Molecular Tumor Board in Non-Small Cell Lung Cancer

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CIOCC Barcelona – HM Delfos
@JordiRemon
Disclosure Information

- I do not have COI related to this specific presentation
Why do we need a MTB in NSCLC?

• **Introduction**

• To understand the genomic profile from NGS reports

• To prioritize the druggable genomic alteration: baseline / resistant

• Increasing the detection of potential druggable genomic alterations

• To include patients in basket trials

• NGS is a reality but MTB and precision approach have challenges
MTB is included in one equation
MTB is included in one equation
MTB is included in one equation
Precision oncology in practice

Find actionable gens with approved therapy

Find actionable genes for clinical trials

<table>
<thead>
<tr>
<th>Genes</th>
<th>TKIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>EGFR TKI</td>
</tr>
<tr>
<td>ALK/ROS1</td>
<td>ALK/ROS1 TKI</td>
</tr>
<tr>
<td>BRAF</td>
<td>BRAF TKI</td>
</tr>
<tr>
<td>RET / NTRK</td>
<td>RET / NTRK TKI</td>
</tr>
<tr>
<td>MET</td>
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</tr>
</tbody>
</table>
Precision oncology in practice

Find actionable gens with approved therapy

Find actionable genes for clinical trials

Additional information about non-actionable gene mutations

Prognostic markers of sensitivity
Two major steps in NSCLC outcome

**Immunotherapy**
5-y OS, KEYNOTE 024 Trial

<table>
<thead>
<tr>
<th>Median OS, mo</th>
<th>HR, (95%CI)</th>
<th>5-Year OS Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>26.3</td>
<td>0.62</td>
<td>31.9</td>
</tr>
<tr>
<td>13.4</td>
<td>(0.48-0.81)</td>
<td>16.7</td>
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</table>

Brahmer – ESMO 2020

**Personalised treatment, ALK+:**
5-y OS, ALEX trial

<table>
<thead>
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<th>Median OS, mo</th>
<th>HR, (95%CI)</th>
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<tbody>
<tr>
<td>Not reached</td>
<td>0.67</td>
<td>63</td>
</tr>
<tr>
<td>57.4</td>
<td>(0.46-0.98)</td>
<td>46</td>
</tr>
</tbody>
</table>

Mok – Annls of Oncology 2020

Chemotherapy
Crizotinib
Pembrolizumab
Alectinib
Number of oncogenes increases over time

Non-small cell lung carcinomas (advanced stage)

Squamous cell carcinomas

- Never- or light-smokers or < 50 years-old

Non-squamous cell carcinomas

- (AC, tumors with an AC component or tumors where an AC cannot be reasonably excluded)

PD-L1 expression

EGFR mutation

ALK rearrangement

ROS1 rearrangement

BRAF V600E mutation

NTRK rearrangement

Figure from Garrido – CTO 2019 (modified based on updated ESMO guidelines 2020 by Planchard et al.)
Number of oncogenes increases over time

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Coming Future.....

Figure from Garrido – CTO 2019 (modified based on updated ESMO guidelines 2020 by Planchard et al.)
Why is it important to get molecular data?

- **EGFR**
- **ALK**
- **ROS1**
- **BRAF**
- **MET**
- **RET**
- **NTRK**
- **HER2**

<table>
<thead>
<tr>
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<td>Dacomitinib</td>
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<td>Trametinib</td>
<td>Tepotinib</td>
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<td>Lorlatinib</td>
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Why is it important to get molecular data?

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</table>

For these known genomic alterations in NSCLC with approved targeted therapies, probably do we need a MTB?

Why do we need a MTB in NSCLC?

- Introduction

- To understand the genomic profile from NGS reports

- To prioritize the druggable genomic alteration: baseline / resistant

- Increasing the detection of potential druggable genomic alterations

- To include patients in basket trials

- NGS is a reality but MTB and precision approach have challenges
X in the equation: Huge Genomic profile

Best technology? Is it available? ("OVER") information
Tissue vs. Liquid, DNA vs. RNA
Primary vs. Metastatic
Germline Mutations

Will I treat better my patient?
## Next Generation Sequencing Platforms & Panels for solid tumor

<table>
<thead>
<tr>
<th>Provider</th>
<th>Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermo Fisher Scientific</td>
<td>Ion S5 /S5 XL</td>
</tr>
<tr>
<td></td>
<td>Ion Proton</td>
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<td></td>
<td>Ion PGM</td>
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<tr>
<td>illumina</td>
<td>HiSeq 2500/3000/4000</td>
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<td></td>
<td>HiSeq X</td>
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<td></td>
<td>MiSeq</td>
</tr>
<tr>
<td></td>
<td>MiSeqDX/ MiSeq FGX</td>
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<tr>
<td></td>
<td>NextSeq 500/550</td>
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<tr>
<td></td>
<td>NovaSeq 5000 /6000</td>
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<tr>
<td>NanoString Technologies</td>
<td>nCounter MAX</td>
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<td>nCounter FLEX</td>
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<tr>
<td>Qiagen</td>
<td>GeneReader</td>
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<tr>
<td>Fluidigm</td>
<td>Biomark HD</td>
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<td></td>
<td>Helios, a CyTOF</td>
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<tr>
<td>Pacific Biosciences</td>
<td>Pac Bio RS II</td>
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<tr>
<td>Oxford Nanopore Technologies</td>
<td>MinION</td>
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<tr>
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<td>PromethION</td>
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### Cancer gene panel

<table>
<thead>
<tr>
<th>Provider</th>
<th>Cancer gene panel</th>
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<tbody>
<tr>
<td>Thermo Fisher Scientific</td>
<td>Oncomine Solid Tumor DNA Kit</td>
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<tr>
<td></td>
<td>Ion AmpliSeq Colon and Lung Cancer Research Panel v2</td>
</tr>
<tr>
<td></td>
<td>Oncomine Solid Tumor Fusion Transcript Kit</td>
</tr>
<tr>
<td></td>
<td>Ion AmpliSeq RNA Fusion Lung Cancer Research Panel</td>
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<tr>
<td></td>
<td>Oncomine focus assay</td>
</tr>
<tr>
<td></td>
<td>Ion AmpliSeq Cancer Hotspot Panel v2</td>
</tr>
<tr>
<td></td>
<td>Oncomine Comprehensive Assay v3</td>
</tr>
<tr>
<td>illumina</td>
<td>TruSight Tumor 15</td>
</tr>
<tr>
<td></td>
<td>TruSight Tumor 26</td>
</tr>
<tr>
<td></td>
<td>TruSight tumor 170</td>
</tr>
<tr>
<td></td>
<td>TruSeq Amplicon – Cancer Panel</td>
</tr>
<tr>
<td></td>
<td>TruSeq RNA fusion</td>
</tr>
<tr>
<td></td>
<td>TruSight RNA pan-cancer</td>
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<tr>
<td>NanoString Technologies</td>
<td>nCounter Vantage Lung Fusion Panel</td>
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<tr>
<td></td>
<td>nCounter® Vantage 3D DNA SNV Solid Tumor Panel (CSO)</td>
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<td></td>
<td>nCounter Vantage 3D SNV:Fusions Lung Assay</td>
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<td></td>
<td>nCounter® Vantage 3D DNA:Fusion:Protein Lung Assay for FFPE</td>
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<tr>
<td>Qiagen</td>
<td>Human Lung Cancer GeneRead DNAseq Targeted Panel V2</td>
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<td></td>
<td>Human Clinically Relevant Tumor GeneRead DNAseq Targeted Panel</td>
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<td>Human Comprehensive Cancer GeneRead DNAseq Targeted Panel V2</td>
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<tr>
<td>Knight Diagnostic Laboratories</td>
<td>GeneTrails® NSCLC Panel</td>
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<td>GeneTrails Comprehensive Solid Tumor Panel</td>
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<td>Arup Laboratories</td>
<td>Solid Tumor Mutation Panel</td>
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<tr>
<td>Vela Diagnostics</td>
<td>Sentosa SQ Non-Small Cell Lung Cancer Panel</td>
</tr>
</tbody>
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### Questions

- Number of genes?
- Global gene panel vs. Gene panel by tumor?

(Slide courtesy of Dr Reguart)
Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group


Routine use of NGS on tumour samples in NSCLC, prostate cancers, ovarian cancers and cholangiocarcinoma
<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Prevalence</th>
<th>ESCAT</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acquired T790M exon 25</td>
<td>60% of EGFR mutant</td>
<td>IA</td>
<td>Mok T, et al. <em>J Clin Oncol</em>. 2018[^27]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heymach J, et al. <em>J Thorac Oncol</em>. 2018[^34]</td>
</tr>
<tr>
<td>ROS1</td>
<td>Fusions (mutations as mechanism of resistance)</td>
<td>1%–2%</td>
<td>IB</td>
<td>Tong J, et al. <em>Clin Cancer Res</em>. 2016[^40]</td>
</tr>
<tr>
<td>RET</td>
<td>Fusions</td>
<td>0.23%–3%</td>
<td>IC</td>
<td>Drilon A, et al. <em>Nat Med</em>. 2020[^41]</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Hotspot mutations</td>
<td>1.2%–7%</td>
<td>IIA</td>
<td>Cancer Genome Research Network. <em>Nature</em>. 2014[^53]</td>
</tr>
</tbody>
</table>

[^34]: Heymach J, et al. *J Thorac Oncol*. 2018
Tissue is the issue and liquid biopsy helps

~30% of NSCLC tissue samples not optimal for genomic profiling

Peripheral blood remains the most studied liquid biopsy
tCTDNA assesses spatial and temporal tumor heterogeneity

In NSCLC, higher baseline cfDNA levels, higher risk of death (HR 1.76, p<0.001).

Survey of precision medicine in cancer

Use of Next-Generation Sequencing Tests to Guide Cancer Treatment: Results From a Nationally Representative Survey of Oncologists in the United States

~76% oncologists use NGS test for guiding treatment decisions

Freedman – JCO PO 2018 * Moor – JCO PO 2020 * Buckenmaier- J Cancer Educt 2020
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Oncologist Confidence in Genomic Testing and Implications for Using Multimarker Tumor Panel Tests in Practice

Most oncologists are not very confident in using NGS to guide treatment decisions

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Oncologist Confidence in Genomic Testing and Implications for Using Multimarker Tumor Panel Tests in Practice

Most oncologists are not very confident in using NGS to guide treatment decisions

Oncologists use a variety of sources for understanding NGS

Freedman – JCO PO 2018 * Moor – JCO PO 2020 * Buckenmaier- J Cancer Educt 2020
NGS co-mutations treatment responsiveness

Genomic Alterations Identified
- **EGFR** amplification, G598V, L858R
- SMARCBI Q323*
- KEAP1 R362Q
- RB1 S829*
- SOX9 E75K – subclonal
- TP53 splice site 672G>A
- VHL S68L

Genomic Alterations Identified
- **EGFR** L858R
- **ERBB2** amplification
- **KDR** amplification – equivocal
- **KIT** amplification – equivocal
- **CDK12** rearrangement exon 13
- **SUFU** deletion exons 4-12
- **ARFPA1** amplification – equivocal
- **BCL2L2** amplification – equivocal
- **NFkBIA** amplification – equivocal
- **NXX2-1** amplification – equivocal
- **RB1 P777fs*33**
- **SMARCA4 E661K** – subclonal
- **TP53 P250L**

**Baseline**

- **MRCA**
- **EGFR T790M**
- **APC**-related hypermutation

**EGFR** mut. with Rb and p53 mut: x 43 risk of SCLC
This phenotype is ~5% of all EGFR mutant tumors

---

Why do we need a MTB in NSCLC?

• Introduction

• To understand the genomic profile from NGS reports

• To prioritize the druggable genomic alteration: baseline / resistant

• Increasing the detection of potential druggable genomic alterations

• To include patients in basket trials

• NGS is a reality but MTB and precision approach have challenges
Treatment decisions may be complex

The mean number of total driver was 5.7

Clinical association and actionability

Priestley – Nature 2019
How do facilitate implementation as standard of care the personalised medicine?

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

(ESCAT) Tier I: target suitable for routine use and recommend specific drug when specific molecular alteration is detected (Table 2).

ESCAT Tier II: Investigational targets that likely define a patient population that benefits from a targeted drug but additional data are needed.

ESCAT Tier III: clinical benefit previously demonstrated in other tumour types or for related molecular targets.

Working on progress

- EGFR, ALK, ROS, BRAF, RET, NTRK, MET ex^{14}
- KRAS G12C, uncommon EGFR, MET ampl., HER2
- NRG fusions

Mateo – Ann Oncol 2018
NGS, are all actionable alterations?

Kelly – PER Lung Cancer Congress 2020
MTB for rare suspects or at TKI resistance

Discussing complex mechanisms of AR

Discussing no (un)-suspect alterations
Why do we need a MTB in NSCLC?

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OBJECTIVE: DE-ADDICTION, < 10% OF PRIMARY ACQUIRED RESISTANCE
And not all genomic alterations are drivers and not all drugs strong

Approved targets:
- B-RAF + MEK inhibitor in NSCLC (V600E BRAF mutation) *Lancet Oncol* 2016
  - ~1-2% NSCLC
- ALK inhibitor in NSCLC (ALK rearrangement) *NEJM* 2010
  - ~4% NSCLC
- EGFR inhibitor in NSCLC (EGFR mutation) *Lancet Oncol* 2012
  - ~11% NSCLC

Not-approved targets:
- ROS1 inhibitor in NSCLC (ROS1 rearrangement) *NEJM* 2014
  - ~1-2% NSCLC
National Lung Matrix Trial

4000 NSCLC screened by 28-gene NGS. N=315 (22 biomarkers / 8 treatments)

A1: FGFR2/3 mutation
B1: TSC1/2 mutation
B2: LKB1 mut/del
B2: LKB1 mut/del + KRAS mut
C1: CDKN2A/2B loss SCC
C2: CDKN2A/2B loss NonSCC
C3: CDK4 mutation
C4: CCND1 mutation
C5: LKB1 mut/del TSC1/2 mutation
C6: KRAS mutation
D1: MET amplification
D2: ROS1 fusion
D3: MET ex 14 skipping
D4: MET exon 14 skipping
E1: NFI mutation SCC
E2: NFI mutation NonSCC
E3: NFI mutation SCC
F1: PIK3CA mutation SCC
F2: PIK3CA mutation NonSCC
F3: PIK3CA/PTEN NonSCC
F4: PTEN SCC
G1: EGFR mutation + T790M mutation
H1: RET rearrangements
N1: Non-actionable

A: AZD4547 (FGFR inhibitor)
B: Vistusertib (MTORC1/2 inhibitor)
C: Palbociclib (CDK4/6 inhibitor)
D: Crizotinib (ALK inhibitor)
E: Selumetinib (MEK inhibitor) + Docetaxel
F: Capivasertib (AKT inhibitor)
G: Osimertinib (EGFR T790M inhibitor)
H: Sitravatinib (VEGF inhibitor)
M: Durvalumab (PDL1 inhibitor)

Median PFS

- A1: FGFR mutation
- G1: EGFR T790M mutation
- D1: MET amplification
- D2: ROS1 gene fusions
- D3: MET exon 14 skipping

24% Sq. 10% PS 2. 60% stage IV

Middleton – Nature 2020
MOSCATO trial

RR on targeted therapies

RR: 11%, mOS: 11.9 mo., 1-y OS: 49%

COURTESY OF PROF. SORIA & MASSARD – CANCER DISCOVERY 2017
~10% of benefit with precision medicine in cancer

2018: 50,811 out of 609,640 (8.3%)

31 drugs with 38 FDA-approved indications

Marquart – JAMA Oncol 2018
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New view in clinical trials

Clinical Experiment
Traditional Design

Innovative Designs
(basket study)

Patients with cancer -> Histological classification -> Direct target therapy -> Response evaluation

Overall response 20%
80% Without response

Patients with cancer -> Genomic classification -> Direct target therapy -> Response evaluation

Overall response 80%
20% Without response


Cardona – Ther Adv in Resp Dis 2020
Agnostic approval paradigm

- Pembrolizumab: MSI-H / TMB-H
- Selpercatinib: RET-alterations
- Larotrectinib / Entrectinib: NTRK-fusions

Precision medicine in rare malignancies

* NTRK-positive tumors and Selpercatinib efficacy

PARP inhibitors in *BRCA*-mutant

**OlympiAD: Breast (olaparib)**

**POLO trial: Pancreas (olaparib)**

**SOLO-1: Ovarian (olaparib)**

**PROfound trial: Prostate (olaparib)**

Robson – NEJM 2017 * Moore – NEJM 2018

Oh – ESMO Asia 2019 * Hussain – ESMO 2019
BRCA-mutant not driver in NSCLC

| RR to CT | PD | SD | SD | SD | PR | SD | SD | SD | SD | SD | SD | PR | SD | SD | SD | PD | PD | PD | SD |
| Smoking status | CS | CS | CS | CS | CS | CS | CS | NS | FS | CS | CS | FS | NS | CS | FS | CS | CS | CS | CS |
| Biallelic inactivation (LOH) | N | N | N | N | U | U | Y | Y | Y | Y | N/Y | U | Y | N | Y | N | Y | Y | N | N | U |
| HRD score | H | U | H | U | U | H | U | U | U | U | U | L | U | H | U | U | L | H | L | H | L |
| BRCA VUS | 1s | 1s | 2s | 2s | 2s | 2s | 2s | 2g | 2g | 2g | 2g | 2s | 2g | 2s | 2s | 2s | 2s | 2s | 2s |
| BRCA mut. | 1s | 1s | 2s | 2s | 2s | 2s | 2g | 2g | 1/2u | 1s | 1g | 1g | 2g | 2g | 2s | 2s | 2s | 2s | 2s | 2s |
| TP53 mut. | | | | | | | | | | | | | | | | | | | | |
| KRAS mut. | | | | | | | | | | | | | | | | | | | | |
| STK11 mut. | | | | | | | | | | | | | | | | | | | | |

Remon – JTO Clinical Research Reports 2020
TDM-1 in *HER-2* deregulated NSCLC

**HER2 Mutant Lung Cancer**

- Confirmed Partial Response
- Stable/Progressive Disease

**HER2 Mutant PERCIST**

- Confirmed Partial Response
- Stable/Progressive Disease

Li – WCLC 2017
Why do we need a MTB in NSCLC?

- Introduction

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- Increasing the detection of potential druggable genomic alterations

- To include patients in basket trials

- NGS is a reality but MTB and precision approach have challenges
All parts in the equation are relevant

GENOMIC PROFILE

TUMOR MOLECULAR BOARD

MULTIDISCIPLINARY COMMITTEE

PERSONALISED TREATMENT

Medical Oncologists, Radiation Oncologist, Phase 1 team, Biologists, Pharmacists, Pathologists and Translational Research Group, Cancer hereditary unit

Is this approach available worldwide?
Just in specific centers?
Are we generating more inequalities?
Is NGS a reality in Spain?

Do all centers with NGS technology have TMB?

Should it be performed just in specific centers with NGS and TMB?

Performed in Phase I vs. Daily clinical practice Baseline (diagnosis) or in pre-treated/unselected

No Tumor Molecular Board
The clue is sharing, virtual MTB

Rao – JCO Clin Cancer Infrom 2020
MTB objectives: Therapeutic decisions and Data sharing

A Data Sharing Platform to Promote Precision Oncology
The Genomic Data Commons
Are we ready for surprises?

N=10,888 Unselected stage III/IV cancer patients who underwent Guardant360 Germline mutations in 1.4%. In patients < 50 years, increased to 3.0%

Table 1. Putative Germline Mutation Occurrences by Cancer Type

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>All</th>
<th>Ovarian</th>
<th>Prostate</th>
<th>Pancreatic</th>
<th>Breast</th>
<th>Lung</th>
<th>Colorectal*</th>
<th>Other†</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>10,888</td>
<td>210</td>
<td>617</td>
<td>332</td>
<td>2,064</td>
<td>4,459</td>
<td>878</td>
<td>2,328</td>
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<tr>
<td>Female</td>
<td>6,242 (57.3)</td>
<td>210 (100)</td>
<td>0 (0)</td>
<td>143 (43.1)</td>
<td>2,037 (98.7)</td>
<td>2,449 (54.9)</td>
<td>397 (45.2)</td>
<td>1,006 (43.2)</td>
</tr>
<tr>
<td>Male</td>
<td>4,646 (42.7)</td>
<td>0 (0)</td>
<td>617 (100)</td>
<td>169 (56.9)</td>
<td>27 (1.3)</td>
<td>2010 (45.1)</td>
<td>481 (54.8)</td>
<td>1,322 (56.8)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>63.6 (18-95)</td>
<td>62.3 (25-89)</td>
<td>68.7 (35-89)</td>
<td>64.5 (34-89)</td>
<td>58.6 (25-95)</td>
<td>66.4 (20-89)</td>
<td>59.5 (21-89)</td>
<td>62.4 (18-89)</td>
</tr>
<tr>
<td>Patients with putative germline mutation</td>
<td>156 (1.4)</td>
<td>17 (6.1)</td>
<td>21 (3.4)</td>
<td>11 (3.3)</td>
<td>45 (2.2)</td>
<td>33 (0.7)</td>
<td>5 (0.6)</td>
<td>24 (1)</td>
</tr>
</tbody>
</table>

Number of genetic counsels units in Spain?

Slavin – JCO 2018
Patients’ psychological impact

Precision medicine initiatives have a responsibility to anticipate potential barriers to implementation of sequencing findings and at least ask the question whether disclosure of results is ethically justifiable if those results are not actionable in practical terms.

And the outcome does not reach our expectations!

Zikmund-Fisher – JAMA Oncology 2017
Drug access inequalities in EU

Within Europe, huge inequalities exist in time to Market Access and Patient Access to new oncology therapies. The average time to market access is 462 days. The graph illustrates the time to market access for different countries, categorized into three access challenges:

- **Access challenge I**: Short delay & Low patient access
- **Access challenge II**: Long delay & Low patient access
- **Access challenge III**: Long delay & High patient access

The optimal access is to have short delay and high patient access. The graph also indicates the percentage of patient access for each country, with an average of 50%..

Conclusions

• NGS is becoming a reality in NSCLC, and other tumor types.

• However, if we request a NGS test it should probably be discussed in a MTB.

• MTB for deciding upfront treatment in uncommon or at TKI progression.

• MTB requires the NGS and drug access.

• Precision approach is a good, but may increase inequalities.