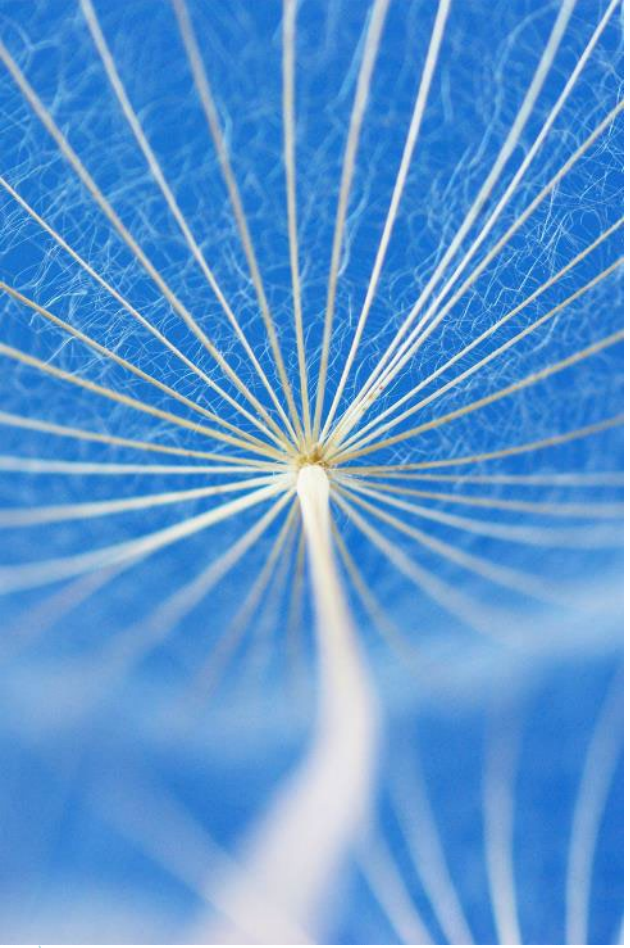



MOLECULAR MDT AND YOU

Dr Brian Bird FRCPI Consultant Medical Oncologist

Bon Secours Hospital

Cork, Ireland

ucc
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

BON SECOURS HEALTH SYSTEM

Dr Brian Healey Bird FRCPI

Consultant Medical Oncologist, Bon Secours Cork

Senior Lecturer in Clinical Education, University College Cork

Principal Investigator Cancer Trials Cork

CANCER TRIALS CORK

ESMO Designated Centres of Integrated Oncology and Palliative Care

DR BRIAN HEALEY BIRD FRCPI

- Trained in Ireland 1998-2005
- Clinical Fellowship National Cancer Institute USA 2005-2008
- Specialize in Lymphoma, GI malignancies and Lung Cancer
- Participate in Clinical Trials with my 2 colleagues
- Currently leading on-site immunotherapy biomarker research with laboratory collaborators in UCC and TCD
- Teach Medical Students in UCC
- Not an expert in interpreting molecular data – yet!

NAVIGATING

Which patients benefit most from Mol MDT?

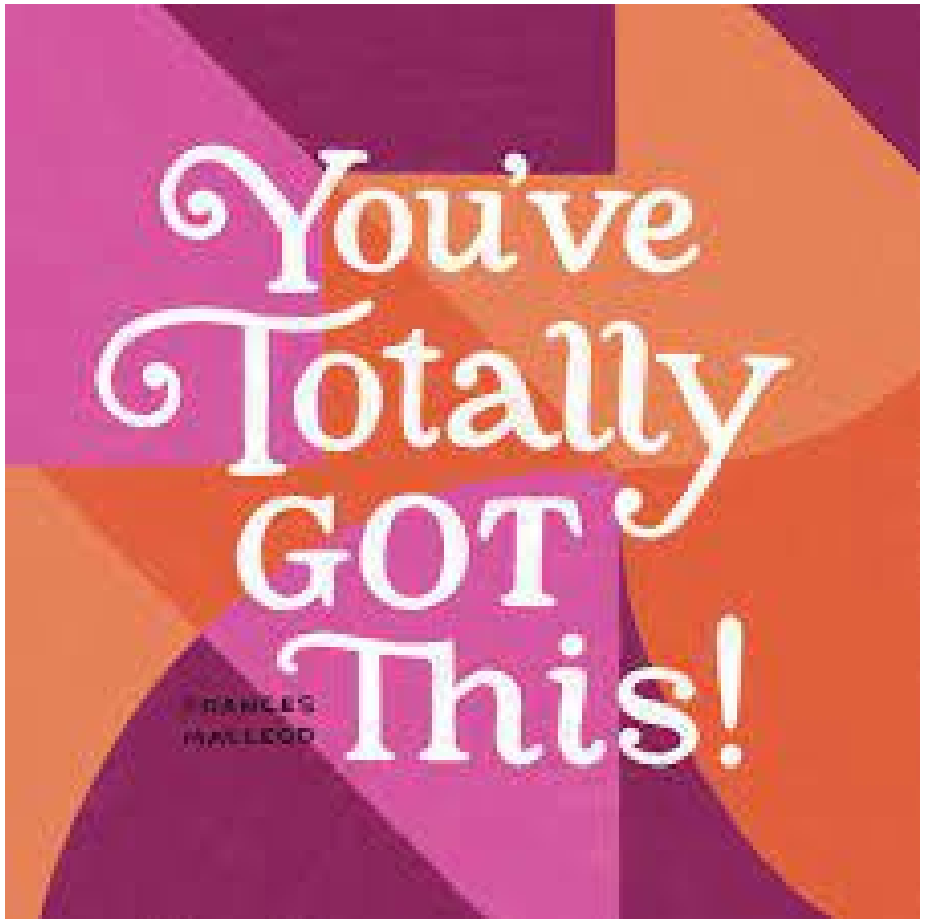
1 example

Personal Reflections

Future Directions

CASES THAT DO NOT NEED MOL MDT

- EGFR Exon 19 mutated lung cancer – first line therapy
- KRAS G12 C mutated lung cancer – unless it helps get compassionate access drug?
- PIK3CA mutated breast cancer
- RAS/RAF wildtype colon cancer



NGS REPORTS – PEARLS AND POISONS?

Not every molecular result is actionable

Not every result comes from the cancer – hereditary mutations, clonal hematopoiesis

Experience is needed to interpret modern NGS results especially after progression on first line Tyrosine Kinase Inhibitors

If you treat multiple types of malignancy it's hard to stay current with test interpretation

Outside large institutions difficult to have all the scientific and clinical genetic expertise required

LEARN TO LOVE THE CHECKLIST

Divers have a checklist

The Mol MDT template slides allow you to present the patient data in a structured way

Your clinical expertise AND

The expert panel's scientific expertise

TOGETHER HELP THE PATIENT

REAL CASE

Adenocarcinoma of Lung

Dr Brian Bird – Stage IV Met Exon 14 mutated NSCLC

General Description

Gender	*female*
Age range	*65-70*
Cancer Type and stage	*Lung Stage IV*
Test type	*solid AND serial liquid*
About the test	*SJH Oncomine Panel FoundationOne®Liquid CDx,*
Date of test	*23/2/2023*

Patient / Treatment History

- 69-year-old female on DOAC for A FIB who presented in January 2022 with haemoptysis. PET showed single rib met, never smoker
- Imaging revealed a Right Upper Lobe mass with mediastinal nodes. EBUS was consistent with metastatic adenocarcinoma of lung (TTF1 pos, p40neg) . Subsequent CT guided biopsy and initial ctDNA test
- MET mutation: c.3028+1delGp.?@33%VAF Mol MDT recommended Tepotonib on progression
- Patient developed brain mets and had XRT then started on first line chemo, and immunotherapy with a modest response until July 2022. Stopped for poor QoL
- Treated with comp access Tepotinib – complicated by prolonged QTc (responded to dose reduction) and thrombocytopenia. Partial Response 18/11/2022
- Visceral Disease Progression on Tepotinib → Repeat Foundation Liquid Test 2/2/23
- Rechallenge with Carbo/Pemetrexed/Pembro

Initial Foundation Liquid ctDNA test April 2022

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** See Genomic Signatures section
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Genomic Signatures section).**

GENE ALTERATIONS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET - exon 14 splice site (3028delG)	1.0%	Crizotinib	2A	Cabozantinib
		Tepotinib	2A	

10 Trials see p. 11

NCCN category

Repeat Foundation Liquid Test Feb 2023

Blood Tumor Mutational Burden - 5 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Gene Alterations

For a complete list of the genes assayed, please refer to the Appendix.

MET D1228H, exon 14 splice site (3028delG)
NF1 M1149V
ATM splice site 2921+1G>A
MSH2 Y408fs*9
RB1 splice site 1668_1695+51>G
TET2 Q810*, R1216*
TP53 R280T

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Capmatinib** (p. 13), **Crizotinib** (p. 13)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 17)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***ATM*** **splice site 2921+1G>A** (p. 9), ***TET2*** **Q810*, R1216*** (p. 11)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 5 Muts/Mb	**No therapies or clinical trials. See Genomic Signatures section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Genomic Signatures section).**

GENE ALTERATIONS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
MET -	D1228H	1.7%	Capmatinib 2A	Cabozantinib
	exon 14 splice site (3028delG)	3.8%	Crizotinib 2A	
			Tepotinib ?	
10 Trials see p. 19				
NF1 -	M1149V	0.21%	None	Selumetinib
				Trametinib
10 Trials see p. 21				
ATM -	splice site 2921+1G>A	0.20%	None	None
10 Trials see p. 17				

? *Limited evidence showing variant(s) in this sample may confer resistance to this therapy*

☐ *NCCN category*

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

ATM - splice site 2921+1G>A ..... p. 9

TET2 - Q810*, R1216* ..... p. 11

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

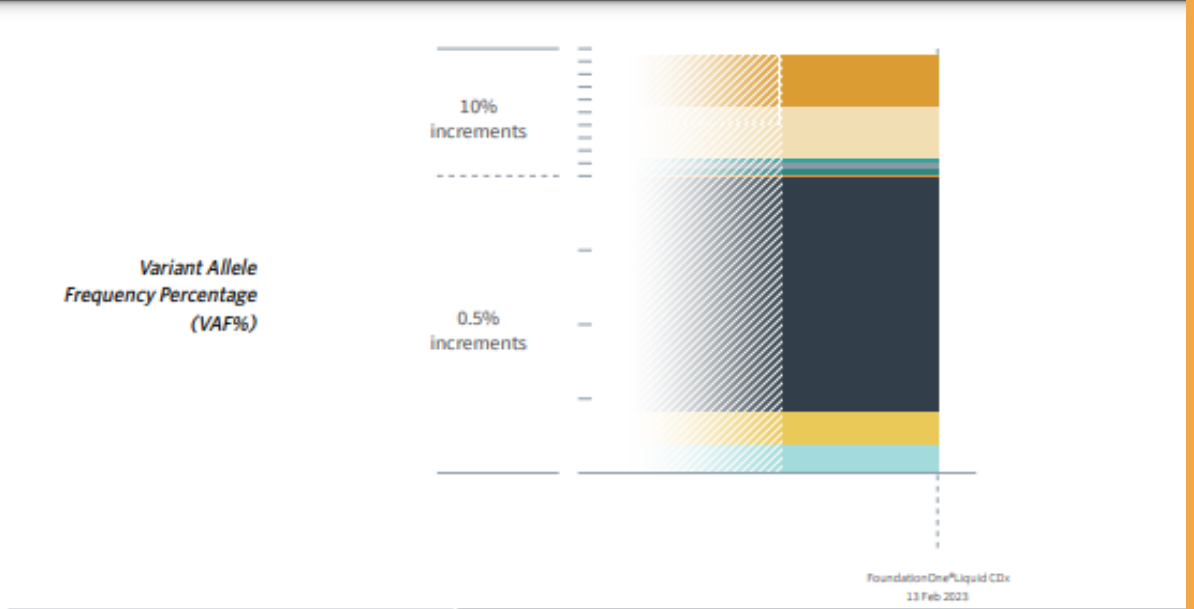
For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Gene Alterations section.

MSH2 - Y408fs*9 ..... p. 10

RB1 - splice site 1668_1695+51>G ..... p. 10

TET2 - Q810*, R1216* ..... p. 11

TP53 - R280T ..... p. 12



HISTORIC PATIENT FINDINGS		ORD-1559150-01 VAF%
Blood Tumor Mutational Burden		5 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
MET	● D1228H	1.7%
	● exon 14 splice site (3028delG)	3.8%
NF1	● M1149V	0.21%
ATM	● splice site 2921+1G>A	0.20%
MSH2	● Y408fs*9	4.3%
RB1	● splice site 1668_1695+51>G	1.9%
TET2	● R1216*	39.8%
	● Q810*	40.5%
TP53	● R280T	4.5%

WHAT WOULD YOU DO?

I phoned a friend!

Dr Brian Bird Stage IV Met Exon 14 mutated NSCLC

Key questions

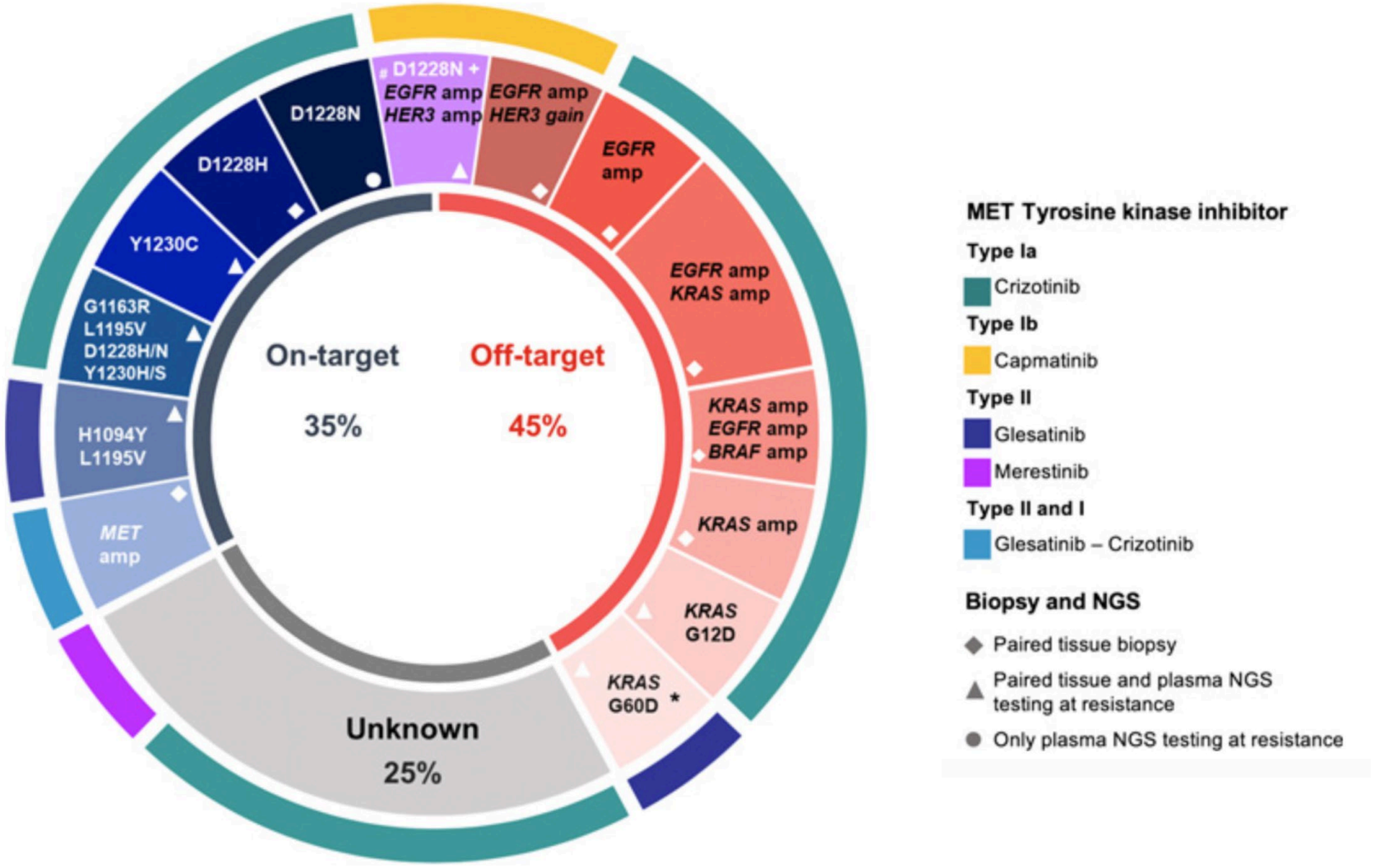
General methodology questions

- What are the mechanisms of Tepotinib resistance?
- Would another tissue biopsy be helpful here?

Questions tailored to the patient case

- Is there any benefit to targeting NF1 with dual TKI here?
- Is the next line of systemic therapy cytotoxic like Docetaxel or are there better alternatives?

Distribution of on-target / off-target & unknown mechanisms of resistance to MET TKI



Recondo et al., Clin Cancer Res; 26(11) June 1, 2020

Mechanisms of resistance to MET-inhibitors

On-Target resistance : secondary MET kinase domain mutations, MET amplification

- The solvent front G1163R mutation
=> resistance to **Type Ia** MET inhibitors (crizotinib), but not to type Ib

- D1228 and Y1230 mutations
=> resistance to **Type I MET** TKIs
=> in vitro by weakening chemical bonds between the drug and the MET kinase domain (crizotinib, capmatinib, tepotinib, and savolitinib)

- L1195 and F1200 mutations
=> Resistance to **Type II MET** inhibitors (cabozantinib, merestinib, and glesatinib)

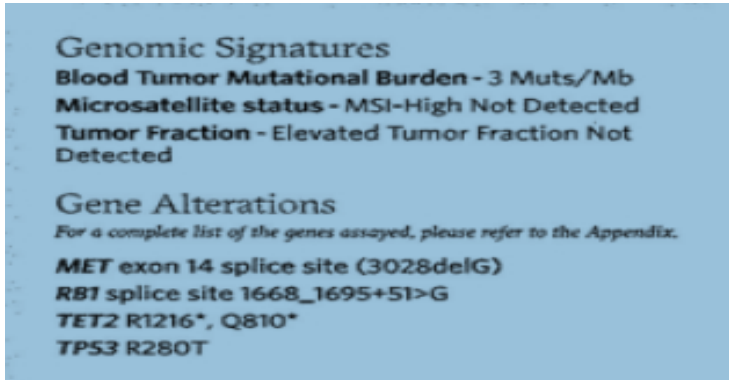
Mechanisms of resistance to Tepotinib

Tepotinib : Type Ib MET TKi

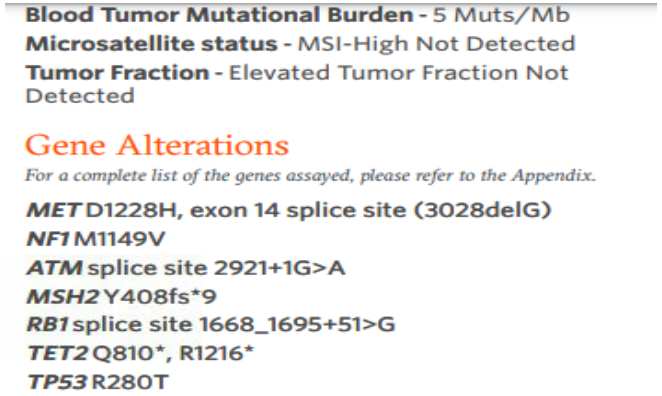
- On-target mutations: D1228 and Y1230 mutations

- Off-target activation

Patient Blood Test 2022



2023 under Tepotinib



=> NF1 mutation:

M1149V : Likely pathogenic (MobiDetails)

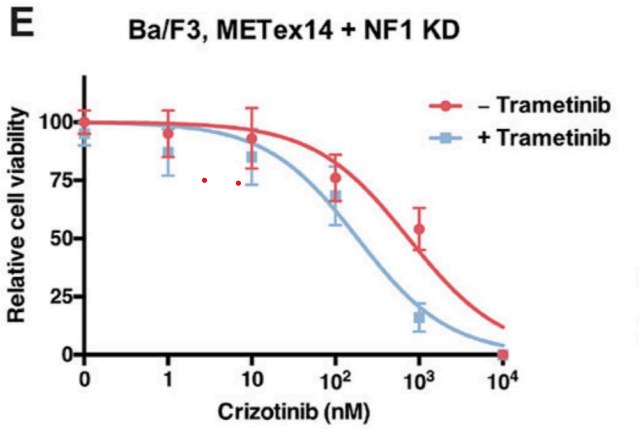
Tissu : VAF?

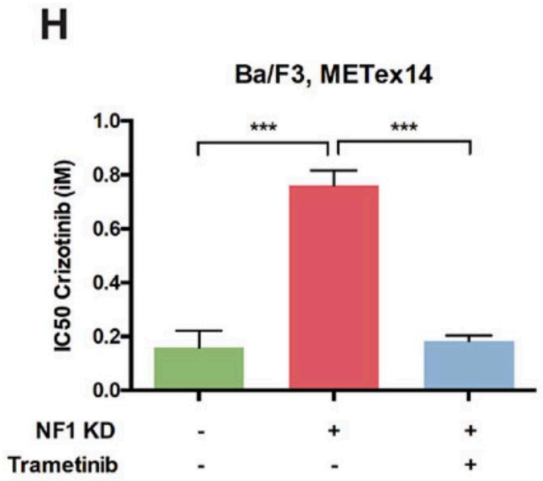
Pre-clinical data : METi/ MEKi

Co-treatment with both trametinib and crizotinib
of cells harboring both METex14 and NF1 downregulation

=> restored sensitivity to treatment (crizotinib monotherapy IC50 0.75 µM versus 0.18 µM upon addition of trametinib, p-value < 0.001 (Figure 4E, 4H).

The selected trametinib dose modestly reduced but did not eliminate cell growth in the absence of crizotinib





Molecular MDT Consensus (my summary)

Reasonable to rechallenge with cytotoxics and immune checkpoint inhibitor

Ideally get tissue on progression to rule out Small Cell transformation

Could try Cabozantinib in the absence of Small Cell transformation

Clinical Outcome

Oligo-progression after 3 cycles of Carbo/Pemetrexed/Pembrolizumab
May 2023

Biopsy of right adrenal mass shows lung adenocarcinoma

Rapid progression of brain mets and lung primary

Not fit for Cabozantinib

Dies June 2023

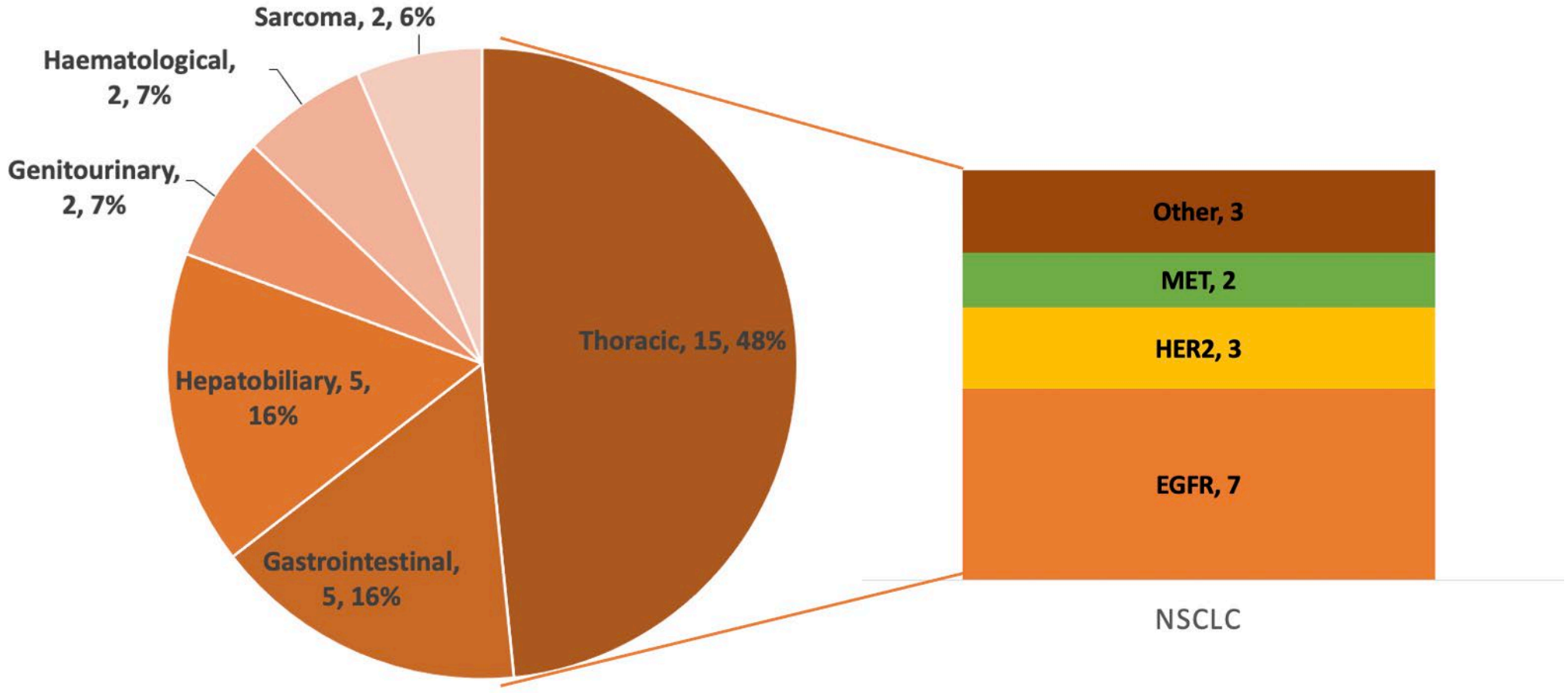
Reflections on this case

Currently gathering data from May 2022 – Sept 2023 (16 cases (includes 2 rediscussions)

A lot of patients on 2nd line standard of care treatment or rechallenge with first line agents never get recommended MTB treatment

?Should I consider early rescan and switch to MTB recommendation?

MTB Experience May 2022 – June 2023



What has been our MTB journey?

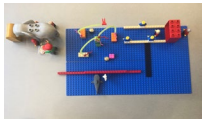
2019

Meeting with government stakeholders

Met NCCP, HRB, HIQA, Novartis and a patient organization to transparently communicate the programme objectives and get their input

Ideation session

Initial MTB program co-designed with Roche, Irish clinicians, and local patient organisation (SJK)



2020

Co-creation of an MTB Pilot

Collected insights and needs from selected HCPs to jointly design the MTB Pilot in Ireland

First MTB Session

1st MTB pilot session in November with 2 patient cases and 5 participants

2021

Extension of the MTB pilot

MTB pilot extended as the number of patient cases, participants and program appreciation increased

Collaboration agreement signed with CTI

Cancer Trials Ireland onboarded for handover of operations for program

2022

Cancer Trials Ireland MTB

July: Full operating of MTB program by CTI, no more involvement of Roche in operations or access to MTB information

2023

Evolution of CTI MTB

Introduction of Haem/Onc MTBs, Educational webinars, Research studies in development

Next steps

Participation in European MTB network to develop consensus standards and patient outcome registry

To date: 66 solid tumour and 5 haem/onc **cases discussed**

HEREDITARY GERMLINE MUTATIONS

ATM in 2 pancreatic cancer cases

MUTYH carrier in EGFR mutated lung cancer

Families now being screened

Suspect with VAF 40-60%

May not be linked to the patient's cancer but relevant to their children etc

PERSONAL REFLECTIONS

Mol MDT can make you and your trainees stronger

Formally preparing the case helps me think objectively

I became less bad at understanding these results

My patients benefit from the expertise the Mol MDT provides

FUTURE DIRECTIONS

Develop National and Regional Expertise

- Ideally government will fund data scientists and clinical geneticists in every cancer center
- Our current trainees will develop expertise in interpreting these complex results
- Online courses in clinical genetics for oncologists
- Government funded molecular testing for all?

Artificial Intelligence

- Can we train AI to help us understand what the results mean for each individual case?

THANK YOU

Dr Brian Healey Bird
FRCPI

@DrHealeyBird

bbird@bonsecours.ie