癌症個人化醫療的現在與未來
Personalized Healthcare in Oncology: A Story of NTRK Fusion Gene

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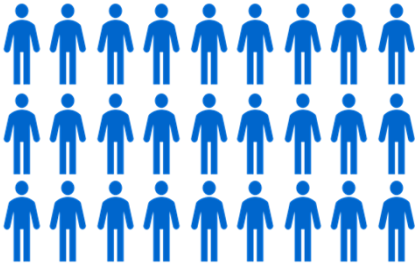
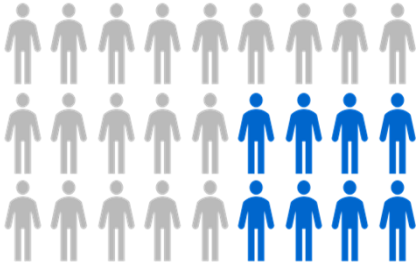
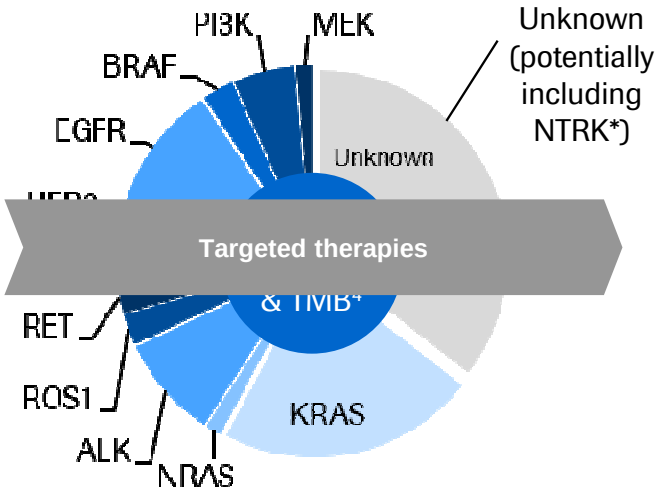
什麼是個人化醫療?

Treatment evolution towards more personalized health care

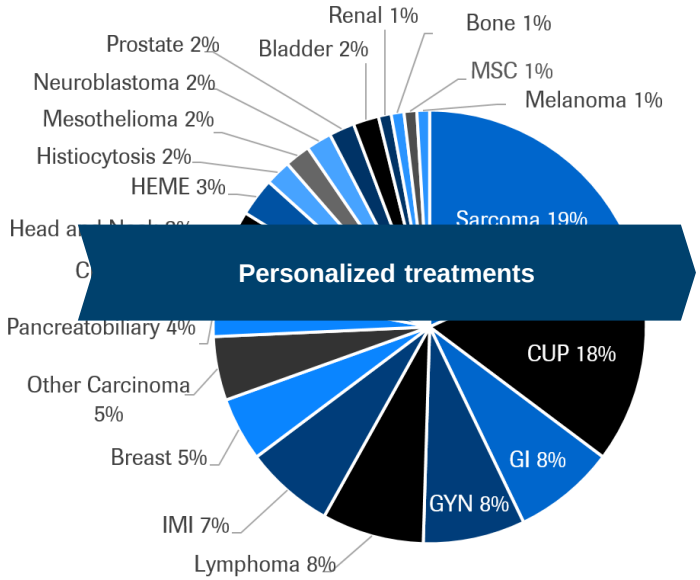
	Blockbuster medicines	Targeted therapies	Personalized treatments
			
Target population	Large: Unspecified	Medium: Sub-group	Small: Individual patient
Diagnostics	No specific biomarkers	Single disease marker	Comprehensive NGS & response monitoring
Treatment	One medicine fits all	Targeted agents	Personalised combos of targeted & immunotherapy agents

Molecular Diagnosis Leads to Smaller Patient Populations

In a single tumour type:
Molecular subtypes in NSCLC



Alterations in the *ALK* gene in different tumour types



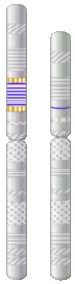
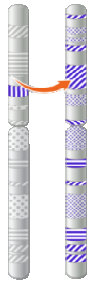
With the increased complexity of tumour pattern, we also need a different diagnostic approach with more granularity on genomic alterations linked with cancer

*NTRK and TMB are potential new biomarkers that are not currently included in the NCCN guidelines. CNS: central nervous system; CUP: cancer of unknown primary site; GI: gastrointestinal; GYN: gynaecological; HEME: haematological; NSCLC: non-small cell lung cancer. 1. NSCLC NCCN Guidelines Version 4.2017; 2. Image modified and adapted from Baumgart, M. (2015) *Am J Hematol Oncol* 11:10-3; 3. Image modified and adapted from Ross J.S. et al. (2017) *Oncologist* 22:1444–50; 4. Bristol-Myers Squibb press release 2018 [Accessed February 2018 from https://news.bms.com/press-release/bms/pivotal-phase-3-checkmate-227-study-demonstrates-superior-progression-free-surviva].

3

可能造成腫瘤發展的四種基因變異型態

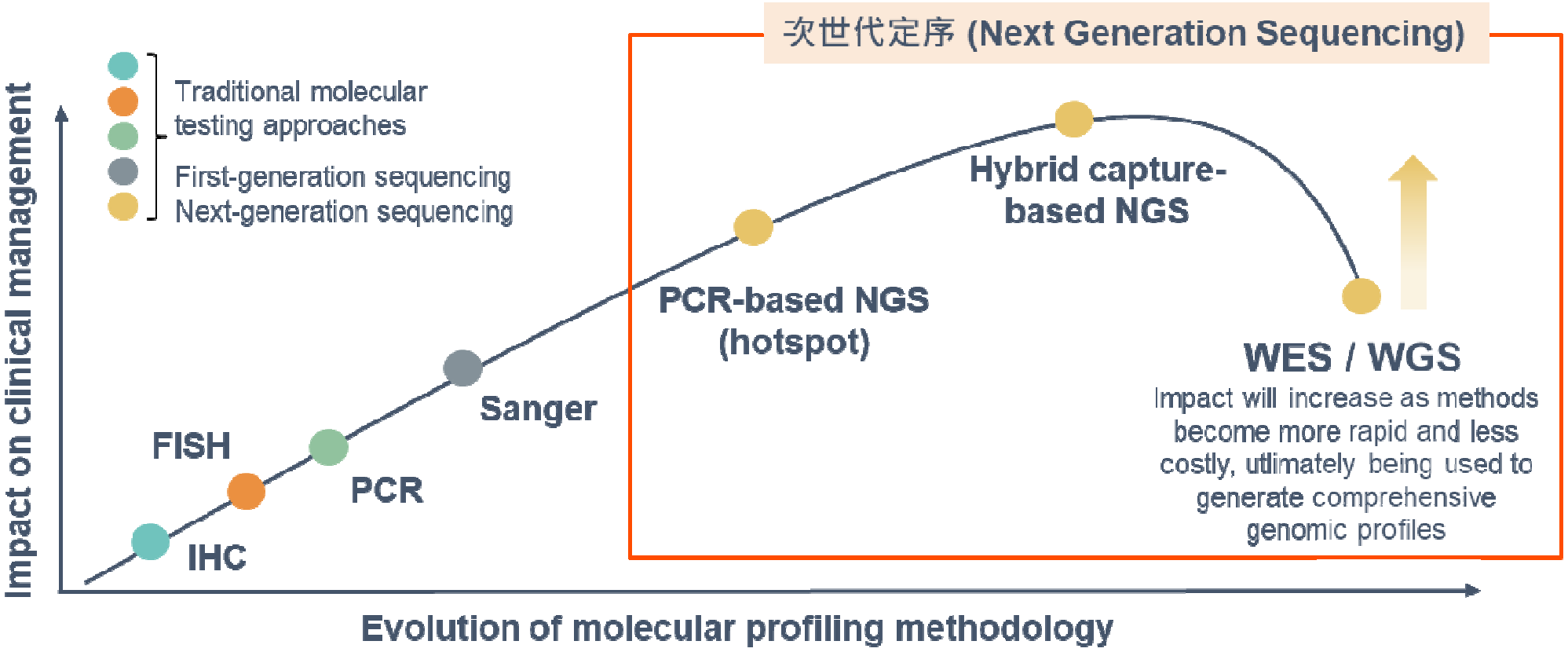
傳統分子檢測與次世代熱點檢測，無法全面掌握所有基因變異型態

BRAF V600E (BRAF inhibitor)	**EGFR Exon 19 deletion (EGFR inhibitor)**	**HER2 amplification (HER2 inhibitor)**	**ALK fusion (ALK inhibitor)**
• 鹼基取代	• 插入及缺失	• 拷貝數變異	• 重組
			

檢測類型	可偵測	無法偵測
IHC	Protein expression	Any alteration not known of ahead of time
FISH	Copy number alterations, Rearrangements	Insertions & deletions, Substitutions
Hotspot NGS* 次世代定序熱點檢測	Substitutions	Insertions & deletions, Copy number alterations, Rearrangements

次世代定序技術 (NGS) 突破以往分子檢測之限制

大幅加速對基因變異了解也推動癌症治療的進步



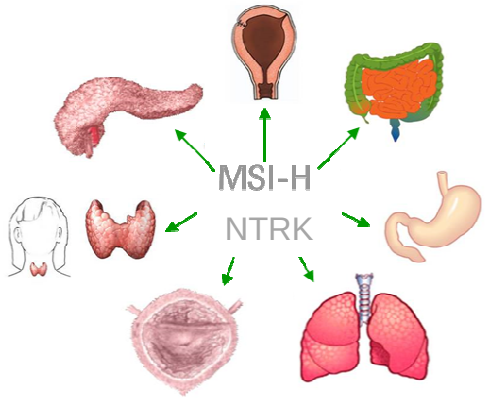
FISH: fluorescence *in situ* hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing;
PCR: polymerase chain reaction; RNA: ribonucleic acid; WES: whole exome sequencing; WGS: whole genome sequencing.

Netto, G.J., et al. (2003) *Proc Bayl Univ Med Cent* 16:379-83; de Matos, L.L., et al. (2010) *Biomark Insights* 5:9-20; Dong, L., et al. (2015) *Curr Genomics* 16:253-63.

Apply NGS to Tumor-Agnostic Treatments

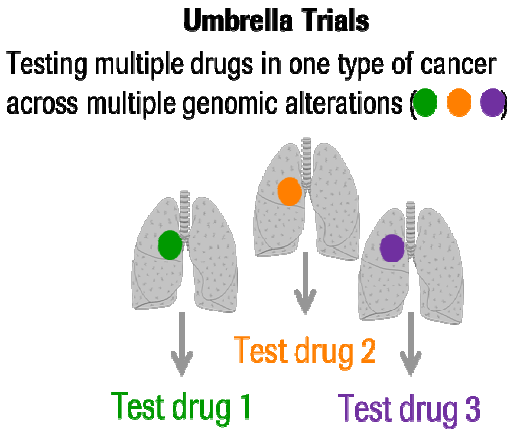
NGS and tumour agnostic therapy[1]

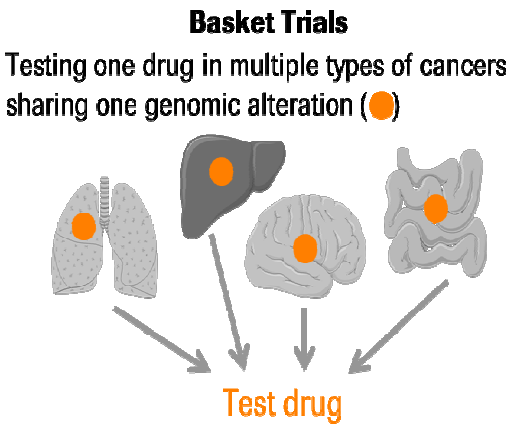
- The FDA has approved pembrolizumab **based on tumour biomarkers without regard for the tumour's origin**[2]



- **TRK inhibitors,** entrectinib and larotrectinib, demonstrates the **tumour type-agnostic** development path
- **NGS platforms** will further facilitate the adaptation of these medicines in clinical practice

Basket studies strengthen the value of genomic profiling and precision oncology



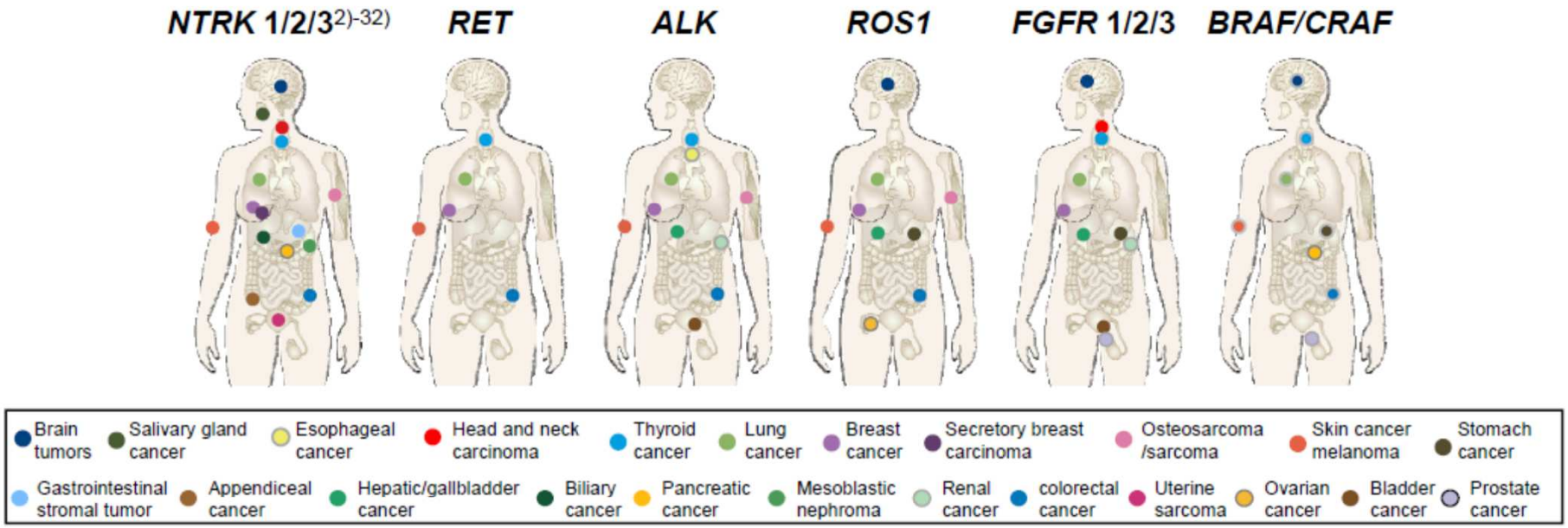


dMMR: mismatch repair deficient; DNA-R: DNA repair; MSI-H: microsatellite instability high; NGS: next-generation sequencing; TRK: tropomyosin receptor kinase.

1. Yan, L., and Zhang, W. (2018) Cancer Commun 38:6; 2. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm (Accessed on August 6, 2018). Image adapted from presentation by Steven Lemery at 2017 ASCO Annual Meeting. 3. West H.J. (2017) JAMA Oncol 3:423

Fusion Genes Expressed Across Cancer Types

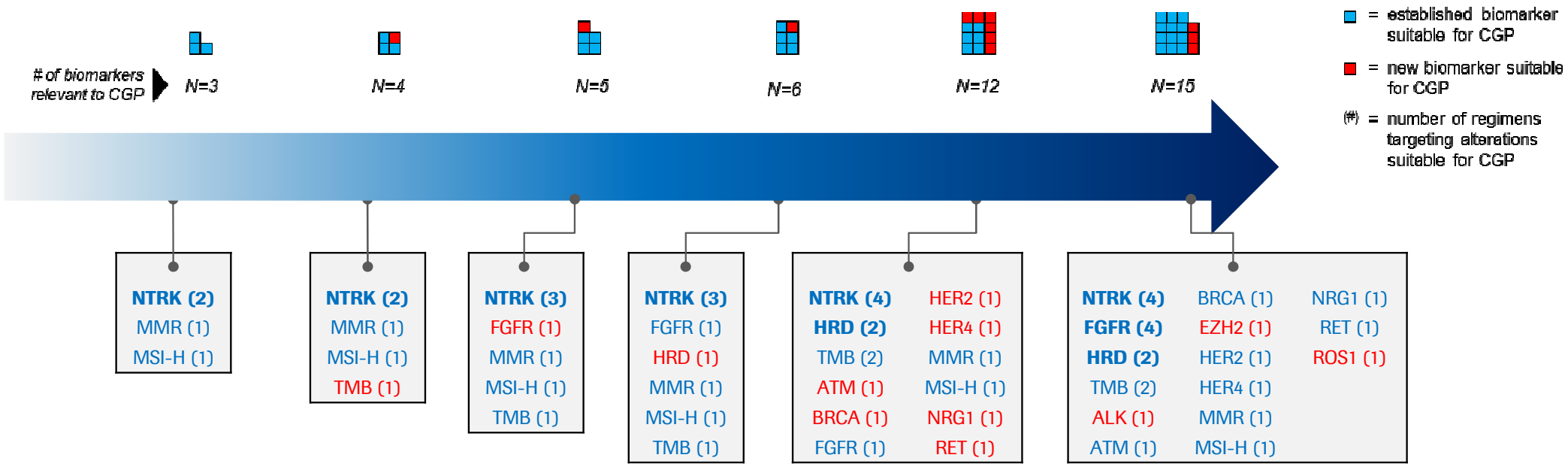
Cancer types expressing fusion genes[1)]



1）Schram AM, et al.: Nat Rev Clin Oncol. 2017; 14（12）: 735-748 2）Orbach D, et al.: Eur J Cancer. 2016; 57: 1-9 3）Knezevich SR, et al.: Nat Genet. 1998; 18（2）: 184-187 4）Rubin BP, et al.: Am J Pathol. 1998; 153（5）: 1451-1458 5）Bourgeois JM, et al.: Am J Surg Pathol. 2000; 24（7）: 937-946 6）Del Castillo M, et al.: Am J Surg Pathol. 2015; 39（11）: 1458-1467 7）Makretsov N, et al.: Genes Chromosomes Cancer. 2004; 40（2）: 152-157 8）Tognon C, et al.: Cancer Cell. 2002; 2（5）: 367-376 9）Laé M, et al.: Mod Pathol. 2009; 22（2）: 291-298 10）Skálová A, et al.: Am J Surg Pathol. 2016; 40（1）: 3-13 11）Bishop JA, et al.: Hum Pathol. 2013; 44（10）: 1982-1988 12）Knezevich SR, et al.: Cancer Res. 1998; 58（22）: 5046-5048 13）Wu G, et al.: Nat Genet. 2014; 46（5）: 444-450 14）Prasad ML, et al.: Cancer. 2016; 122（7）: 1097-1107 15）Wiesner T, et al.: Nat Commun. 2014; 5: 3116 16）Musholt TJ, et al.: Surgery. 2000; 128（6）: 984-993 17）Leeman-Neill RJ, et al.: Cancer. 2014; 120（6）: 799-807 18）Chiang S, et al.: Am J Surg Pathol. 2018; 42（6）: 791-798 19）Ross JS, et al.: Oncologist. 2014; 19（3）: 235-242 20）Jones DT, et al.: Nat Genet. 2013; 45（8）: 927-932 21）Yamamoto H, et al.: Histopathology. 2016; 69（1）: 72-83 22）Stransky N, et al.: Nat Commun. 2014; 5: 4846 23）Vaishnavi A, et al.: Nat Med. 2013; 19（11）: 1469-1472 24）Shi E, et al.: J Transl Med. 2016; 14（1）: 339 25）Brenca M, et al.: J Pathol. 2016; 238（4）: 543-549 26）Kim J, et al.: PLoS One. 2014; 9（3）: e91940 27）Frattini V, et al.: Nat Genet. 2013; 45（10）: 1141-1149 28）Zheng Z, et al.: Nat Med. 2014; 20（12）: 1479-1484 29）Chen Y, et al.: J Hematol Oncol. 2018; 11（1）: 78 30）Ardini E, et al.: Mol Oncol. 2014; 8（8）: 1495-1507 31）Creancier L, et al.: Cancer Lett. 2015; 365（1）: 107-111 32）Zehir A, et al.: Nat Med. 2017; 23（6）: 703-713

Four tumour agnostic indications exist as of 2020, and up to eight more could gain approvals by 2023

*Biomarkers Likely to Have Approved Targeted Therapies with Tumour Agnostic Indications**



Analysis includes Ph2 & Ph3 trials initiated before Feb 1, 2020, and information for those trials was updated as of June 1, 2020.
Projection is based on the assumption that all ongoing PhII and II trials will lead to approvals.
Actual number of approvals expected to be lower.

*Multiple secondary sources used to cross validate information, including Trialtrove, CT.gov, EudraCT, ChiCTR; FDA approval timelines estimation based on Ph3 PCD + 8 months review; analysis based on current phase 2 and 3 trials with inclusion criteria requiring patient selection based on alterations to specific biomarkers; assumption made that all ongoing phase 2 and 3 trials will lead to approval; "biomarker" defined as any biological molecule found in blood or tissues that has either pronostic or predictive significance in cancer treatment, and for which the effectiveness of a therapy in a patient population defined by the detection of this molecule or molecular aberration is currently being tested or has already been approved; **biomarkers without immediate relevance for CGP are primarily those for which detection of protein expression via IHC or other immunology approaches is more appropriate (e.g., PD-L1)

12 companies are projected to have tumour agnostic approvals, across 12 unique biomarkers relevant to CGP, by 2023

*Companies Likely to Have Approved Therapies Targeting Each Biomarker in 2023**

ATM
- **Pfizer** (talazoparib + avelumab)

BRCA
s/gBRCA
- **Pfizer** (talazoparib)

FGFR CGP+
FGFR1/2/3
- **Debiopharm** (Debio 1347)

HER2 CGP+
HER2 fusion
- **Rain Therapeutics** (tarloxotinib)

HER4 CGP+
HER4 fusion
- **Rain Therapeutics** (tarloxotinib)

HRD CGP+
- **AstraZeneca/Merck** (olaparib)
- **Clovis** (rucaparib)

MMR
- **Merck** (pembrolizumab)

MSI-H
- **Merck** (pembrolizumab)

NRG1 CGP+
- **Rain Therapeutics** (tarloxotinib)

NTRK CGP+
- **Roche** (entrectinib)
- **Bayer** (larotrectinib; selitrectinib)
- **Turning Point** (repotrectinib)

RET CGP+
- **Eli Lilly** (selpercatinib)

TMB CGP+
- **Merck** (pembrolizumab)
- **BMS** (ipilimumab; nivolumab)

CGP+ = CGP advantageous relative to other tests (e.g., for translocations, fusions, TMB, LOH, HRD)

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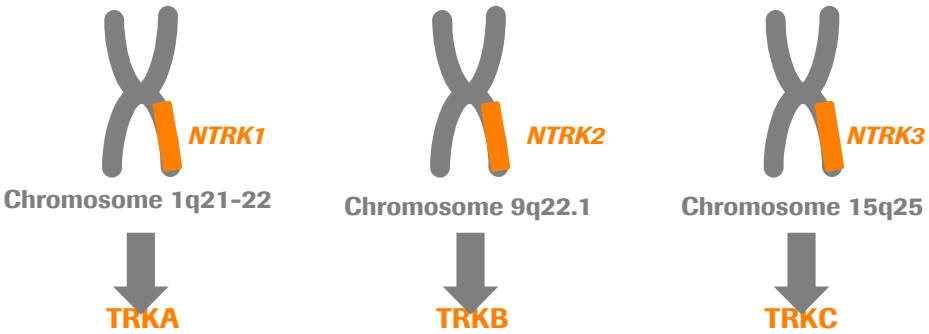
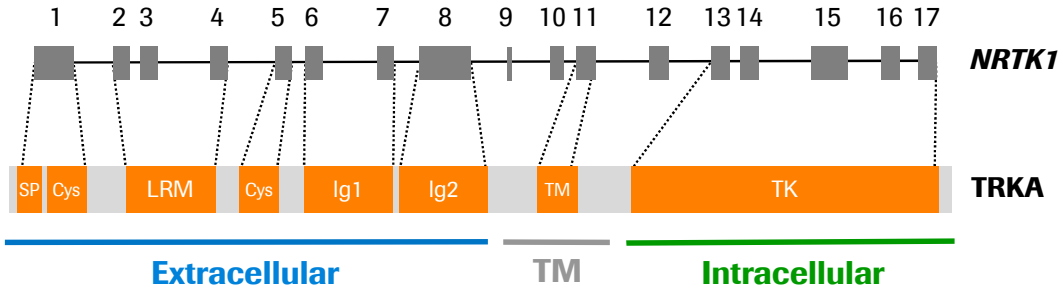
NTRK - The neurotrophic tyrosine receptor kinase gene family

- ***NTRK1, 2*** and *3* encode TRKA, TRKB and TRKC, respectively, each located on a different chromosome[1]
- The ***NTRK*** genes have a similar general organisation with extracellular domains in the N terminus and intracellular domains in the C terminus[1,2,3]
- ***NTRK1, 2*** and ***3*** comprise 17, 24 and 20 exons, respectively[1,2,3]
- The varying number of introns and different splicing patterns of the three genes make detection of oncogenic fusions using DNA methods challenging



NTRK1 **gene with 17 exon sequences and respective TRKA protein regions**[1]

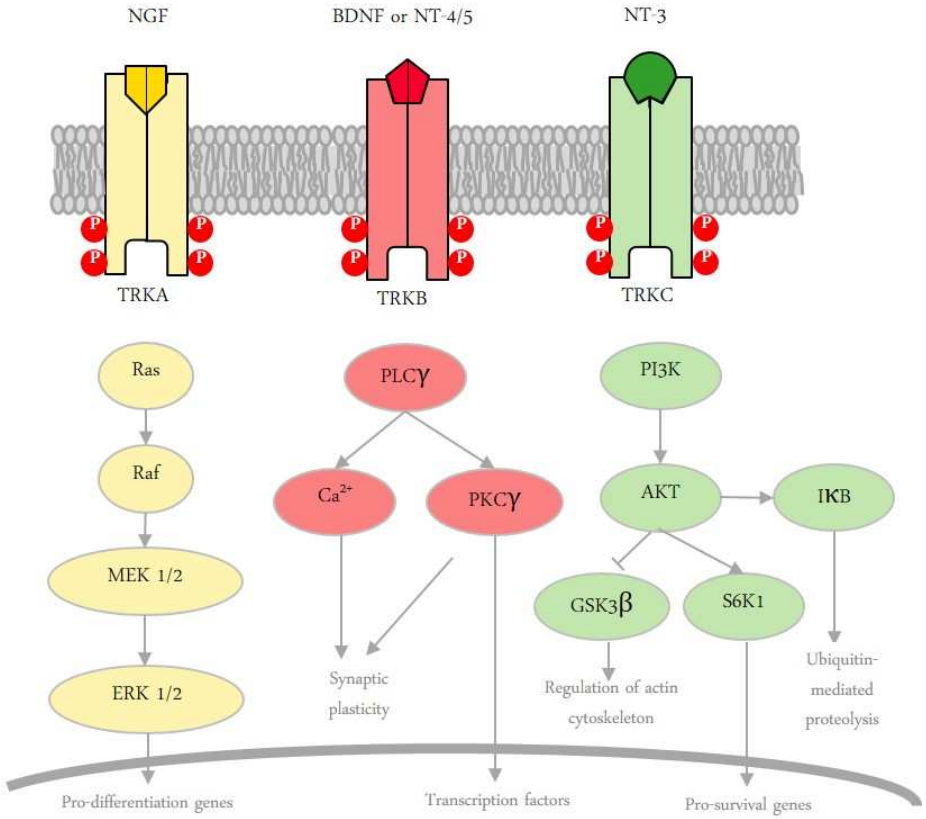


Cys: cysteine clusters; Ig: immunoglobulin-like motif; LRM: leucine-rich motifs; NTRK: neurotrophic TRK; SP: signal peptide; TK: tyrosine kinase; TM: transmembrane domain; TRK: tyrosine receptor kinase.

1. Amatu A. et al. (2016) *ESMO Open* 1:e000023; 2. Luberg K. et al. (2010) *J Neurochem* 113:952–964; 3. Ichaso N. etl al. (1998) *Oncogene* 17:1871–1875.

TRK signalling leads to cell proliferation, differentiation and survival

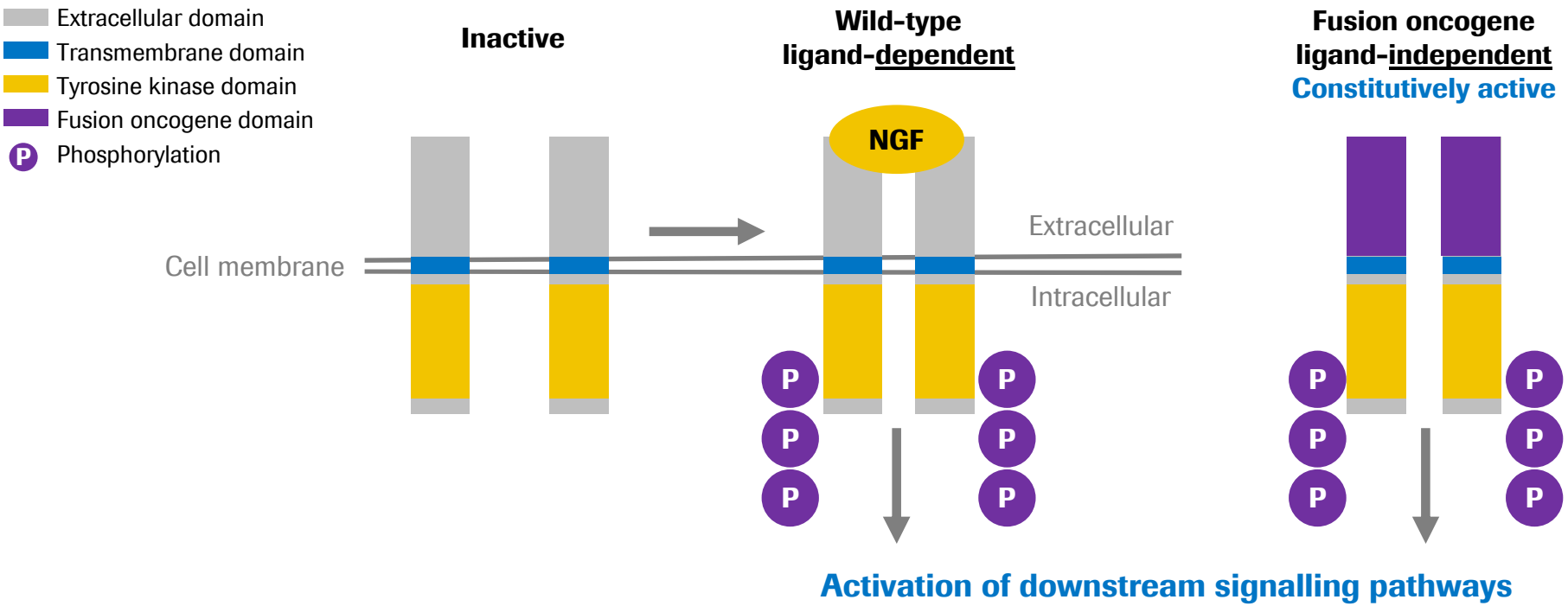
- NGF/TRKA supports survival and differentiation of sympathetic and sensory neurons responsive to temperature and pain[1]
- BDNF/TRKB supports survival and differentiation of sensory neurons responsive to tactile stimuli[1]
- NT-4/TRKB supports survival and differentiation of motor neurons[1]
- NT-3/TRKC supports survival and differentiation of sensory neurons responsive to limb movement and position[1]



AKT: v-akt murine thymoma viral oncogene homologue; BDNF: brain-derived neutrophic factor; ERK: extracellular signal-regulated kinase; GSK3β: glycogen synthase kinase β; IκB: inhibitor of nuclear factor κ B; MEK: mitogen-activated protein kinase; NGF: nerve growth factor; NT: neurotrophin; NTRK: neutrophic TRK; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC: protein kinase C; PLC: phospholipase C; RAF: rapidly accelerated fibrosarcoma kinase; RAS: rat sarcoma kinase; S6K1, ribosomal protein S6 kinase beta-1; TRK: tropomyosin receptor kinase.

1. Nakagawara A. (2001) *Cancer Lett* 169:107-14; figure modified from Khotskaya Y.B. et al. (2017) *Pharmacol Therap* 173:58-66.

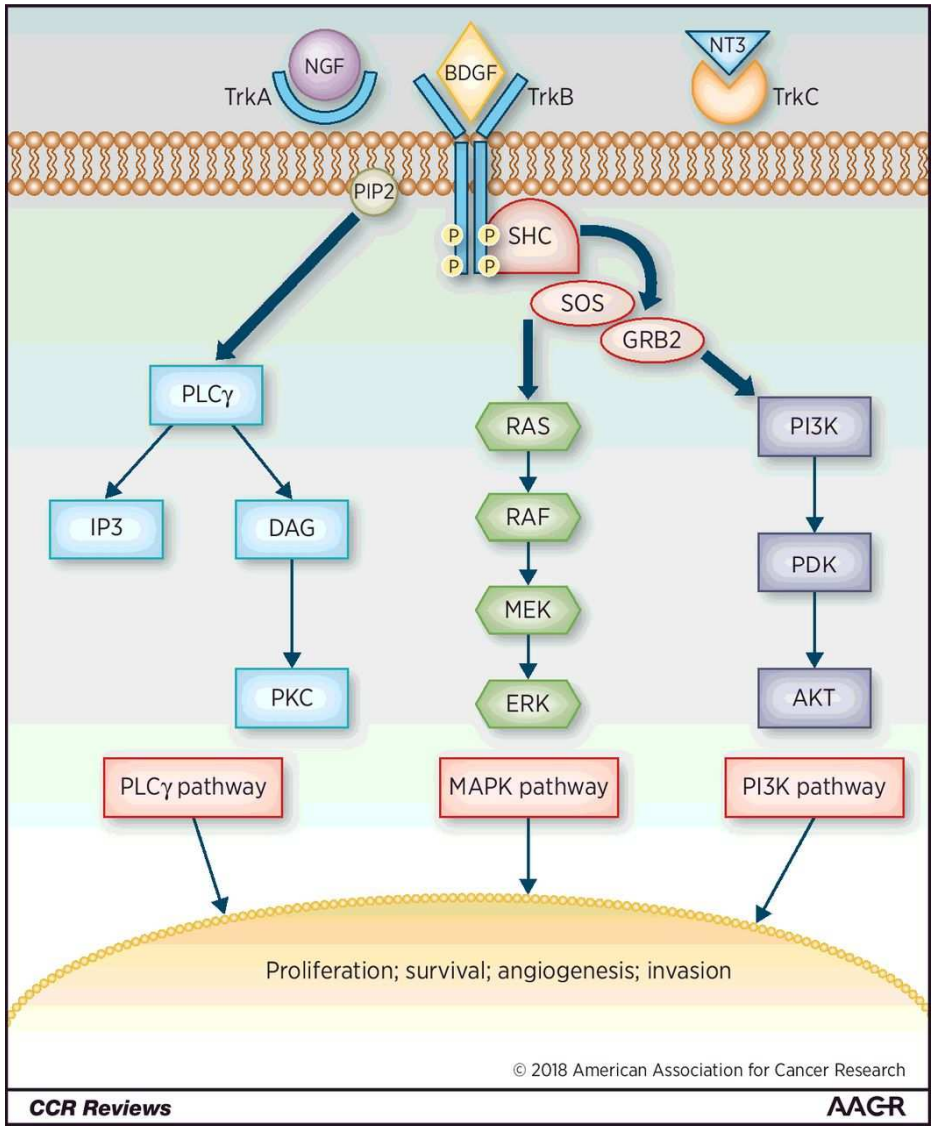
NTRK gene fusions may generate constitutively activated tropomyosin receptor kinases (TRK) fusion proteins



Constitutive activation can lead to cancer cell transformation, proliferation, migration and invasiveness[1]

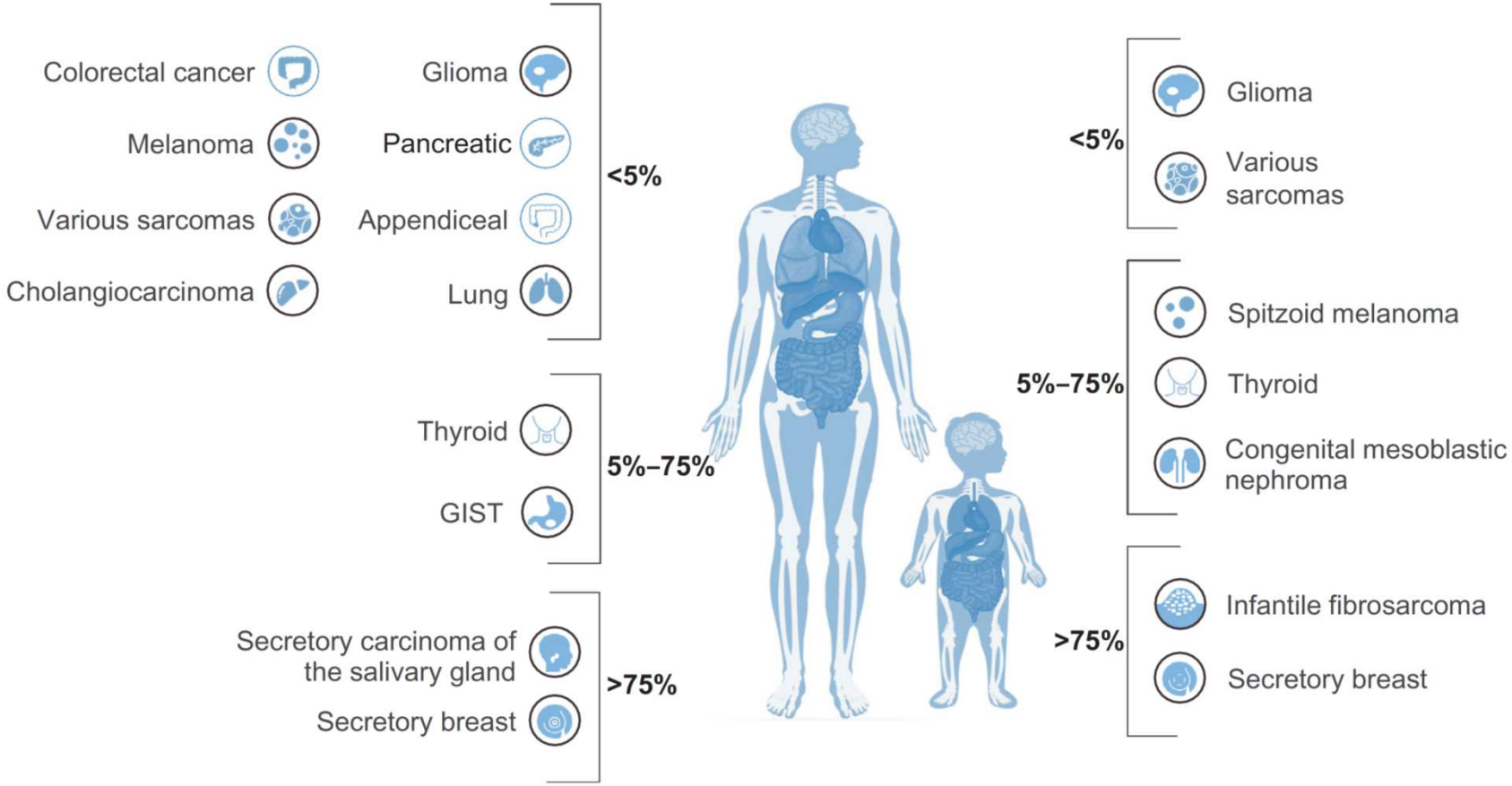
The cellular location of fusion proteins and the signalling pathways they activate may vary and can be dependent on the specific fusion partner

Ntrk signaling and oncogenesis



Clin Cancer Res. 2018 Dec 1;24(23):5807-5814.

TRK Fusions are Found in Diverse Tumor Types in Adult and Pediatric Patients[1,2]



GIST: gastrointestinal stromal tumor; MASC: mammary analogue secretory carcinoma; TRK: tropomyosin receptor kinase.

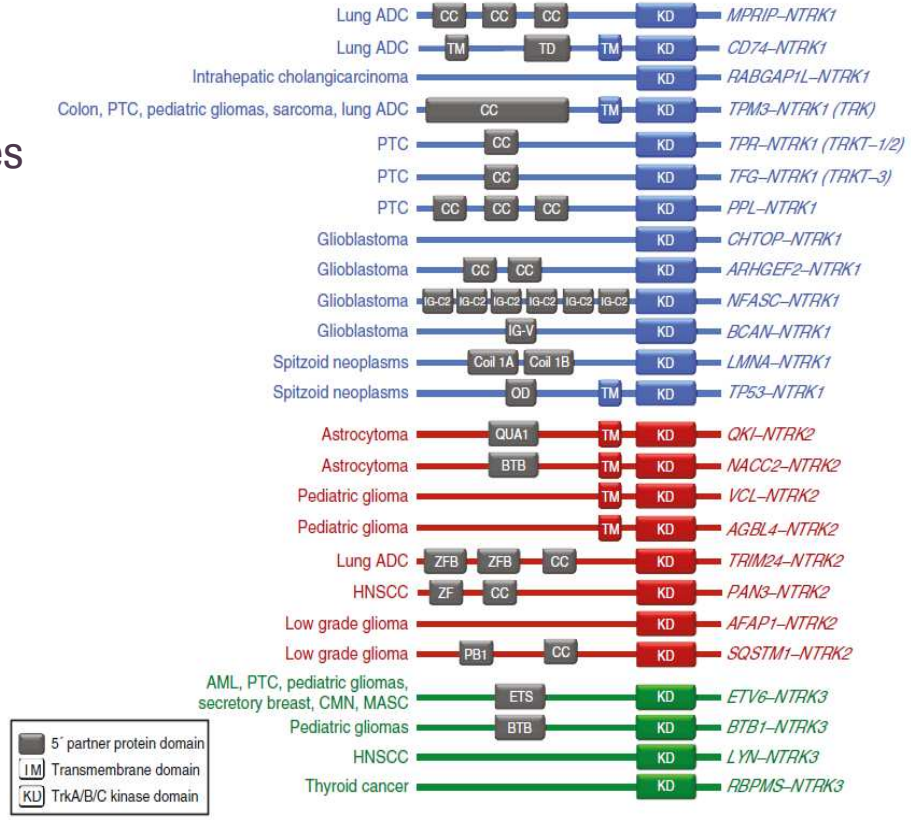
1. Vaishnavi A. et al. (2015) *Cancer Discov 5:25-34*; 2. Amatu A, et al. ESMO Open. 2016.

NTRK gene fusions are particularly problematic to detect

- Large intronic regions[1,2]
- Many break points and fusion partners
- Is endogenously expressed in some tissue types

What does this means for testing?

- IHC may lack specificity
- RT-PCR is not comprehensive
- FISH requires at least 3 assays
- NGS DNA-only panels may lack sensitivity



1, Sigal D et al. *J Natl Compr Canc Netw* 2017;15:1317-22; 2. Gagan J, Van Allen EM. *Genome Med* 2015;7:80; 3. Vaishnavi A et al. *Cancer Discov* 2015;5:25-34

NGS has advantages over other methods for detecting NTRK gene fusions

Method	Sensitivity	Specificity	Detection of all fusion genes	Detection of partner	Detection of expression	Screening
IHC	High	Moderate/high	Yes	No	Yes	Yes*
FISH	High	High	One per probe	No	No	No
RNA Seq NGS	High	High	Yes	Yes	Yes	Yes
DNA Seq NGS	Moderate	High	Yes	Yes	No	Yes

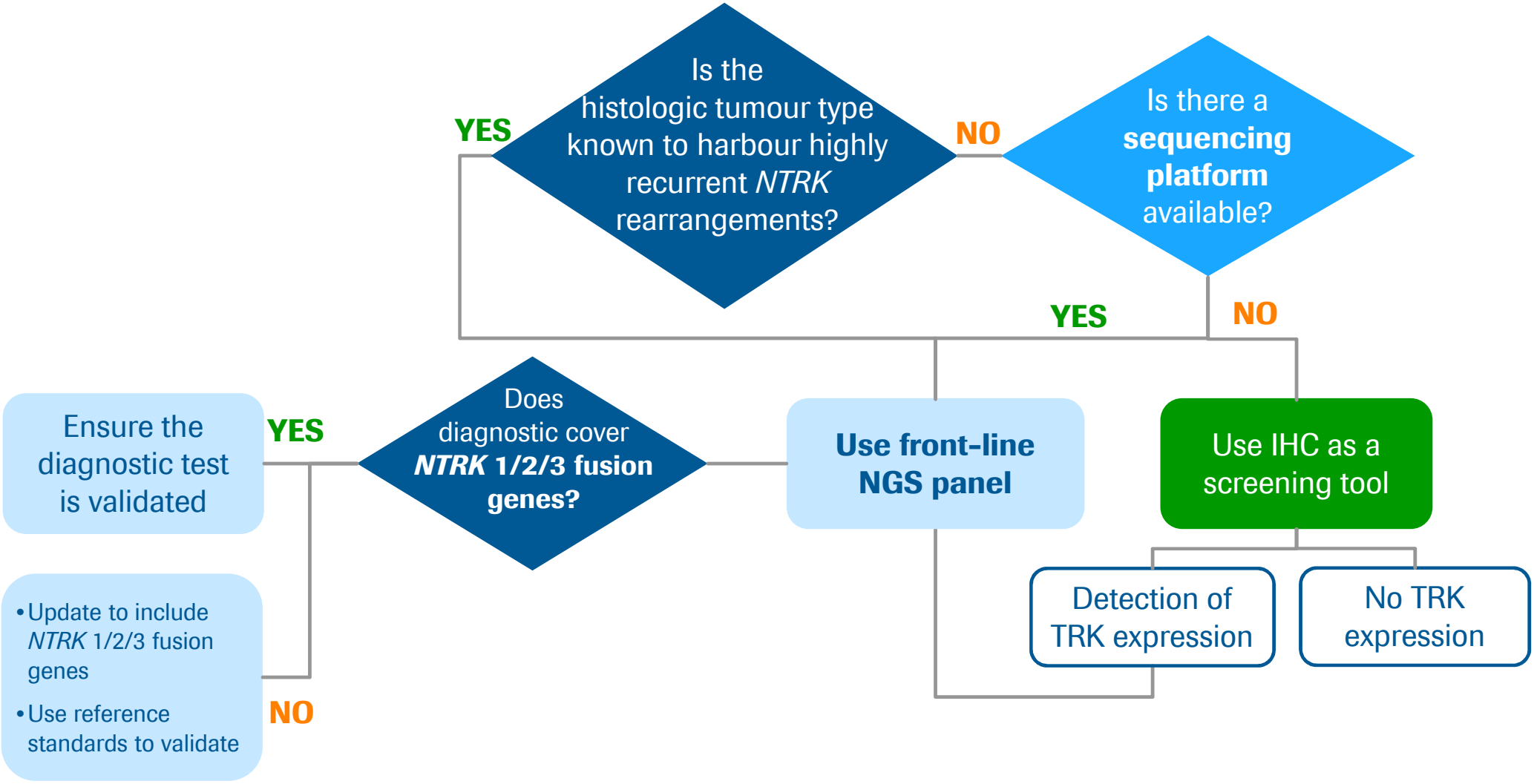
IHC can be used to screen for TRK expression but NGS is needed to confirm the presence of an *NTRK* gene fusion

Some NGS assays do not detect all three *NTRK* fusion genes. Detection of all fusion proteins depends on selection of a targeted panel that includes *NTRK* 1/2/3

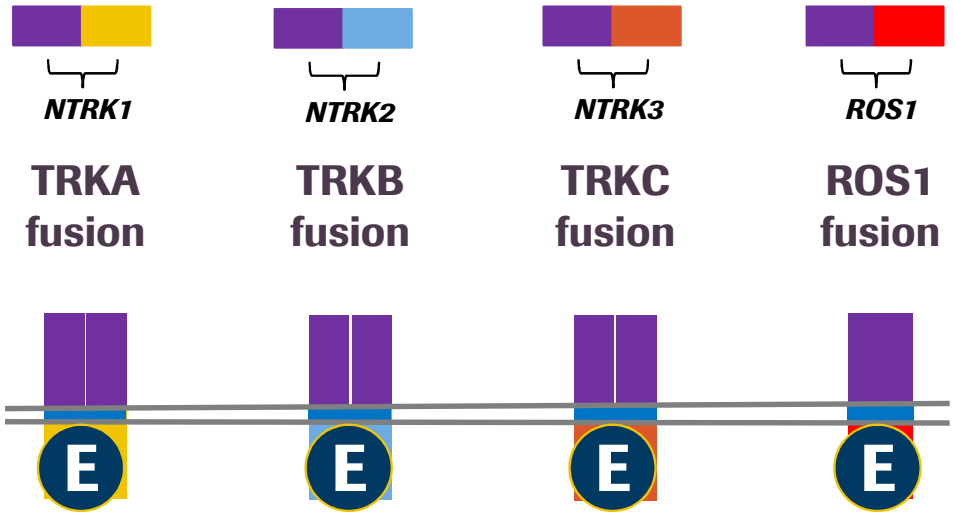
*NGS is needed to confirm the presence of an *NTRK* gene fusion detected by IHC

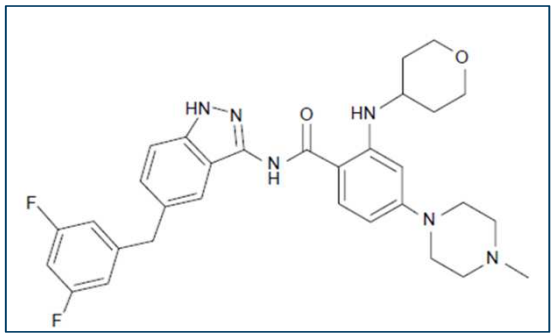
Adapted from Reis-Filho. ESMO 2018

ESMO Recommendation for *NTRK* testing



Entrectinib inhibits TRK and ROS1 tyrosine kinase activity





E ntrectinib

Constitutive activation of intracellular signalling pathways
e.g. MAPK, PI3K-AKT, PLCγ-PKC

Cell proliferation **Cell survival**

Cancer

Entrectinib binds receptor tyrosine kinase domains in TRK and ROS1 fusion proteins and inhibits signalling

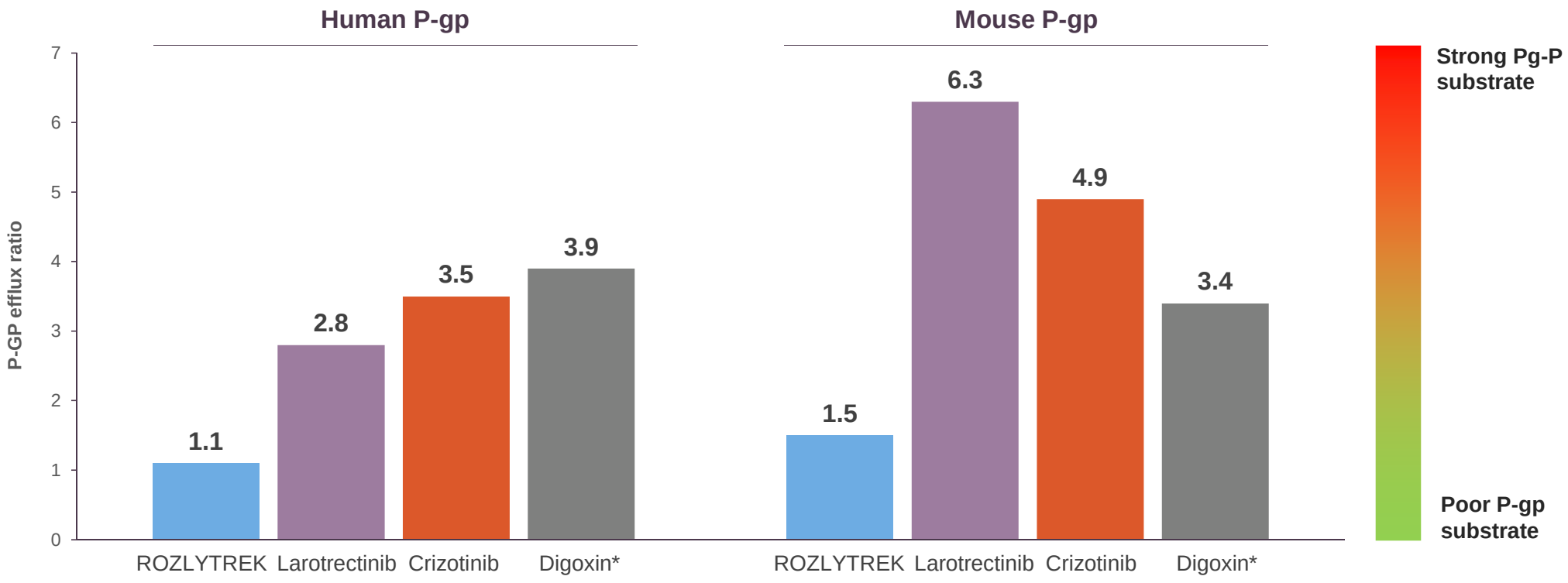
Inhibition of cancer cell growth

Clinical tumour responses

Vaishnavi, et al. Cancer Discov 2015; Lin, et al. J Thorac Oncol 2017
ROZYLYTREK US PI, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000lbl.pdf [last accessed Sept 2020]

ROZLYTREK is an Effective Brain Penetrant and a Weak P-gp Substrate

Drug efflux through P-gp in model system



P-gp efflux assay was performed at steady-state using LLC-PK1 cell monolayers over-expressing human or mouse P-gp

*In vitro control P-gp substrate

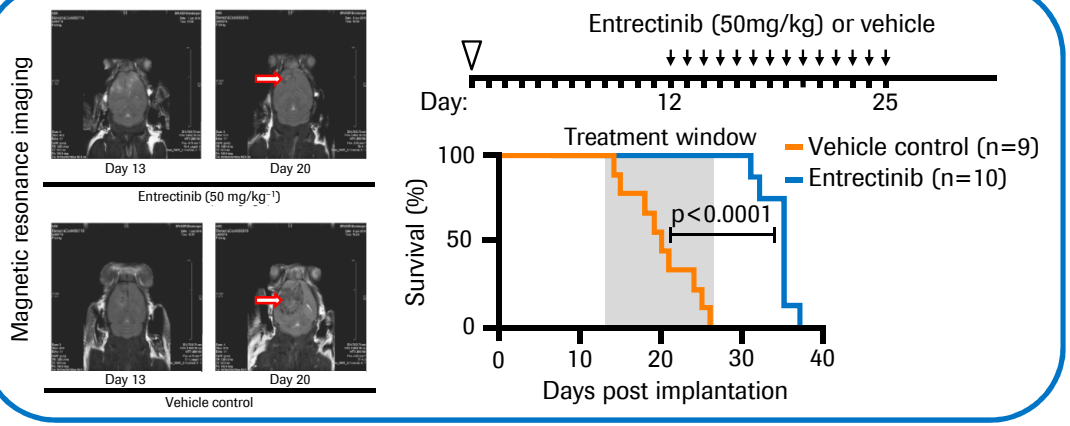
H. Fischer et al, Neuro Oncol. 2020 Jun 9;22(6):819-829. doi: 10.1093/neuonc/noaa052

ROZLYTREK Crosses the Blood–brain Barrier and Achieves Tumor Shrinkage

Entrectinib is designed to cross the blood–brain barrier to control CNS disease,[1] a frequent complication of advanced solid tumours

Entrectinib has substantial exposure in the CNS (brain-to-blood ratios of 0.4–2.2) that is sufficient to achieve durable target inhibition and tumour shrinkage[2]

Entrectinib demonstrated antitumour activity and survival benefit in a preclinical *NTRK*+ glioma model[3]



- BNN4 (*BCAN-NTRK1*+ glioma) cells implanted orthotopically by IC injection
- Mice received oral entrectinib 50mg/kg, once daily for 14 days
- All mice in the control group succumbed to brain tumours within the 14-day treatment window, while all mice in the entrectinib group survived

1. Menichincheri, et al. J Med Chem 2016; 2. Rangaraju, et al. Neuro-oncol 2017; 3. Cook, et al. Nat Commun 2017

Updated integrated efficacy and safety analysis of entrectinib▼: *NTRK* fusion-positive solid tumors (Aug 2020 cut-off)

Efficacy population*
Adult patients with *NTRK* fusion-positive, TRK-inhibitor-naïve solid tumours
N=121

ALKA-372-001
Phase I, dose-escalation study
n=1

STARTRK-1
Phase I, dose-escalation study
n=2

STARTRK-2
Phase II, multicentre, global basket study
Entrectinib 600mg once daily, 28-day cycle
n=118

Co-primary endpoints:†
- ORR
- DoR

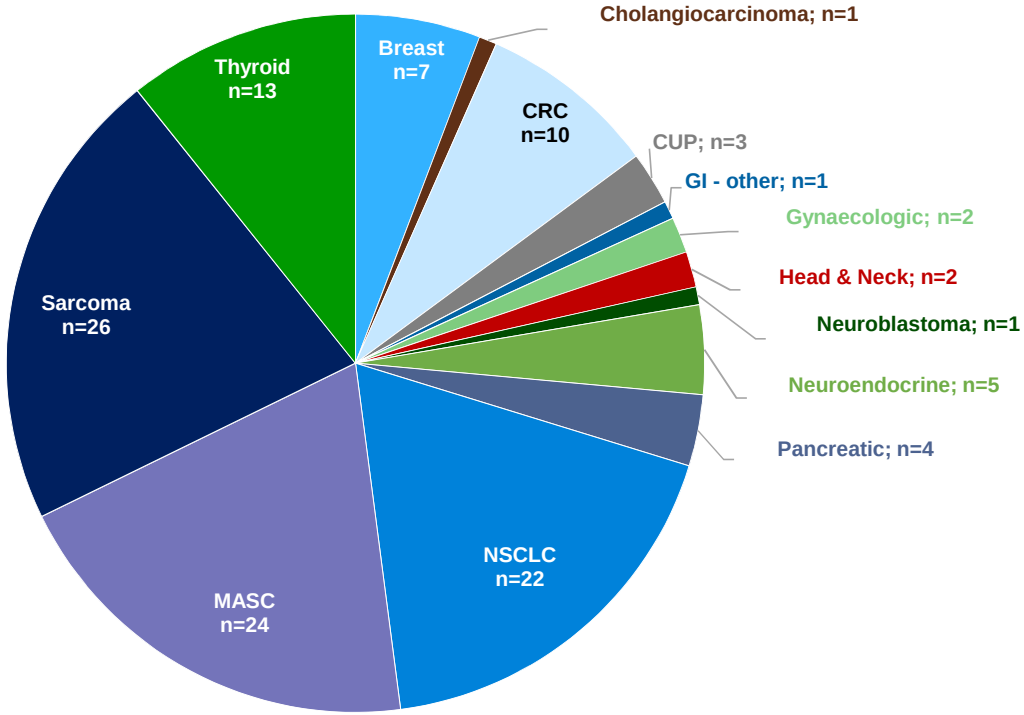
Secondary endpoints:
- PFS† and OS
- intracranial ORR† and DoR †,‡
- safety and tolerability

Safety population§
Patients receiving entrectinib (all tumour types and gene rearrangements)
N=626, including **193** adult patients with *NTRK+,* TRK-inhibitor naïve solid tumours who received ≥1 dose of entrectinib

Bazhenova, et al. Presented at ESMO 2021 (Poster 533P)
Enrolment cut-off (efficacy population): 31 July 2019; Data cut-off (all patients): 31 Aug 2020. *Patients with at least 12 months of follow-up; †Per blinded independent central review (RECIST v1.1) ‡Patients with measurable and non-measurable baseline CNS lesions; §Patients from ALKA-372-001, STARTRK-1, STARTRK-2 and STARTRK-NG

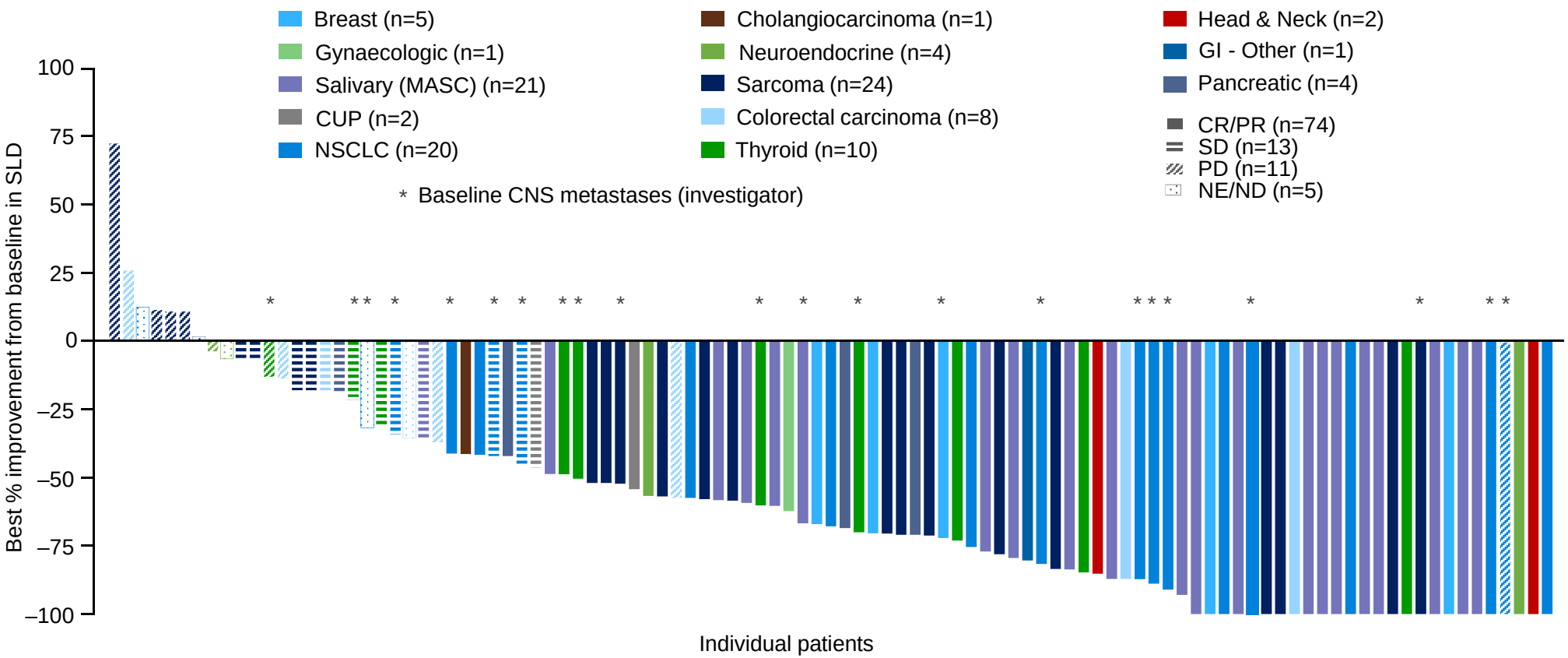
The efficacy population included 121 patients with 14 different tumour types

- Overall safety population: N=626 (adult and paediatric patients), including **n=193** patients with *NTRK* fusion-positive solid tumours
- Efficacy population: **n=121** patients with 14 different tumour types
- Median survival follow-up was **25.8 months**



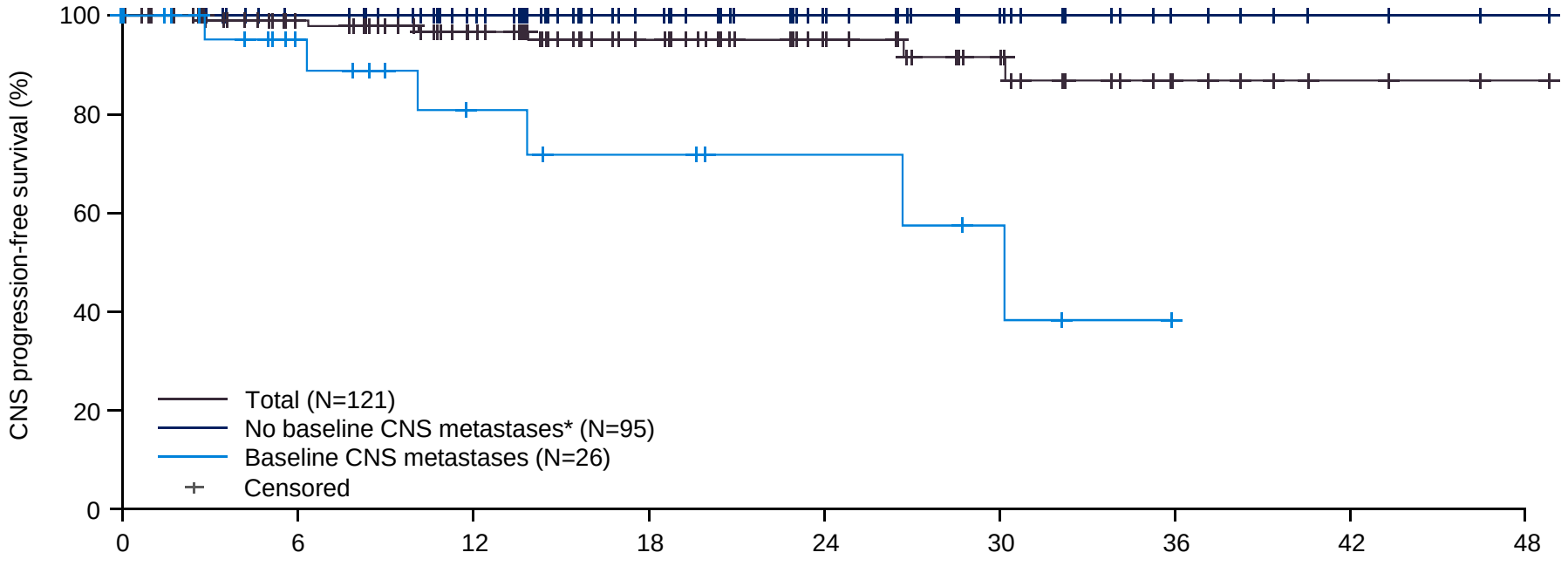
Bazhenova, et al. Presented at ESMO 2021 (Poster 533P)
CRC, colorectal carcinoma; CUP, cancer of unknown primary; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer

Responses with entrectinib▼ by tumour type



Bazhenova, et al. Presented at ESMO 2021 (Poster 533P). **Enrolment cut-off: 31 July 2019; Data cut-off: 31 Aug 2020**
Patients with missing SLD percent change were excluded from the plot.
GI, gastrointestinal; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; MASC, mammary analogue secretory carcinoma; SLD, sum of longest diameters

CNS progression (deaths censored) in patients treated with entrectinib▼ per baseline CNS metastases status



No. at risk

Total	121	101	91	82	71	55	47	37	31	24	20	13	7	5	3	2	1
No CNS mets	95	81	76	71	62	48	40	32	26	20	17	12	7	5	3	2	1
CNS mets	26	20	15	11	9	7	7	5	5	4	3	1					

Bazhenova, et al. Presented at ESMO 2021 (Poster 533P). **Enrolment cut-off: 31 July 2019; Data cut-off: 31 Aug 2020**
*Regular CNS scans of patients without baseline CNS disease were not mandated by the protocol but only required if clinically indicated.

Entrectinib▼: safety overview (Aug 2020 cut-off)

- Median dose intensity: 91.3% (IQR 65.9–99.6) in the *NTRK* fusion-positive safety population
  94.2% (IQR 67.8–100.0) in the overall safety population

TRAEs reported in ≥10% of patients Patients, %	*NTRK* fusion-positive safety population (n=193)	Overall safety population (N=626)
Dysgeusia	35.2	35.9
Diarrhoea	31.1	25.9
Fatigue	27.5	28.8
Weight increase	27.5	27.3
Constipation	25.9	25.1
Blood creatinine increase	25.9	21.2
Dizziness	24.9	26.8
Oedema peripheral	18.1	16.1
Anaemia	17.1	15.7
Nausea	16.6	20.3
AST increase	16.6	13.1
ALT increase	15.5	12.5
Paraesthesia	11.9	15.8
Myalgia	10.9	14.4
Vomiting	10.9	13.6
Arthralgia	5.2	10.2

Bazhenova, et al. Presented at ESMO 2021 (Poster 533P). **Data cut-off: 31 Aug 2020**
IQR, interquartile range; *NTRK*, neurotrophic tyrosine receptor kinase

Patient history

Timeline

March 2019

Initial symptoms

Age, gender and medical information

- 62-year-old male
- Presented with jaundice

Case provided courtesy of Dr Ming-Huang Chen.

Patient history

Timeline

March 2019	April 2019
Initial symptoms	Pancreatic head NEC

Age, gender and medical information

- 62-year-old male
- Presented with jaundice

Pathology results

Liver biopsy:

- Liver tissue infiltrated with poorly differentiated carcinoma cells in nested and cord-like patterns
- Tumour cells are positive for **creatin kinase and INSM1** negative for CD56, CK7, trypsin and synaptophycin
- **Ki-67 index is 70%**

Diagnosis

- Pancreatic head NEC, grade 3
- cT4N1M1 with liver metastases

CK: creatine kinase; INSM1: insulinoma-associated protein 1; NEC: neuroendocrine.
Case provided courtesy of Dr Ming-Huang Chen.

Patient history

Treatment and response

- ERCP and metallic stent insertion
- Chemotherapy with atezolizumab, etoposide and cisplatin, 4 cycles
  - Progressive disease
- FOLFIRINOX, 4 cycles
  - Progressive disease
- Gemcitabine and nab-paclitaxel, 8 cycles
  - Progressive disease
- Dacarbazine and fluorouracil, 3 cycles
  - Progressive disease
- Ipilimumab and nivolumab, 3 cycles
  - Progressive disease with complicated type 1 DM

DM: diabetes mellitus; ERCP: endoscopic retrograde cholangiopancreatography; FOLFIRINOX: fluorouracil, leucovorin, irinotecan, and oxaliplatin; NEC: neuroendocrine.
Case provided courtesy of Dr Ming-Huang Chen.

Patient history

Timeline

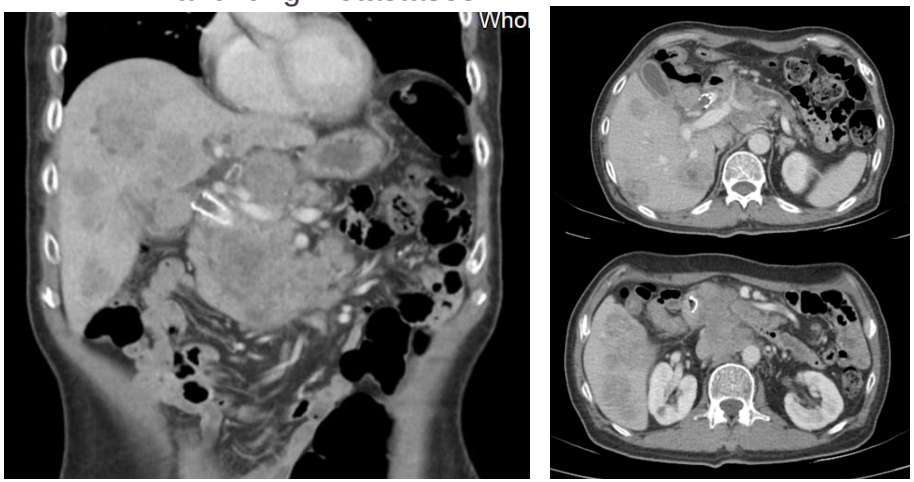
March 2019	April 2019	April 2019 – July 2020	September 2020
Initial symptoms	Pancreatic head NEC	Treatment and response	CT scan showed progressive disease

Treatment and response

- ERCP and metallic stent insertion
- Chemotherapy with atezolizumab, etoposide and cisplatin, 4 cycles
  - Progressive disease
- FOLFIRINOX, 4 cycles
  - Progressive disease
- Gemcitabine and nab-paclitaxel, 8 cycles
  - Progressive disease
- Dacarbazine and fluorouracil, 3 cycles
  - Progressive disease
- Ipilimumab and nivolumab, 3 cycles
  - Progressive disease with complicated type 1 DM

Test results

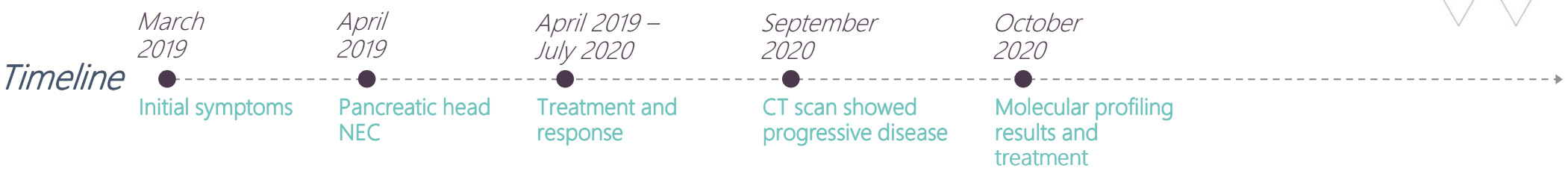
- CT scan showed pancreas head tumour (4.2 x 2.8 cm), multiple liver, multiple lymph node and lung metastases



CT: computed tomography; DM: diabetes mellitus; ERCP: endoscopic retrograde cholangiopancreatography; FOLFIRINOX: fluorouracil, leucovorin, irinotecan, and oxaliplatin; NEC: neuroendocrine

Case provided courtesy of Dr Ming-Huang Chen

Patient history



Molecular profiling results

Results based on liquid-based CGP:

Genomic alterations	VAF%
ETV6-NTRK3 fusion	24.3%
KRAS K117N	0.23%
RB1 R320*	50.9%
TP53 R213*	65.8%

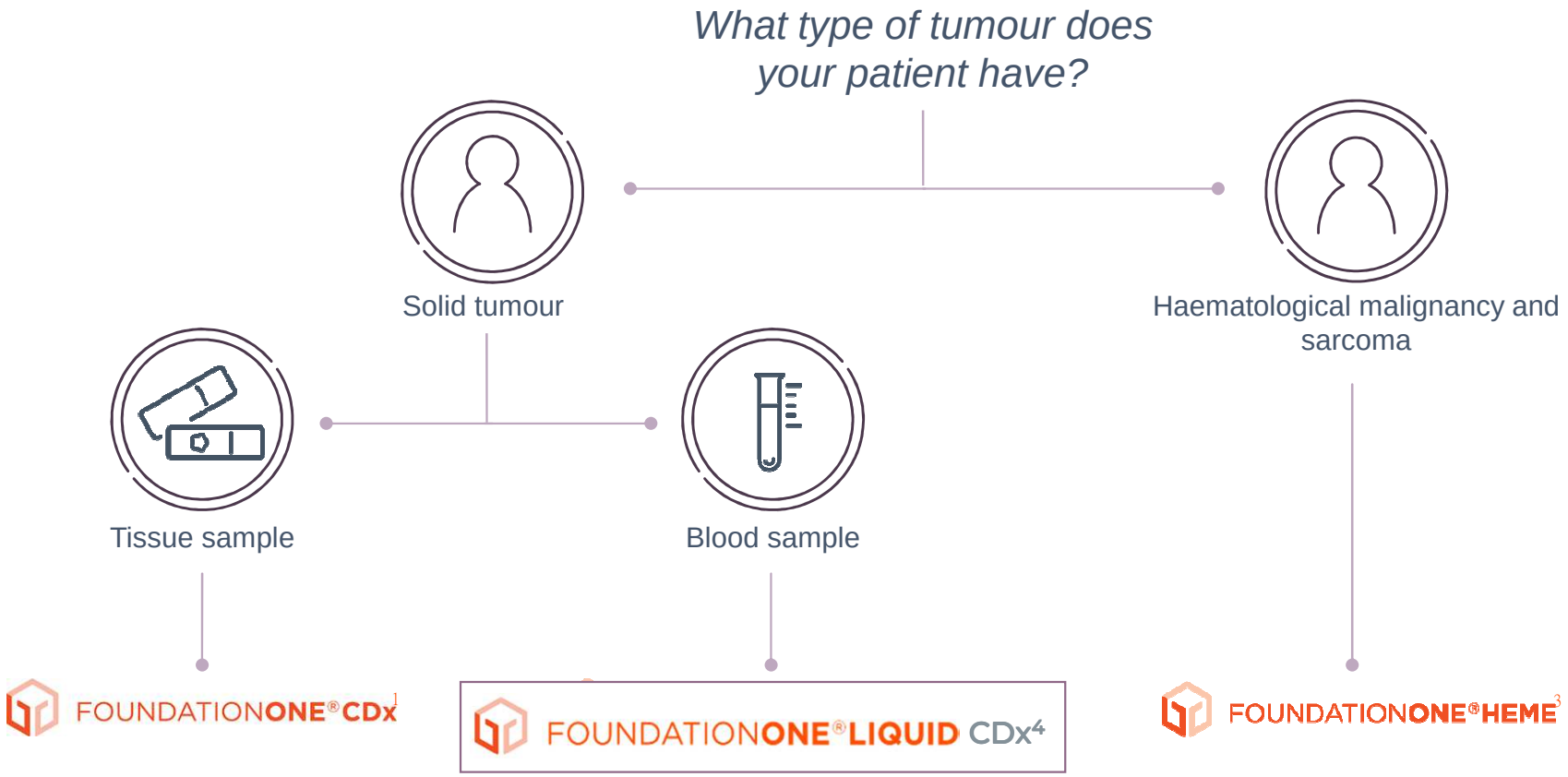
TF: 62%
MSI: Cannot be determined
TMB: 10 muts/Mb

Treatment

- Received entrectinib (600 mg)

CDx: companion diagnostic; Mb: megabase; MSI: microsatellite instability; muts: mutations; NEC: neuroendocrine; PD-L1: programmed death-ligand 1; TF: tumour fraction; TMB: tumour mutational burden; VAF: variant allele frequency.
Case provided courtesy of Dr Ming-Huang Chen.

F1LCDx will complement the current FMI offering to better support patient care



CGP: comprehensive genomic profiling.

1. Foundation Medicine, Inc. (2019) FoundationOne CDx Technical Specifications; 2. Foundation Medicine, Inc. (2019) FoundationOne Liquid Technical Specifications; 3. Foundation Medicine, Inc. (2019) FoundationOne Heme Technical Specifications.4. Foundation Medicine, Inc. (2020) Data on file: Internal development;

FoundationOne® CDx and NTRK detection

FoundationOne ® CDx (F1CDx) is estimated to detect approx. 90% of all NTRK fusions. This detection rate is based on coverage of all exons for NTRK1/2/3 and selected introns for NTRK1/2 and for ETV6**.

F1CDx *NTRK* gene coverage		
Gene	**Captured exons**	**Captured introns**
NTRK1 (NM_002529)	all	7-11
NTRK2 (NM_006180)	all	12
NTRK3 (NM_002530)	all	none*
*ETV6*** (NM_001987)	none	5-6

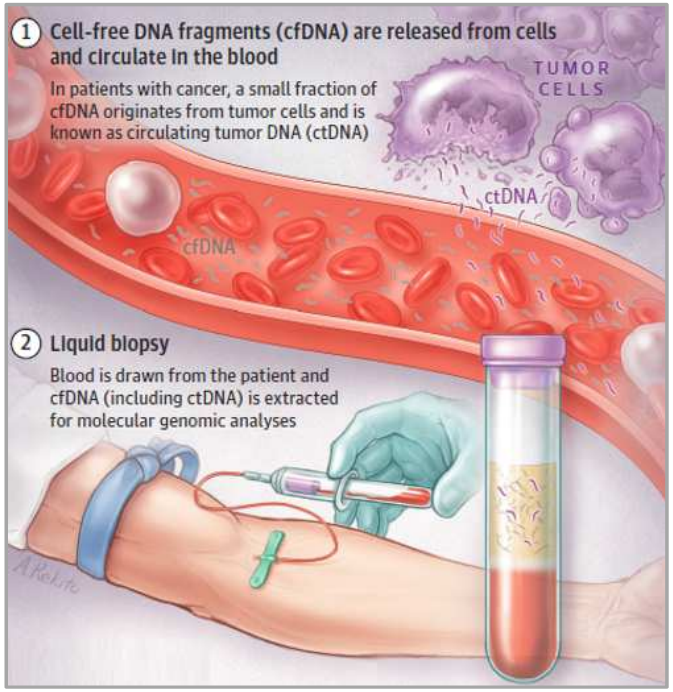
*Select regions of *NTRK3* intron 14 and intron 17 are captured due to overlaps with alternate isoforms
***ETV6* is the most frequent fusion partner of *NTRK3*

F1CDx estimated *NTRK* detection***		
Fusion pair	**Total # in COSMIC[1]**	**Estimated detection**
TPM3-NTRK1	38	100.0%
TPR-NTRK1 variant I	2	100.0%
TPR-NTRK1 variant II	2	96.6%
TFG-NTRK1	1	100.0%
TFG-NTRK1	1	100.0%
LMNA-NTRK1	2	100.0%
TP53-NTRK1	1	100.0%
QKI-NTRK2	2	48.9%
NACC2-NTRK2	1	100.0%
ETV6-NTRK3 variant I	119	100.0%
ETV6-NTRK3 variant II****	15	0.4%
ETV6-NTRK3 variant III	1	100.0%
ETV6-NTRK3 variant IV****	1	3.7%
Overall F1CDx detection rate of *NTRK* fusions[2]		**90.9%**

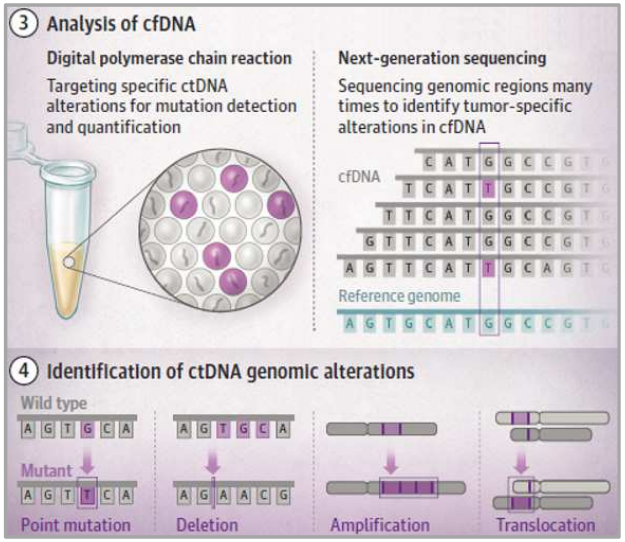
***This estimate is based on fusions with annotated breakpoints in the COSMIC v92 database and average empirical sequence depth of F1CDx
****Poor detection due to lack of *ETV6* intron 4 capture in F1CDx

1.COSMIC: Catalogue Of Somatic Mutations In Cancer; 2. Internal data on file as of October 2020; Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important; **ETV6* is the most frequent fusion partner of *NTRK3*

Liquid biopsy: test ctDNA



破碎的腫瘤細胞釋放DNA碎片到血液中，經由抽血分離這些游離DNA，並進行次世代基因定序(NGS)，有機會能夠得知腫瘤的基因變異資訊



ROZLYTREK™ entrectinib

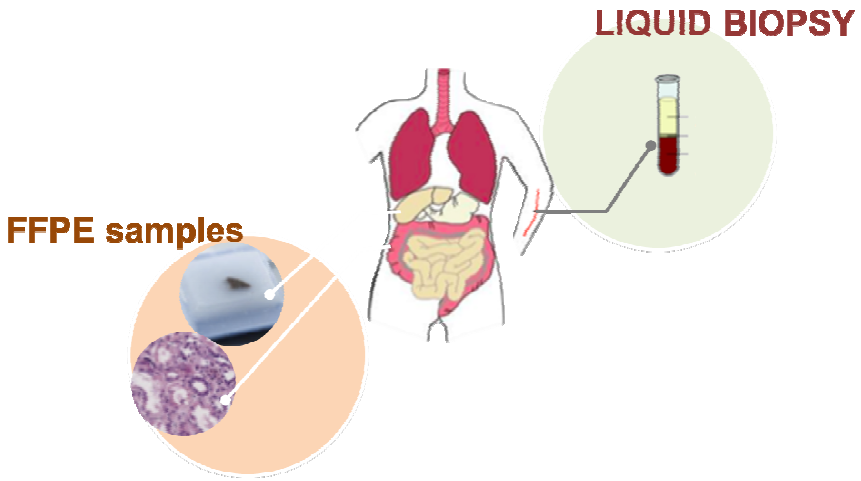
Liquid Biopsy and Tissue Biopsy

腫瘤組織

- 標準的癌症病理檢查樣本
- 提供完整的組織形態資訊
- 檢測上相對容易操作
- 樣本可以長期保存

液態採檢

- 低侵入性的檢體採集
- 可重複並多次採集檢體
- 有機會偵測癌症復發
- 可動態監控癌症的進展、治療效果評估、癌細胞抗藥性



ROZLYTREK™ entrectinib

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F1LCDx *NTRK* gene coverage

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***ETV6* is the most frequent fusion partner of *NTRK3*

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Fusion pair	Total # in COSMIC	Estimated detection
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TFG-NTRK1	1	100.0%
LMNA-NTRK1	2	100.0%
TP53-NTRK1	1	100.0%
QKI-NTRK2	2	48.9%
NACC2-NTRK2	1	100.0%
ETV6-NTRK3 variant I	119	100.0%
ETV6-NTRK3 variant II****	15	0.3%
ETV6-NTRK3 variant III	1	100.0%
ETV6-NTRK3 variant IV****	1	3.4%
Overall F1LCDx detection rate of *NTRK* fusions		**90.6%**

***This estimate is based on fusions with annotated breakpoints in the COSMIC v92 database and average empirical sequence depth of F1LCDx
****Poor detection due to lack of *ETV6* intron 4 capture in F1LCDx

1.COSMIC: Catalogue Of Somatic Mutations In Cancer; 2. Internal data on file as of October 2020; **ETV6 is the most frequent fusion partner of NTRK3

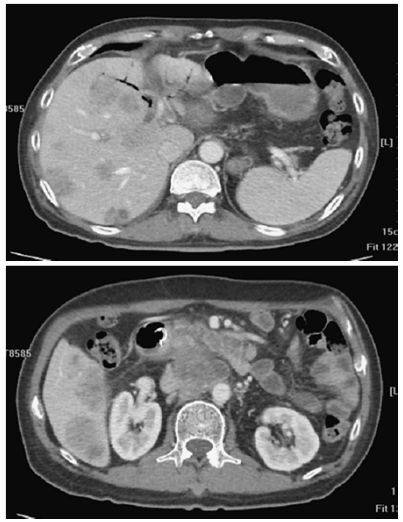
Patient history

Timeline

March 2019	*April 2019*	*April 2019 – July 2020*	*September 2020*	*October 2020*	*January 2021*
Initial symptoms	Pancreatic head NEC	Treatment and response	CT scan showed progressive disease	Molecular profiling results and treatment	Partial response

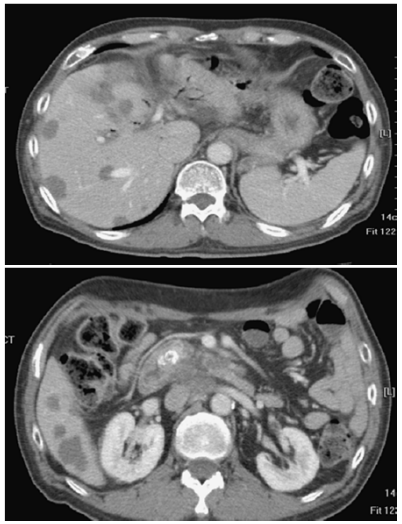
Test results

August 2020



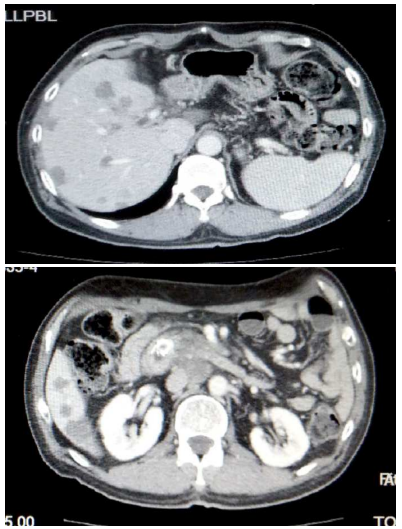
600 mg entrectinib

November 2020



400/600 mg entrectinib

January 2021



- Tx-related AE: grade 1 fatigue, BW increase 3 kg/month

AE: adverse event; BW: body weight; CT: computed tomography: NEC: neuroendocrine; Tx: treatment.
Case provided courtesy of Dr Ming-Huang Chen.

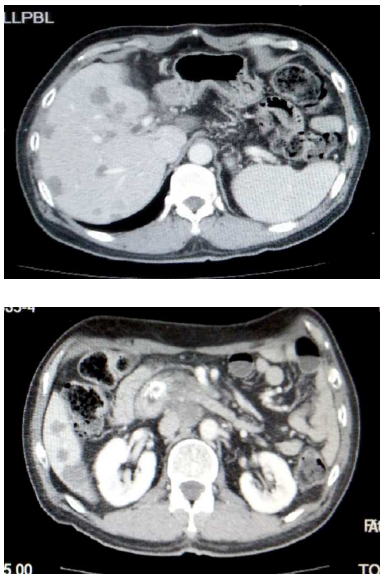
Patient history

Timeline

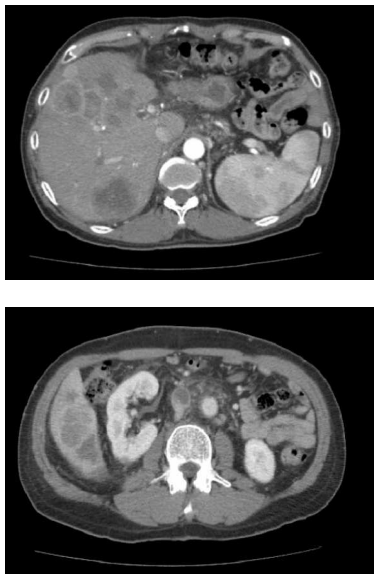
March 2019	April 2019	April 2019 – July 2020	September 2020	October 2020	January 2021	April 2021
Initial symptoms	Pancreatic head NEC	Treatment and response	CT scan showed progressive disease	Molecular profiling results and treatment	Partial response	Progressive disease; liquid biopsy results

Test results

January 2021



April 2021



Molecular profiling results

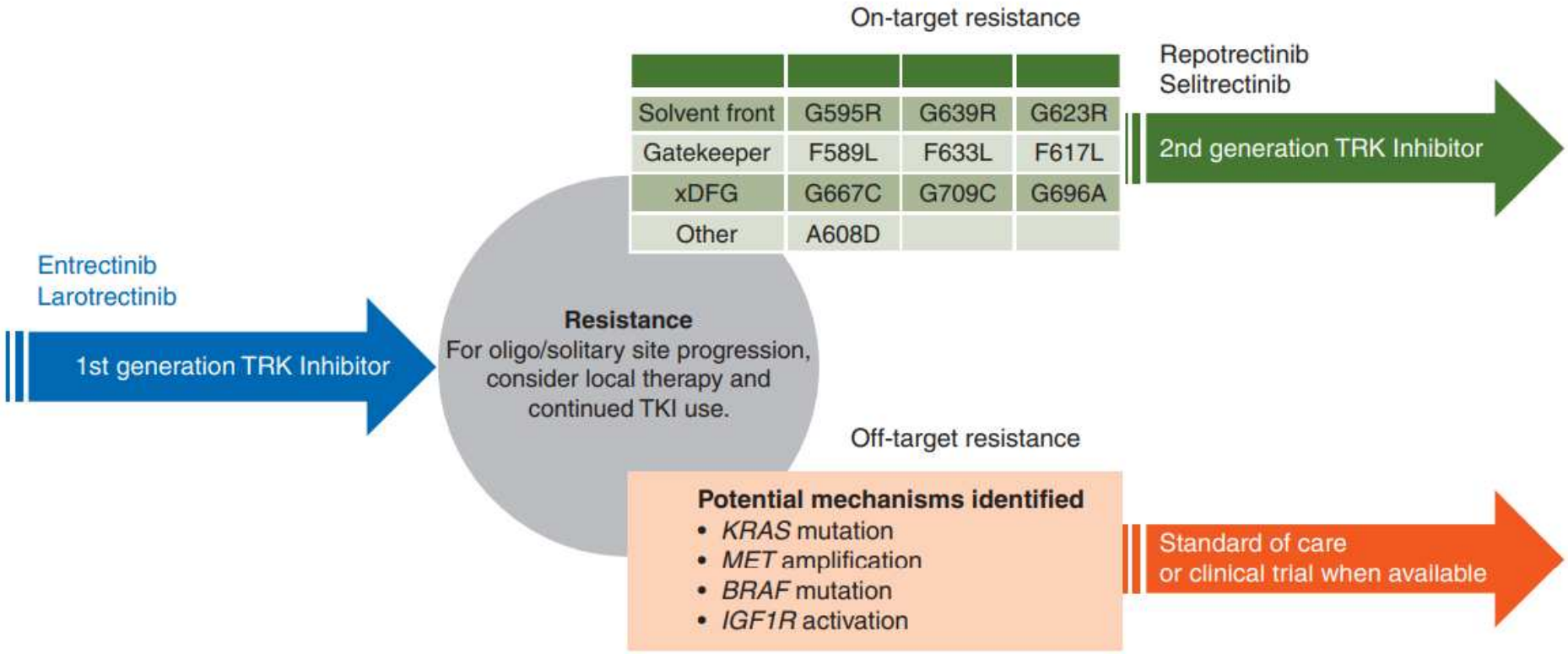
Results based on liquid-based CGP:

Genomic alterations	VAF%
ETV6-NTRK3 fusion	24.3%
NTRK3 G623R	5.3%
NTRK3 G623E	7.7%
*RB1 R320**	77%
*TP53 R213**	88.5%
BRCA2 rearrangement exon 14	0.15%

CDx: companion diagnostic; CT: computed tomography: NEC: neuroendocrine; Tx: treatment; VAF: variant allele frequency.
Case provided courtesy of Dr Ming-Huang Chen.

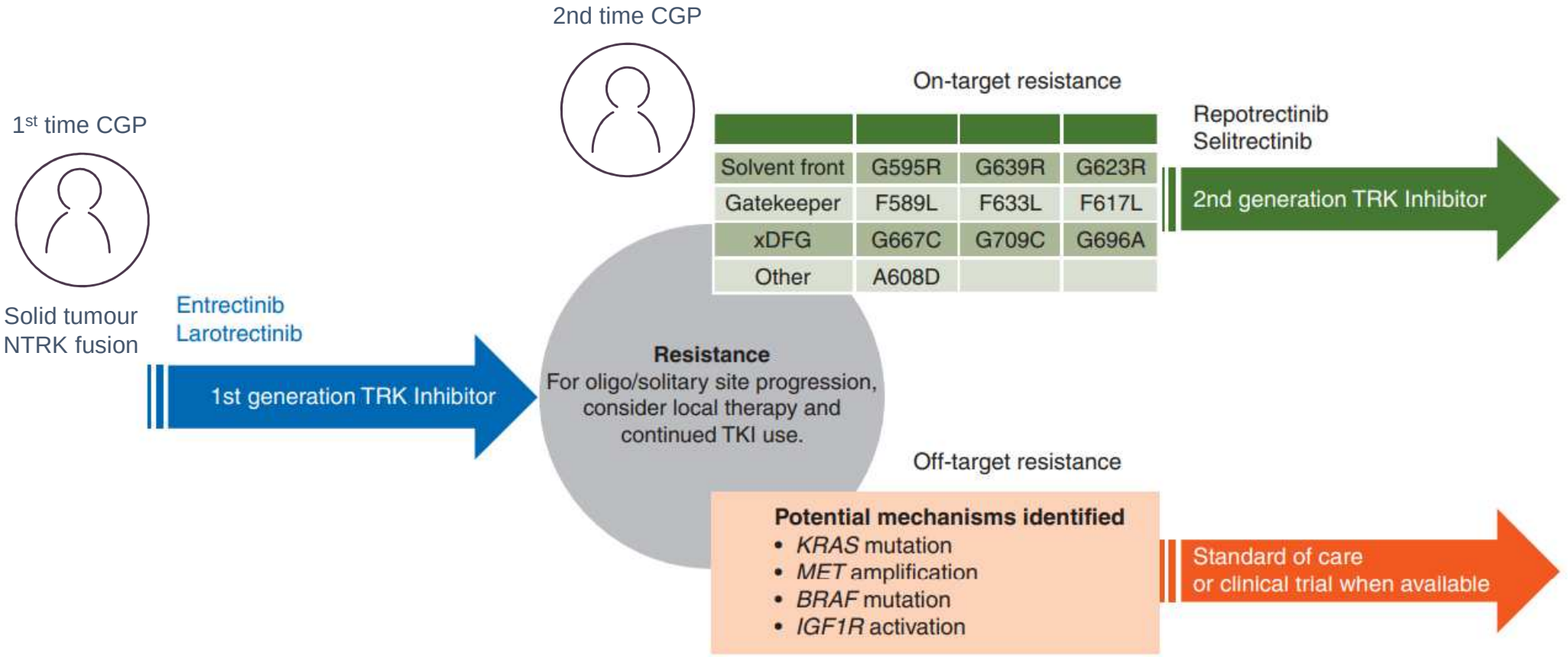
Potential resistance mechanism of NTRK inhibitors

Off-target resistance



Annals of Oncology 30 (Supplement 8): viii23–viii30, 2019 doi:10.1093/annonc/mdz282

Future Personalized Treatment (CGP after PD)



Annals of Oncology 30 (Supplement 8): viii23–viii30, 2019 doi:10.1093/annonc/mdz282

Conclusions

- Personalized therapy is the future therapy in cancer treatment.
- Comprehensive Gene profiling (CGP) is a key to success for personalized therapy
- *NTRK* fusion gene alterations happens in several cancer types and NTRK inhibitor, like entrectinib,

  demonstrate durable overall and intracranial responses, regardless of CNS status at baseline:
  - In patients without baseline CNS metastases, ORR was **62.1%** (17 CR) and median DoR was **29.0 months**
  - In patients with baseline CNS metastases, ORR was **57.7%** and median DoR was **17.2 months**

Bazhenova, et al. Presented at ESMO 2021 (Poster 533P)
NTRK, neurotrophic tyrosine receptor kinase

Thanks for Your Attention!