

Treatment initiation based on liquid biopsy results

Week 6 | Week 7 | Week 8

Treatment initiation based on tissue biopsy results

Week 6 | Week 7 | Week 8

PROPOSED STRATEGIES TO ADDRESS CHALLENGES IN NSCLC DIAGNOSIS

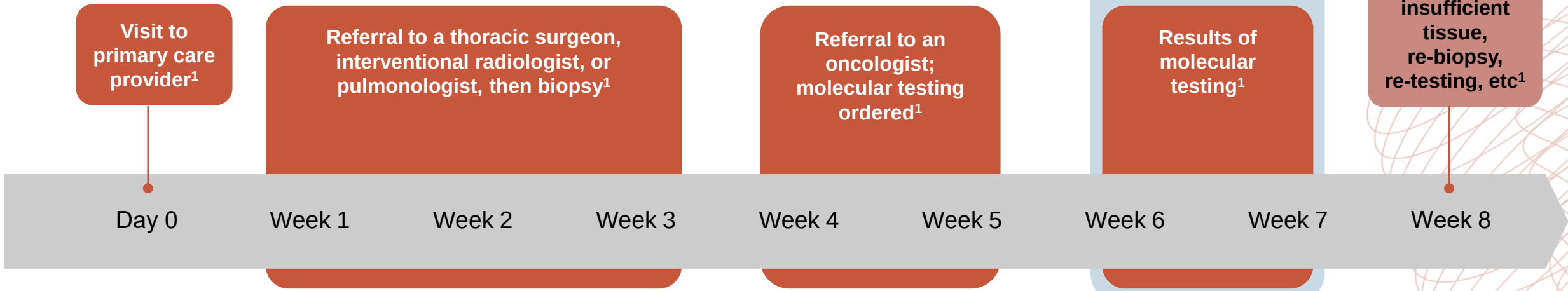
Clinical suspicion of advanced NSCLC prompts specialist to order molecular testing

Pathologists conduct “reflex-testing” immediately after histologic diagnosis of adenocarcinoma in NSCLC patients

Liquid biopsies to detect ctDNA are conducted immediately after pathologic-confirmation of NSCLC

Broad-range biomarker testing modalities take longer to release results[2]

PCR-based tests:
1-4 days
NGS: 7-20 days/weeks

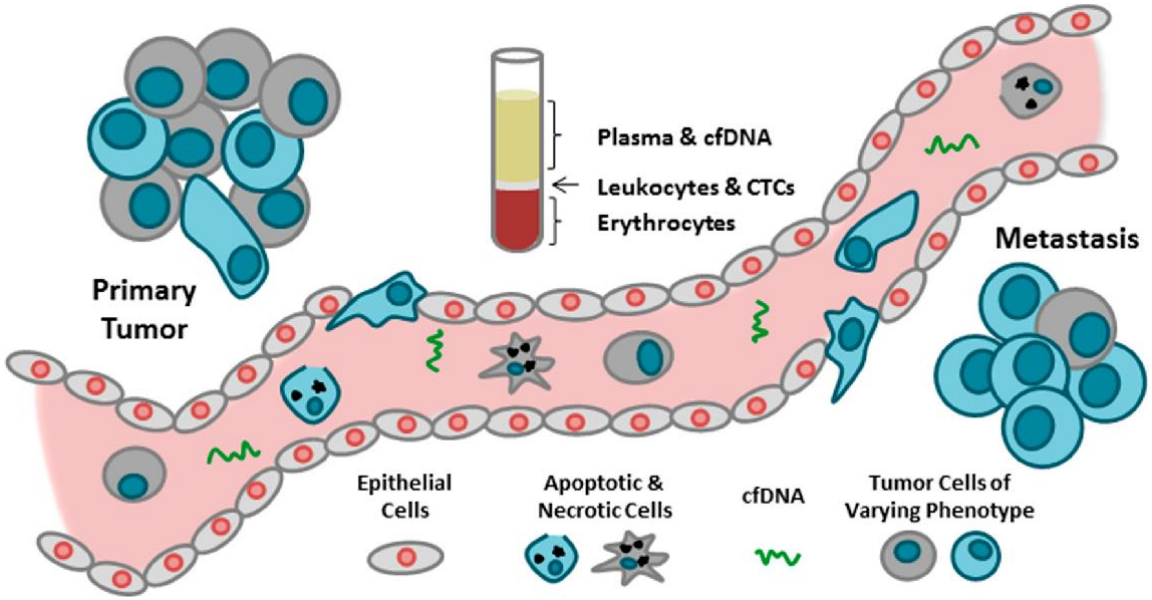


ctDNA, circulating tumour DNA; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction

1. Gregg JP, et al. Transl Lung Cancer Res. 2019;8:286-301; 2. Pennell NA, et al. Am Soc Clin Oncol Educ Book. 2019;39:531-542; 3. 3. Loong H, personal experience

ROLE OF LIQUID BIOPSY IN DIAGNOSIS AND MANAGEMENT OF NSCLC

- **What is liquid biopsy?**
  - Blood sample containing cell-free DNA from multiple sources, including DNA shed from tumour



- **When do we use liquid biopsy?**
  - Molecular testing is needed but amount of available biopsy tissue is inadequate or unknown, or tissue biopsy not possible
  - Resistance to TKIs
- **Advantages**
  - Minimally invasive
  - May overcome tumour heterogenicity
- **Limitations**
  - Sensitivity: 70%-80%; specificity: near 100%
  - Negative result is non-informative

cfDNA, cell-free DNA; CTC, circulating tumour cell; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitors

Bauml J, et al. Clin Cancer Res. 2018;24:4352-4354; Lowes LE, et al. Int J Mol Sci. 2016:17:E1505; Bonanno L, et al. Br J Cancer 2022; 127: 383-393

HIGHLIGHTS FROM ESMO LIQUID BIOPSY GUIDELINES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20]*

[1]Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Malaga, Spain; [2]Urological Cancer Research, University College London, London, UK; [3]Department of Medical Oncology, Institut Curie, Paris; [4]University of Versailles Saint-Quentin-en-Yvelines (UVSQ)/Paris-Saclay University, Saint Cloud, France; [5]Department of Oncology and Hemato-Oncology, University of Milano, Milan; [6]Division of Early Drug Development, European Institute of Oncology, IRCCS, Milan, Italy; [7]IrsiCaixa, Hospital Universitari Trias i Pujol, Badalona; [8]Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain; [9]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, USA; [10]Early Phase Trials and Sarcoma Units, Institut Bergonie, Bordeaux; [11]DITEP, Gustave Roussy, Villejuif; [12]Faculty of Medicine, University of Bordeaux, Bordeaux, France; [13]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden; [14]Departments of Pathology and Laboratory Medicine & Genetics, UNC School of Medicine, Chapel Hill, USA; [15]Medical Oncology Department, Hospital del Mar-IMIM, CIBERONC, Universitat Pompeu Fabra, Barcelona, Spain; [16]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori, 'Fondazione G. Pascale' – IRCCS, Naples, Italy; [17]Institute for Tumour Biology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; [18]Scientific and Medical Division, European Society for Medical Oncology, Lugano, Switzerland; [19]Royal Marsden Hospital, London; [20]Institute of Cancer Research, London, UK; [21]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA; [22]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne; [23]Division of Personalised Oncology, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; [24]Preclinical and Translational Research Programme, Vall d'Hebron Institute of Oncology (VHIO), ICREA, CIBERONC, Barcelona; [25]Medical School, Universitat Autònoma de Barcelona, Barcelona, Spain; [26]Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Valencia; [27]Instituto de Salud Carlos III, CIBERONC, Madrid, Spain; [28]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan

Available online 6 July 2022

Circulating tumour DNA (ctDNA) assays conducted on plasma are rapidly developing a strong evidence base for use in patients with cancer. The European Society for Medical Oncology convened an expert working group to review the analytical and clinical validity and utility of ctDNA assays. For patients with advanced cancer, validated and adequately sensitive ctDNA assays have utility in identifying actionable mutations to direct targeted therapy, and may be used in routine clinical practice, provided the limitations of the assays are taken into account. Tissue-based testing remains the preferred test for many cancer patients, due to limitations of ctDNA assays detecting fusion events and copy number changes, although ctDNA assays may be routinely used when faster results will be clinically important, or when tissue biopsies are not possible or inappropriate. Reflex tumour testing should be considered following a non-informative ctDNA result, due to false-negative results with ctDNA testing. In patients treated for early-stage cancers, detection of molecular residual disease or molecular relapse, has high evidence of clinical validity in anticipating future relapse in many cancers. Molecular residual disease/molecular relapse detection cannot be recommended in routine clinical practice, as currently there is no evidence for clinical utility in directing treatment. Additional potential applications of ctDNA assays, under research development and not recommended for routine practice, include identifying patients not responding to therapy with early dynamic changes in ctDNA levels, monitoring therapy for the development of resistance mutations before clinical progression, and in screening asymptomatic people for cancer. Recommendations for reporting of results, future development of ctDNA assays and future clinical research are made.

Key words: circulating tumour DNA (ctDNA), liquid biopsy, precision medicine

*"Liquid biopsy assays with **very high analytical and clinical specificity** may be used in practice **with limitations considered**"*

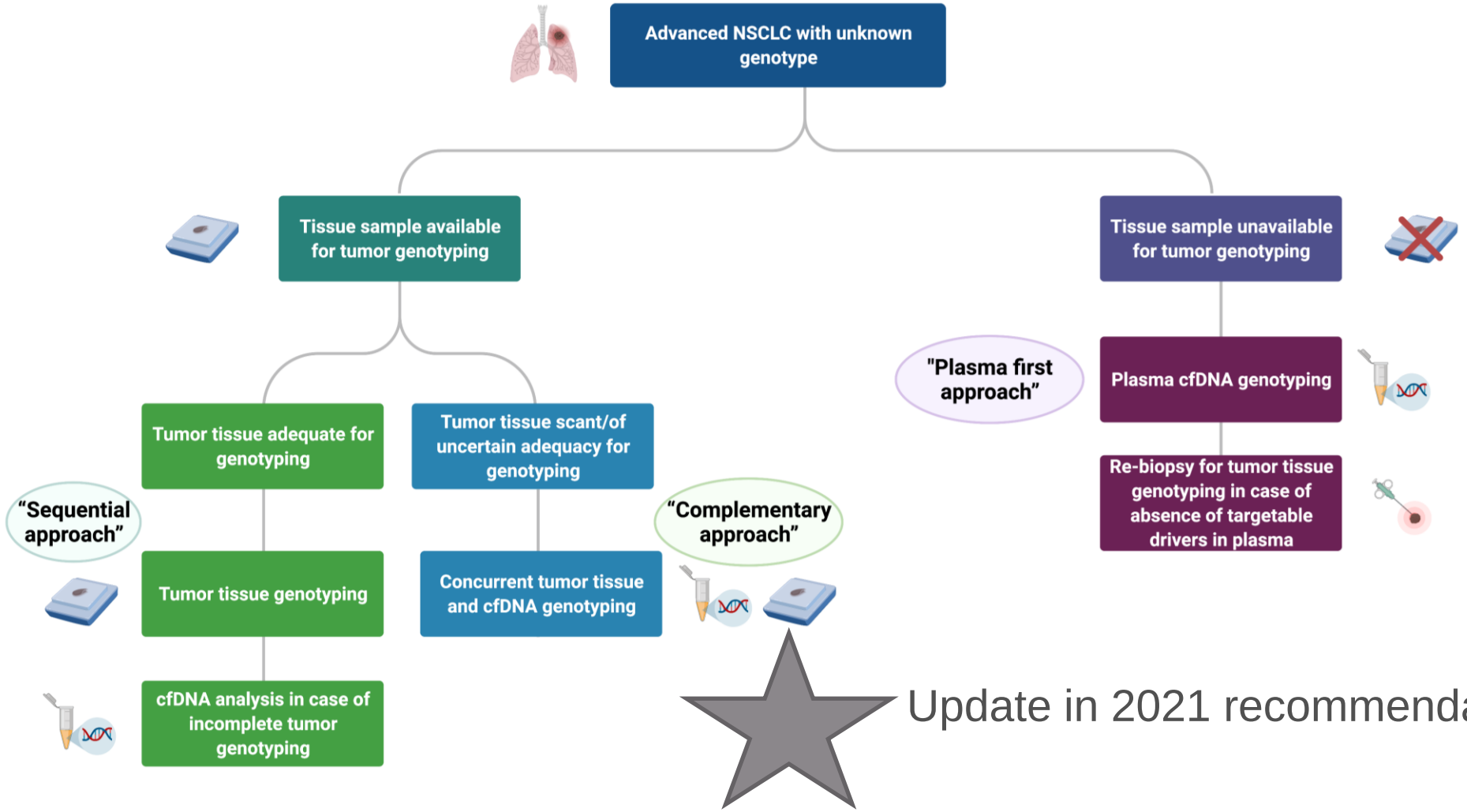
*"A liquid first strategy is recommended as an alternative option to tissue genotyping **where time to result is clinically important or tissue biopsy is unavailable or inappropriate**"*

*"Blood samples should be **collected when cancer is progressing**, either treatment naive or after prior lines of therapy"*

ESMO, European Society for Medical Oncology

Pascual J, et al. Ann Oncol. 2022;33:750-768

POSITIONING cfDNA GENOTYPING IN NSCLC



Update in 2021 recommendation

cfDNA, cell-free DNA; NSCLC, non-small cell lung cancer

International Association for the Study of Lung Cancer (IASLC) Atlas of Molecular Testing for Targeted Therapy in Lung Cancer 2023
Rolfo C, et al. J Thorac Oncol. 2021;16:1647-1662

WE NEED …

- Good QUALITY biopsies taken at 1st attempt
- Incorporation of molecular testing as REFLEX testing in pathology department
- Costs of NGS to come further down …
- For NGS: REFLEX Workflow to incorporate RNA-based testing either concurrently with DNA or in event of DNA non-conclusive
- Establish the role of liquid biopsies as a complementary testing method

With this in place – upfront NGS becomes more effective!

NGS, next-generation sequencing

ADDRESSING THE CHALLENGES OF BIOMARKER TESTING IN LUNG CANCER

Q&A SESSION

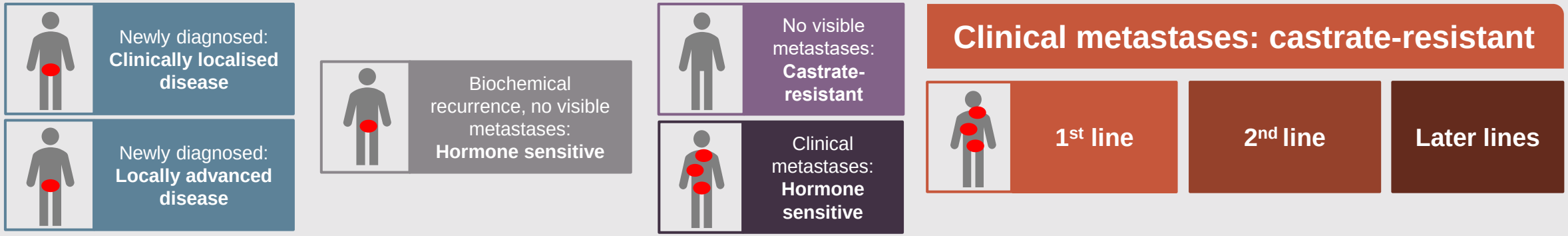
ADDRESSING THE CHALLENGES OF BIOMARKER TESTING IN PROSTATE CANCER

Assoc. Prof. Alicia Morgans

GU Medical Oncologist
Dana-Farber Cancer Institute, Boston, USA

DESPITE TREATMENT OPTIONS, OUTCOMES REMAIN POOR FOR PATIENTS WITH METASTATIC PROSTATE CANCER[1,2]

Clinical states of prostate cancer[1]



Relative 5-year survival by Stage[1,2]

Stage I	Stage II	Stage III	Stage IV (metastases)
~100%	~100%	~95%	~30%

1.Scher H, et al. PLoS One. 2015;10:e0139440; 2. Prostate cancer survival statistics. Available at https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/survival#ref-3. Accessed 21-Mar-2024

MUTATIONS IN THE HRR PATHWAY MAY BE ASSOCIATED WITH DEVELOPMENT AND PROGRESSION OF PROSTATE CANCER

Increased risk of developing prostate cancer by age 65 years with germline mutations in *BRCA1* and/or *BRCA2*

BRCA1	*BRCA2*
1.8X	8.6X

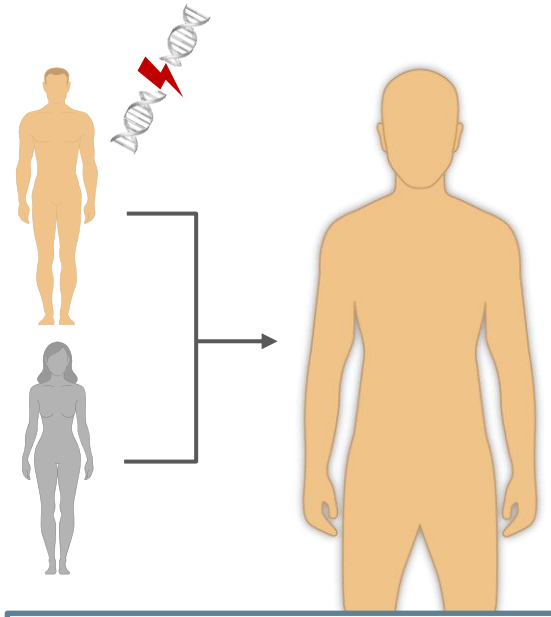
- Mutations in the HRR pathway may play a role in progression of prostate cancer to the lethal castration-resistant form, and *BRCA2* mutations appear to have a negative impact on response to first-line taxane treatment in castration-resistant prostate cancer

Up to **1 in 3** men diagnosed with advanced prostate cancer harbour HRR mutations.

BRCA1/2, breast cancer gene 1/2; HRR, homologous recombination repair

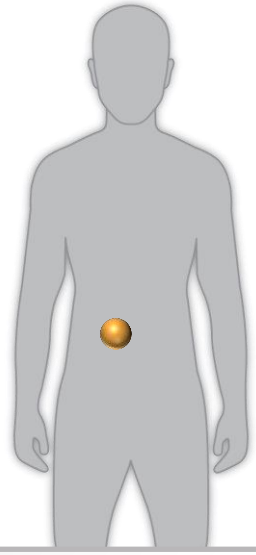
Palmbos PL and Hussain MH. Oncology (Williston Park). 2016;30(5):377-85; Castro E, et al. J Clin Oncol. 2019;37(6):490-503; Page E, et al. European Urology. 2019;76:831-42

MUTATIONS IN HRR GENES CAN BE GERMLINE OR SOMATIC



Germline mutations are inherited from a parent[1]

- Hereditary[1]
- Present in germ cells from parents; in every cell of offspring (constitutional)[1]
- Can be detected by saliva, buccal swab, blood, or tumour testing[2]



Somatic mutations can arise from DNA damage caused by internal or external insults[1]

- Acquired[1]
- Present only in certain somatic cells; do not impact reproductive cells[1]
- Can be detected by tumour testing or liquid biopsy[2,3,a]

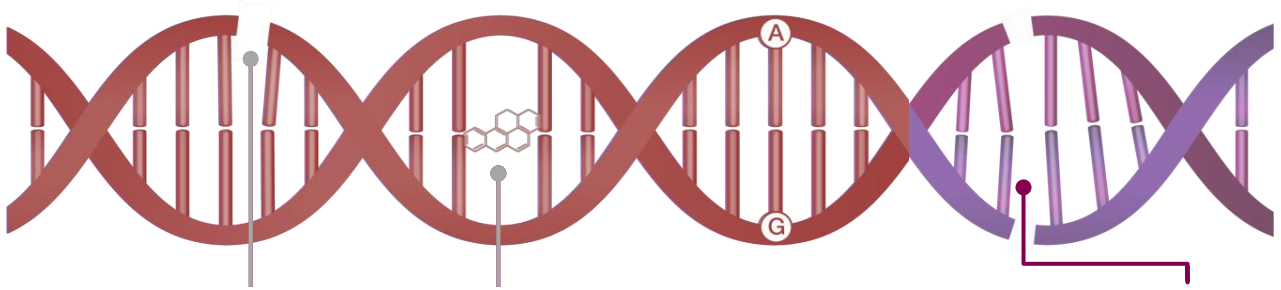
Cells with HRR mutations Cells without HRR mutations Tumour with HRR-mutated cells

[a] Blood testing could theoretically capture circulating tumour cells; however, tumour testing is the only reliable method of detecting somatic mutations.[2,4]

HRR, homologous recombination repair

1. National Institutes of Health. https://medlineplus.gov/genetics/understanding/mutationsanddisorders/genemutation/. Accessed 17-Mar-24;
2. Wu H, et al. Gene Ther. 2017;24(10):601-9; 3. Fiala C, Diamandis EP. BMC Med. 2018;16(1):166;
4. BRACAnalysis CDx® | Myriad International (myriadgenetics.eu). Accessed 17-Mar-24

MUTATIONS IN DNA REPAIR PATHWAYS CAN LEAD TO GENETIC INSTABILITY AND DRIVE TUMOUR GROWTH1,2



	DNA single strand breaks	Bulky adducts	Base mismatches, insertions & deletions	DNA double strand breaks
Repair pathway	Base excision repair (BER)	Nucleotide excision repair (NER)	Mismatch repair ***(including MSH2 MLH1)***	Non-homologous end joining (NHEJ); **Homologous recombination repair (HRR)** ***including ATM, BRCA1/2, PALB2, CHEK1/2, RAD51***

Homologous recombination repair (HRR) is a key mechanism for the repair of DNA double strand breaks[1,2]

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CHEK1/2, checkpoint kinase 1/2; MLH1, MutL Homolog 1; MSH2, MutS protein homolog 2; PALB2, partner and localizer of BRCA2

1. Lord CJ and Ashworth A. Nature. 2012;481:287-93; 2. O'Connor MJ. Mol Cell. 2015;60:547-60

GENETIC TESTING INFORMS DECISION MAKING

Clinical questions and decisions:

- Understanding familial risk (germline mutations)
- Estimating disease prognosis
- Informing treatment decisions, including eligibility for clinical trials
- Evaluating genomic alterations for other research purposes

Testing considerations:

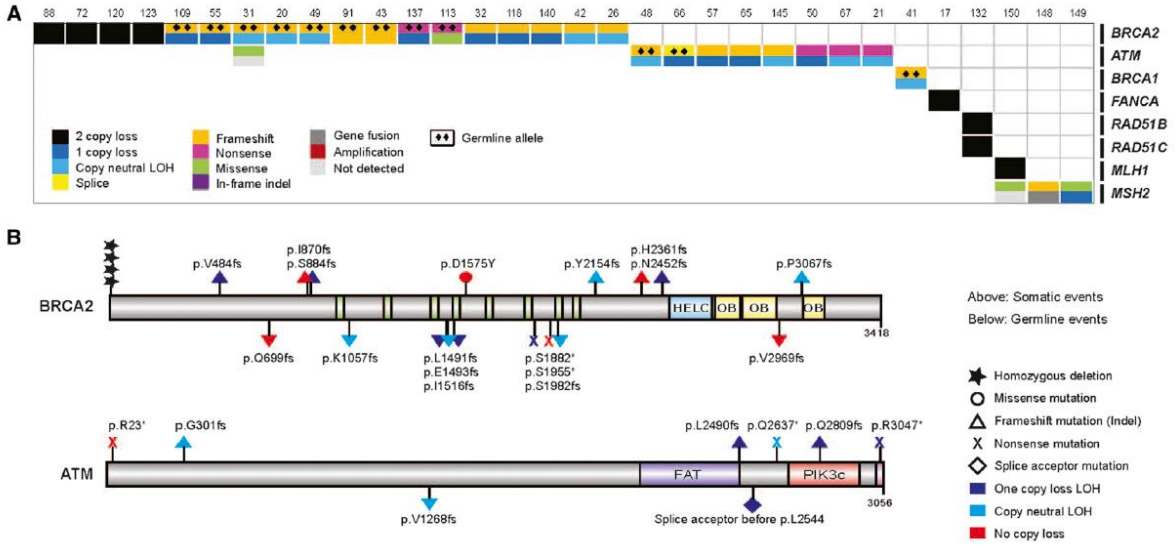
- Technical limitation and sample availability
- Detection of germline only, or both germline and somatic mutations
- Test availability/access
- Turnaround time
- Access to and availability of testing and genetic counselling

Bilkey GA, et al. Front Public Health. 2019;7:40; Katsanis SH and Katsanis N. Nat Rev Genet. 2013;14(6):415-26

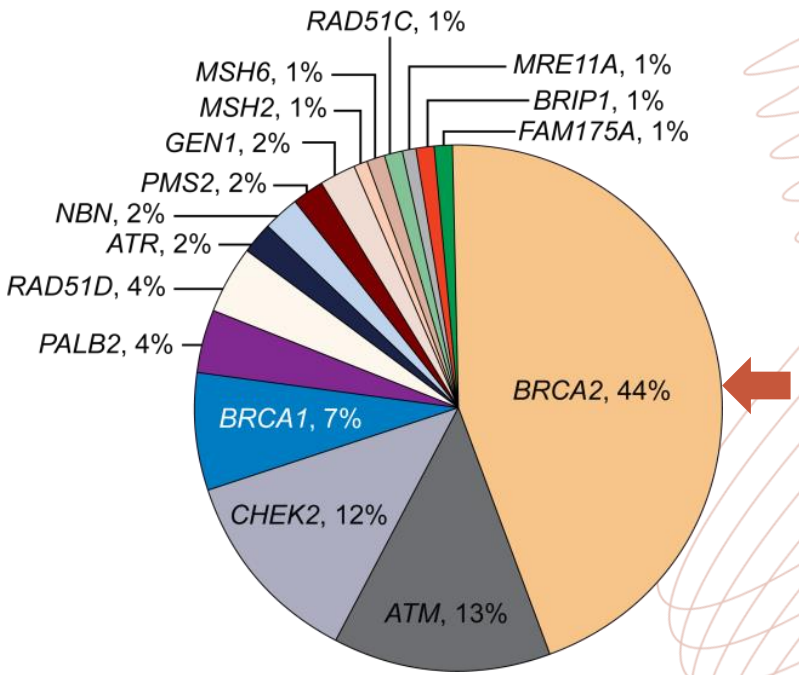
DNA REPAIR ALTERATIONS ARE COMMON IN ADVANCED PROSTATE CANCER

SOMATIC

- **~23%** of men with mCRPC have DNA repair pathway aberrations
- The incidence of DNA repair alterations is higher in men with **metastatic prostate cancer** than those with **localised disease**



GERMLINE



- **~12%** of men with metastatic prostate cancer have germline mutations in one or more of the 16 DNA repair genes

LOH, loss of heterozygosity; mCRPC, metastatic castration resistant prostate cancer; PC, prostate cancer

1. Robinson D, et al. Cell. 2015;161:1215-1228; 2. Pritchard CC, et al. N Engl J Med. 2016;375:443-453; 3. Antonarakis ES, et al. Eur Urol. 2018;74:218-225

ESTIMATED GERMLINE AND SOMATIC MUTATIONS IN METASTATIC PROSTATE CANCER

	Somatic Mutation	Germline Mutation	Combined Rate
BRCA1	1%	1%	2%
BRCA2	5%	5.4%	10-11%
PALB2	4%[a]	0.4%	4.4%
ATM	2-3%	1.6%	3.5-4.5%
MSH2/6	4-5%	1.5%	5.5-6.5%

[a]mCRPC rate

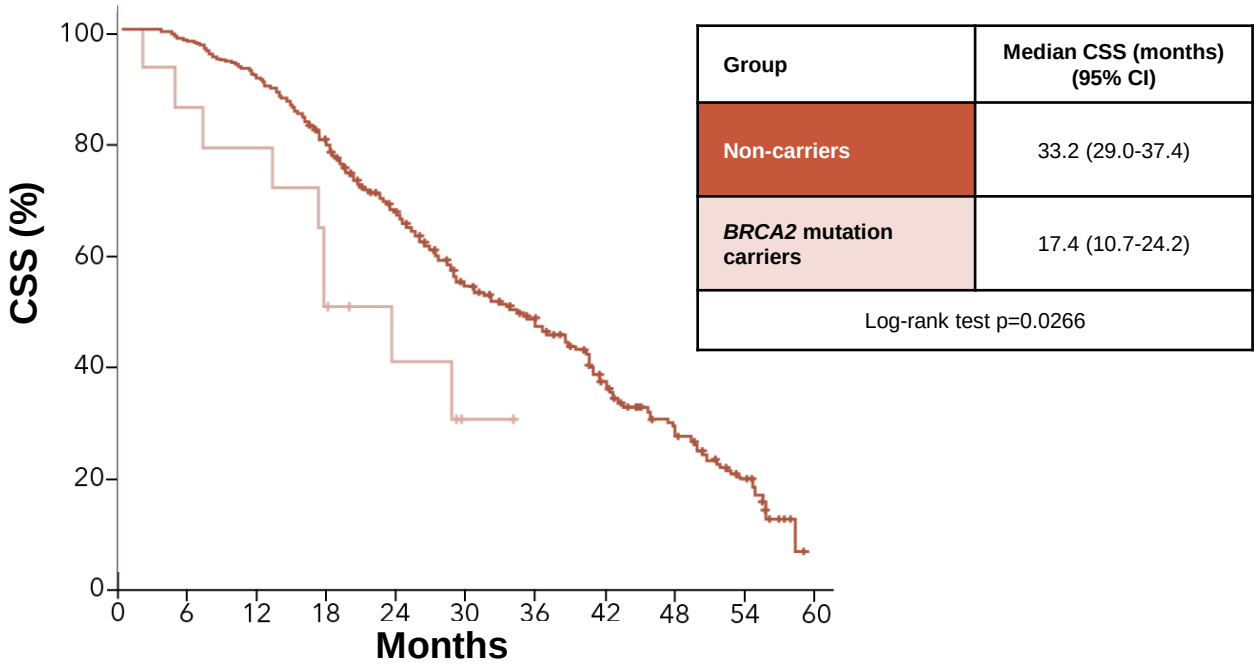
ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; mCRPC, metastatic castration resistant prostate cancer; *MSH2/6*, MutS protein homolog 2/6; *PALB2*, partner and localizer of *BRCA2*

Adapted from Pritchard C, APCCC Basel 2019, Cheng H, et al. J. Natl Compr Canc Netw. 2019: 17: 515-521; Lang S, et al. Int J Onc 2019; 55: 597-616 (Supplementary material)

PATIENTS WITH HRR MUTATIONS (INCLUDING *BRCA2* MUTATIONS) ARE MORE LIKELY TO HAVE POOR OUTCOMES ON STANDARD-OF-CARE THERAPIES[1-3]

Patients with **germline HRR mutations** including *BRCA2* mutations are more likely to have **poor outcomes** on standard-of care-therapies[1,2]

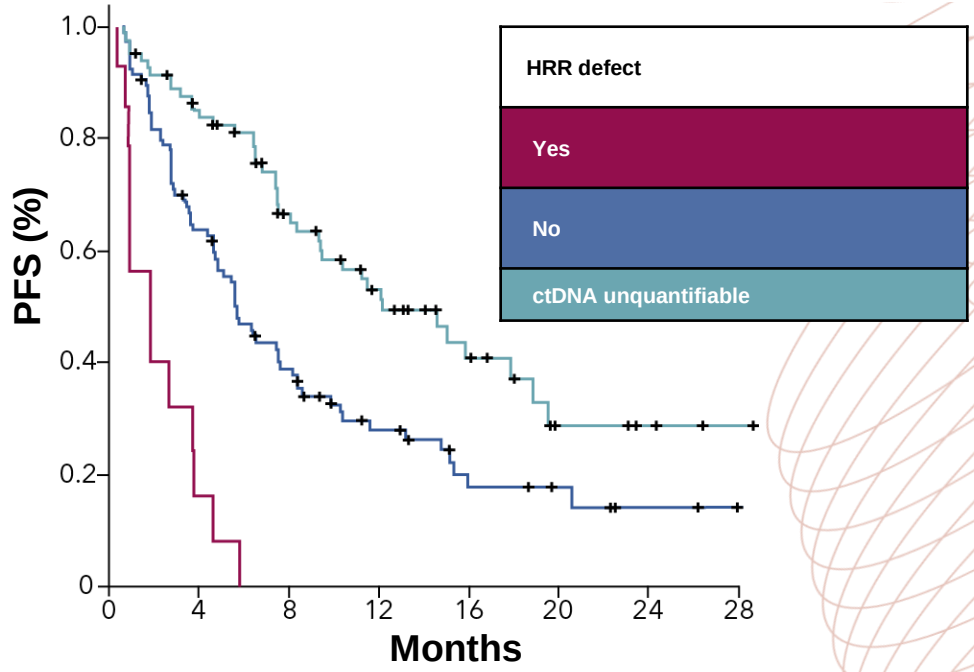
Cancer-specific survival in patients with mCRPC with *BRCA2* mutation[1]



Group	Median CSS (months) (95% CI)
Non-carriers	33.2 (29.0-37.4)
BRCA2 mutation carriers	17.4 (10.7-24.2)
Log-rank test p=0.0266	

Poor responses to standard therapy also seen for **tumour HRR mutations**[2]

Time to progression in patients with mCRPC with HRR mutations[3]

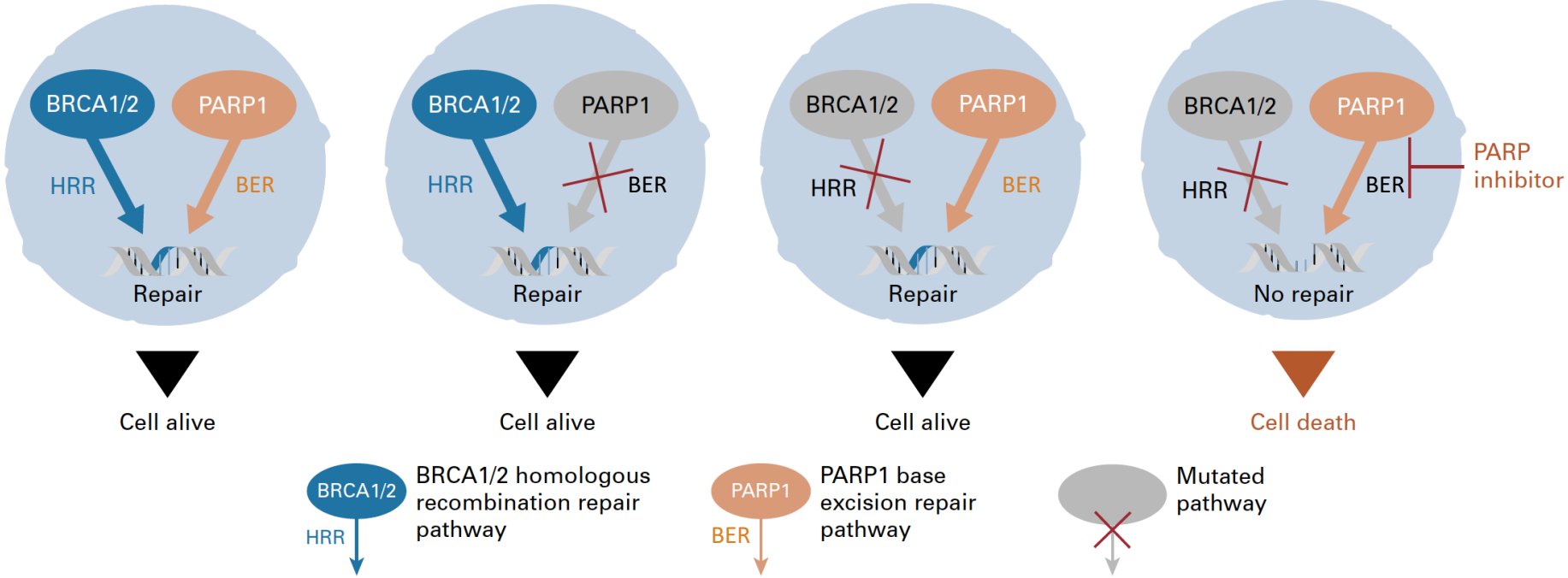


BRCA2, breast cancer gene 2; CI, confidence interval; CSS, cause-specific survival; ctDNA, circulating tumour DNA; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PFS, progression-free survival

1. Adapted from: Castro E, et al. J Clin Oncol. 2019;6:490-503; 2. Annala M, et al. Eur Urol. 2017;72:34-42; 3. Annala M, et al. Cancer Discov. 2018;8:444-57

PARP INHIBITORS: ‘SYNTHETIC LETHALITY’ IN CANCER

- ***BRCA*: “copy editor”;** homologous recombination repair (HRR)
- **PARP: “spell check”;** base excision repair (BER)

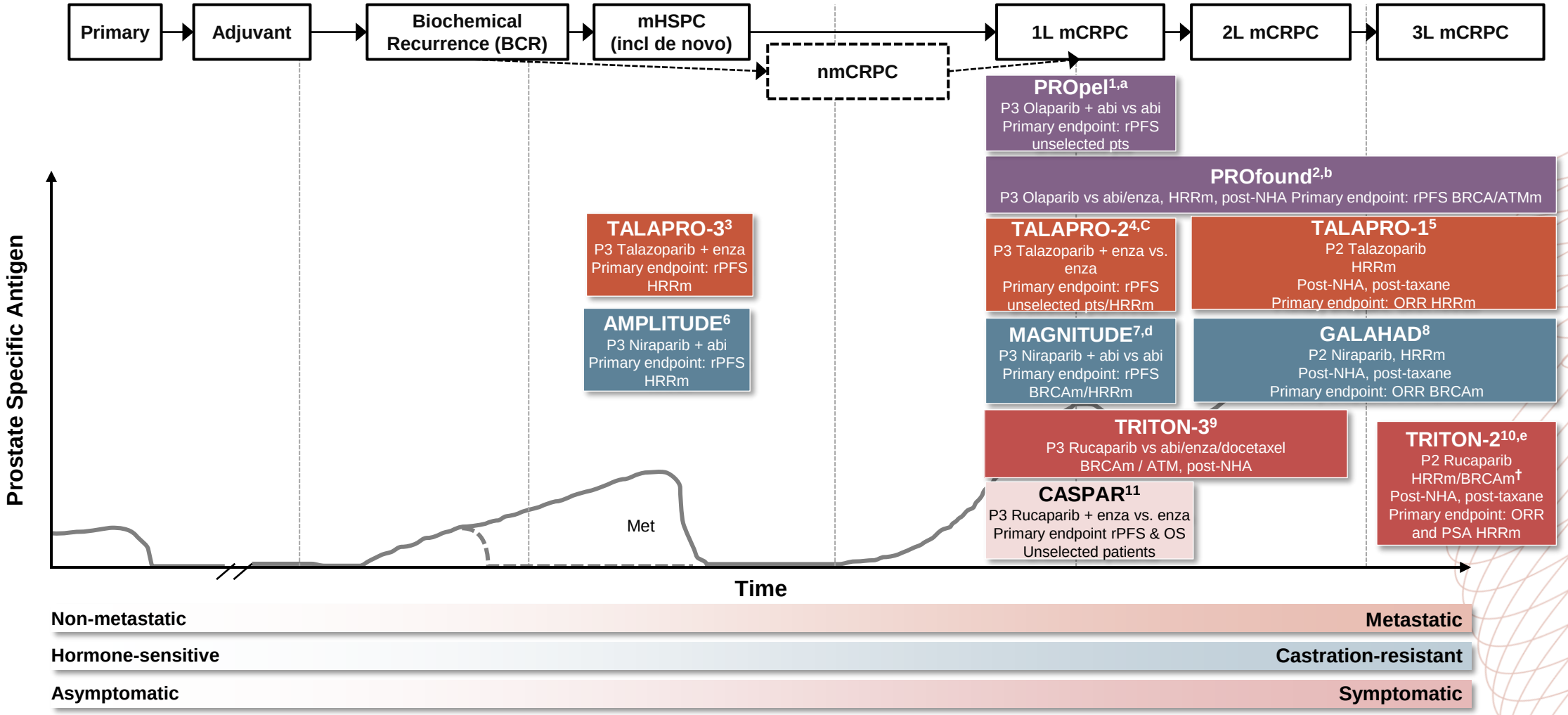


PARP is required for single-strand break repair (e.g. via BER)
MOA – inhibiting SSB/BER is synthetic lethal with HRD

BER, base excision repair; BRCA1/2, breast cancer type 1/2 susceptibility protein; HRD, homologous recombination deficiency; HRR, homologous recombination repair; MOA, mode of action; PARP, poly-ADP ribose polymerase; SSB, single-strand break

Adapted from Gourley C, et al. J Clin Oncol. 2019;37(25):2257-69; Banerjee S, et al. Nat Rev Clin Oncol. 2010;7:508-19

TRIALS INVESTIGATING PARPI IN ADVANCED PROSTATE CANCER



Please see slide notes for references. [a] PROpel led to the approval of olaparib in combination with abiraterone in patients with *BRCA*m mCRPC (FDA approval) or in patients for whom chemotherapy is not clinically indicated (EMA approval); [b] PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRR mutations (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA; [c] Talapro-2 led to the approval of talazoparib in combination with enzalutamide for HRR gene-mutated mCRPC (FDA approval); [d] MAGNITUDE led to the approval of niraparib in combination with abiraterone in patients with *BRCA*m mCRPC (FDA approval) or patients with mCRPC and *BRCA1/2* mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated; [e] As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane
1/23L, first/second/third line; abi, abiraterone; AR, androgen receptor; *ATM*, ataxia telangiectasia mutated; BRCA, breast cancer gene; EMA, European Medicines Agency; enza, enzalutamide; FDA, US Food and Drug Administration; HRR, homologous recombination repair; m, mutation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NHA, new hormonal agent; nmCRPC, non-metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; P, phase; PARP, poly (ADP-ribose) polymerase; PSA, prostate-specific antigen; pts, patients; rPFS, radiographic progression-free survival

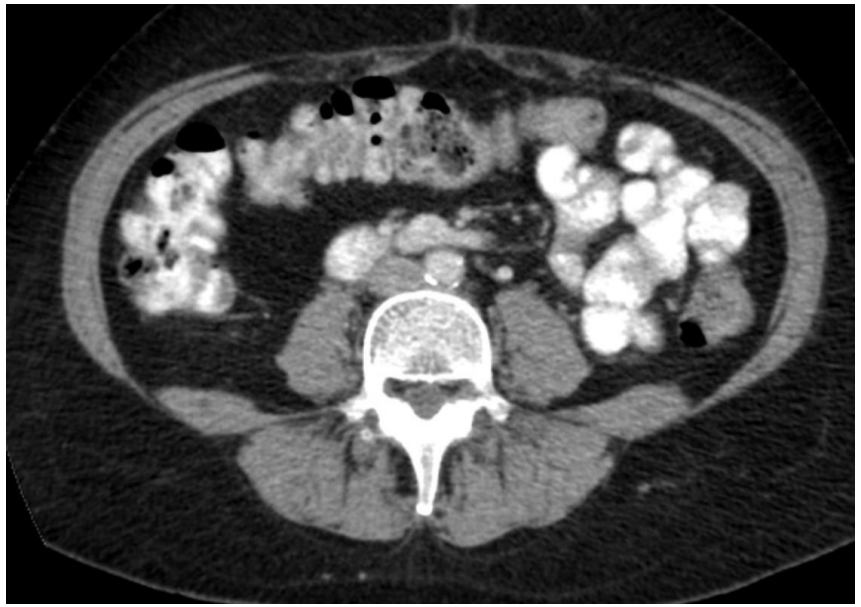
PATIENT CASE

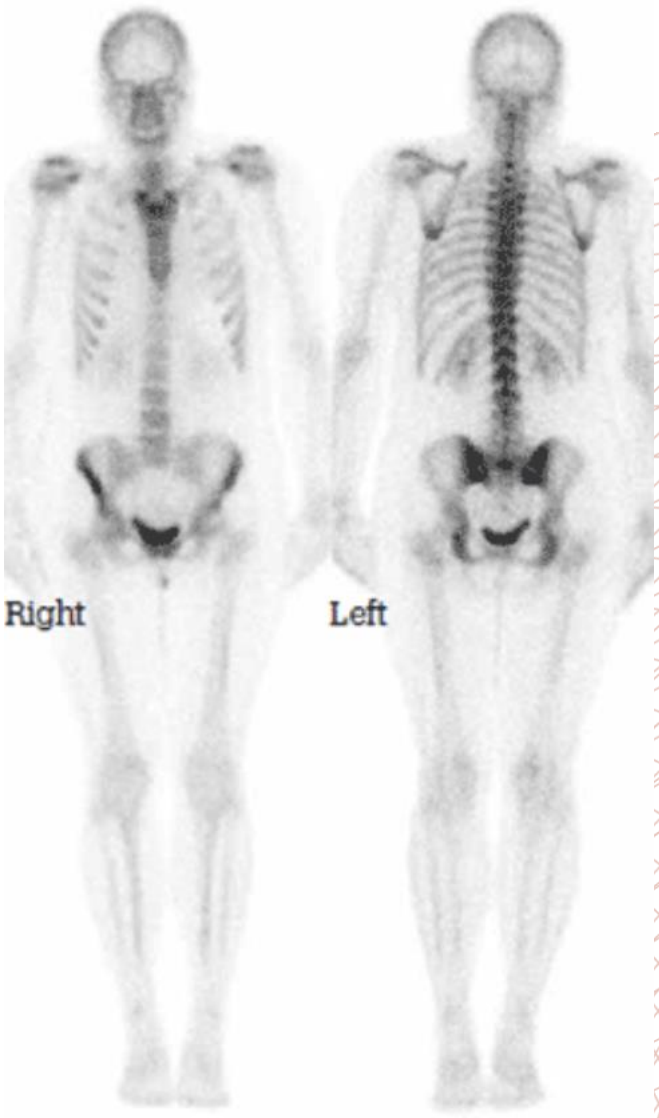
- Mr. GC is a **68 yo man** who presented to his primary care physician for his annual visit
- PMH: **Hyperlipidaemia**
- Meds: **simvastatin**
- Family History: **Grandmother had breast cancer**
- He is married and has good family support. He recently retired from being a high school history teacher
- Routine labs were unremarkable other than a **PSA of 12.6 ng/mL**
- He was referred to a urologist for further evaluation. His urologist proceeded with MRI of the prostate that demonstrated a **12 mm PI-RADS 5 lesion on the right**

MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting & Data System; PMH, prior medical history; PSA, prostate specific antigen; yo, year-old

PATIENT CASE

- MRI guided biopsy was performed. This demonstrated Gleason 4+5, GG 5, prostate adenocarcinoma in 5 of 12 cores
- He completed staging work up, which was negative for evidence of metastatic disease





MRI, magnetic resonance imaging; GG, grade group

POLLING QUESTION

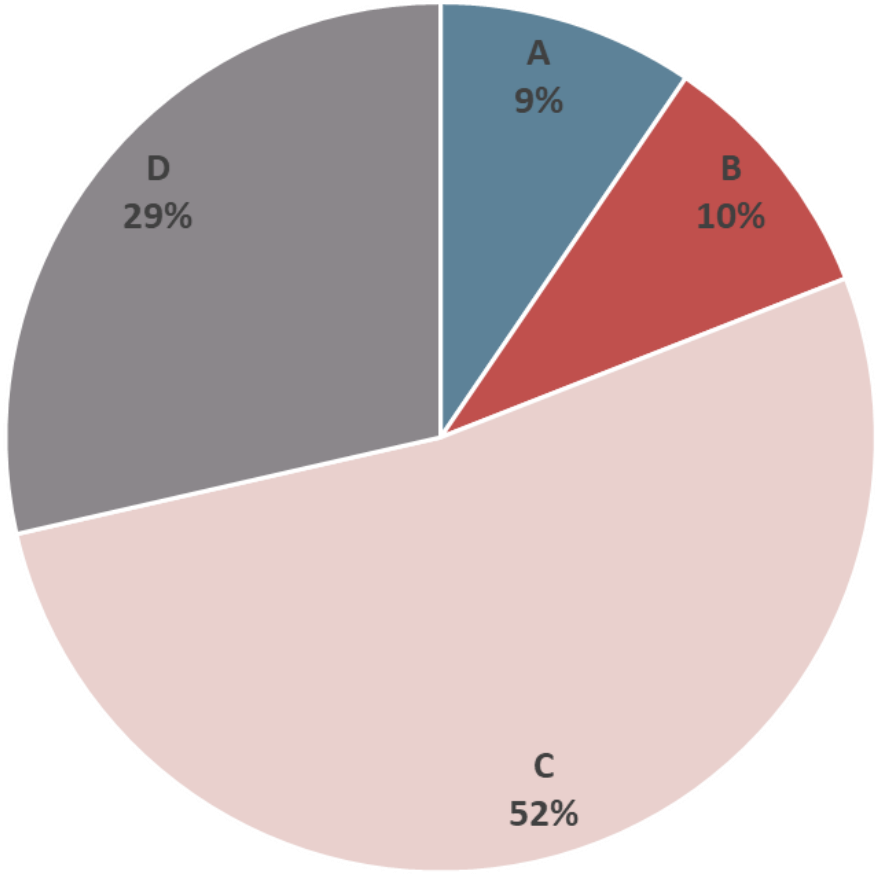
SHOULD HE UNDERGO GENETIC TESTING AT THIS TIME?

A. No, he does not have a family history of prostate cancer

B. No, he does not have enough first-degree relatives with cancer and was not diagnosed at a young age

C. Yes, he has high risk localised prostate cancer and should get germline testing ✅

D. Yes, all patients with prostate cancer should undergo germline genetic testing



POLLING QUESTION: RESPONSE

SHOULD HE UNDERGO GENETIC TESTING AT THIS TIME?

A. No, he does not have a family history of prostate cancer

B. No, he does not have enough first-degree relatives with cancer and was not diagnosed at a young age

C. Yes, he has high risk localised prostate cancer and should get germline testing

D. Yes, all patients with prostate cancer should undergo germline genetic testing

NCCN Guidelines Version 3.2024
Hereditary Cancer Testing Criteria

TESTING CRITERIA FOR PROSTATE CANCER SUSCEPTIBILITY GENES
(Specifically *ATM, BRCA1, BRCA2, CHEK2,* and *HOXB13*[z]) (GENE-A)[a,aa,bb]

Testing is clinically indicated in the following scenarios:

- See General Tumor Criteria on CRIT-1.
- Personal history of prostate cancer with specific features:
  - By tumor characteristics (any age)
    - ◊ Metastatic[p]
    - ◊ Histology
      - – high- or very-high-risk group (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
  - By family history and ancestry
    - ◊ ≥1 close blood relative[o] with:
      - – breast cancer at age ≤50 y
      - – triple-negative breast cancer at any age
      - – male breast cancer at any age
      - – ovarian cancer at any age
      - – pancreatic cancer at any age
      - – metastatic,[p] high-, or very-high-risk group (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age
    - ◊ ≥3 close blood relatives[o] with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer
    - ◊ Ashkenazi Jewish ancestry
- Family history of cancer
  - ◊ An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)[q]

Criteria met → GENE-1

If testing criteria not met, consider testing criteria for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

Testing *may be* considered in the following scenario:

- Personal history of prostate cancer with intermediate-risk prostate cancer with intraductal/cribriform histology (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age

Footnotes on CRIT-6A

https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed 14-Mar-2024

NCCN Guidelines Version 3.2024
Prostate Cancer

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

GERMLINE TESTING

For details regarding the nuances of genetic counseling and testing, see Principles of Cancer Risk Assessment and Counseling (EVAL-A) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

- **Pre-test Considerations**
  - The panel recommends inquiring about family and personal history of cancer, and known germline variants at time of initial diagnosis. Criteria for germline testing (see CRIT-6 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and LS-1 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal) should be reviewed at time of initial diagnosis and, if relevant, at recurrence.
  - Germline testing should be considered in appropriate individuals where it is likely to impact the prostate cancer treatment and clinical trial options, management of risk of other cancers, and/or potential risk of cancer in family members.
- **Testing**
  - If criteria are met, germline multigene testing that includes at least *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6,* and *PMS2* is recommended.
- **Post-test Considerations**
  - Post-test genetic counseling is strongly recommended if a germline mutation (pathogenic/likely pathogenic variant) is identified. Cascade testing for relatives is critical to inform the risk for familial cancers in all relatives.
  - Post-test genetic counseling is recommended if positive family history but no pathogenic variant OR if only germline variants of uncertain significance (VUS) are identified. This is to ensure accurate understanding of family implications and review indications for additional testing and/or follow-up (including clinical trials of reclassification).
  - Resources are available to review the available data supporting pathogenic consequences of specific variants (eg, https://www.ncbi.nlm.nih.gov/clinvar/; https://brcaexchange.org/about/app).
  - Individuals should be counseled to inform providers of any updates to family cancer history.

PATIENT CASE *CONTINUED*

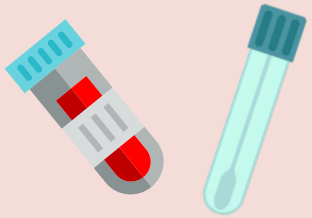
- He completes germline testing by blood-based assay, and it was negative for HRR alterations

HRR, homologous recombination repair

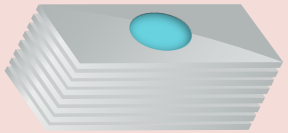
DIAGNOSTIC OPTIONS FOR MOLECULAR TESTING IN PROSTATE CANCER[1,2]

Germline

Somatic



Blood or buccal swab testing



Tissue testing

ctDNA testing

CTC testing

Tumour molecular testing can identify both germline and somatic HRR mutations, while germline testing detects only germline HRR mutations[3]

CTC, circulating tumour cell; ctDNA, circulating tumour DNA; HRR, homologous recombination repair

1. Cheng H, et al. ASCO Educational Book. 2018;38:372-381; 2. Haber DA and Velculescu VE. Cancer Discov. 2014;4:650-661;
3. Raymond VM, et al. J Natl Cancer Inst. 2015;108(4):djv351; 4. Wu H, et al. Gene Ther. 2017;24(10):601-609

PATIENT CASE *CONTINUED*

- He discussed his high-risk localised disease at length, and proceeded with prostatectomy, and tolerated well
  - PSA undetectable post-operatively
- PSA rose to 0.2 ng/mL approximately 6 months after surgery. Underwent salvage radiation with ADT PSA nadir was 0.05 ng/mL
- 10 months later, testosterone was 35 ng/dL and PSA started to rise
  - PSA 0.9 ng/mL
  - PSA 1.48 ng/mL
  - PSA 2.59 ng/mL

ADT, androgen deprivation therapy; PSA, prostate specific antigen

PATIENT CASE *CONTINUED*

- He undergoes repeat imaging for restaging
- Bone scan demonstrated sternal lesion concerning for metastatic disease
- His CT scan is negative for lymph node and visceral involvement but demonstrates several bone lesions in the pelvis
- PSA 4.23 ng/mL, testosterone in castrate range
- He declines biopsy that was requested due to relatively low PSA in the setting of metastatic disease

CT, computed tomography; PSA, prostate specific antigen

POLLING QUESTION

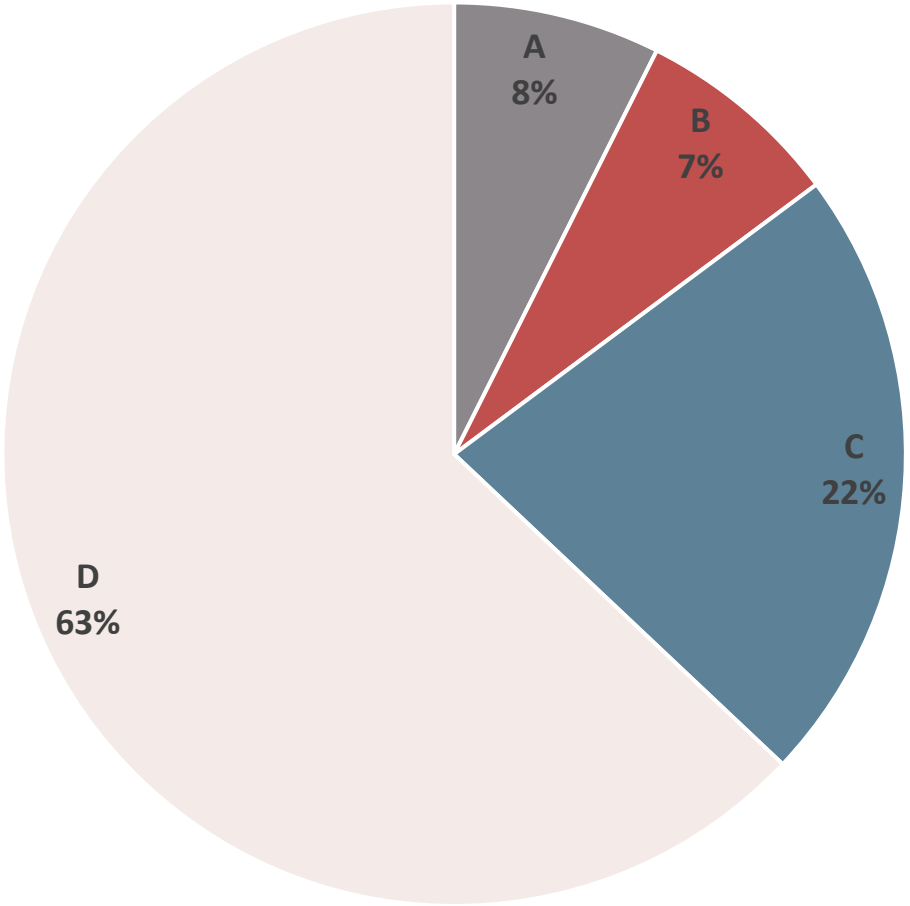
SHOULD HE UNDERGO ADDITIONAL GENETIC TESTING AT THIS TIME?

A. No, he already completed genetic testing

B. No, he has declined a biopsy

C. No, he only has bone lesions and it is not possible to do genetic testing with bone biopsy tissue

D. Yes, he should undergo somatic testing ✅



POLLING QUESTION: RESPONSE

SHOULD HE UNDERGO ADDITIONAL GENETIC TESTING AT THIS TIME?

A. No, he already completed genetic testing

B. No, he has declined a biopsy

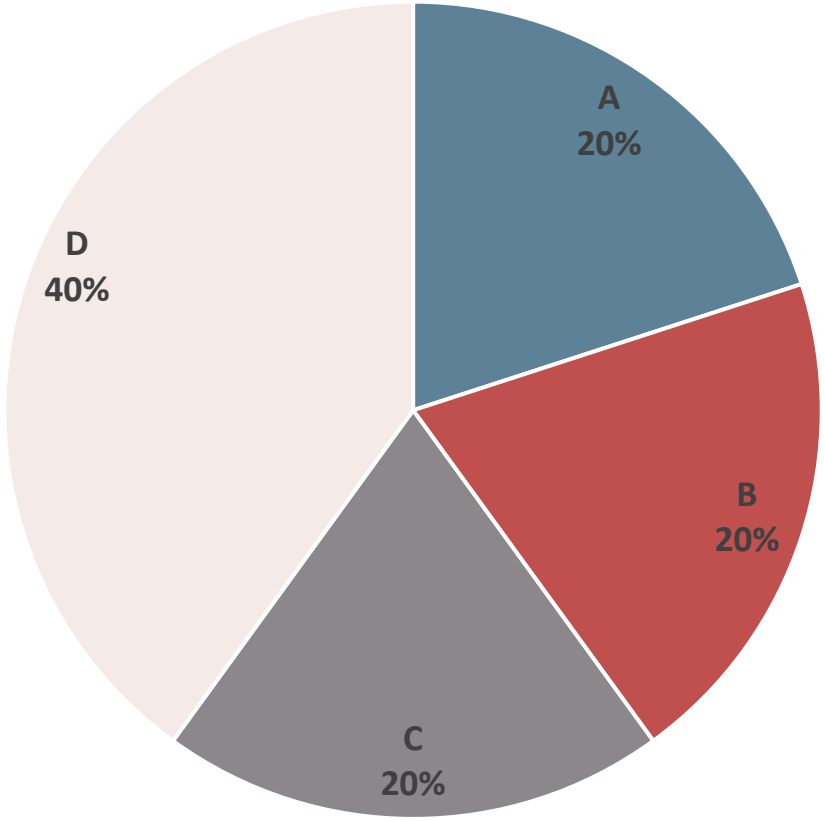
C. No, he only has bone lesions and it is not possible to do genetic testing with bone biopsy tissue

D. Yes, he should undergo somatic testing

POLLING QUESTION

WHICH OPTION IS NOT SUITABLE FOR SOMATIC GENETIC TESTING FOR THIS PATIENT?

A. **Buccal swab testing** ✅
B. Metastatic bone biopsy
C. Circulating tumour DNA (liquid biopsy)
D. Prostatectomy specimen tissue testing



POLLING QUESTION: RESPONSE

WHICH OPTION IS NOT SUITABLE FOR SOMATIC GENETIC TESTING FOR THIS PATIENT?

A. **Buccal swab testing**
B. Metastatic bone biopsy
C. Circulating tumour DNA (liquid biopsy)
D. Prostatectomy specimen tissue testing

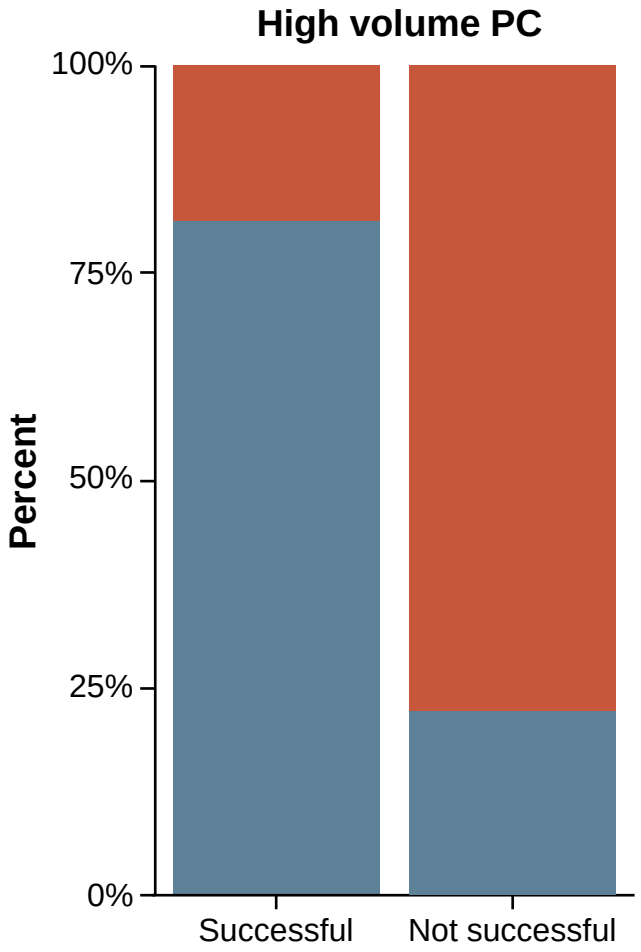
GENETIC TESTING APPROACHES: STRENGTHS AND WEAKNESSES

	Tumour testing	Germline testing	ctDNA testing
Advantages	• Most validated technique that allows **somatic and germline mutations** detection	• Easy to obtain **whole blood** or **buccal swab** samples to test for germline mutations • Can only detect germline mutations	• **Plasma ctDNA** is tested with easy-to-obtain **blood** samples • Can detect germline mutations • Plasma testing can also detect **somatic mutations** if there is an appreciable level of ctDNA
Disadvantages	• Requires invasive biopsies which may provide only limited tissue quantity and quality • Prostate cancer primary spreads to bone; tissue samples from bone metastases are difficult to obtain and process • A biopsy may miss within-tumour genetic heterogeneity	• Unable to identify somatic mutations	• Tests not currently widely available • Highly sensitive tests are required • May miss patients who do not shed sufficient ctDNA

ctDNA, circulating tumour DNA

Capoluongo E, et al. Oncotarget. 2018;9:19463-19468; Cheng H, et al. Am Soc Clin Oncol Educ Book. 2018;38:372-381; Ossandon MR, et al. J Natl Cancer Inst. 2018;110:929-934; Kammesheidt A, et al. Int J Mol Epidemiol Genet. 2018;9(1):1-12

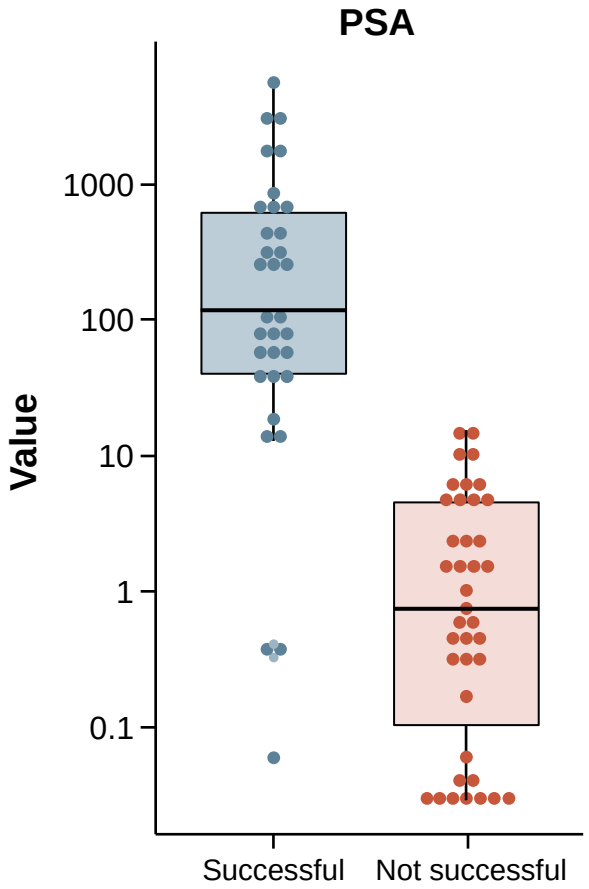
FACTORS AFFECTING SUCCESS FOR cfDNA



NOTE: Blue bars indicate percentage of patients with high-volume PC

Characteristic	OR	95% CI	P
Intercept	0.0	0.0-0.3	0.007
Log PSA	2.0	1.4-2.9	<0.001
Castration-resistant PC	6.5	1.0-41.5	0.050
Metastatic PC	2.7	0.1-69.9	0.550
High volume PC	6.3	1.3-31.9	0.026

- Somatic mutations were identified in cfDNA in 91% of patients with PSA >10 ng/mL



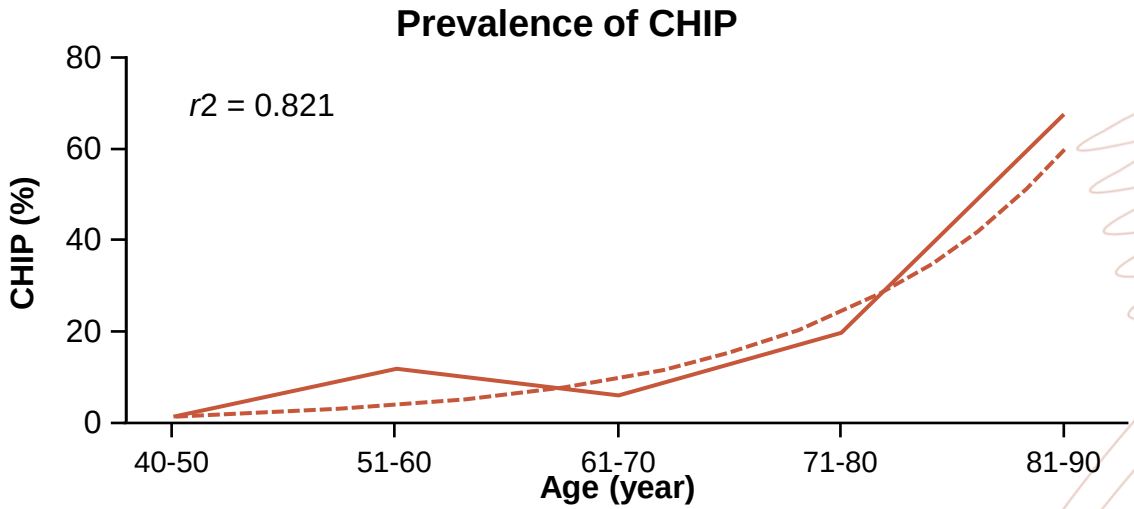
Detection of somatic alterations in plasma by PSA level

cfDNA, cell-free DNA; CI, confidence interval; OR, odds ratio; PC, prostate cancer; PSA, prostate specific antigen

Schweizer MT, et al. Prostate. 2019;79(7):701-708

MEN WITH PC ARE AT HIGH RISK OF BEING MISDIAGNOSED AS BEING ELIGIBLE FOR PARPi THERAPY USING CURRENT cfDNA TESTS

- Prostate cancer mutations are identified in plasma only
- CHIP can be detected in plasma and whole blood
- Use of a whole blood control can distinguish CHIP from PC variants



CHIP clones detected in DNA repair genes used for PARPi eligibility

Age, y	Gene	CHIP variants(s)	VAF cfDNA	VAF blood control	Notes
81	*ATM*	p.R3008C, p.E3007D	16%; 5%	16%; 5%	CHIP hotspot by outside lab in bone marrow
54	*ATM*	p.S305*	2%	3%	
82	*ATM*	p.G2891D	12%	13%	Kinase domain
81	*ATM*	c.2921 + 1G>A	78%	65%	Not germline based on tumour testing
87	*ATM*	p.L2492R	7%	9%	CHIP hotspot
76	*BRCA2*	p.T3310Nfs*17	3%	3%	Reported by outside lab, recommending PARPi
74	*CHEK2*	p.P426H	19%	18%	Kinase domain

ATM, ataxia telangiectasia mutated; BRCA2, breast cancer gene 2; cfDNA, cell free DNA; *CHEK2*, checkpoint kinase 2; CHIP, clonal haematopoiesis of indeterminate potential; PARPi, poly(ADP) ribose polymerase inhibitor; PC, prostate cancer; VAF, variant allele fraction

Jensen K, et al. JAMA Oncol. 2021;7(1):107-110

NCCN Guidelines Version 3.2024
Prostate Cancer

- **Tumor Specimen and Assay Considerations**
  - **The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. This could include lymph node biopsy for patients with N1 disease. When unsafe or unfeasible, plasma circulating tumor (ctDNA) assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.**
  - **Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.**
  - **DNA analysis for MSI and immunohistochemistry for mismatch repair (MMR) are different assays measuring different biological effects caused by dMMR function. If MSI is used, testing using a next-generation sequencing assay validated for prostate cancer is preferred.**
- **Post-test Considerations**
  - **Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, PMS2*).**
  - **Post-test genetic counseling to assess for the possibility of Lynch syndrome is recommended if MSI-H or dMMR is found.**

ctDNA, circulating tumour DNA; MMR, mismatch repair; MSI, microsatellite instability; PSA, prostate specific antigen

https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 14-Mar-2024

NCCN Guidelines Version 3.2024
Prostate Cancer

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

SOMATIC TUMOR TESTING

- **Pre-test Considerations**
  - **At present, tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. Clinical trials may include established and/or candidate molecular biomarkers for eligibility.**
  - **Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making.**
  - **Patients should be informed that tumor molecular analysis by DNA sequencing has the potential to uncover germline findings. Confirmatory germline testing may be recommended [see Post-test Considerations (below) and Tumor Testing: Potential Implications for Germline Testing in the Principles of Cancer Risk Assessment and Counseling (EVAL-A) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic].**
- **Testing**
  - **Somatic testing for alterations in DNA damage response:**
    - **Multigene tumor testing for alterations in HRR genes, including but not limited to *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*, and *CDK12*, is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.**
    - **Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC and may be considered in patients with regional or castration-sensitive metastatic prostate cancer.**
    - **TMB testing may be considered in patients with mCRPC.**

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; *CHEK1/2*, checkpoint kinase 1/2; *PALB2*, partner and localizer of *BRCA2;* TMB, tumour mutational burden

https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 14-Mar-2024

BIOMARKER DRIVEN TREATMENT FOR mCRPC

mCRPC, metastatic castration resistant prostate cancer

KEY PARPi INVESTIGATIONS IN PROSTATE CANCER

PARP Inhibitor Monotherapy		
Olaparib	PROfound[1]	FDA approved for HRR-mutated mCRPC[a]
Rucaparib	TRITON2[2]	FDA approved for *BRCA*-mutated mCRPC[a]
Talazoparib	TALAPRO-1[3]	Clinical activity in *BRCA*-mutated mCRPC
Niraparib	GALAHAD[4]	Clinical activity in *BRCA*-mutated mCRPC
PARP Inhibitor Combination Therapy		
Olaparib + Abiraterone	PROpel[5]	FDA approved for *BRCA*-mutated mCRPC[a] (May 2023)
Talazoparib + Enzalutamide	TALAPRO-2[6]	FDA approved for HRR-mutated mCRPC[a] (June 2023)
Niraparib + Abiraterone[b]	MAGNITUDE[7]	FDA approved for *BRCA*-mutated mCRPC[a] (August 2023)

[a] Information taken from product prescribing information; [b] Approved as a fixed dose combination

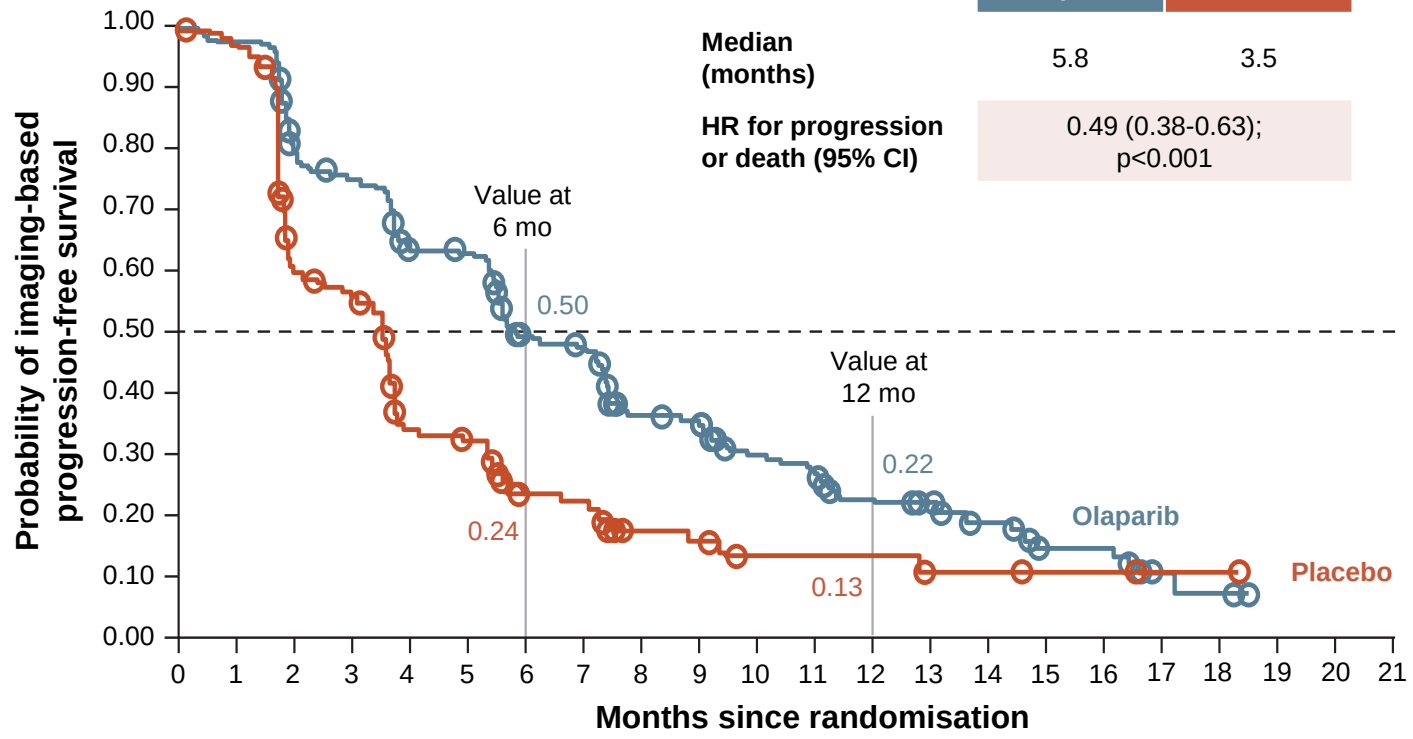
BRCA, breast cancer gene; FDA, US Food and Drug Administration; HRR, homologous recombination repair; mCRPC, metastatic castration resistant prostate cancer; PARP(i), poly (ADP-ribose) polymerase (inhibitor)

1. de Bono J, et al. N Engl J Med. 2020;382:2091-2102; 2. Abida W, et al. J Clin Oncol. 2020;38:3763-3772; 3. de Bono JS, et al. Lancet Oncol. 2021;22:1250-1264; 4. Smith M, et al. Lancet Oncol. 2022;23:362-373; 5. Clarke N, et al. NEJM Evidence 2022;1(9): doi: https://doi.org/10.1056/EVIDoa2200043; 6. Agarwal A, et al. Lancet. 2023;402:291-303; 7. Chi KN, et al. J Clin Oncol. 2023;41:3339-3351

PROFOUND: EFFICACY IN COHORT A AND OVERALL POPULATION

Overall[1,a]

	Olaparib	Placebo
Median (months)	5.8	3.5
HR for progression or death (95% CI)	0.49 (0.38-0.63); p<0.001	

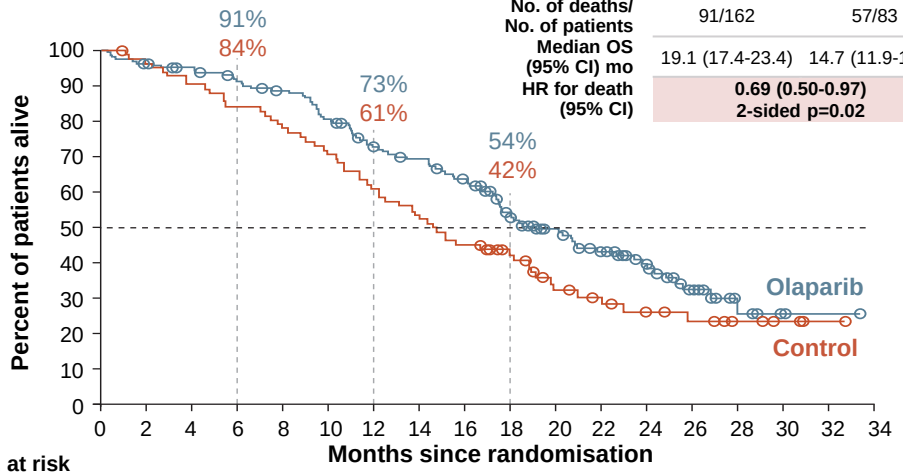


No. at risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

Cohort A (*BRCA1/2* or *ATM*)[2]

No. of deaths/ No. of patients	Olaparib	Control
	91/162	57/83
Median OS (95% CI) mo	19.1 (17.4-23.4)	14.7 (11.9-18.8)
HR for death (95% CI)	0.69 (0.50-0.97) 2-sided p=0.02	

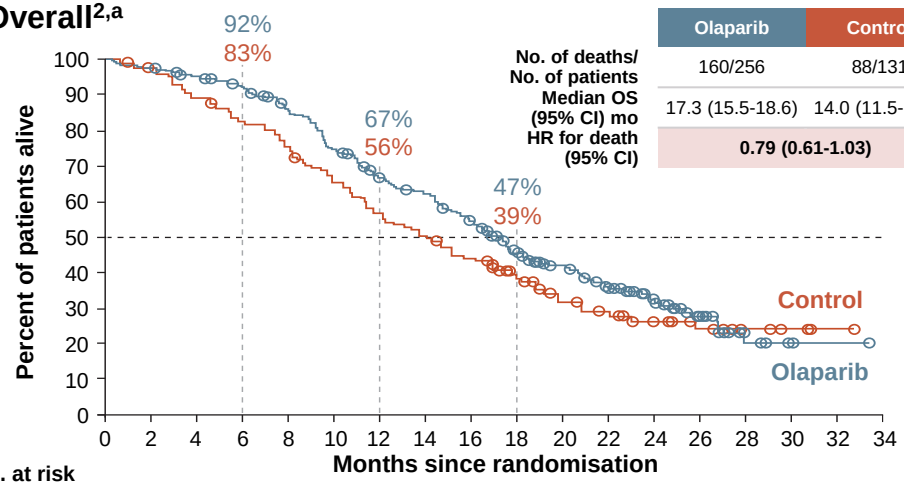


No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0				
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0				

Overall[2,a]

No. of deaths/ No. of patients	Olaparib	Control
	160/256	88/131
Median OS (95% CI) mo	17.3 (15.5-18.6)	14.0 (11.5-17.1)
HR for death (95% CI)	0.79 (0.61-1.03)	



No. at risk

Olaparib	256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0				
Control	131	125	115	106	96	83	71	63	55	37	27	22	15	11	6	3	1	0				

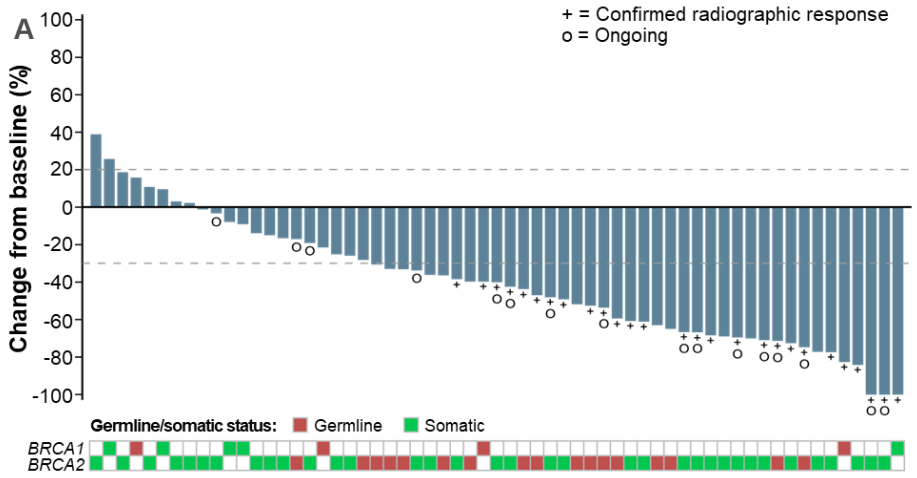
[a] mCRPC patients with alterations of *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* in their tumour tissue

ATM, ataxia telangiectasia mutated; BRCA1/2, breast cancer gene 1/2; CDK12, cyclin-dependent kinase 12; CHEK1/2, checkpoint kinase 1/2; CI, confidence interval; HR, hazard ratio; mCRPC, metastatic castration resistant prostate cancer; mo, months; OS, overall survival; PALB2, partner and localiser of BRCA2;

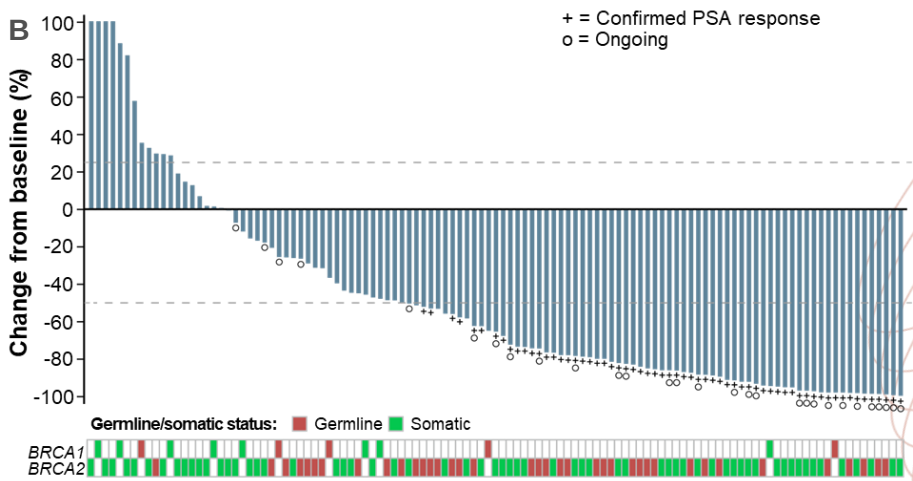
1. de Bono J, et al. N Engl J Med. 2020;382:2091-2102; 2. Hussain M, et al. N Engl J Med. 2020;383:2345-2357

TRITON2: POST NHA AND CHEMO RUCAPARIB MONOTHERAPY IN mCRPC WITH *BRCA1* OR *BRCA2* ALTERATIONS

Best change from baseline in sum of target lesion(s) in the IRR-evaluable population



Best change from baseline in PSA in the overall efficacy population

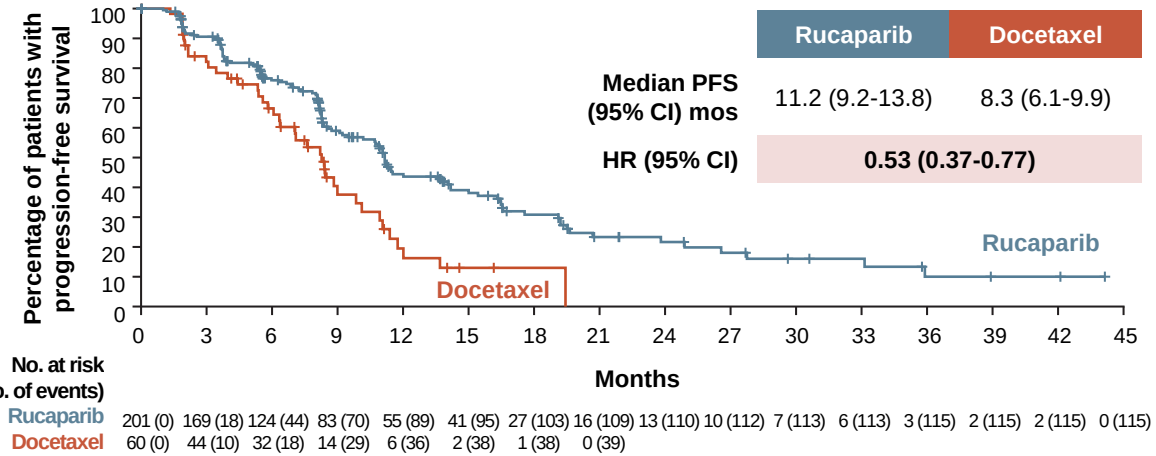


BRCA1/2, breast cancer gene 1/2; chemo, chemotherapy; CI, confidence interval; IRR, independent radiology review; mCRPC, metastatic castration resistant prostate cancer; NHA, new hormonal agent; PSA, prostate-specific antigen, rPFS, radiographic progression-free survival

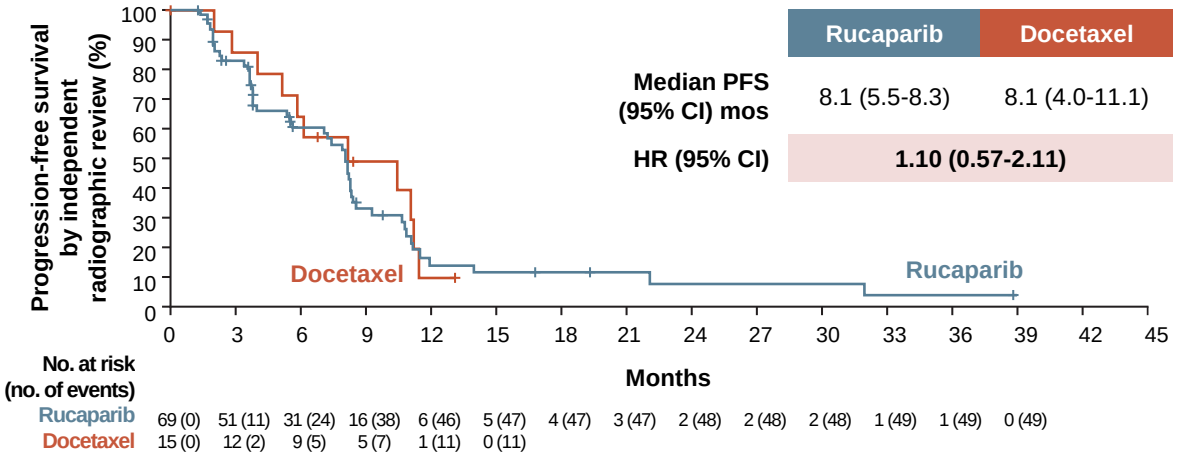
Adapted from: Abida W, et al. J Clin Oncol. 2020;38:3763-72

TRITON3 STUDY: RUCAPARIB VS PHYSICIAN'S CHOICE IN PATIENTS WITH *BRCA1/2* OR *ATM* ALTERATIONS

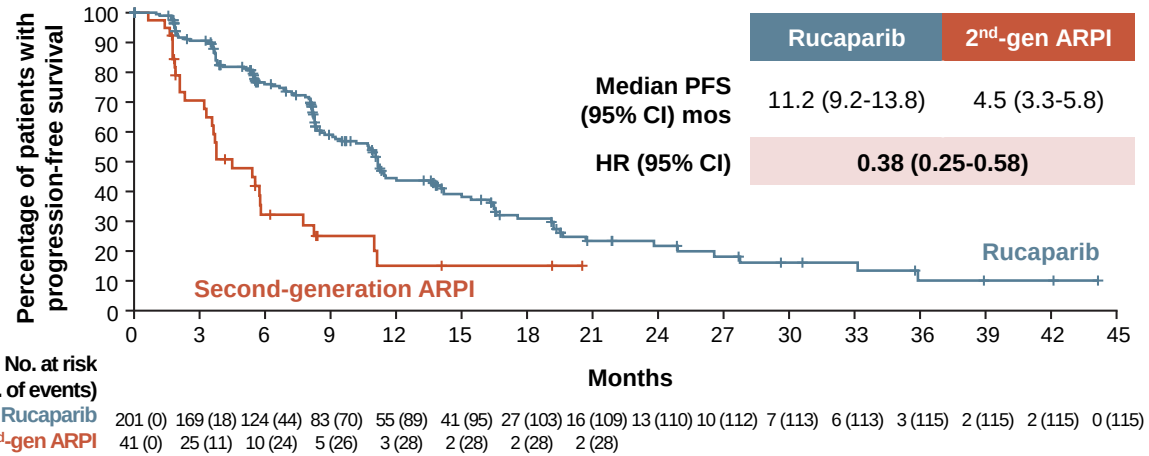
Rucaparib vs. docetaxel in the *BRCA* subgroup



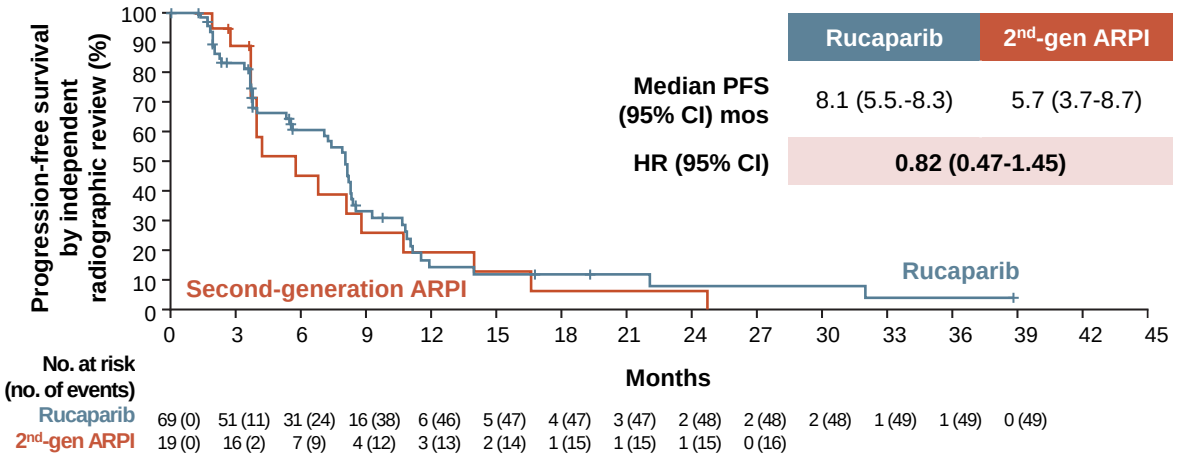
Rucaparib vs. docetaxel in the *ATM* subgroup



Rucaparib vs. second-generation ARPI therapies in the *BRCA* subgroup



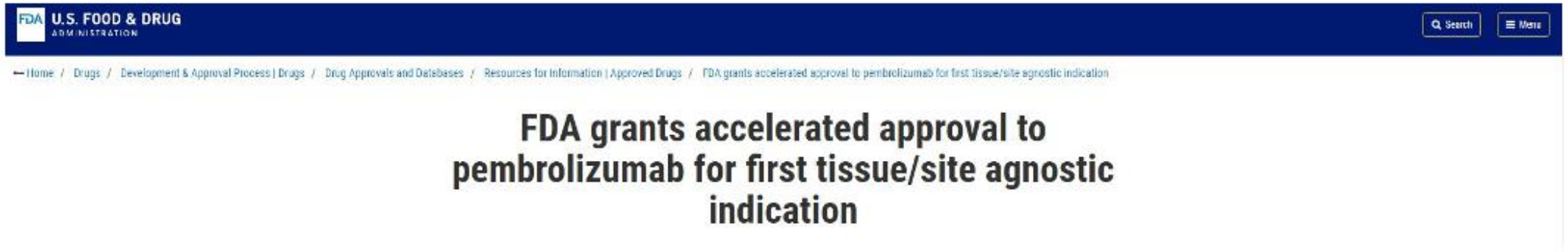
Rucaparib vs. second-generation ARPI therapies in the *ATM* subgroup



ARPI, androgen receptor pathway inhibitor; *ATM*, ataxia telangiectasia mutated; BRCA(1/2), breast cancer gene (1/2); CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Fizazi K, et al. N Engl J Med. 2023;388(8):719-732 (including supplementary appendix)

PEMBROLIZUMAB: APPROVED FOR MSI-H, TMB ≥10, AND MSH/dMMR MUTATIONS



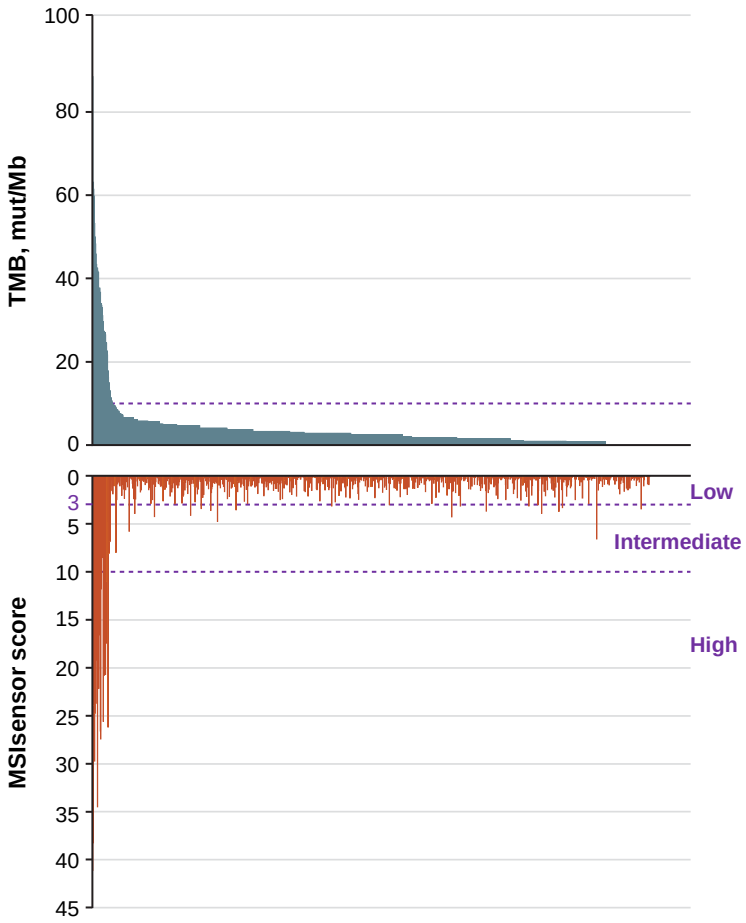
FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication [press release]. Silver Spring, MD: US Food and Drug Administration; May 23, 2017.

dMMR, deficient DNA mismatch repair; FDA, Food and Drug Administration; MSH, MutS protein homolog; MSH, mismatch repair genes; MSI-H, microsatellite instability high; TMB, tumour mutational burden

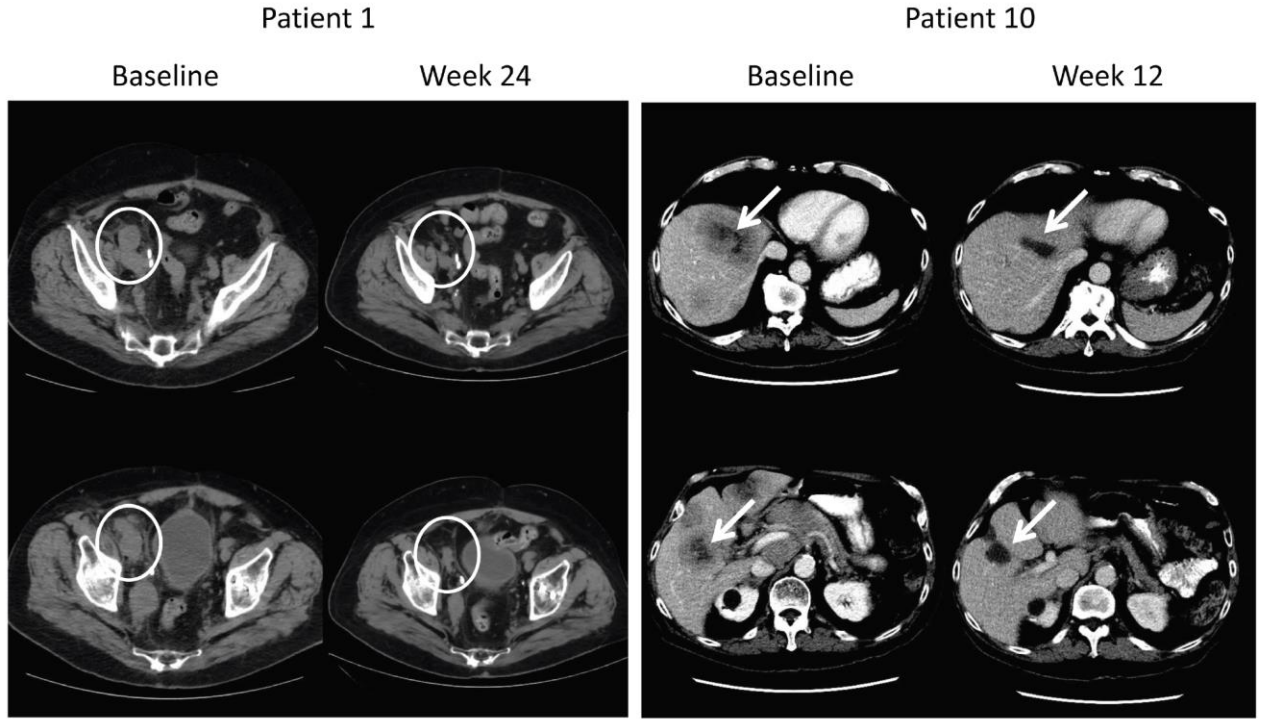
FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication [press release]
Silver Spring, MD: US Food and Drug Administration; May 23, 2017; Pembrolizumab Prescribing Information, March 2024

PEMBROLIZUMAB: CONSIDER FOR MSI-H, TMB >10, AND MSH/MLH MUTATIONS

TMB and MSIsensor score in 1033 patients with prostate cancer[1]



- Approximately 2-3% of men with prostate cancer have MSI-H tumours (left)[1,2] and can have radiographic responses to pembrolizumab (right)[3]



MLH, MutL homolog; MSH, MutS protein homolog; MSI-H, microsatellite instability high; mut/Mb, mutations per megabase; TMB, tumour mutational burden

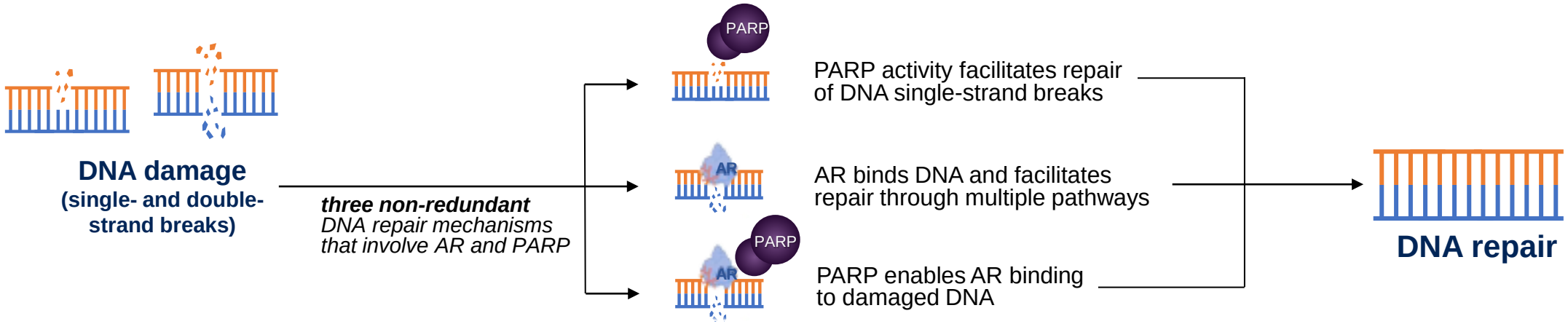
1. Abida W, et al. JAMA Oncol. 2019;5(4):471-478; 2. Abida W, et al. J Clin Oncol 2018; 36 (15)_Suppl: 5020; 3. Graff J, et al. Oncotarget. 2016;7(33):52810-52817

COMBINATION PARPi DATA IN mCRPC

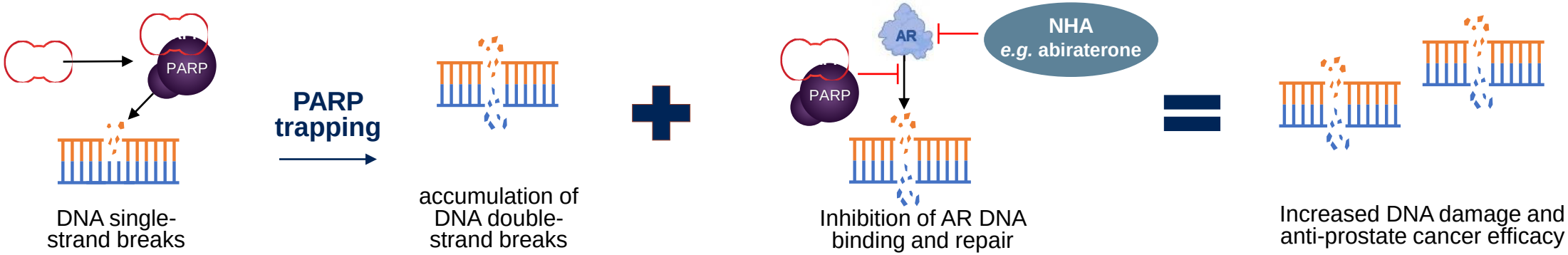
mCRPC, metastatic castration resistant prostate cancer; PARPi, poly-ADP ribose polymerase inhibitor

INTERACTIONS BETWEEN PARP SIGNALING AND AR SIGNALING

PARP and AR are important for DNA repair in prostate cancer



Inhibition of PARP and AR in combination results in more DNA damage in AR-driven cancer cells



AR, androgen receptor; DNA, deoxyribonucleic acid; NHA, novel hormonal agent; PARP, poly(ADP-ribose) polymerase

1.Chaudhuri AR, et al. Nat Rev Mol Cell Biol. 2017;18:610-21; 2. Polkinghorn WR, et al. Cancer Discov. 2013;3:1245-53; 3. Lord CJ, et al. Science 2017;355:1152-8; 4. Pommier Y, et al. Sci Transl Med 2016;8:p362ps17; 5. Schiewer MJ, et al. Cancer Discov. 2012;2:1134-49; 6. Asim M, et al. Nat Commun. 2017;8:374; 7. Li L, et al. Sci Transl Med. 2017;10:10.1126/scisignal.aam7479; 8. Clarke N, et al. GU ASCO 2023; 9. Clarke N, et al. NEJM Evidence 2022.EVIDoa2200043

rPFS ACROSS AR-PARP INHIBITOR COMBINATION TRIALS (PRIMARY ENDPOINT)

		TALAPRO-2 (BICR)[1]		PROpel (invest. review)[2,3]		Magnitude (BICR)[4]	
		TALA+ ENZA	Placebo+ ENZA	OLA+ ABI	Placebo+ ABI	NIRA+ ABI	Placebo+ ABI
All comers/unselected	n	402	403	399	397	Not applicable	
	Median rPFS, mo	Not reached	21.9	24.8	16.6		
	HR	**0.63**		**0.66**			
HRR deficient	n	85	84	111	115	212	211
	Median rPFS, mo	27.9	16.4	Not reached	13.9	16.5	13.7
	HR	**0.46**		**0.50**		**0.73**	
HRR non-deficient[a]	n	198	214	279	273	117	116
	Median rPFS, mo	Not reached	22.1	24.1	19.0	NA	NA
	HR	**0.66**		**0.76**		**(1.09)**	
*BRCA*m	n	27	32	47	38	113	112
	Median rPFS, mo	Not reported	Not reported	Not reached	8.4	16.6	10.9
	HR	**0.23**		**0.23**		**0.53**	
Non-*BRCA*m	n	58	52	343	350	99	99
	Median rPFS, mo	Not reported	Not reported	24.1	19.0	14.8	16.4
	HR	**0.66**		**0.76**		**0.99**	

[a]in TALAPRO-2 determined by prospective tumour tissue testing.

Please note that these studies cannot be directly compared. The data are presented for information purposes only

ABI, abiraterone acetate; AR, androgen receptor; BICR, blinded independent central review; BRCAm, breast cancer gene mutation; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; mo, months; NIRA, niraparib; OLA, olaparib; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Agarwal A, et al. The Lancet 2023: https://doi.org/10.1016/S0140-6736(23)01055-3; 2. Clarke N, et al. NEJM Evidence 2022; 1(9): DOI: 10.1056/EVIDoa2200043; 3. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); 4. Chi K, et al. J Clin Oncol 2023: DOI: 10.1200/JCO.22.01649

mOS ACROSS AR-PARP INHIBITOR COMBINATION TRIALS

		TALAPRO-2 (BICR)[1]		**PROpel** (invest. review)[2]		**Magnitude** (BICR)[3,4]	
		TALA+ ENZA	**Placebo+ ENZA**	**OLA+ ABI**	**Placebo+ ABI**	**NIRA+ ABI**	**Placebo+ ABI**
All comers/unselected	n	402	403	399	397	Not applicable	
	Median OS, mo	36.4	Not reached	42.1	34.7		
	HR	**0.89** *(31% mature)*		**0.81** *(47.9% mature)*			
HRR deficient	N	Not reported		111	115	212	211
	Median OS, mo			Not reached	28.5	Not reached	Not reached
	HR			**0.66**		**0.94** *(46.3% mature)*	
HRR non-deficient	n	Not reported		279	273	Not reported	
	Median OS, mo			42.1	38.9		
	HR			**0.89**			
*BRCA*m	n	Not reported		47	38	113	112
	Median OS, mo			Not reached	23.0	29.3	28.6
	HR			**0.29**		**0.88**	
Non-*BRCA*m	n	Not reported		343	350	Not reported	
	Median OS, mo			39.6	38.0		
	HR			**0.91**			

Please note that these studies cannot be directly compared. The data are presented for information purposes only

ABI, abiraterone acetate; AR, androgen receptor; BICR, blinded independent central review; BRCAm, breast cancer gene mutation; CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; HRR, homologous recombination repair; mo, months; NA, not applicable (not reported); NIRA, niraparib; OLA, olaparib; PARP, poly-ADP ribose polymerase; rPFS, radiographic progression-free survival; TALA, talazoparib

1. Agarwal A, et al. The Lancet 2023: https://doi.org/10.1016/S0140-6736(23)01055-3 (Data supplement); 2. Clarke N, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16) (ASCO GU 2023 oral presentation); 3. Chi K, et al. J Clin Oncol 2023: DOI: 10.1200/JCO.22.01649; 4. Efstathiou E, et al. J Clin Oncol 41, 2023 (suppl 6; abstr 170) (ASCO GU 2023 oral presentation);

PARP INHIBITORS ARE APPROVED IN PROSTATE CANCER

Olaparib FDA-approved indication[1]

- Indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and **HRRm**, who have **progressed** on enzalutamide or abiraterone acetate
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with ***BRCAm* mCRPC**

Niraparib FDA-approved indication[3]

- Indicated as **a fixed-dose combination of niraparib/abiraterone acetate** with prednisone for the treatment of adult patients with ***BRCAm* mCRPC**

Rucaparib FDA-approved indication[5]

- Indicated as **monotherapy** for the treatment of adult patients with ***BRCAm* mCRPC** who have **progressed on** AR-directed therapy and a **taxane[a]**

Talazoparib FDA-approved indication

- In combination with enzalutamide for the treatment of adult patients with HRRm **mCRPC**

Olaparib EMA-approved indication[2]

- Indicated as **monotherapy** for the treatment of adult patients with **mCRPC** and a ***BRCAm***, who have **progressed** on prior therapy, including an **NHA**
- In **combination with abiraterone** and prednisone or prednisolone for the treatment of adult patients with **mCRPC in whom chemotherapy is not clinically indicated**

Niraparib EMA-approved indication[4]

- Indicated as **a fixed-dose combination of niraparib/abiraterone acetate** with prednisone or prednisolone for the treatment of adult patients with **mCRPC and *BRCA1/2* gene mutations** (germline and/or somatic) **in whom chemotherapy is not clinically indicated**

[a]Rucaparib has no current approval in prostate cancer in Europe

Talazoparib EMA-approved indication

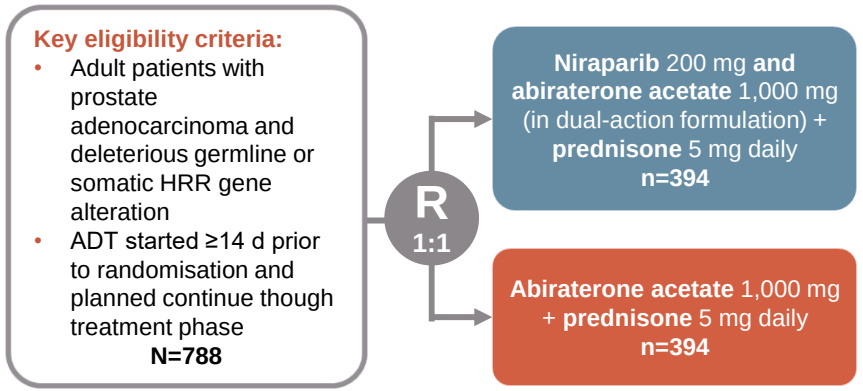
- In combination with enzalutamide for the treatment of adult patients with **mCRPC** in whom chemotherapy Is not clinically indicated

AR, androgen receptor; BRCAm, breast cancer gene mutation; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HRRm, homologous recombination repair mutation; LHRH, luteinising hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; PARP, poly-ADP ribose polymerase

1. Lynparza (olaparib) US prescribing information (Sep-2023); 2. Lynparza (olaparib) summary of product characteristics (Mar 2023); 3. FDA approves niraparib and abiraterone acetate plus prednisone for BRCA-mutated metastatic castration-resistant prostate cancer | FDA; 4. https://www.esmo.org/oncology-news/ema-recommends-granting-a-marketing-authorisation-for-akeega-fixed-dose-combinations-of-niraparib-abiraterone-acetate; 5. Rubraca (rucaparib) US prescribing information (Jun 2022); 6. Talzenna (talazoparib) summary of product characteristics (Apr 2024)

EXPANDING REACH OF COMBINATION APPROACHES EARLIER IN DISEASE

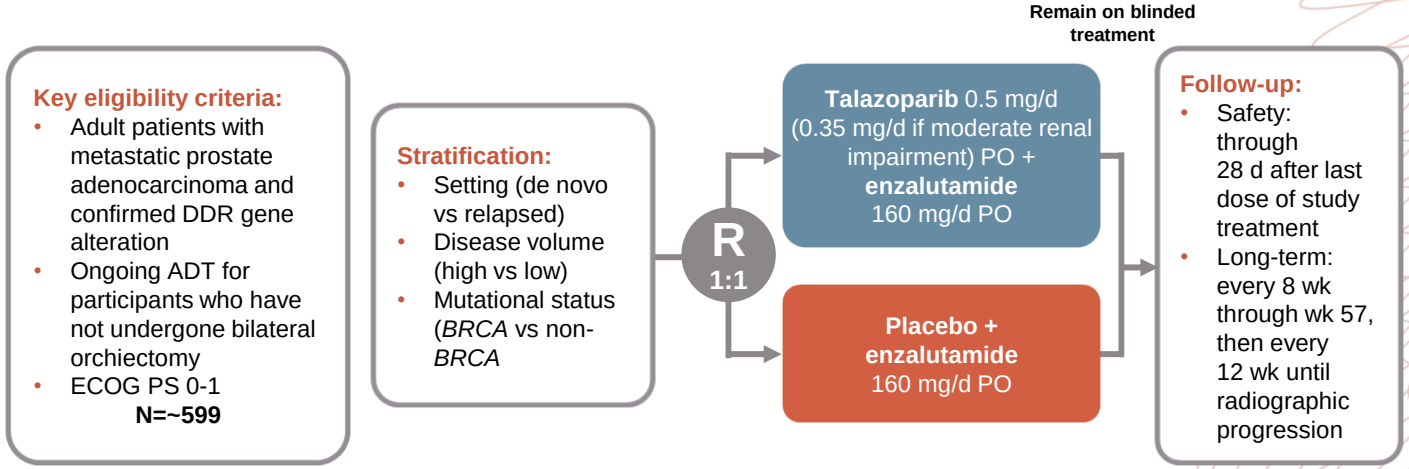
mHSPC: Phase 3 AMPLITUDE



- **Primary endpoint:** Investigator-assessed radiographic PFS
- **Secondary endpoints:** OS, symptomatic PFS, time to subsequent therapy

mHSPC: Phase 3 TALAPRO-3

Talazoparib + enzalutamide in mHSPC



- **Primary endpoint:** Radiologic PFS
- **Secondary endpoints:** OS, objective response and DoR in soft-tissue disease, PSA response, time to PSA progression, time to PFS

ADT, androgen deprivation therapy; BRCA, breast cancer gene; d, day; DDR, DNA damage response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRR, homologous recombination repair; mHSPC, metastatic hormone sensitive prostate cancer; OS, overall survival; PFS, progression free survival; PO, orally; PSA, prostate-specific antigen; R, randomisation; wk, weeks

Clinicaltrials.gov (NCT04497844; NCT04821622); TALAPRO-3 clinical trial protocol: phase III study of talazoparib plus enzalutamide in metastatic castration-sensitive prostate cancer | Future Oncology (futuremedicine.com), Accessed 17-Mar-24

PATIENT CASE *CONTINUED*

RESULTS OF GENOMIC TESTING

- Somatic tissue testing of the prostatectomy specimen demonstrated a *BRCA2* mutation

Patient results

4 genomic findings

5 therapies associated with potential clinical benefit

0 therapies associated with lack of response

15 clinical trials

Tumour type: Prostate acinar adenocarcinoma

Genomic alterations identified
BRCA2 loss
PTEN loss exons 2-9

Additional findings†
Microsatellite status: MS-Stable
Tumour Mutational Burden: TMB-Low; 4 Muts/Mb

Therapeutic implications

Genomic findings detected	FDA-approved therapies (in patient's tumour type)	FDA-approved therapies (in another tumour type)	Potential clinical trials
BRCA2 loss	None	Niraparib Olaparib Rucaparib	Yes, see clinical trials section
PTEN loss exons 2-9	None	Everolimus Temsirolimus	Yes, see clinical trials section
Microsatellite status MS-Stable	None	None	None
Tumour Mutational Burden TMB-Low; 4 Muts/Mb	None	None	None

Example genetic testing report

BRCA2, breast cancer gene 2; FDA, US Food and Drug Administration; MS, microsatellite; Muts/Mb, mutations per megabase; PTEN, phosphatase and tensin homolog; TMB, tumour mutational burden

Julika P, et al. Case Rep Oncol 2020; 13: 55-61

PATIENT CASE *CONTINUED*

- He now meets criteria for treatment of mCRPC with abiraterone acetate plus prednisone, enzalutamide, docetaxel, olaparib, or PARPi and novel hormonal treatment combination
- He and his team consider the options in a shared decision
  - He feels strongly that he does not want to lose his hair
  - He prefers oral treatment
  - He would like to be as aggressive as possible in terms of getting cancer control given the rapid progression to mCRPC
  - He likes the idea of targeted therapy for his *BRCA2* mutation

BRCA2, breast cancer gene 2; mCRPC, metastatic castration resistant prostate cancer; PARPi, poly(ADP-ribose) polymerase inhibitor

PATIENT CASE *CONTINUED*

- After considering his options, he proceeds with treatment with abiraterone acetate plus olaparib
- He favoured the combination of an oral option, aggressiveness against the *BRCA2* target, and no hair loss
- He feels improvement in fatigue, and tolerates treatment well
- PSA decreased in 8 weeks (PSA 4.23 → 1.67 ng/mL)

BRCA2, breast cancer gene 2; PSA, prostate specific antigen

CONCLUSIONS

- Germline testing in patients with advanced prostate cancer can be used to identify patients whose families need cascade testing
- Multiple options for testing are available
  - Somatic testing using primary prostatectomy tissue, prostate biopsy, metastatic biopsy, or ctDNA testing
  - Germline testing with buccal swab or plasma testing
- Genetic testing in patients with advanced prostate cancer may identify patients for highly effective targeted agents
  - Germline and somatic genetic testing are may identify patients who are eligible for treatment with PARPi and pembrolizumab
  - Both forms of genetic testing are recommended

ctDNA, circulating tumour DNA; PARPi, poly(ADP-ribose) polymerase inhibitor

ADDRESSING THE CHALLENGES OF BIOMARKER TESTING IN PROSTATE CANCER

Q&A SESSION

PANEL DISCUSSION
AND
AUDIENCE QUESTIONS

FUTURE PERSPECTIVES AND SUMMARY

Fernando López-Ríos MD, PhD

Department of Pathology
Hospital Universitario 12 de Octubre
Madrid, Spain

FINAL COMMENTS

- Molecular testing is now standard of care
  - Preserve and prioritise tissue
  - A more comprehensive perspective of predictive biomarker testing
- Lung
  - Organise your testing strategy: upfront NGS *versus* sequential testing
  - Patient-centered workflows: reflex testing and integrate liquid biopsies
- Prostate
  - Importance of HRR mutations and MSI-H
  - Germline and somatic testing are recommended

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