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A regulator's view on rare cancer drug development: Histology independent indications

Disclaimers

- the views presented are personal and may not be understood or quoted as being made on behalf of or reflecting the position of PEI, EMA or one of its committees or working parties

- data presented have been sourced from published literature

Road Map

- Introduction
  - What defines the disease and populations ?
    - global revolution of classical concepts
- Cases
  - **Keytruda** *(Pembrolizumab)* - Mismatch repair deficiency
  - **Vitrakvi** *(Larotrectinib)-* Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion proteins

    ✓ **paradigm change in regulatory decision making**
- Regulatory considerations

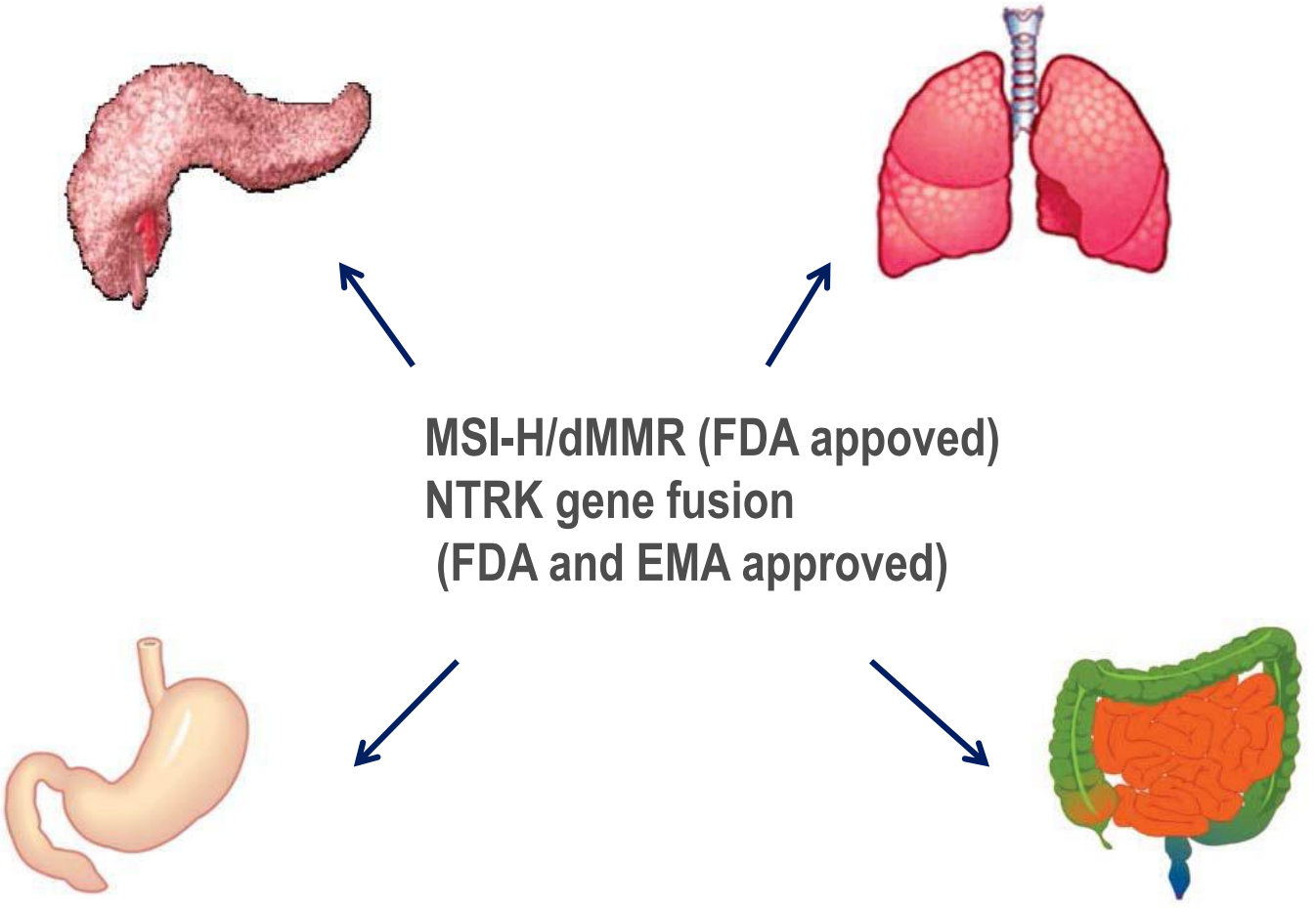
What defines the disease and populations

Traditional development paradigm

- Based on tumor type and line of therapy, e.g.,
  - Previously untreated advanced Non small cell Lung Cancer (NSCLC)
  - Hepato Cellular Carcinoma (HCC) after previous sorafenib treatment
- Based on a biomarker within a tumor type, e.g.,
  - HER-2 positive breast or gastric cancer
  - RAS wild-type colorectal cancer

Histology independent, not the organ, defines the indication

Similar indications, different histologies, anything in common?



Cases

- MSI-H/dMMR / Keytruda-Pembrolizumab
- NTRK gene fusion/ Vitrakvi-Larotrectinib

MSI-H/dMMR

- MSI-H = microsatellite instability
- dMMR = deficient mismatch repair

- Causes of dMMR/MSI-H:
  - Mutation in DNA repair proteins (e.g. Lynch syndrome)
    Inactivation of DNA repair proteins

→ Impairment in mismatch repair causes an increase of mutations (neo-antigens) as potential targets for the immune system

- Biological rationale:

• High mutational burden leads to high neoantigen expression

• High neoantigen expression leads to autologous immune

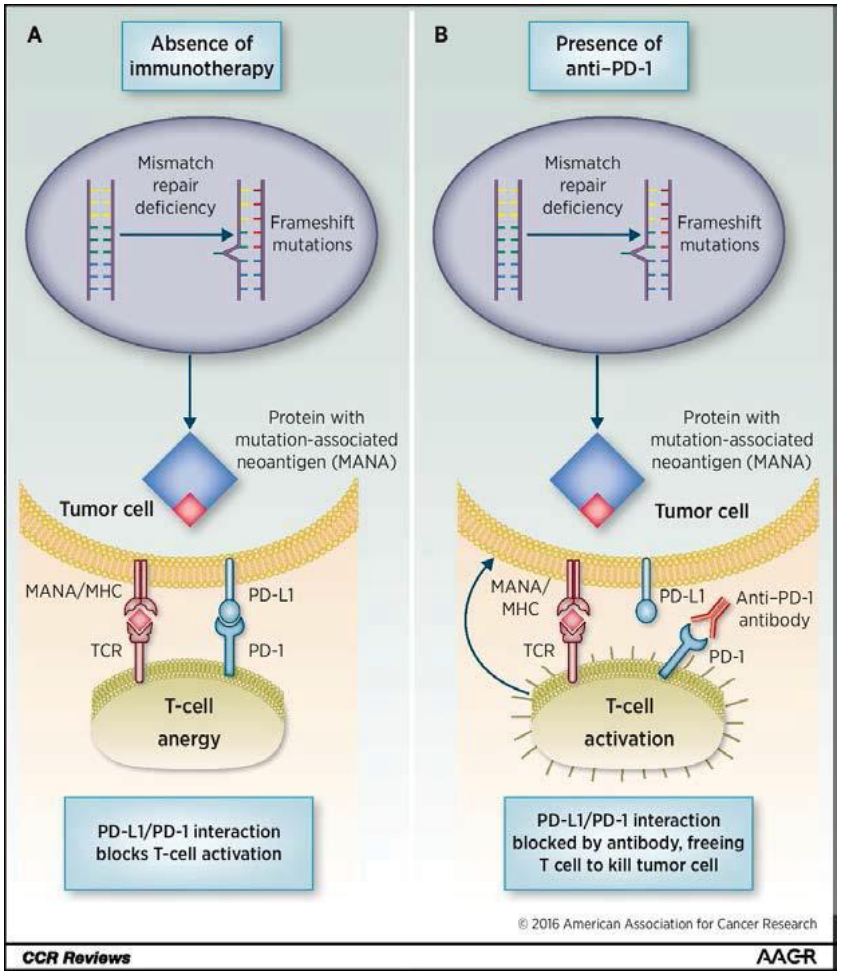
recognition of cancer cells

• By blocking PD-1 on tumor neoantigen-specific T cells,

pembrolizumab can activate anti-tumor immune responses

HYPOTHESIS:

PD-1 blockade with KEYTRUDA can restore effective anti-tumor immunity in MSI-H cancer, **regardless of cancer type**

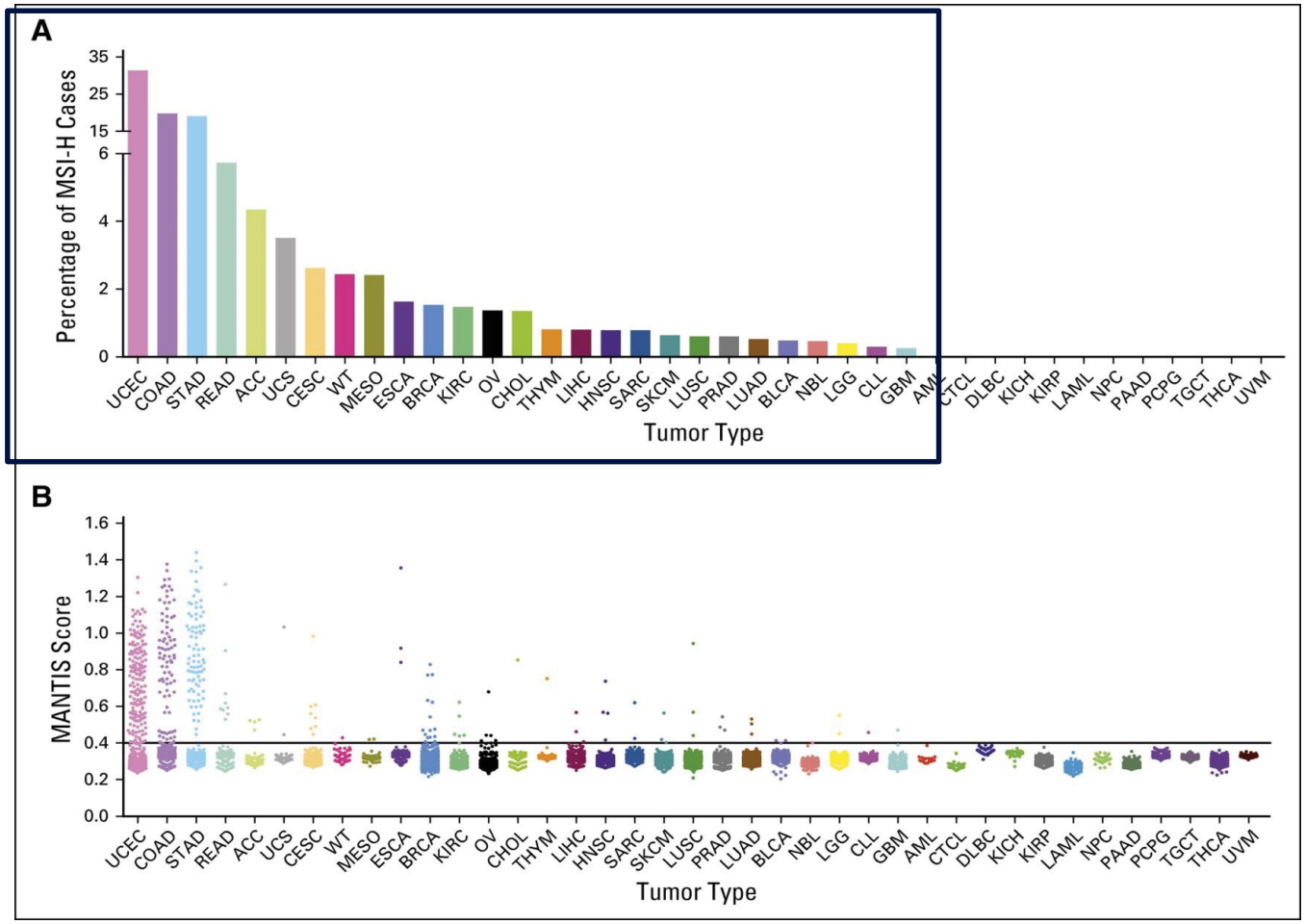


Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

How to demostrate MSI-H or MMR-deficiency

- Clinical testing of tumor tissues for the presence of MMR gene deficiency is standard practice in clinical oncology
- IHC on 4 MMR-proteins (MLH1, PMS2, MSH2 and MSH6)
- PCR-based microsatellite instability analysis
- MSI testing using Next-Generation Sequencing (NGS)
- Comprehensive mutation analysis by WGS

MSI-H in different tumor types



Bonneville et al., JCO Precision Oncology, 2017

Data supporting pembrolizumab approval

- data from 149 patients with MSI-H/dMMR solid tumor
- Most patients (84% for colorectal cancer and 53% for other tumors) had received two or more therapies for metastatic or unresectable disease
- KEYNOTE-16 

Phase 2 in patients with MSI-H tumors

Cohort A
MSI-H/dMMR
n=40

Cohort B
MSS/pMMR
n= 25

colorectal cancers

Cohort C
MSI-H/dMMR
n=40

non-colorectal

Primary endpoint: ORR; Secondary endpoints: PFS by RECIST v1.1, and OS

Data supporting pembrolizumab approval

Study	Design	Number	Prior treatments
KEYNOTE-016	• prospective, investigator-initiated • patients with CRC and other tumors (basket)	28 CRC 30 non-CRC	• CRC: ≥ 2 prior regimens • Non-CRC: ≥1 prior regimen
KEYNOTE-164	• prospective, international • CRC	61	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR
KEYNOTE-012	retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer	6	≥1 prior regimen
KEYNOTE-028	retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC	5	≥1 prior regimen
KEYNOTE-158	• prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC • retrospectively identified patients *who were enrolled in specific rare tumor non-CRC cohorts*	19	1 prior regimen

Data supporting pembrolizumab approval

- Pooled analysis:
  - Primary efficacy endpoint across trials: ORR
  - Key secondary efficacy endpoint: Duration of response

	N=149
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate CR	7.4%
Partial response rate PR	32,2%
DOR Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

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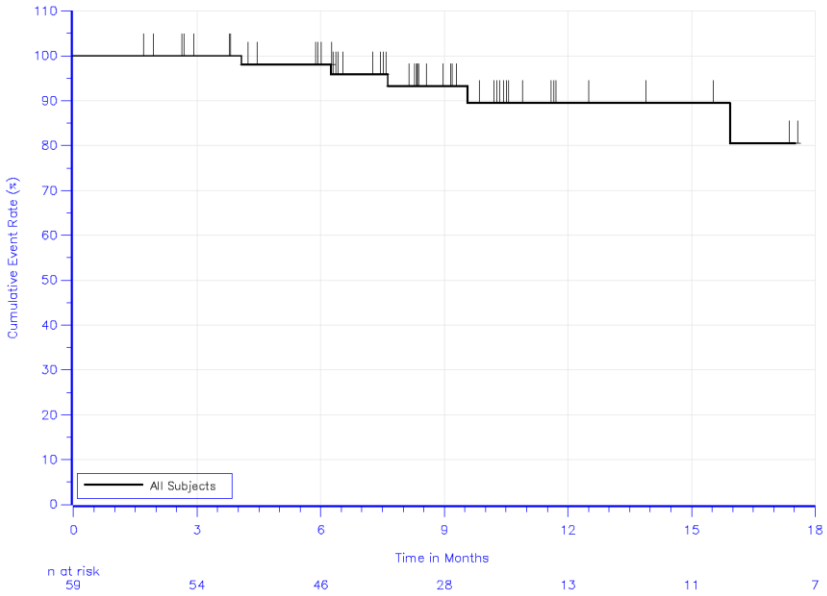


Data supporting pembrolizumab approval

	N	Objective response rate n (%)	95% CI
CRC	90	32(36%)	(26%, 46%)
Non-CRC	59	27 (46%)	(33%, 59%)
Endometrial cancer	14	5 (36%)	(13%, 65%)
Biliary cancer	11	3 (27%)	(6%, 61%)
Gastric or Gejunction cancer	9	5 (56%)	(21%, 86%)
Pancreatic cancer	6	5 (83%)	(36%, 100%)
Small intestinal cancer	8	3 (38%)	(9%, 76%)
Breast cancer	2	PR,PR	
Prostate cancer	2	PR,SD	
Bladder cancer	1	NE	
Esophageal cancer	1	PR	
Sarcoma	1	PD	
Thyrioid cancer	1	NE	
Retroperitoneal adenocarcinoma	1	PR	
Small cell lung cancer	1	CR	
Renal cell cancer	1	PD	

FDA considerations

Approved for MSI-H or dMMR Patients Whose Disease Has Progressed Following Prior Treatment and Who Have No Satisfactory Alternative Treatment Options, Which Includes Patients with Colorectal Cancer That Has Progressed Following Treatment with Fluoropyrimidine, Oxaliplatin, and Irinotecan

- Strong scientific/biological rationale
- Compelling clinical data
- Extensive history of clinical use / safety profile
- Favorable risk/benefit profile with similar ORR in other indications
- **Approved for patients without available therapies**

Regulatory considerations (EU perspective)

Is an histology independent approval justifiable in MSI-H?

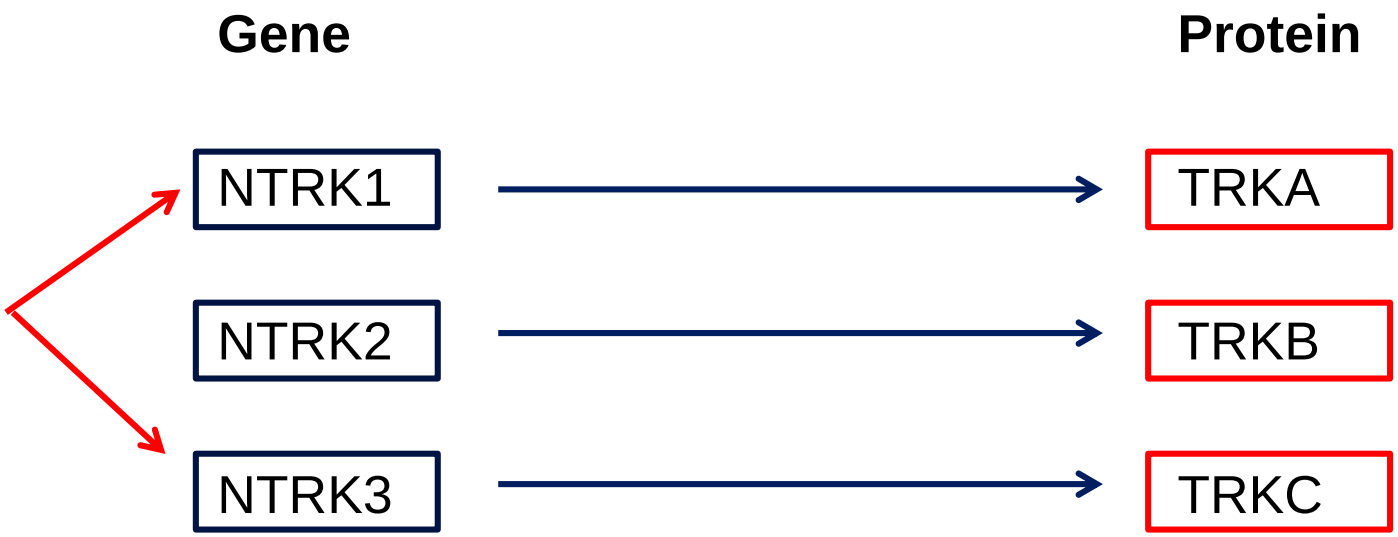
- Etablished MoA (preclinical data proof of principle) ???
- MoA tumor tissue independent ???
- Validated biomarker √
- Clinical proof of priciple (Pivotal randomized study?) Activity across tumor types ???
- Clinical safety √
- Unmed medical need √

Cases

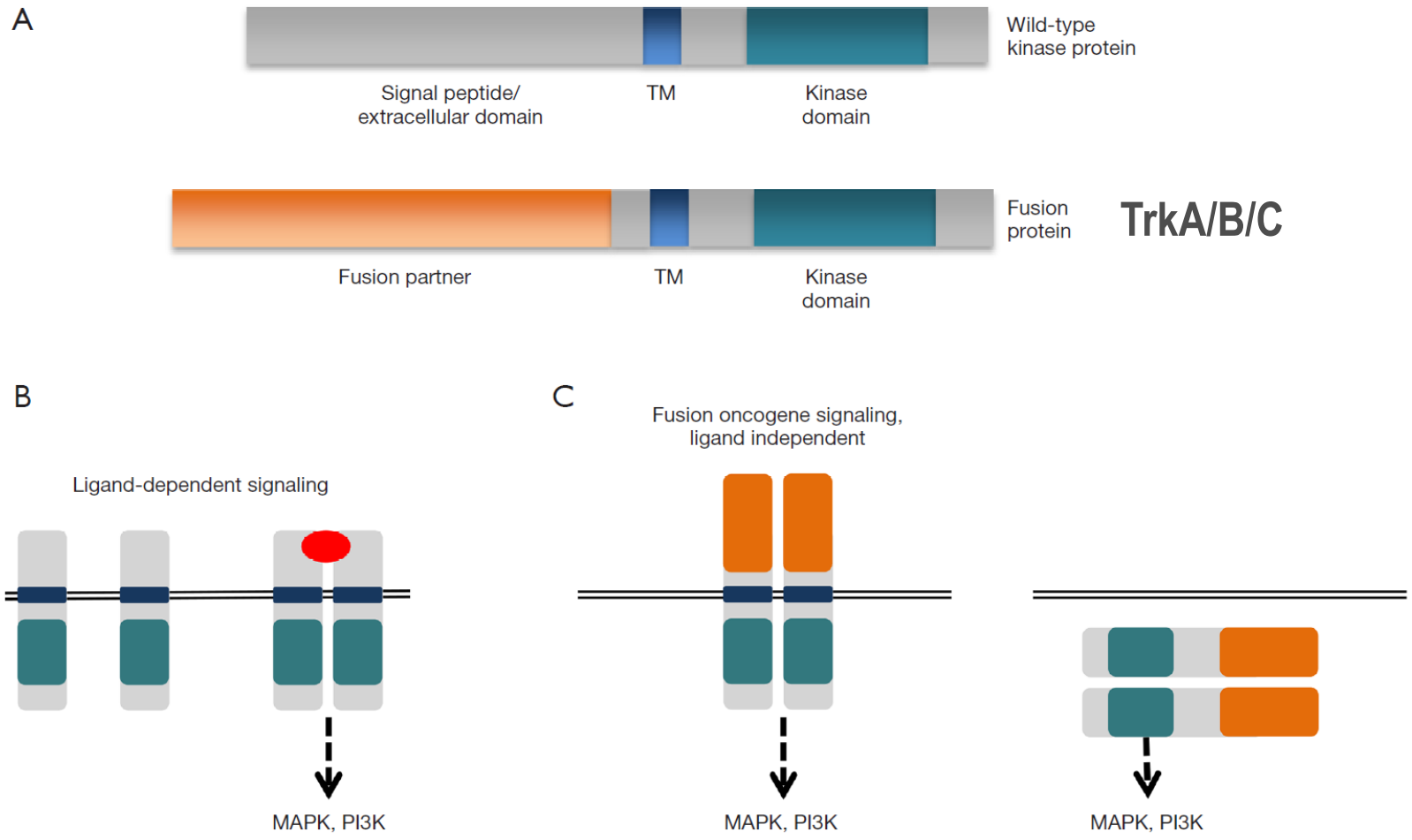
- MSI-H/dMMR
- NTRK gene fusion

NTRK gene fusion

- Terminology



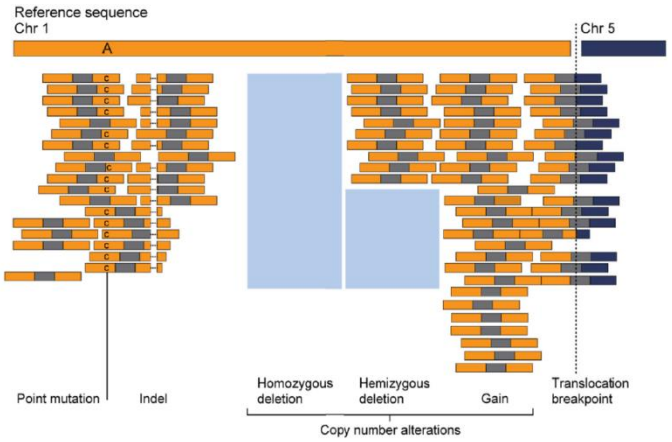
NTRK gene fusion



Source: Farago et al. Translational Lung Cancer Research, Vol 6, No 5 October 2017

Clinical Detection of NTRK Gene Fusions

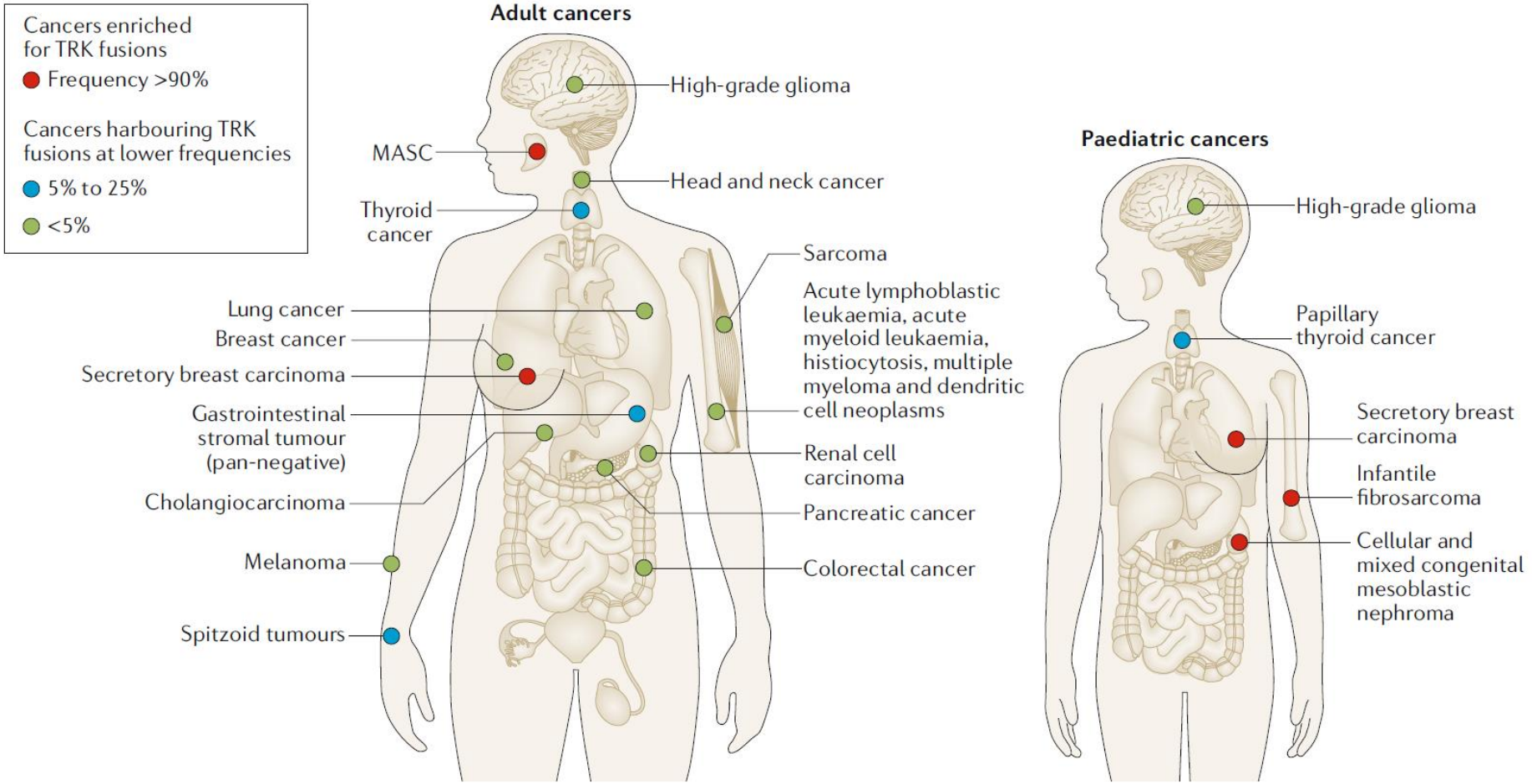
- No companion diagnostics available
- NTRK gene fusions detection via Next generation sequencing



Meyerson et al. Nat Rev Genet 2010;11

- IHC (TRKA/B/C)
- DNA FISH can be used to detect NTRK gene fusions; however, in order to detect fusions at multiple locations, such as the 3 NTRK genes, multiple FISH tests would need to be run.

Prevalence of NTRK gene fusion



Source : Cocco et al. Nature Reviews Clinical Oncology Dez 2018

Data supporting larotrectinib approval

Study	Design	Number	Endpoints
LOXO-TRK-14001 8 sites US	Phase 1, open-label, 3 + 3 dose escalation study with expansion phase in patients with NTRK gene fusions only	8	Primary : Safety, MTD, RP2D. Secondary: ORR (CR + PR) Duration of response
LOXO-TRK-15002 21 sites US, EU, Asia	Phase 2, open-label “basket” study	63 Non-small cell lung cancer 6 Thyroid 9 Sarcoma 12 Colorectal 6 Salivary gland14 Biliary 2 Primary CNS 3 Others 11	Primary :ORR (CR + PR) Secondary: BOR, DOR, PFS, OS, Quality of life Safety
LOXO-TRK-15003 17 sites US, EU, Australia	Phase 1, open-label, dose escalation study Phase 2, single arm open-label study in IFS, other extracranial solid tumours, and primary CNS tumours	43	Phase 1 Primary: Safety, DLT Secondary: BOR, DOR Quality of life Safety Phase 2 Primary: ORR Secondary: DOR, Safety

Data supporting larotrectinib approval

- Pooled analysis:

  Primary efficacy endpoint across trials: ORR

  Key secondary efficacy endpoint: Duration of response

	N=55
ORR (95% CI)	75% (61, 85)
Complete response rate CR	22%
Partial response rate PR	53%
DOR Median in months (range)	NR (1.6+, 33,2+)
% with duration ≥6 months	73%

Data supporting larotrectinib approval

- Pooled analysis:

Primary efficacy endpoint across trials: ORR

	N=55 (PAS)
ORR (95% CI)	75% (61, 85)
Complete response rate CR	22%
Partial response rate PR	53%
DOR Median in months (range)	NR (1.6+, 33,2+)
% with duration ≥6 months	73%

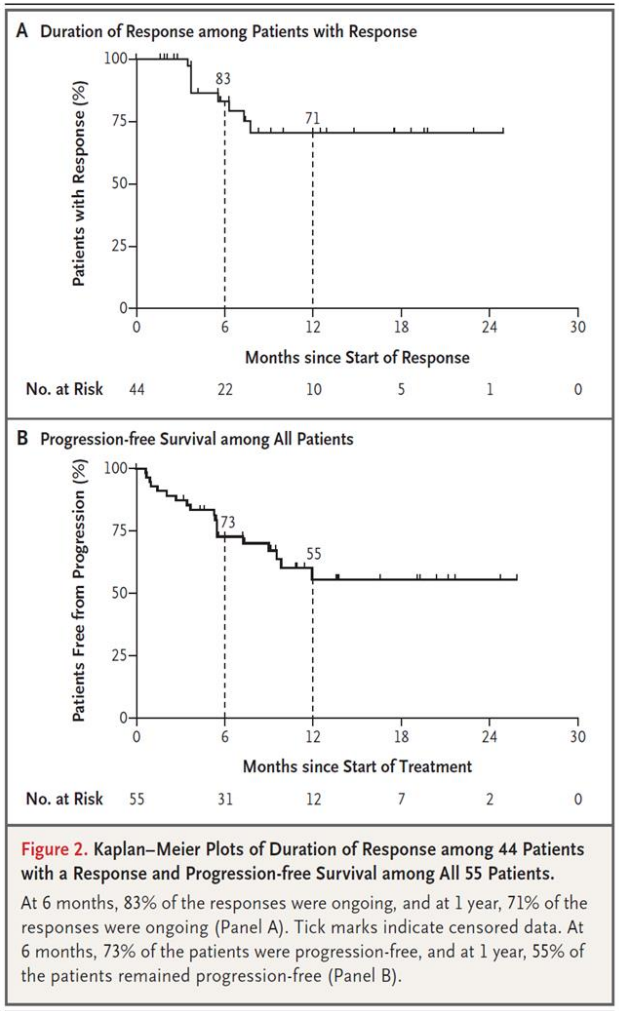


Figure 2. Kaplan–Meier Plots of Duration of Response among 44 Patients with a Response and Progression-free Survival among All 55 Patients.

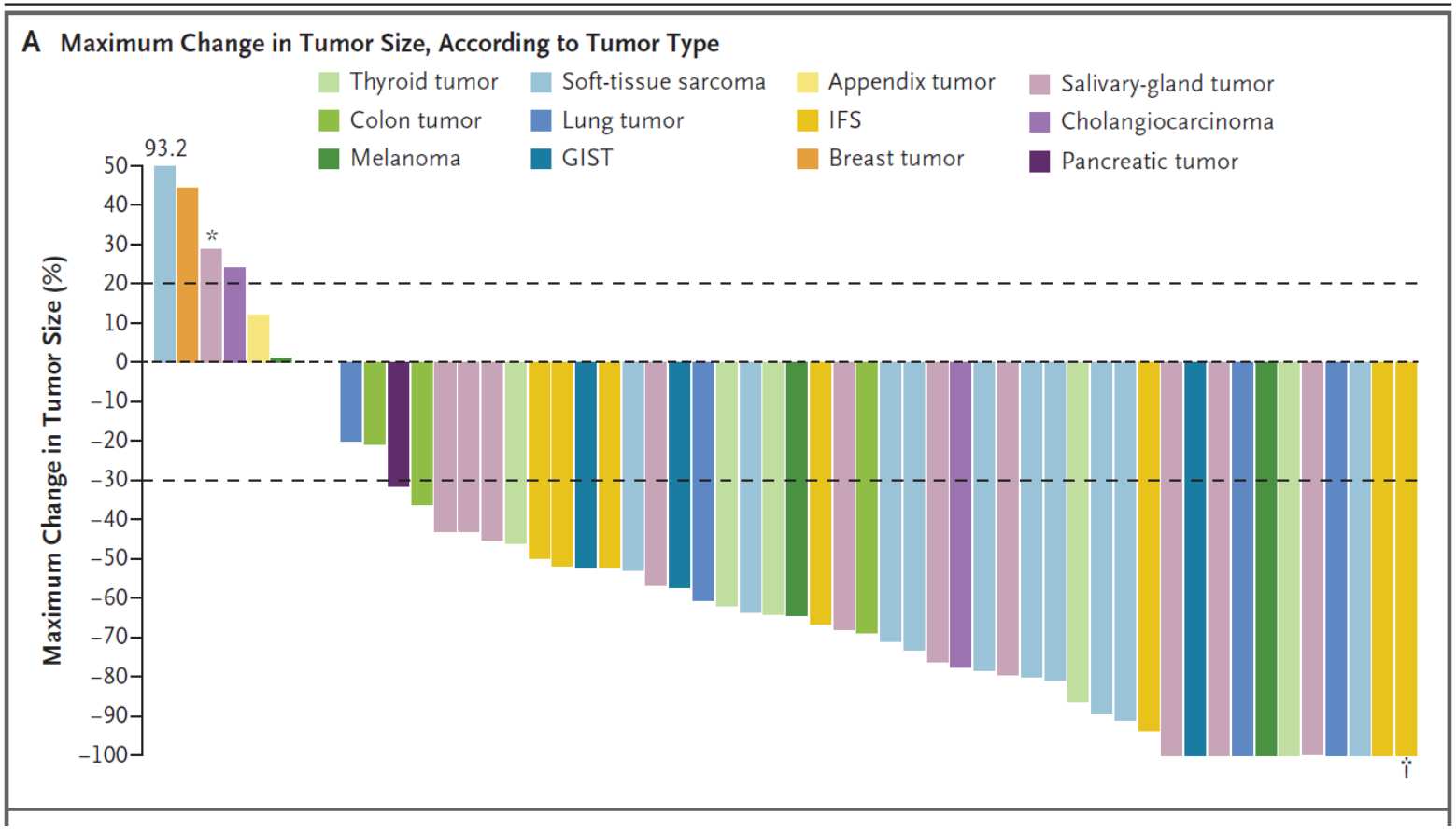
At 6 months, 83% of the responses were ongoing, and at 1 year, 71% of the responses were ongoing (Panel A). Tick marks indicate censored data. At 6 months, 73% of the patients were progression-free, and at 1 year, 55% of the patients remained progression-free (Panel B).

From Drilon et al NEJM, 2018

Data supporting larotrectinib approval

	N	Objective response rate (%)	95% CI
Soft tissue sarcoma	11	10(91%)	(59%, 100%)
Salivary gland	12	10 (83%)	(52%, 98%)
Infantile fibrosarcoma	7	7 (100%)	(59%, 100%)
Thyroid	5	5 (100%)	(48%, 100%)
Lung cancer	4	3 (75%)	(19%, 99%)
Melanoma	4	4 (83%)	NA
Colon cancer	4	1 (25%)	NA
GIST	3	3 (100%)	(29%,100%)
Cholangiocarcinoma	2	NE,SD	
Appendix	1	SD	
Breast cancer	1	PD	
Pancreas	1	SD	

Data supporting larotrectinib approval



From Drilon et al. NEJM, 2018

Regulatory considerations (EU perspective)

Is an histology independent approval justifiable in NTRK fusion positive Tumors?

- Etablished MoA (preclinical data proof of principle) √
- MoA tumor tissue independent ???
- Validated biomarker √
- Clinical proof of priciple (Pivotal randomized study?) Activity across tumor types ???
- Clinical safety √
- Unmed medical need √

FDA:

Vitrakvi is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment.

EMA:

“Vitrakvi as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion,
who have a disease that is *locally advanced*, metastatic or where surgical resection is likely to result in severe morbidity, and
who have no satisfactory treatment options (see sections 4.4 and 5.1).”

Regulatory Considerations

- Solid proof that MoA is tumor context independent is vital
- Such proof may be delivered with representative preclinical models
- These models should be rigorously validated
- Selected biomarker(s) for patient selection should be rigorously validated and cross-validated
- Clinical data to support the proposed MoA.
- Design of the pivotal trial depends on rarity of the condition