IV Simposio

GETHI

La genómica en el diagnóstico molecular de neoplasias

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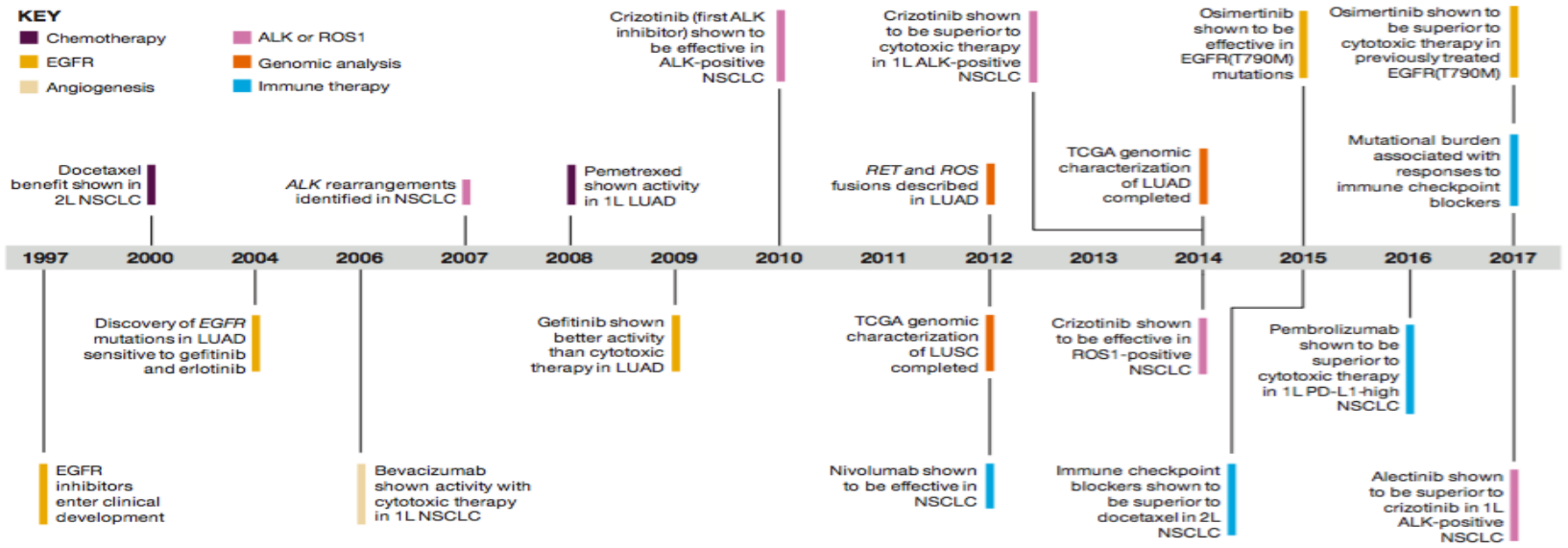
Outline

- Introduction
- Targetable oncogenic drivers in lung cancer
- Biomarkers for IO
- Challenges in NGS implementation
- Take-home messages

Introduction

- Lung cancer is a molecularly heterogeneous disease and understanding its biology is crucial for the development of effective therapies.
- The treatment of advanced NSCLC has changed from the empirical use of chemotherapy to personalize medicine based on genetic alterations and PD-L1 status.



Herbst R, Nature 2018

Genomic landscape and smoking

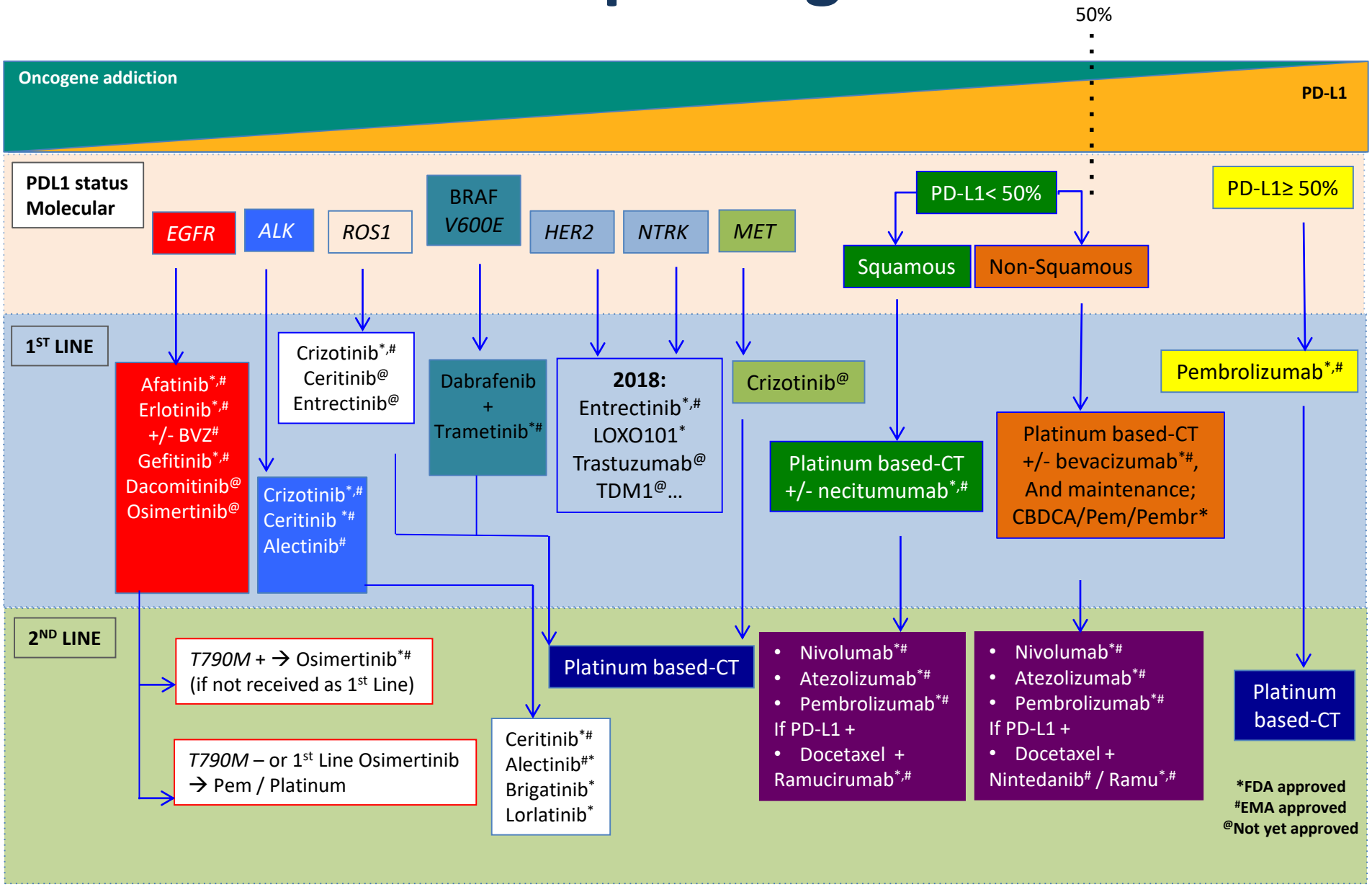
- The genomic landscape is markedly distinct between never smokers and smokers.
  - Smokers have a significantly higher mutation frequency and non-actionable mutations such as those in KRAS and TP53.
  - Never smokers have a higher prevalence of actionable driving gene alterations including EGFR, ALK and ROS1.
- Second ESMO Consensus[1]
  - All non-squamous tumours in patients with advanced/recurrent disease should be tested for EGFRmutation [I, A]
  - Selected squamous tumours (from patients with minimal or remote smoking history) should strongly be considered for testing [IV, B]

[1] Kerr K et al. Ann Oncol 2014

Alterations in targetable oncogenic pathways in NSCLC

- There are, on average, more than 300 non-synonymous mutations per lung cancer but only a minority of these genes can promote tumorigenesis.
- Large scale genomic studies have recognized a variety of potential therapeutic targets including
  - Establish (*EGFR, ALK, ROS*1, BRAF and PD-1/PD-L1)
  - Emerging (*MET, RET, NTRK*)
  - Elusive (*TP53, KRAS*)

New treatment paradigm in NSCLC



ESTABLISH TARGETS

EGFR Mutations

- Found in 10% to 30% of NSCLC patients.
- More common in never-smokers, adenocarcinomas, females, Asians
- Predominantly located in *EGFR* exons 18-21
- Specific *EGFR* mutation identified is important
  - There are sensitive mutations, primary resistance mutations (often exon 20), and acquired resistance mutations (T790M)
- We have first, second and third generation approved agents.
- Osimertinib demonstrated a significant improvement in PFS compared to first generation EGFR TKIs. The overall survival results are largely awaited to establish the best sequence in the first line setting.

ALK Gene Rearrangements

- Most commonly found in younger nonsmokers with adenocarcinoma, adenosquamous carcinoma, and rarely SCC.
- Frequency: 4% overall, 33% in EGFR-negative never-smokers.
- Several ALK variants identified in NSCLC; clinical significance of each is unknown
- Testing
  - Vysis break apart FISH (> 15% cells with split signal in 50 nuclei scored)
  - ALK IHC
  - NGS
- 4 agents approved for ALK-positive NSCLC (first line and/or after progression): Crizotinib, ceritinib, alectinib and brigatinib.
- Alectinib has demonstrated increased ORR and PFS compared to crizotinib in untreated advanced ALK+ patients[1].

[1]Peters S. NEJM 2017

ROS 1 Rearrangements

- Found in < 1% of lung adenocarcinomas.
- Most common in young patients, never smokers.
- Drugs used to treat ALK+ tumours including crizotinb, ceritinib and lorlatinib have also shown marked activity in ROS1+[1].

[1]Herbst R. Nature 2018

BRAF mutations

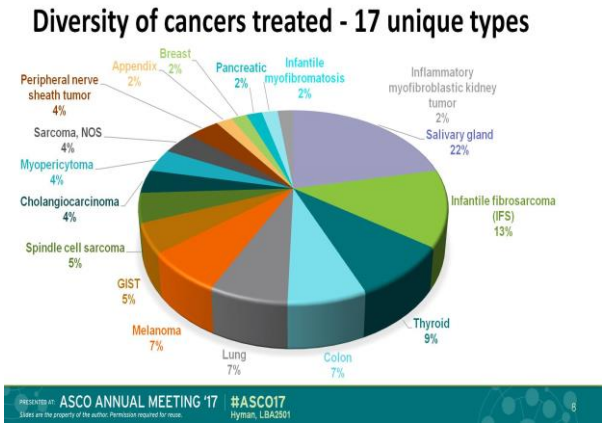
- Genotyping studies in NSCLC have detected mutations in 2-5% of patients, half of whom have a *BRAF* V600E mutation.
- Most patients are former smokers and non-V600E mutations are more common in heavy smokers.
- On 23 February 2017, the CHMP adopted a positive opinion recommending targeted treatment with the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation
- That combination shows a 63.2% ORR and a median PFS 9.7 m[1].

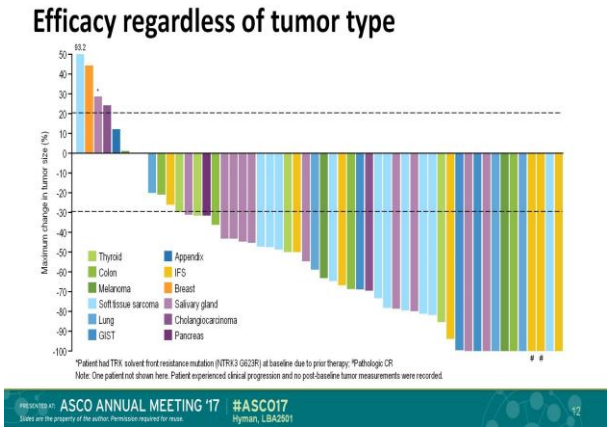
[1]Planchard D. Lancet Oncology 2016

EMERGING TARGETS: BEYOND *EGFR, ALK* AND *ROS*

NTRK rearrangements

- NTRK gene rearrangements have recently emerged as targets.
- TRK fusions occur rarely but broadly in various adult and pediatric solid tumors, including appendiceal cancer, breast cancer, cholangiocarcinoma, colorectal cancer, GIST, infantile fibrosarcoma, lung cancer, mammary analogue secretory carcinoma of the salivary gland, melanoma, pancreatic cancer, thyroid cancer, and various sarcomas.
- Several TRK inhibitors are now in clinical development including Larotrectinib and Entrectinib. For Larotrectininb a Marketing Authorisation Application by the EMA is expected in 2018.





MET alterations

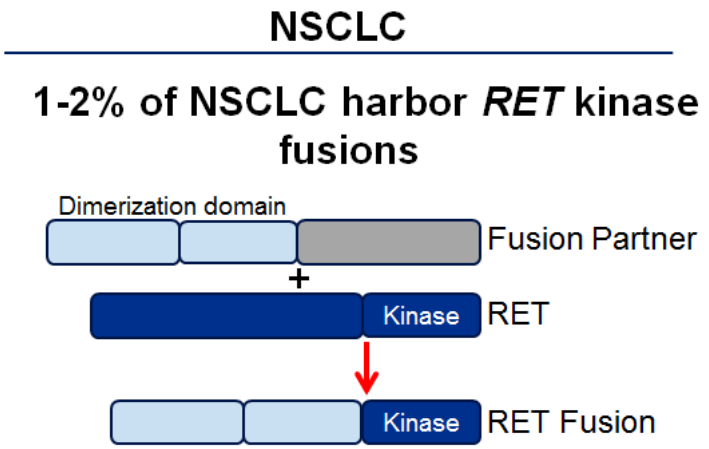
- A variety of alterations have been described including amplifications, exon 14 skipping mutations and gene re-arrangements.
- Clinical outcomes were disappointing until the recognition of MET exon 14 skipping as potential driver.
- The prevalence is around 3% in adenocarcinomas; more common in pulmonary sarcomatoid carcinomas.
- At least five MET-targeted TKIs, including crizotinib, cabozantinib, capmatinib, tepotinib, and glesatinib, are being investigated clinically for patients with MET exon 14 altered-NSCLC[1].

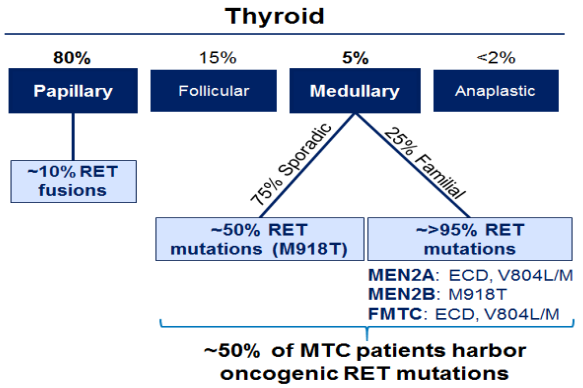
[1]Reungwetwattana T. et al. Lung Cancer 2017

RET rearrangements

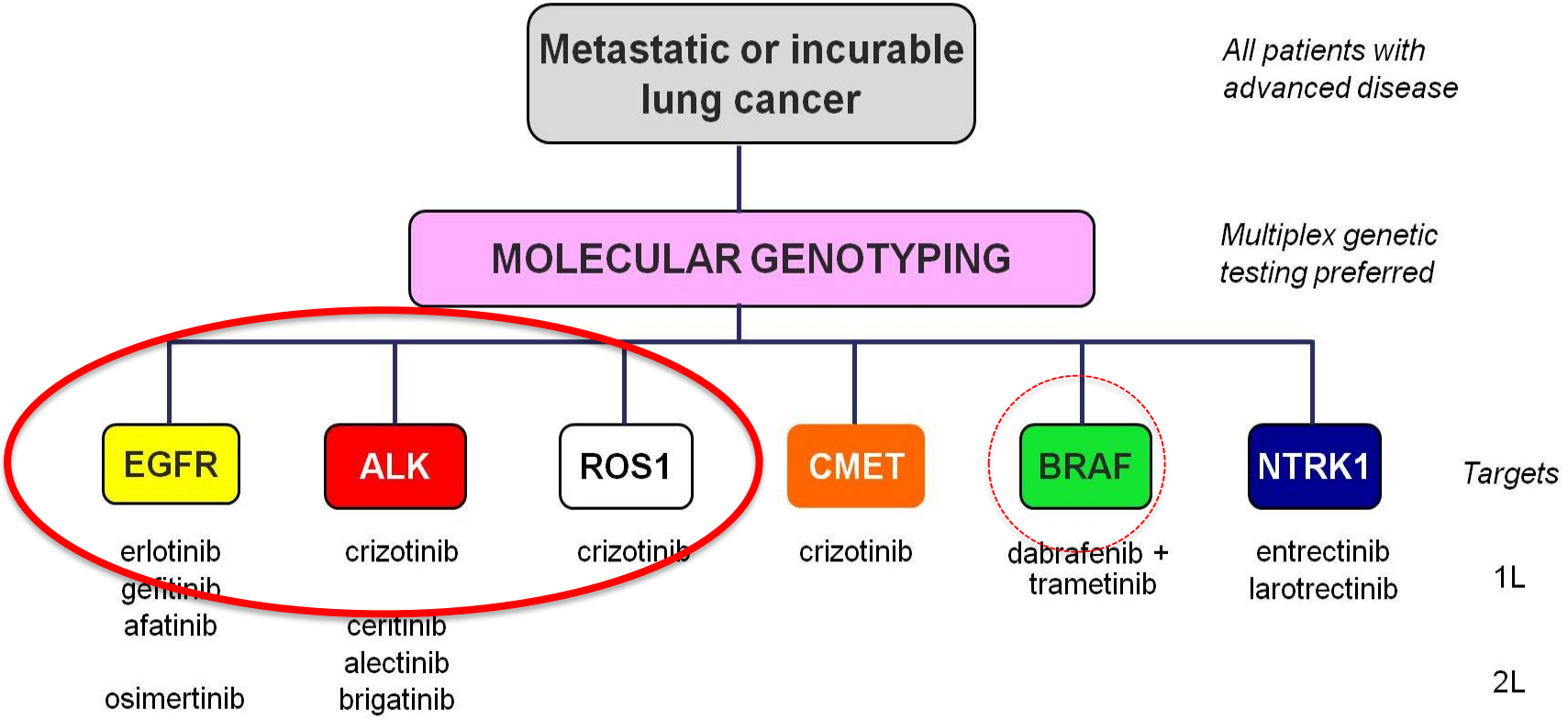
- Observed in 1-2% NSCLC
- Most common in never smokers and advanced disease.
- To date, no highly selective RET has been tested
- There is no clear gold standard for treatment

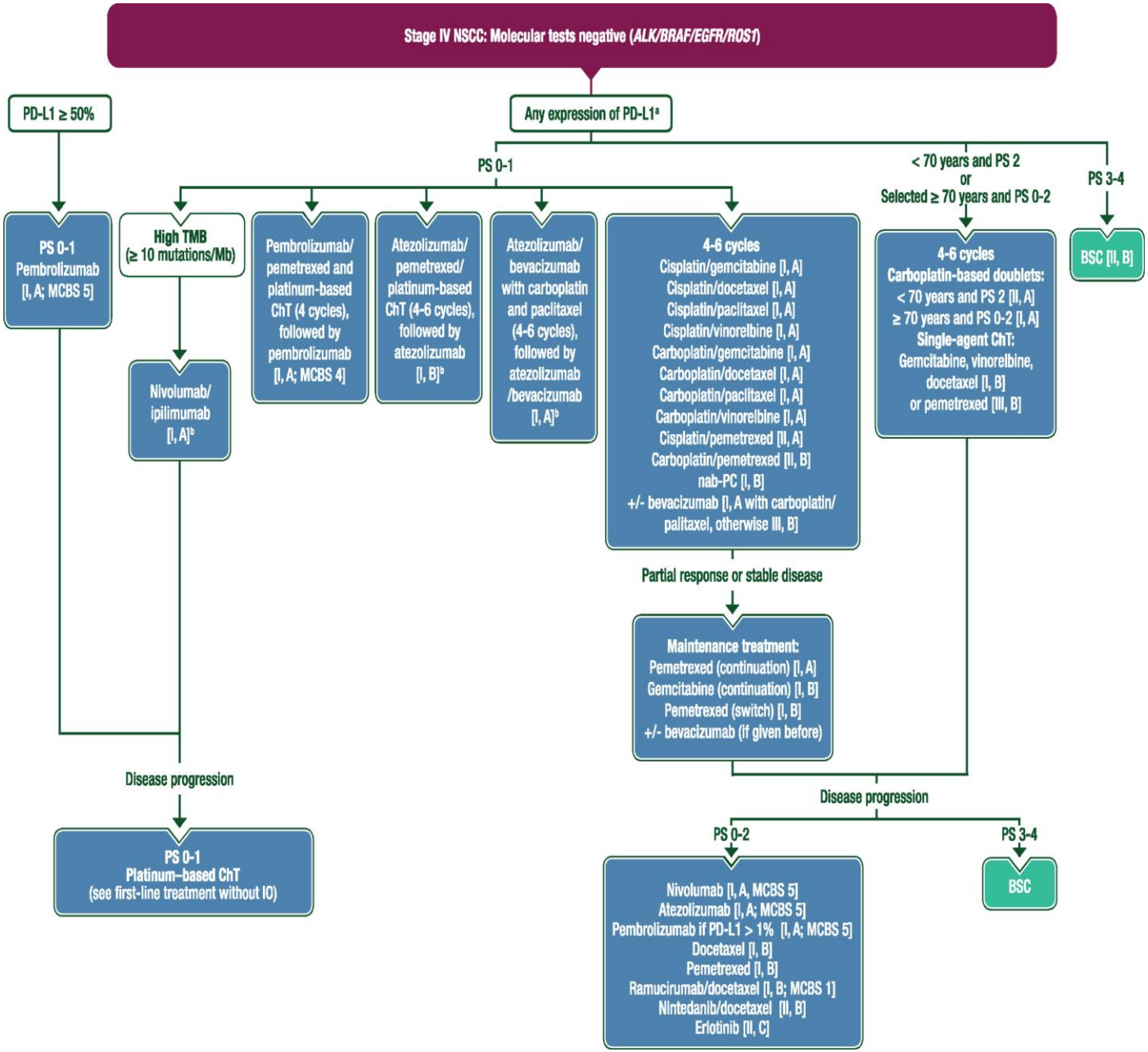
Fusion Partner		RET
KIF5B	*CLIP1*	Cabozantinib
CCDC6	*ERC1*	Vandetanib
NCOA	*RUFY3*	Lenvatinib
TRIM33	*TFG*	Sunitinib
CUX1	*PRKAR1A*	RXDX-105
KIAA1468	*FRMD4A*	BLU-667
		LOXO-292





Upfront genotyping is now an essential step in choosing therapy




Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)
PD-L1 ≥ 50%
Any expression of PD-L1[a]
PS 0-1
< 70 years and PS 2 or Selected ≥ 70 years and PS 0-2
PS 3-4
PS 0-1 Pembrolizumab [I, A; MCBS 5]
High TMB (≥ 10 mutations/Mb)
Pembrolizumab/ pemetrexed and platinum-based ChT (4 cycles), followed by pembrolizumab [I, A; MCBS 4]
Atezolizumab/ pemetrexed/ platinum-based ChT (4-6 cycles), followed by atezolizumab [I, B][b]
Atezolizumab/ bevacizumab with carboplatin and paclitaxel (4-6 cycles), followed by atezolizumab /bevacizumab [I, A][b]
4-6 cycles
Cisplatin/gemcitabine [I, A]
Cisplatin/docetaxel [I, A]
Cisplatin/paclitaxel [I, A]
Cisplatin/vinorelbine [I, A]
Carboplatin/gemcitabine [I, A]
Carboplatin/docetaxel [I, A]
Carboplatin/paclitaxel [I, A]
Carboplatin/vinorelbine [I, A]
Cisplatin/pemetrexed [II, A]
Carboplatin/pemetrexed [II, B]
nab-PC [I, B]
+/- bevacizumab [I, A with carboplatin/ palitaxel, otherwise III, B]
4-6 cycles
Carboplatin-based doublets:
< 70 years and PS 2 [II, A]
≥ 70 years and PS 0-2 [I, A]
Single-agent ChT:
Gemcitabine, vinorelbine, docetaxel [I, B]
or pemetrexed [III, B]
BSC [II, B]
Nivolumab/ ipilimumab [I, A][b]
Partial response or stable disease
Maintenance treatment:
Pemetrexed (continuation) [I, A]
Gemcitabine (continuation) [I, B]
Pemetrexed (switch) [I, B]
+/- bevacizumab (if given before)
Disease progression
Disease progression
PS 0-1
Platinum–based ChT
(see first-line treatment without IO)
PS 0-2
PS 3-4
Nivolumab [I, A, MCBS 5]
Atezolizumab [I, A; MCBS 5]
Pembrolizumab if PD-L1 > 1% [I, A; MCBS 5]
Docetaxel [I, B]
Pemetrexed [I, B]
Ramucirumab/docetaxel [I, B; MCBS 1]
Nintedanib/docetaxel [II, B]
Erlotinib [II, C]
BSC

KRAS co-mutation impact clinical response to IO?

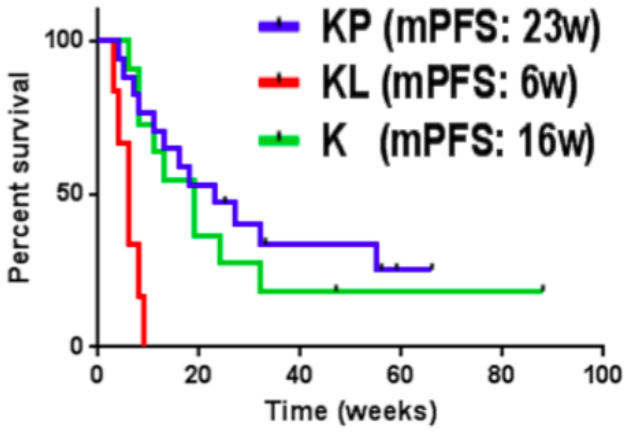
Datasets:

- 229 *KRAS*-mutant NSCLC patients enrolled in the MDACC Moon Shot Gemini Protocol
- 35 patients received immunotherapy and had robust clinical data and at least 46-gene NGS molecular panel

Co-mutations	n=35
STK11/LKB1	6 (17%)
TP53	17 (49%)
Neither (*KRAS* only)	12 (34%)

KRAS alleles	n=35
G12D	7 (20%)
G12V	9 (26%)
G12C	11 (31%)

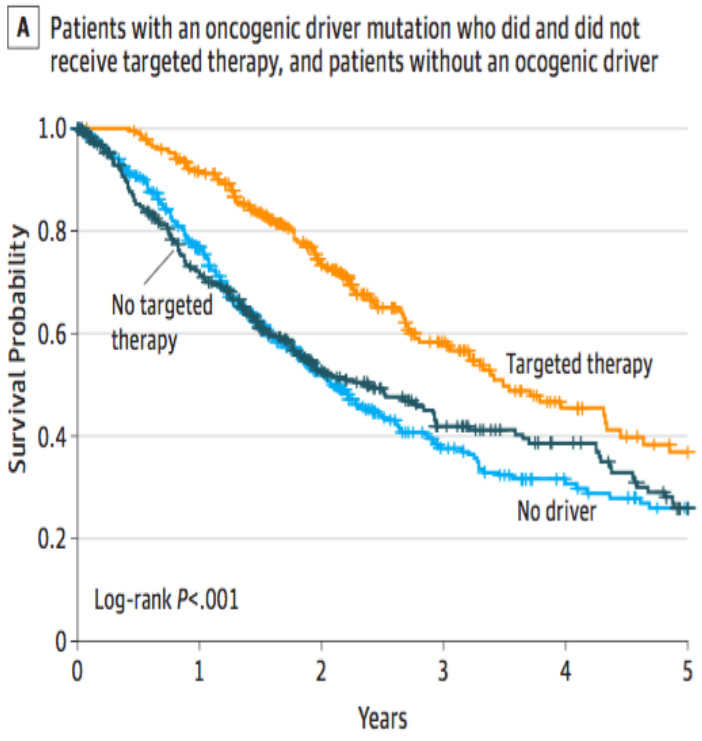
Significantly shorter median PFS with immunotherapy in the KL subgroup

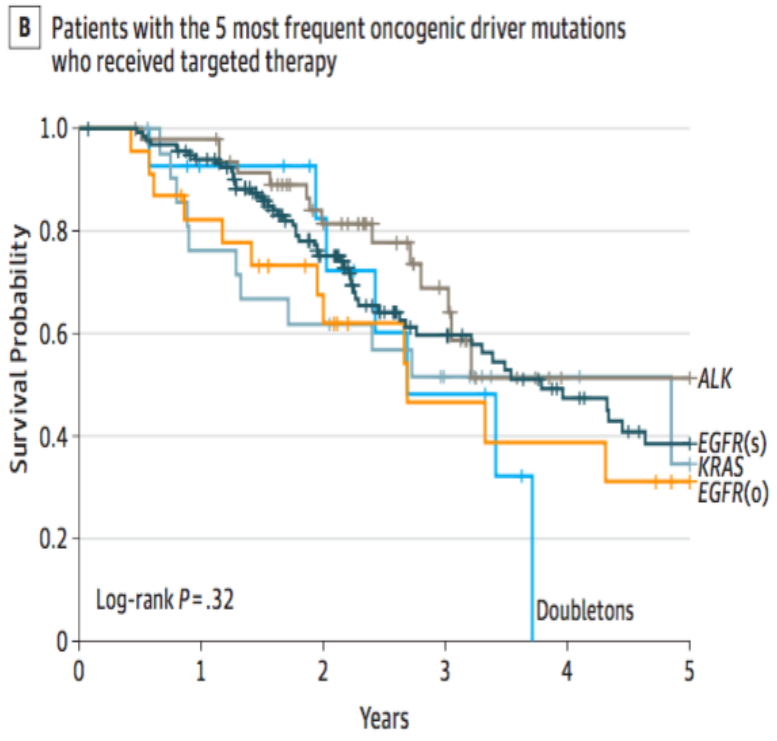


Skoulidis WCLC 2016

Precision medicine is a fact in lung cancer

Long term survival with adequate treatment (2-4 years)

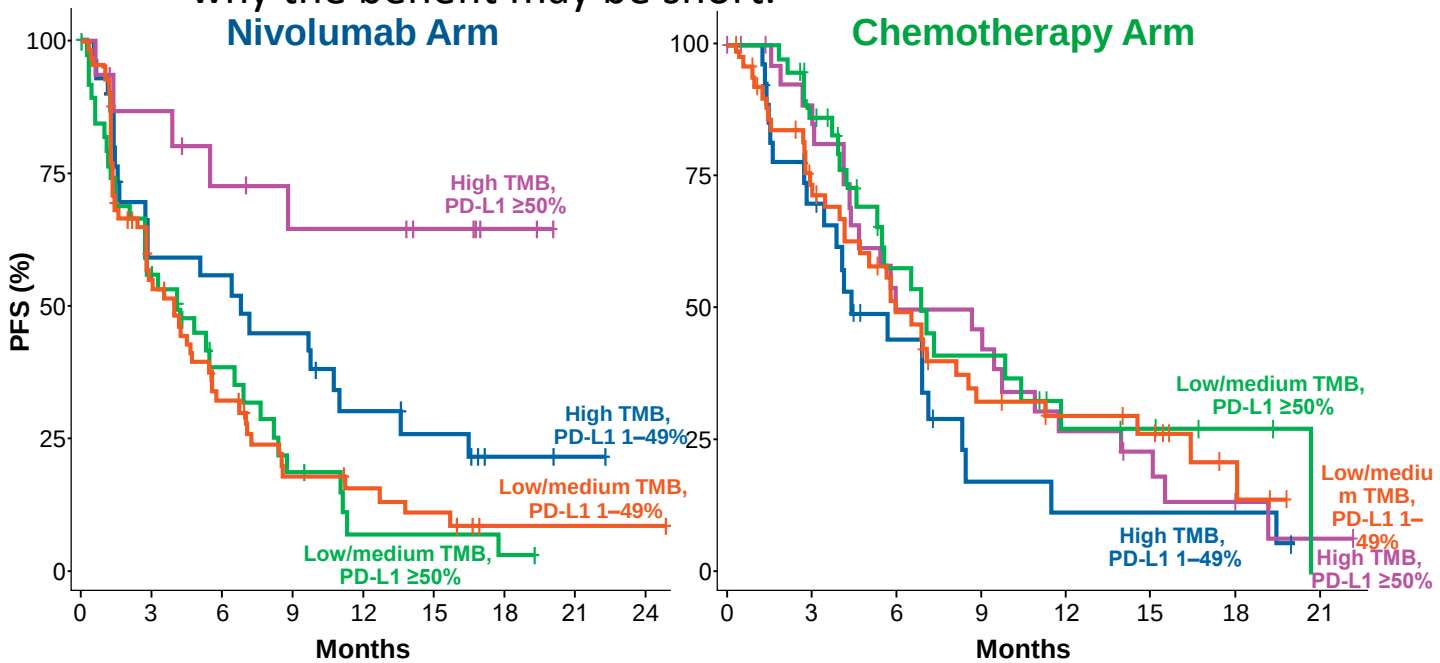




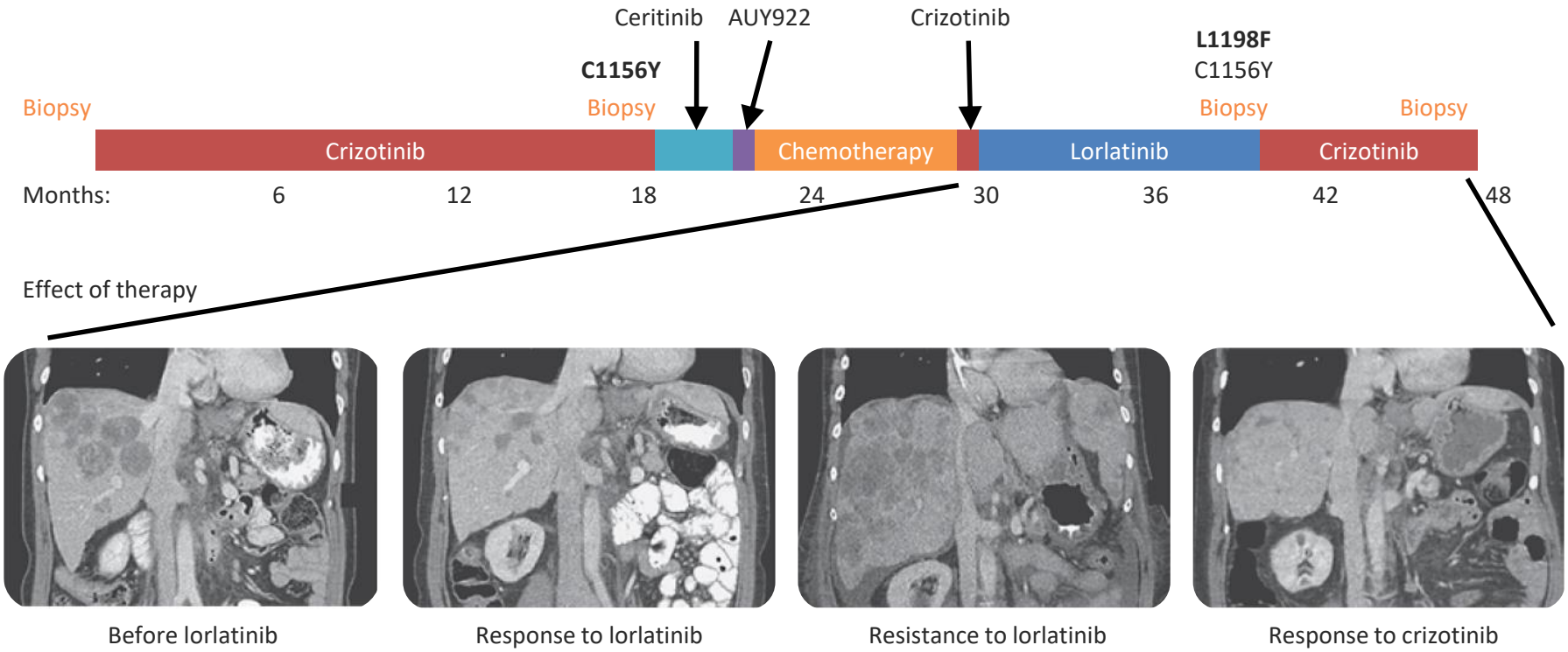
Kris M, JAMA 2014

Precision immunotherapy

- For some NSCLC patients this treatment is truly life changing.
- However, these durable effects have only been demonstrated in a subset of patients
- Key next steps are
  - To identify the patients most likely to benefit.
  - To understand mechanisms of resistance
    - why fewer than half of patients benefit.
    - why the benefit may be short.



Re-genotyping may be key for optimal sequencing strategies



- Sequencing strategies should be flexible; in some cases revisiting previous agents may be the best approach

Shaw AT, et al. N Engl J Med 2016;374:54–61.

Clinical implementation of NGS: Challenges

- Healthcare stakeholders are unclear about the **clinical utility** of NGS and concerned it could be an expense addition rather than an affordable alternative.
- It remains to be proven whether NGS leads to more appropriate use of targeted agents.
- Clinical decisions based only on biological premise or case report…**without the organized collection of efficacy or AEs, each patient could be a clinical trial of a patient[1].**

[1]Stinchcombe T. Ann Oncol 2017

Limits to personalized cancer medicine

Clinical Study	Design	Screened Sample	Patients with Genetic Profile	Patients with Mutation That Might Be Targeted by Drugs	Patients Receiving Matched Drug	Main Outcome Result
SHIVA trial[8]	Randomized, controlled trial of matched molecular targeted agent or physician's choice	741 patients with metastatic solid tumors who were amenable to biopsy	496 (67%)	293 (40%), of whom 195 underwent randomization	96 (100% of experimental-therapy group)	No significant difference in progression-free survival (primary end point); hazard ratio for death or disease progression, 0.88 (95% CI, 0.65–1.19)
Lung Cancer Mutation Consortium	Testing for driver mutations in metastatic lung adenocarcinomas at multiple centers				Many treated as per guidelines for an approved biomarker	Longer overall survival in the subgroups with a mutation treated with directed therapy than in those without the mutation or those that do not receive directed therapy
Study I[5]		1007 patients	733 (73%) tested for ≥10 genes	466 (46%)	260 (26%)	
Study II[6]		1315 patients	919 (70%) tested for ≥8 genes	529 (40%) had mutations, with 187 (14%) of them that could be targeted by drugs and had follow-up	127 (10%)	
SAFIR-01[9]	Treatment chosen after genetic profiling by comparative genomic hybridization and gene sequencing	423 women with metastatic breast cancer	299 (71%)	195 (46%)	55 (13%)	4 patients had a partial response and 9 had stable disease for >16 wk (3% of screened sample)
M.D. Anderson Study[10]	Treatment chosen after gene sequencing of patients with advanced cancer	2601 patients	2000 (77%)	789 (30%)	83 (3%) in genotype-matched trials; 116 (4%) with common mutations not in trial	Not stated
Princess Margaret IMPACT–COMPACT study[11]	Treatment chosen after gene sequencing of archival tissue	1893 patients with advanced solid tumors	1640 (87%)	938 (50%) had mutations, approximately 20% of which could be targeted by drugs	84 (4%) treated in genotype-matched trials	Response rate of 20% in genotype-matched trial vs. 11% in unmatched trials
Cleveland Clinic Study[12]	Treatment chosen after gene sequencing	250 patients	223 (89%)	109 (44%)	24 (10%)	Not stated

* CI denotes confidence interval, COMPACT Community Oncology Molecular Profiling in Advanced Cancers Trial, and IMPACT Integrated Molecular Profiling in Advanced Cancers Trial

Tannock I, NEJM 2016

Clinical applicability and cost of a 46-gene panel: retrospective validation and prospective audit in the UK National Health Service

- 46-gene hotspot cancer panel assay
- 351 patients (108 NSCLC, 88 colorectal and 109 melanoma)
- Median TAT 7 working days
- A locally actionable mutation (available targeted treatment or clinical trial) 35% but targeted treatment only 15%
- At a cost of £339 per patient, the panel was less expensive locally than performing more than 2 o 3 single gene tests

Hamblin A et al. PLOS Medicine 2017

Take-home messages

- The pace of advancement in technology and genome biology is transforming many aspects of diagnosis, clinical trial design and treatment.
- Several challenges and ethical considerations have to be considered including new infrastructural demands, universal standards and educational approaches.
- Addressing these challenges will require the full commitment of all stakeholders.