PERSONALIZED THERAPY BASED ON MUTATION TESTING:

CASE STUDIES AND A CLINICAL PERSPECTIVE

VINOD GANJU

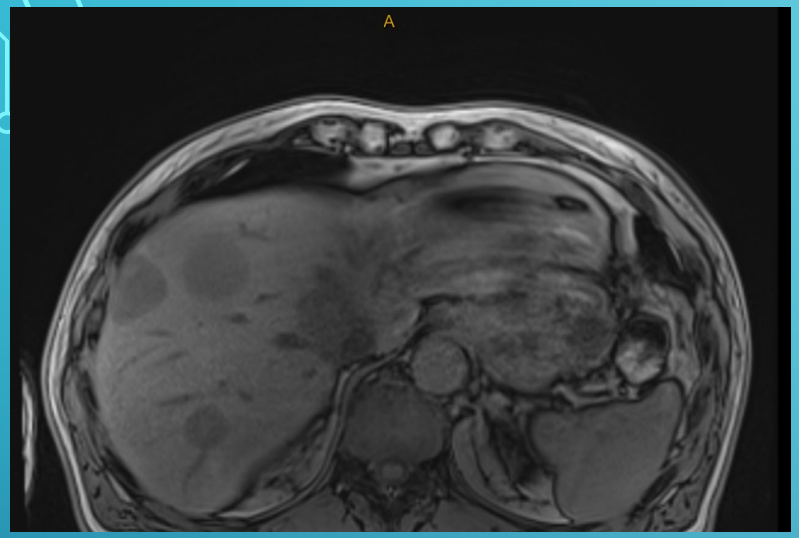
PASO MEDICAL

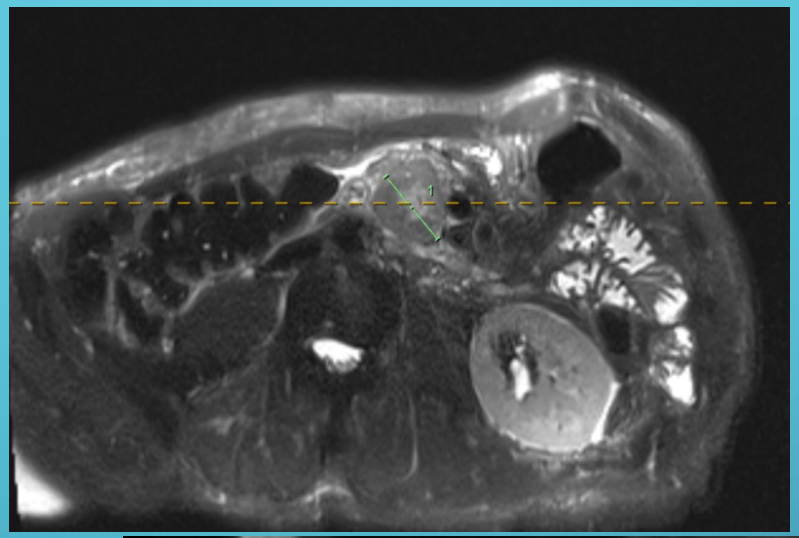
Case 1

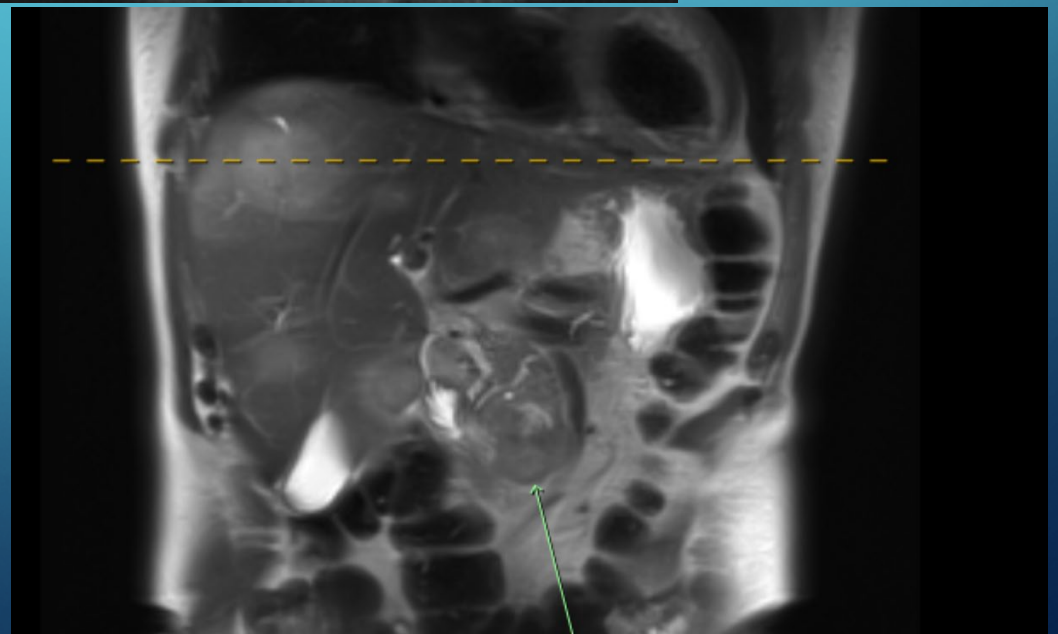
Mr PD
76 yo retired teacher
Active (cycling 100km/week)
April 2020: AMI/STEMI, rapid recovery
Abnormal LFTs
U/S-CT: Pancreatic mass and liver metastases
Referred for EUS Monash Health
Aspiration biopsy of pancreatic mass: Adenocarcinoma
Cytology referred for molecular testing
PH: Ocular melanoma Rx XRT 2007

FH: Father deceased from Ca pancreas age 74, Paternal Niece Breast cancer, Paternal uncle and aunt with cancer
Staging MRI/PET
Germline testing ordered

Case 1: Selected MRI images

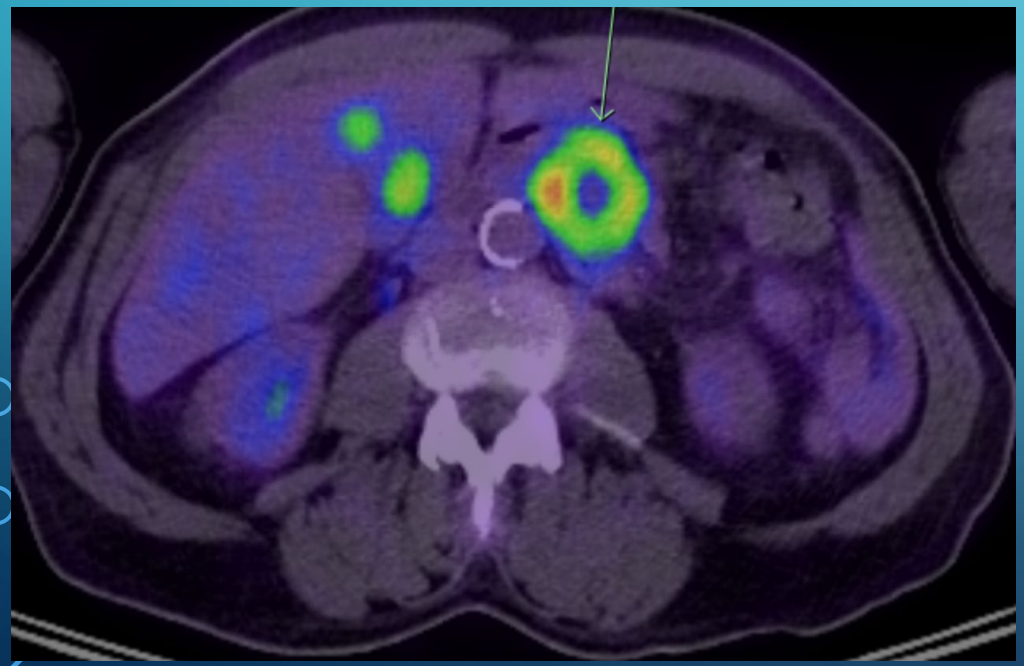


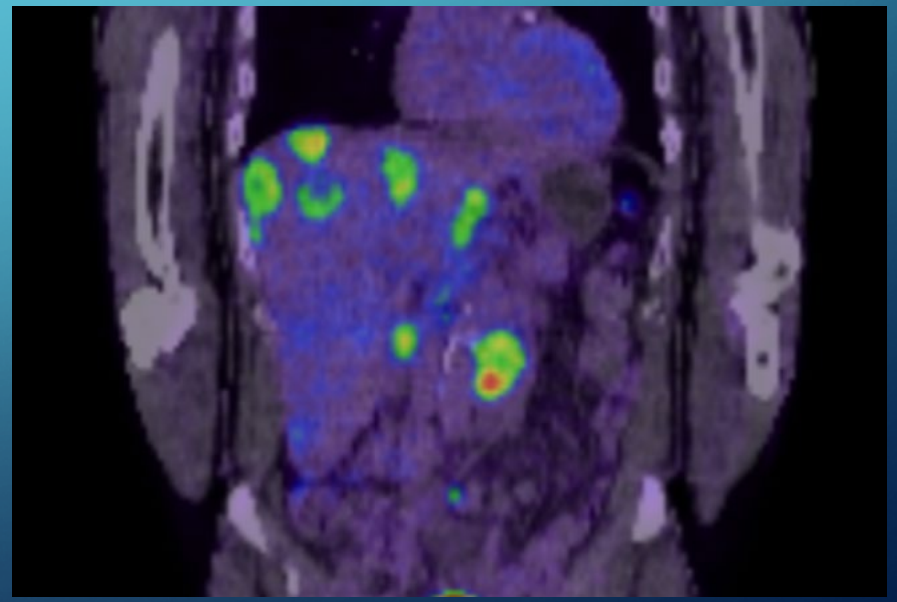




Case 1: Selected FDG-PET images







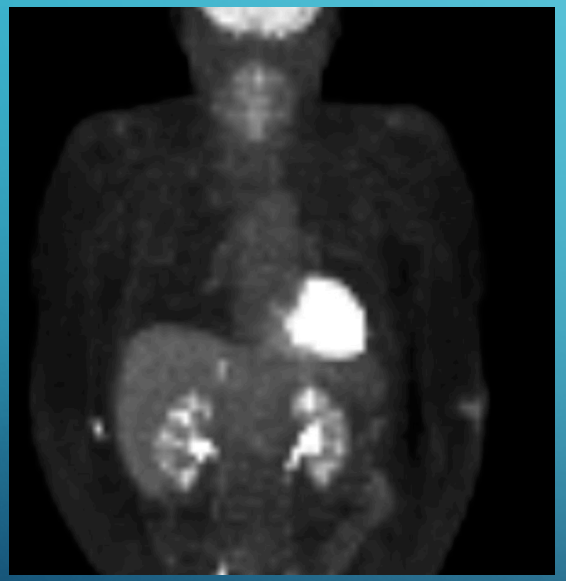
Case 1: Early events

June 2020:
Single dose of Gemcitabine and Abraxane
Admission to hospital with biliary sepsis
- Rx IV antibiotics and ERCP/Biliary stent
Readmission with upper GI bleeding, gastric outlet obstruction
- Duodenal stent, embolization of branches of SMA
- Pall XRT to duodenum/pancreas
- Multiple transfusions

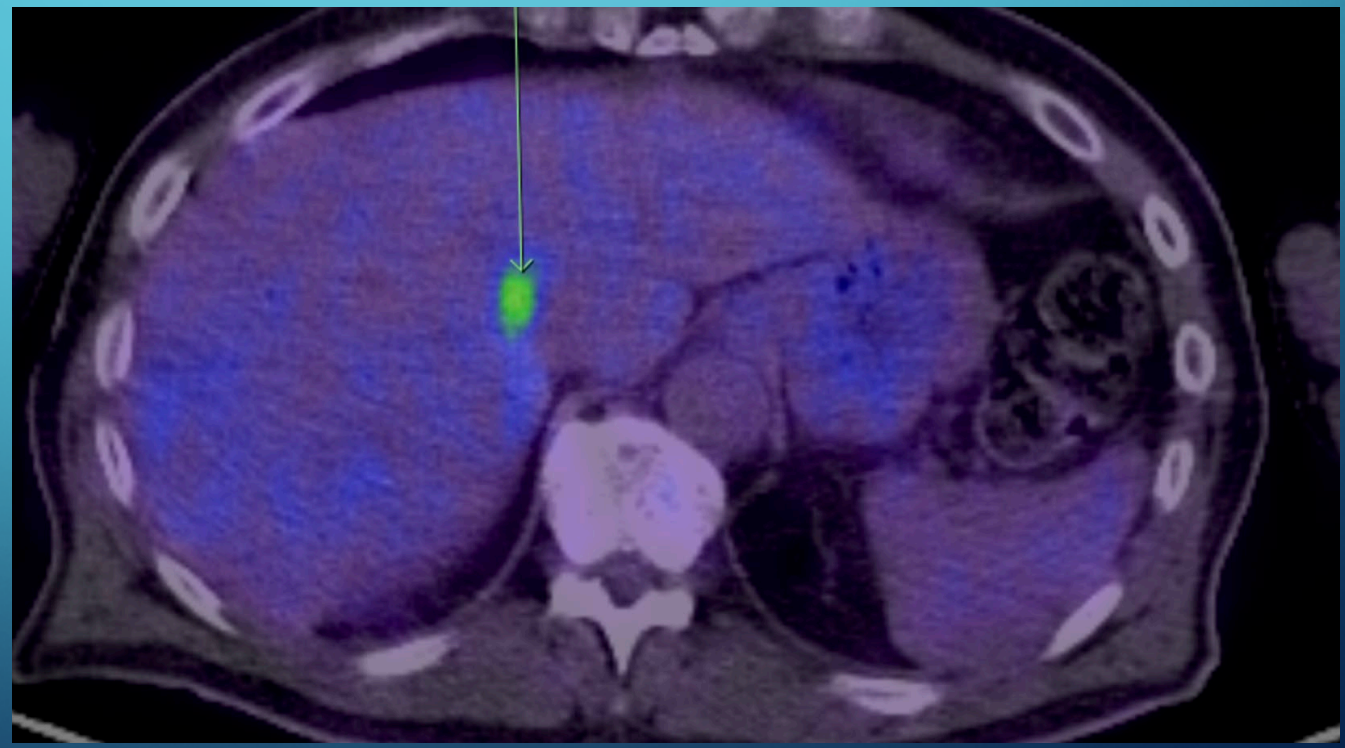
Aug 2020:
Germline test result: BRCA1 Ex 20 mutation identified; pathogenic variant C5
Recovered surprising well from recent crises
- Restarted chemo, chemo altered to include Carboplatin (Gemcitabine omitted)
- Rx better tolerated with symptomatic improvement
- CT showing tumour regression in all sites after 3rd cycle of Abraxane/Carbo

Case 1: Further developments

EBUS biopsy underwent molecular studies (research study at Monash)
Results in Sep 2020: BRCA1, TMB very high
Pembrolizumab added (self funded)
Chemo discontinued in Oct 2020, Pembrolizumab continued

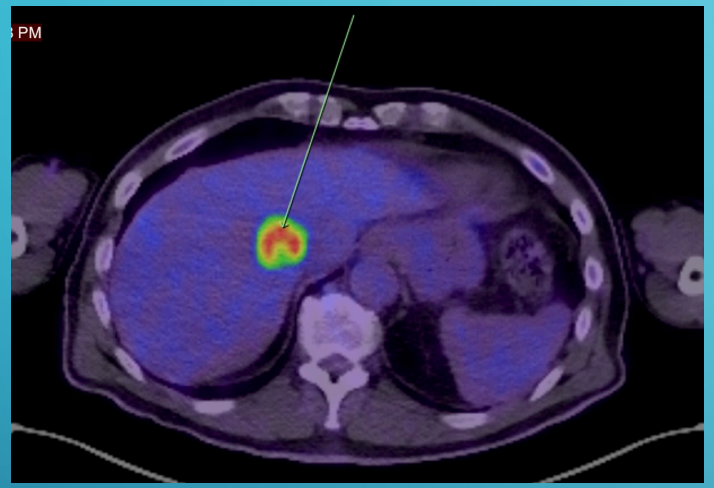


Nov 2020 PET



Case 1: Further developments

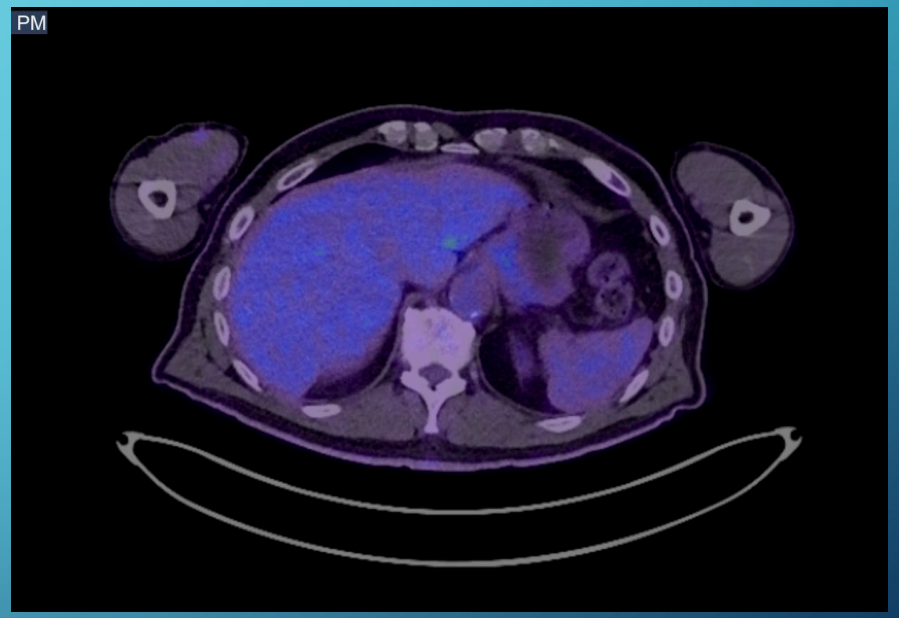
Feb 2021
Isolated disease progression in liver



Pembrolizumab continued
Olapararib added (Compassionate access AZ)

Gradually returned to normal health through first half of 2021

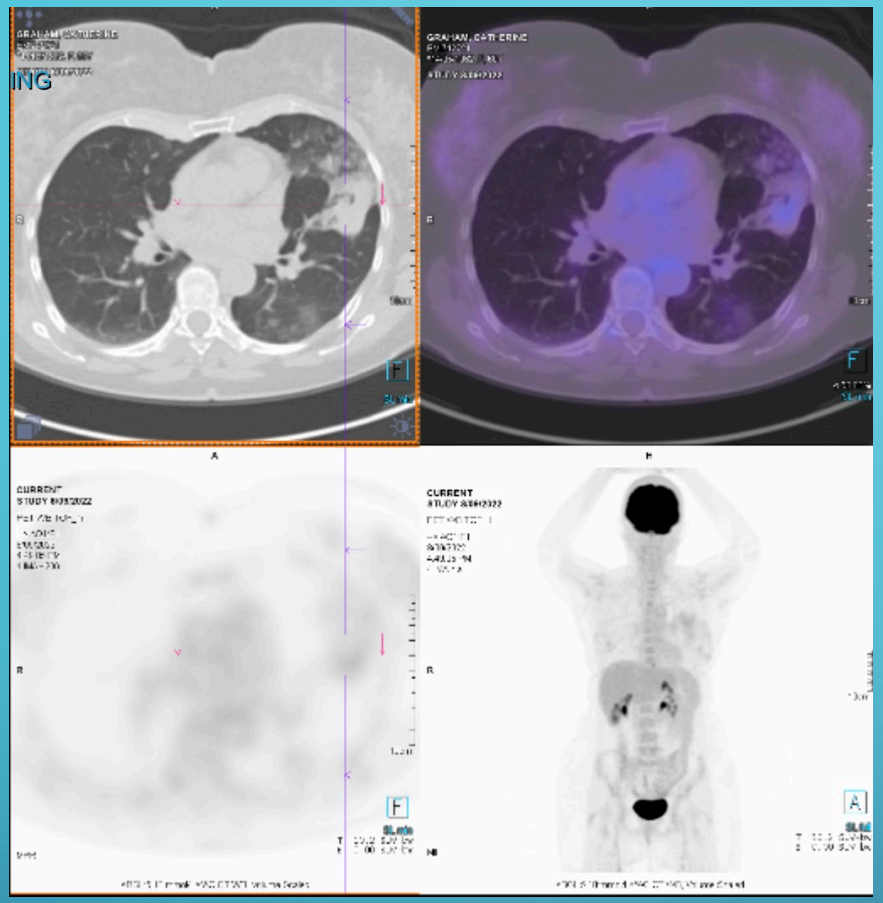
Subsequent CR from June 2021onwards



Pembrolizumab plus Olaparib continued till Feb 2025
February 2025 onward Pembrolizumab only
Pembrolizumab continued with gradually lengthening intervals between treatment over 2025 and finally discontinued in Dec 2025

Case # 2

- 62 y.o. travel manager
- No sig PMH
- Smoker 10-15/d between ages 18-45
- No sig FH
- Well till mid 2021
- Gradually increasing cough, initially treated symptomatically
- Abnormal CXR thought to be reflecting inflammatory changes in late 2021/early 2022
- Multiple courses of antibiotics



- Specialist referral and workup in mid 2022 (CT/PET, biopsy)
- Dx Multifocal adenocarcinoma of L lung
- September 2022: L Pneumonectomy
- Adjuvant chemotherapy x 4 cycles completed Dec 202

Case # 2

F/U in early 2023 R lung nodule noted
Regular imaging through 2023
More nodules emerged and increased in size



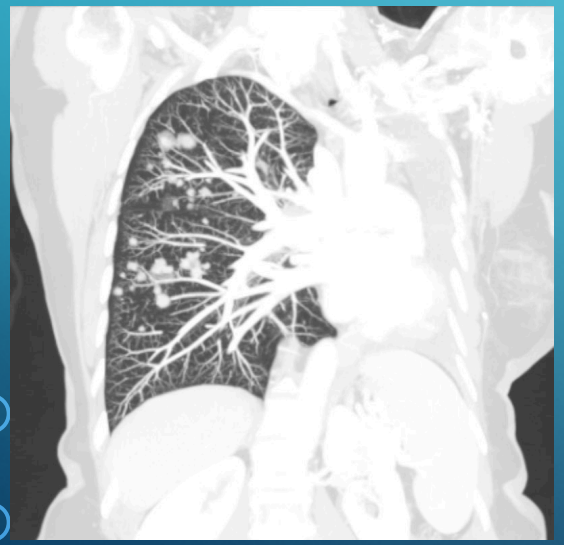


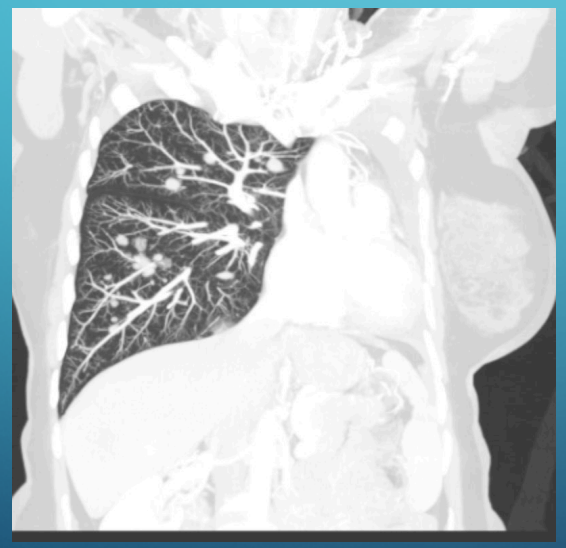




Case # 2

Molecular Testing:
KRAS G12C mutation detected following testing in May 2024 on the original surgical specimen.
Referred for clinical trial in May 2024

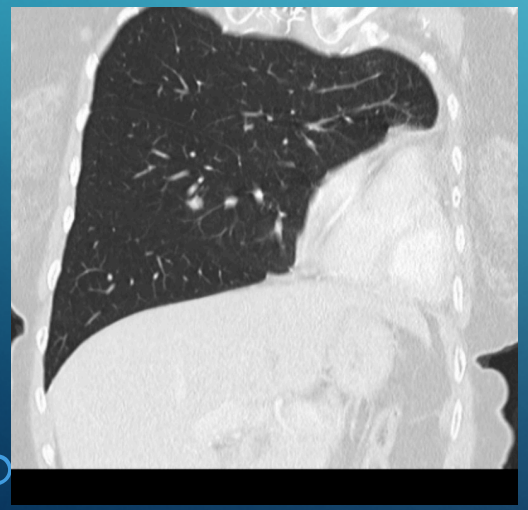






Case # 2

From June 2024: Rx oral TKI(directed to KRAS G12C) plus Pembrolizumab 2 cycles (phase1 clinical trial)
CR on CT imaging but developed immune mediated hepatitis
Hepatitis resolved with oral steroids, TKI continued, Pemboluzimab discontinued
TKI continued thereafter
Radiologic CR last 20+ months
Remains well on Rx
No toxicity or safety signals
Recent setback infected leg wound from a cat bite





Case # 3

Ms LM 28 yo school teacher

PH Superficial Melanoma 2003

FH: 2nd degree cousin with “clear cell sarcoma” age 22

Paternal Aunt Ca Breast age 40

Sep 2013:

Rapidly progressive abdominal distention

Admission to MH with malignant ascites

Clinical Dx of advanced ovarian/peritoneal carcinoma

Radical surgical debulking: BSO/Omentectomy/Lymph node dissection

Histology: Poorly differentiated high-grade cancer (not sarcoma)

Widespread omental nodules, multiple positive. Nodes, no obvious primary in Fallopian tube or uterus

Histology reviewed at multiple centers in Australia and UK

Conclusion: Peritoneal Mesothelioma

Post surgery FDG-PET avid deposits in 3 sites in RUQ and L pelvic side wall

Case 3

Rx Carbo/Pemetrexed for 4 cycles
then continued on maintenance Pemetrexed on and off for next 3 years
mCR on serial FDG-PET scans
Minor progression on scans and gradually increasing fatigue on maintenance Rx in late 2016

Enrolled in a phase 1 clinical trial oral FGFR inhibitor
SD ~ 10 months , but Rx stopped due to ocular toxicity

Whole Genome Sequencing at Garvan Institute (fresh tissue from biobank) in early 2018

- BAP1 loss
- ALK-Fusion

Case 3

Crizotinib accessed on compassionate access program from Pfizer
Rx Aug 2018 onwards
mCR on serial FDG-PET imaging
Rx ceased early 2019: Extreme anticipatory nausea and vomiting
Restaging laparoscopy +ve cytology despite clear scans and macroscopically clear abdomen
S/B clinical psychologist eventually returned to crizotinib but at lower doses from late 2020 onwards
Uninterrupted Rx since then with ongoing clear scans

Table 1. Genetic indications for targeted therapy in cancer

Mutated gene	Common genetic alterations	Tumors implicated	Drugs
ALK	Mutation, fusion	Non–small cell lung cancer	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
ATM	Mutation	Breast	Olaparib
BCR-ABL	Fusion	Chronic lymphocytic leukemia, acute lymphocytic leukemia	Bosutinib, dasatanib, imatinib, nilotinib, ponatinib, asciminib
BRAF	Mutation	Melanoma, colorectal, hairy cell leukemia, thyroid	Dabrafenib, encorafenib, vemurafenib, binimetinib, cobimetinib, trametinib
BRCA1/2	Mutation	Breast, ovarian, prostate	Olaparib, niraparib, rucaparib, talazoparib
CHEK2	Mutation	Breast, ovarian	Olaparib
CSF1R	Mutation, fusion	Giant cell tumor	Pexidartinib, sunitinib[A]
EGFR	Mutation, fusion, amplification	Non–small cell lung cancer	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, brigatinib[A], amivantamab
ERBB2/3/4	Amplification, mutation	Breast	Afatinib[A], lapatinib, neratinib, tucatinib, trastuzumab[B], pertuzumab[B], margetuximab
EZH2	Mutation	Lymphoma	Tazemetostat
FGFR1/2/3	Mutation, fusion	Cholangiocarcinoma	Erdafitinib, lenvatinib[A], pemigatinib, infigratinib
FLT3	Mutation	Myeloid leukemia	Gilteritinib, midostaurin, sorafenib[A]
IDH1/2	Mutation	Myeloid leukemia, cholangiocarcinoma, glioblastoma	Ivosidenib, enasidenib
JAK2	Mutation	Myeloproliferative syndrome	Fedratinib, ruxolitinib
KIT	Mutation, fusion	Gastrointestinal stromal tumor, mastocytosis, melanoma	Avapritinib, imatinib, pazopanib[A], pexidartinib[A], ripretinib, sorafenib, nilotinib[A], sunitinib
KRAS	Mutation	Non–small cell lung cancer	Sotorasib
MET	Mutation, fusion	Non–small cell lung cancer	Cabozantinib[A], capmatinib, crizotinib[A], tepotinib
NTRK	Fusion	Many solid tumors at low frequency	Larotrectinib, entrectinib
PDGFRA/B	Mutation, fusion	Gastrointestinal stromal tumor, mastocytosis, hypereosinophilic syndrome	Avapritinib, imatinib[A], sorafenib[A], sunitinib[A], lenvatinib[A], pazopanib[A], ripretinib[A]
PIK3CA	Mutation	Breast	Umbralisib[A], duvelisib[A], idelalisib[A], copanlisib[A], alpelisib, temsirolimus[A], everolimus[A]
PML-RARA	Fusion	Myeloid leukemia	Arsenic trioxide, retinoic acid
RET	Mutation, fusion	Renal, thyroid, non–small cell lung cancer	Pralsetinib, selpercatinib, cabozantinib[A]
ROS1	Fusion	Non–small cell lung cancer	Entrectinib, crizotinib
SMO/PTCH1	Mutation	Medulloblastoma, basal cell carcinoma	Vismodegib

[A]Mutation-specific treatment supported by National Comprehensive Cancer Network guidelines that does not have full FDA approval. [B]Base antibody used alone or as antibody-drug conjugate.

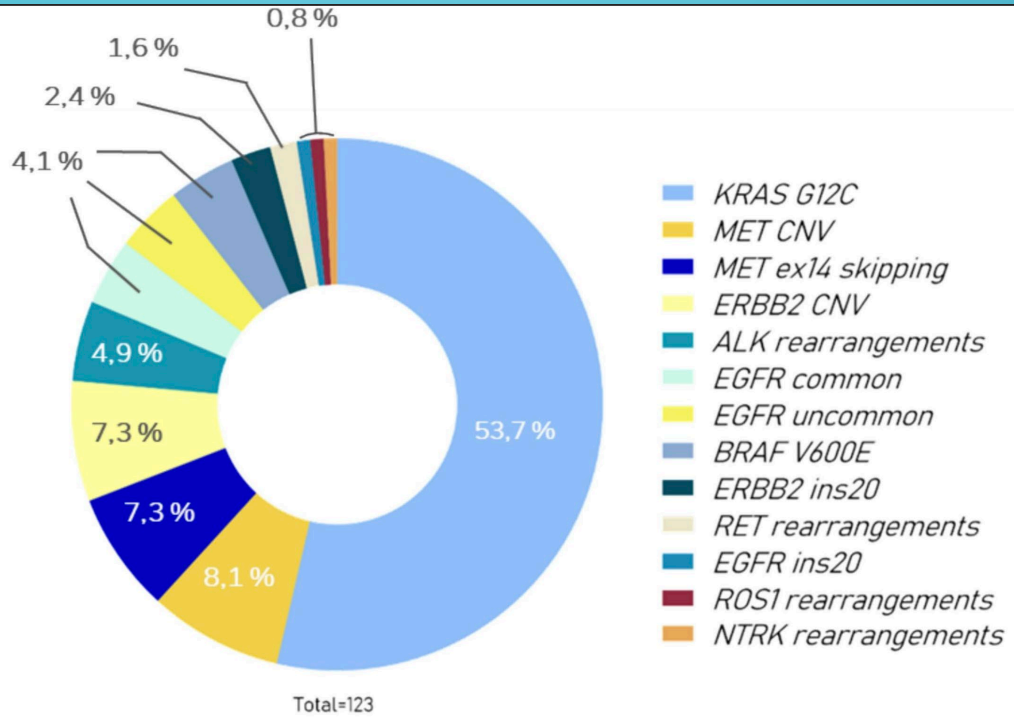
Lung Cancer
Volume 204, June 2025, 108550

Comprehensive molecular profiling of advanced NSCLC using NGS: Prevalence of druggable mutations and clinical trial opportunities in the ATLAS study

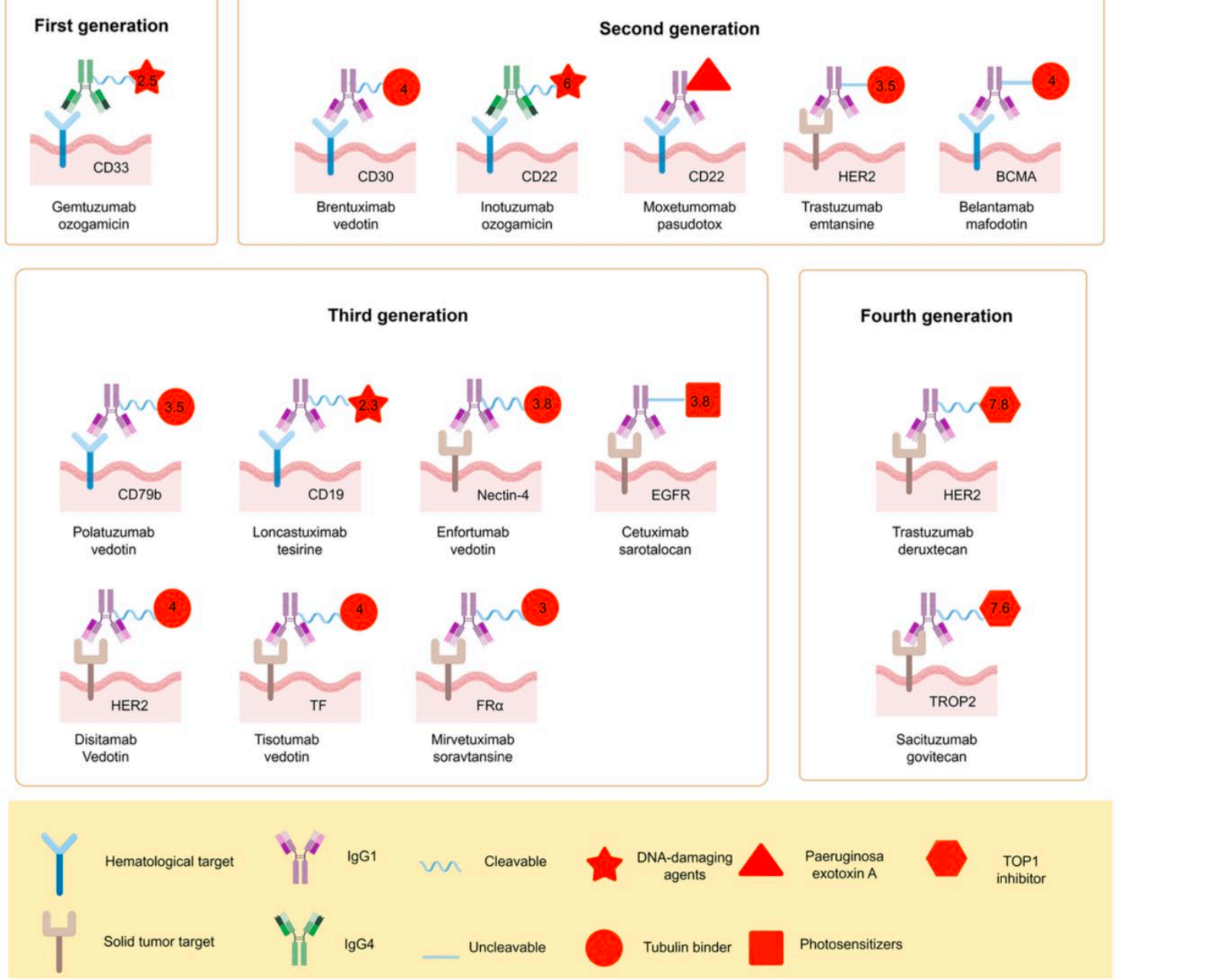
Roberto Serna-Blasco [a], Pilar Mediavilla-Medel [a], Karla Medina [b], María Ángeles Sala [c], David Aguiar [d], Asunción Díaz-Serrano [e], Mónica Antoñanzas [f], Julio Ocaña [g], Xabier Mielgo [h], Inmaculada Fernández [i], Rafael López-Castro [j], Manuel Cobo [k], Mireia Martínez [l], José Carlos Villa [m], Petra Rosado [n], Ana López [o], María Guirado [p], Santiago Viteri [q], Delvys Rodríguez [r], Florencia García [s]...Mariano Provencio [y]

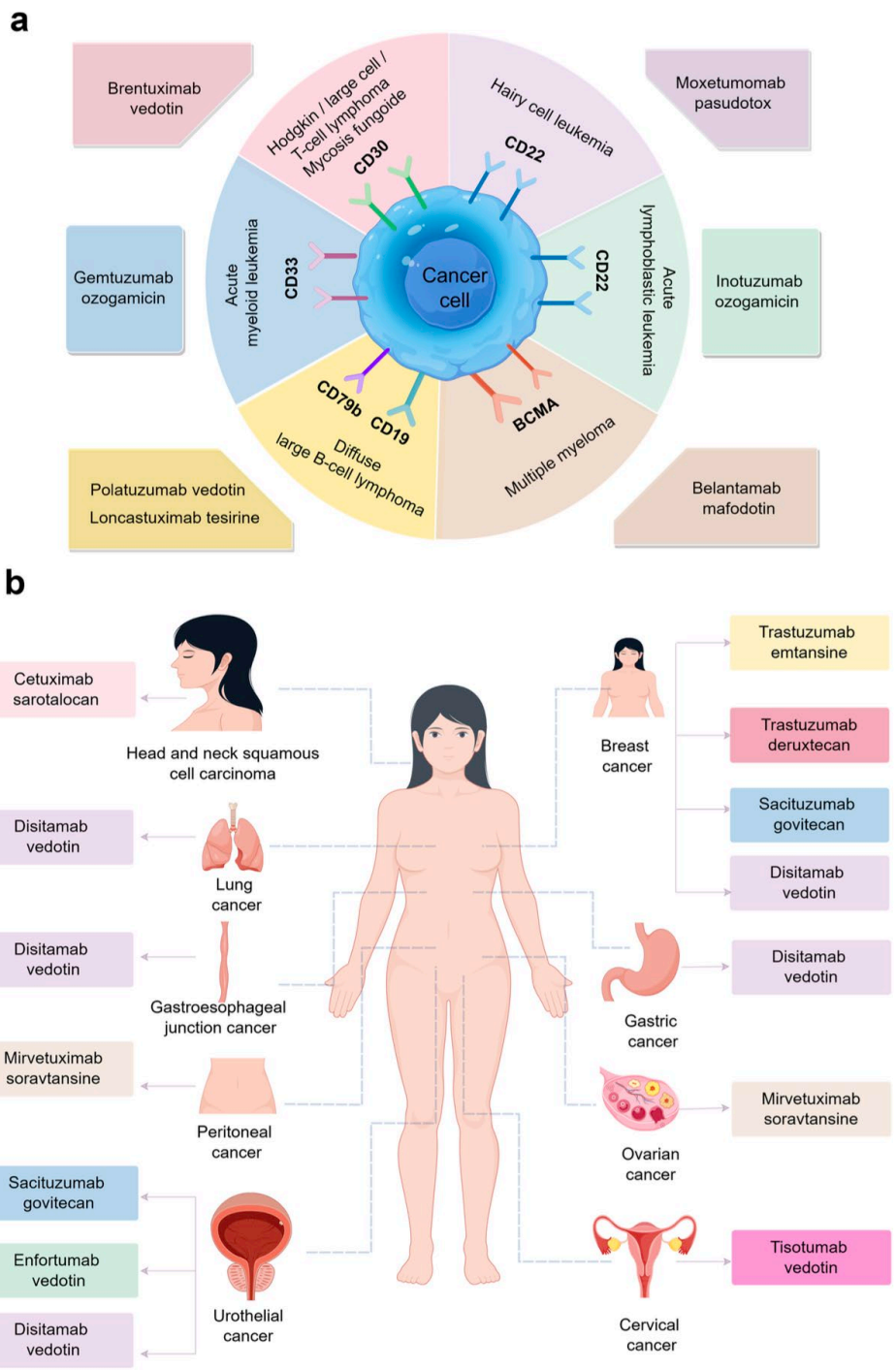
Highlights

- NGS increased detection of druggable mutations from 7.9 % to 25.9 %
- KRAS G12C was the most common druggable alteration.
- 34.5% of patients had mutations matching trials available within the same country.
- Druggable mutations were significantly more frequent in women and non-squamous.



Gene	% total (n=455)	% target (n=123)
KRAS G12C	14.51	53.7
MET CNV	2.2	8.1
MET ex14 Skipping	1.98	7.3
ERBB2 CNV	1.98	7.3
ALK rearrangements	1.32	4.9
EGFR common	1.1	4.1
EGFR uncommon	1.1	4.1
BRAF V600E	1.1	4.1
ERBB2 ins20	0.66	2.4
RET rearrangements	0.44	1.6
EGFR ins20	0.22	0.8
ROS1 rearrangements	0.22	0.8
NTRK rearrangements	0.22	0.8


First generation
2.5
CD33
Gemtuzumab ozogamicin
Second generation
4
CD30
Brentuximab vedotin
6
CD22
Inotuzumab ozogamicin
CD22
Moxetumomab pasudotox
3.5
HER2
Trastuzumab emtansine
4
BCMA
Belantamab mafodotin
Third generation
3.5
CD79b
Polatuzumab vedotin
2.3
CD19
Loncastuximab tesirine
3.8
Nectin-4
Enfortumab vedotin
3.8
EGFR
Cetuximab sarotalocan
4
HER2
Disitamab Vedotin
4
TF
Tisotumab vedotin
3
FRα
Mirvetuximab soravtansine
Fourth generation
7.8
HER2
Trastuzumab deruxtecan
7.6
TROP2
Sacituzumab govitecan
Hematological target
IgG1
Cleavable
DNA-damaging agents
Paeruginosa exotoxin A
TOP1 inhibitor
Solid tumor target
IgG4
Uncleavable
Tubulin binder
Photosensitizers


a
Brentuximab vedotin
Hodgkin / large cell / T-cell lymphoma Mycosis fungoide
CD30
Hairy cell leukemia
CD22
Moxetumomab pasudotox
Gemtuzumab ozogamicin
Acute myeloid leukemia
CD33
Cancer cell
CD22
Acute lymphoblastic leukemia
Inotuzumab ozogamicin
CD79b
CD19
Diffuse large B-cell lymphoma
BCMA
Multiple myeloma
Polatuzumab vedotin
Loncastuximab tesirine
Belantamab mafodotin
b
Cetuximab sarotalocan
Head and neck squamous cell carcinoma
Disitamab vedotin
Lung cancer
Disitamab vedotin
Gastroesophageal junction cancer
Mirvetuximab soravtansine
Peritoneal cancer
Sacituzumab govitecan
Enfortumab vedotin
Disitamab vedotin
Urothelial cancer
Breast cancer
Trastuzumab emtansine
Trastuzumab deruxtecan
Sacituzumab govitecan
Disitamab vedotin
Disitamab vedotin
Gastric cancer
Mirvetuximab soravtansine
Ovarian cancer
Tisotumab vedotin
Cervical cancer

How often can we achieve such results

Mutation testing:

- 5% (all cancers) actionable mutations detected rate 10 years ago
- Current estimates vary from 25-25 % but with variable degree of success with the drugs available

Protein/IHC based marker detection

- Her2 in Breast, Gastric, Bladder, NSCLC, upper GI cancers is identifying 30-50% of cases, but success with ADCs variable
- Other targets such as Claudin, Trop2, Tissue Factor, PDL1, Nectin all under investigation or arriving in the clinic

When I was a "treating the herd" doctor

Considerations for developing treatments for a given patient

- Where did the cancer start its life?
- How far has it spread?
- What proportion of cases will benefit from preventative (Adjuvant) chemotherapy
- Usually at 3-20% benefit (numbers needed to treat)
- Picking the best first systemic therapy from large scale clinical trials, guidelines, prognostic and predictive scoring systems based on "median" levels of benefit or survival

Being a N=1 doctor

How does the new technology help?

Access and costs obviously need to be also considered.

Planning for an intervention

- Patient characteristics
  - Risk factors
  - Occupational exposure
  - Psychosocial circumstances
  - Family dynamics…….?????? Urgently needed assays

- Diagnostic accuracy
  - Limited tissue, uncertain primary……Somatic Mutation Panel

- Genetic background of the patient
  - Inheritable cancer risk……..Germline Mutation Testing
  - Pharmacogenomics (predicting toxicity)

- Looking for targetable pathology….Somatic Mutation Panel, IHC
- Tracking treatment responses……Circulation DNA/RNA assays
- Tracking outcomes……..Minimal Residual Disease Assays