Histology Independent Drug Development Introduction and Successes

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NHS Foundation Trust

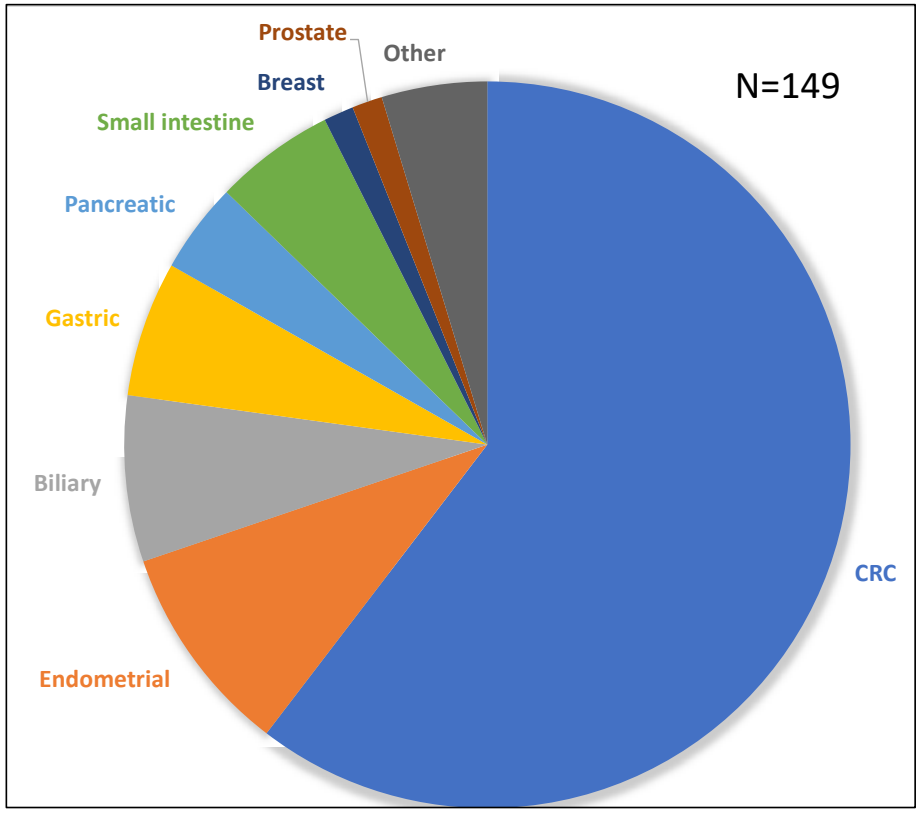
Newcastle University / Centre for Cancer

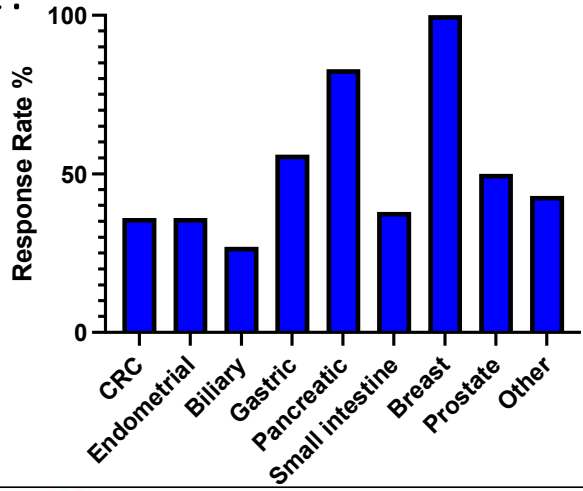
Histology Independent Therapy

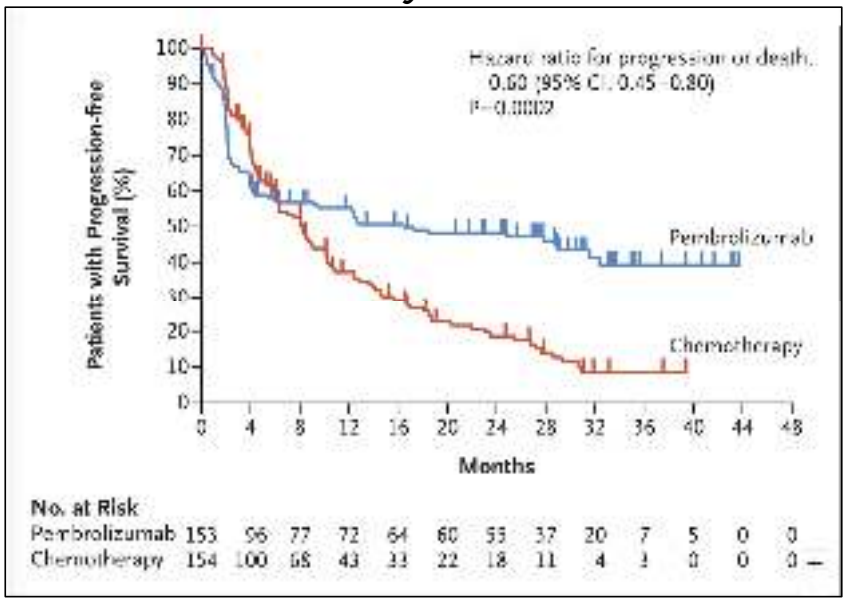
- Prevalent across all histologies?
- Activity identical across all histologies?
- Easy to find in standard of care testing?


2017
2021
2022
FDA approval
Pembrolizumab in
MSI-H/ MMR
FDA approval
Dostarlimab
in MSI-H/ MMR
EMEA approval
Pembrolizumab in
5 tumour types
with MSI-H/ MMR

Response to ICI in MSI-H- Histology Independent?







Lamery et al. N Engl J Med. 377(15), 2017, p 1409-1411

André et al. N Engl J Med. 2020 Dec 3;383(23):2207-2218. doi: 10.1056/NEJMoa2017699.

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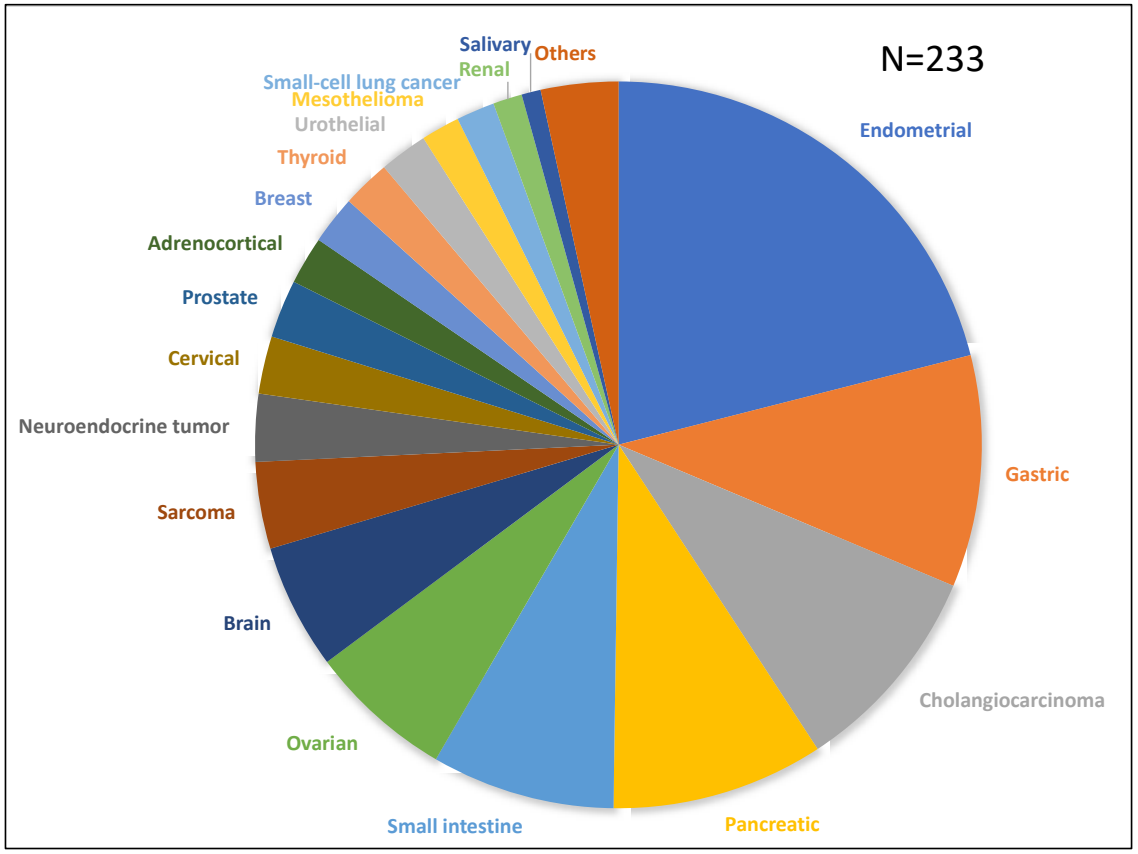
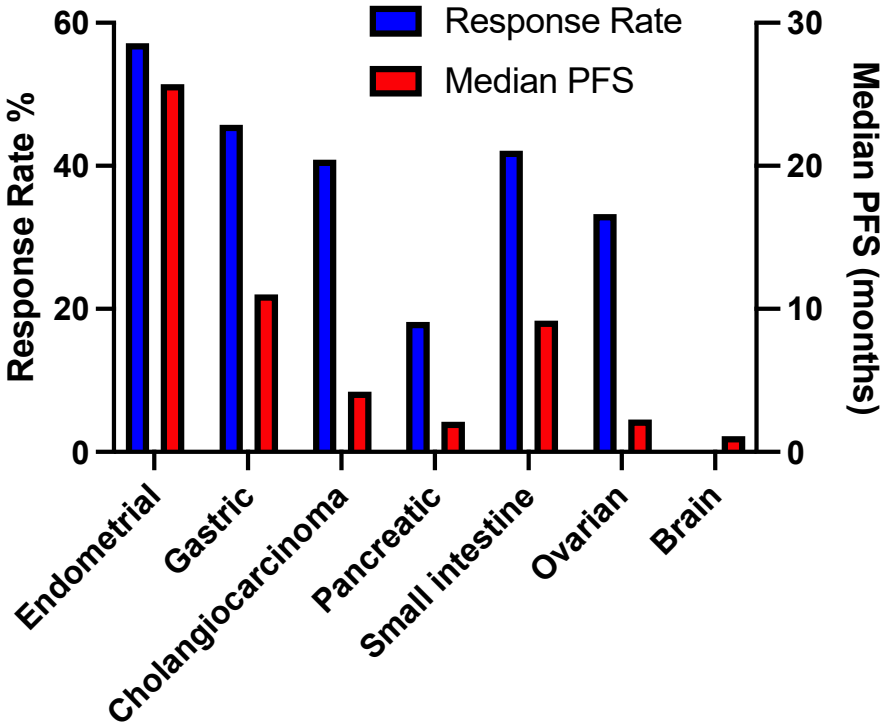
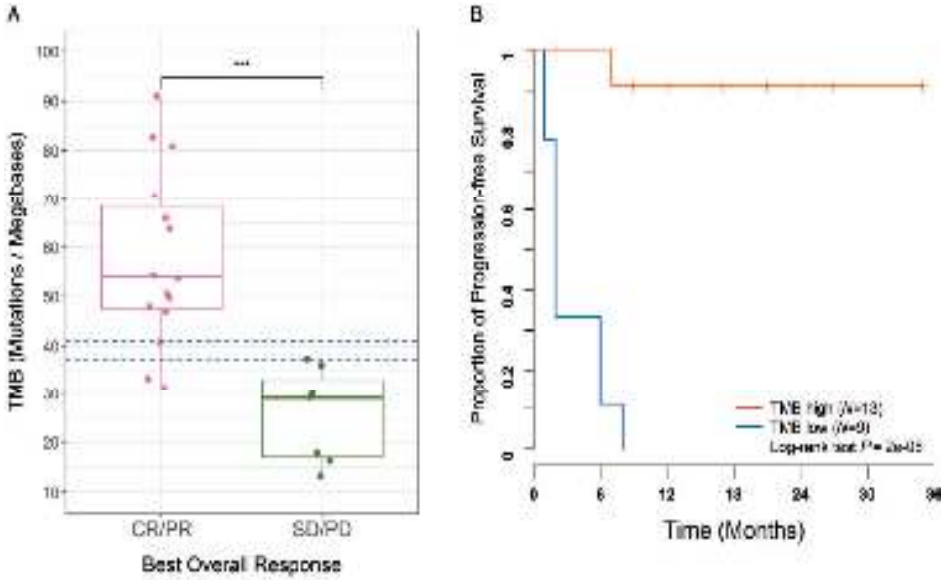




Marabelle et al. J Clin Oncol. 2020 Jan 1;38(1):1-10. doi: 10.1200/JCO.19.02105.

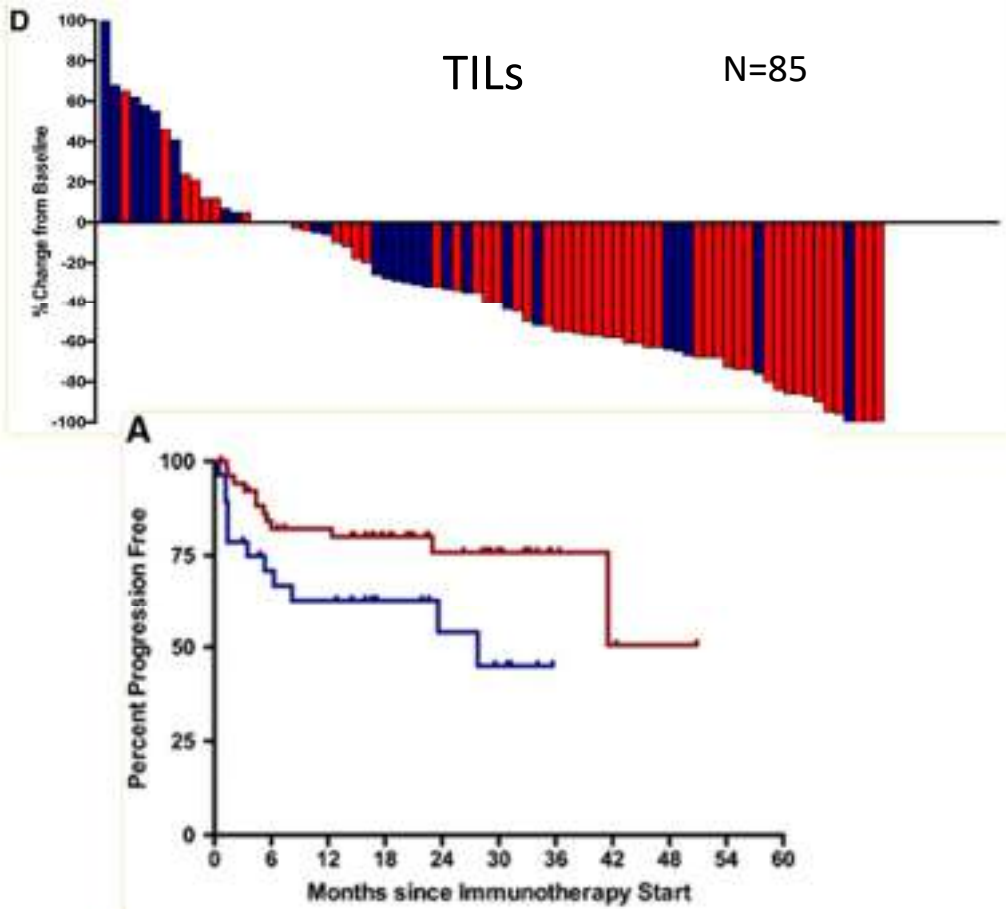
Is MSI-H the best biomarker?

TMB N=22



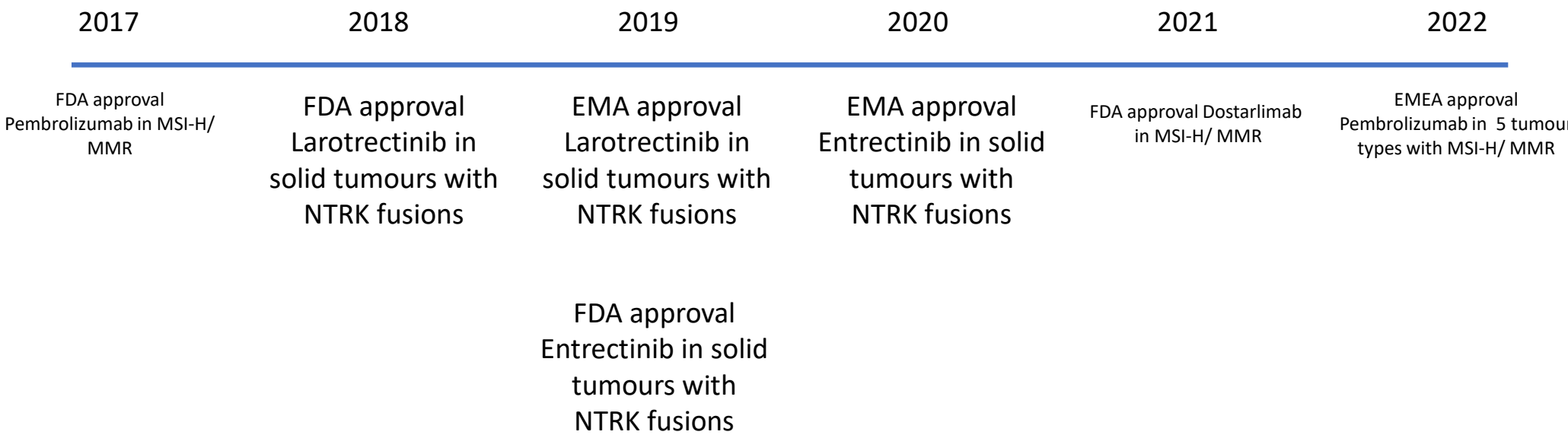
Shrock et al *Annals of Oncology* 2019 301096-1103DOI: (10.1093/annonc/mdz134)

TILs N=85



Loupakis F et al Oncologist. 2020 Jun;25(6):481-487. doi: 10.1634/theoncologist.2019-0611

	FDA Histology Independent Licensed Therapies	Prevalent across malignancies	Activity across malignancies	Ease of diagnosis
Microsatellite instability	Pembrolizumab, Dostarlimab			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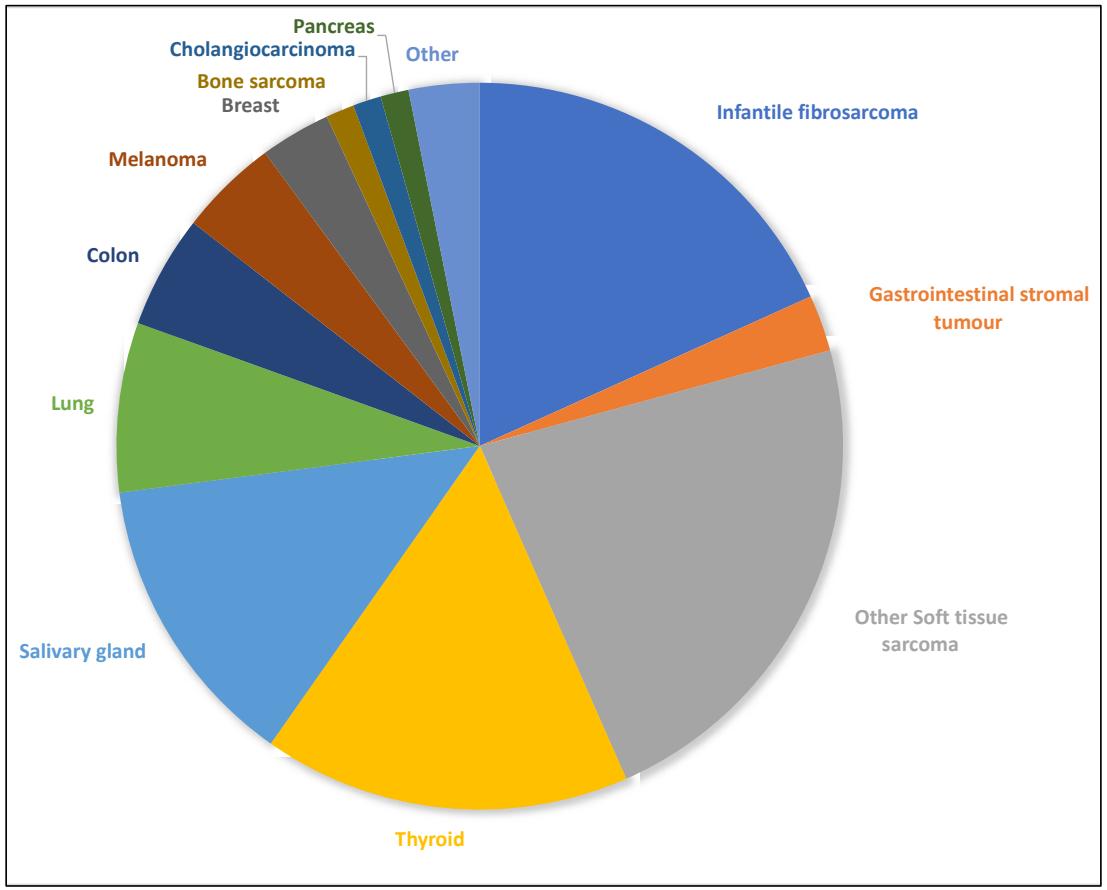
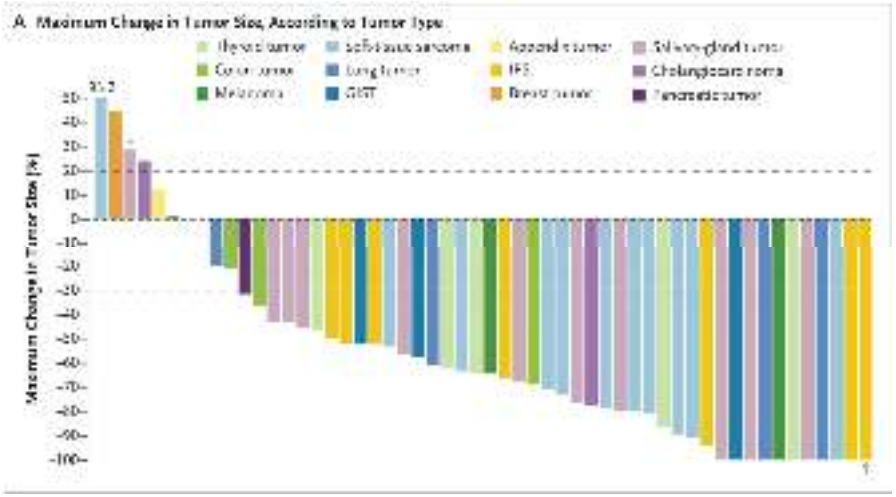
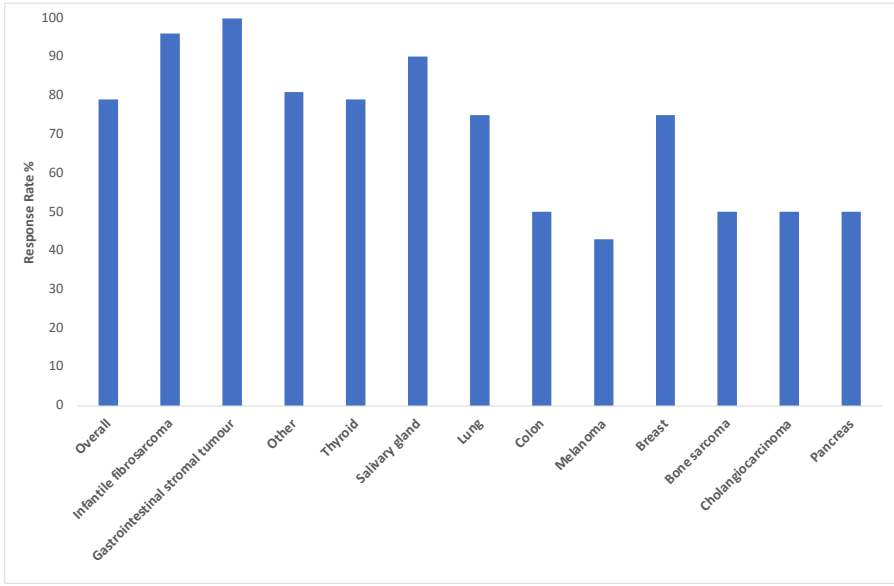
Larotrectinib in NTRK fusion Cancers







Hong et al Lancet Oncol. 2020 Apr;21(4):531-540. doi: 10.1016/S1470-2045(19)30856-3.

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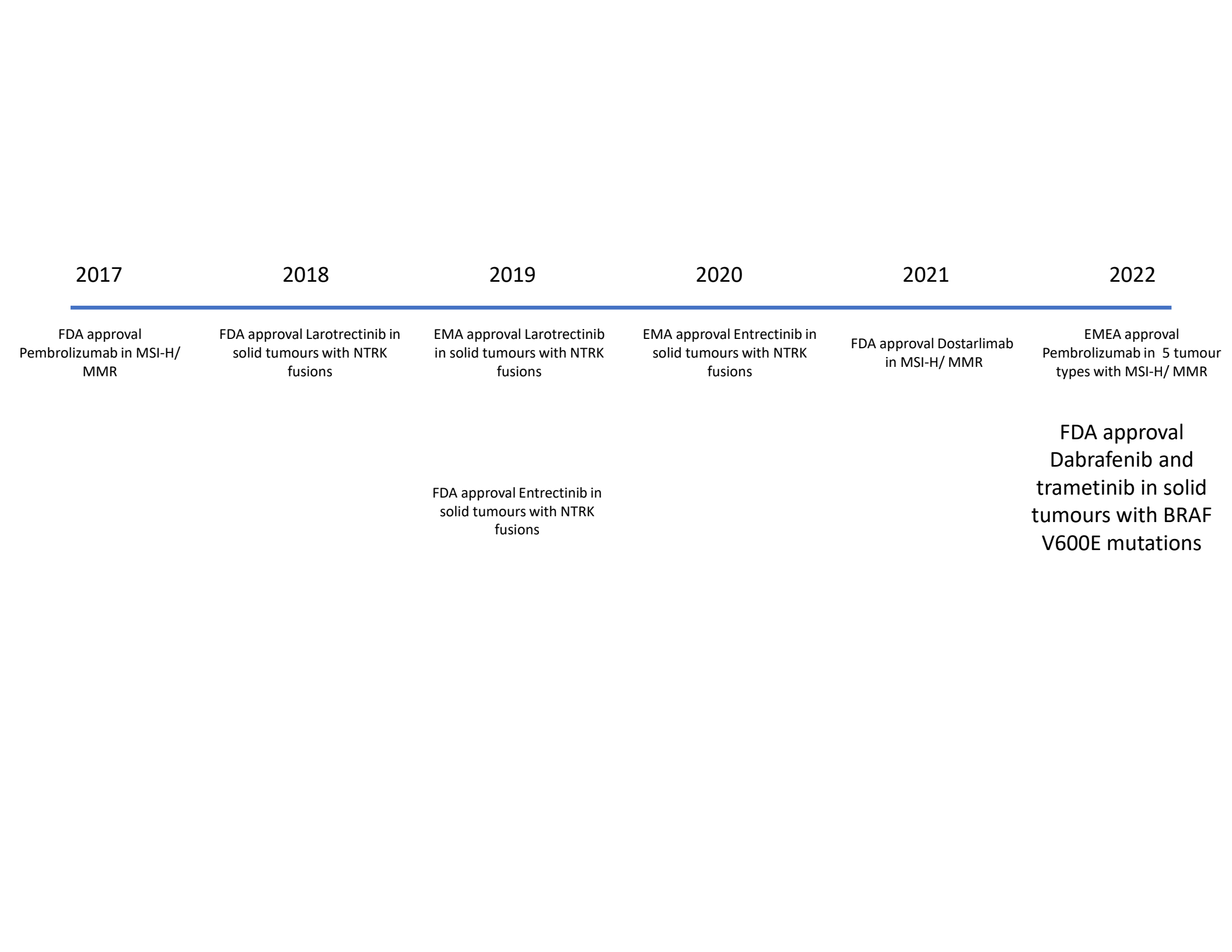
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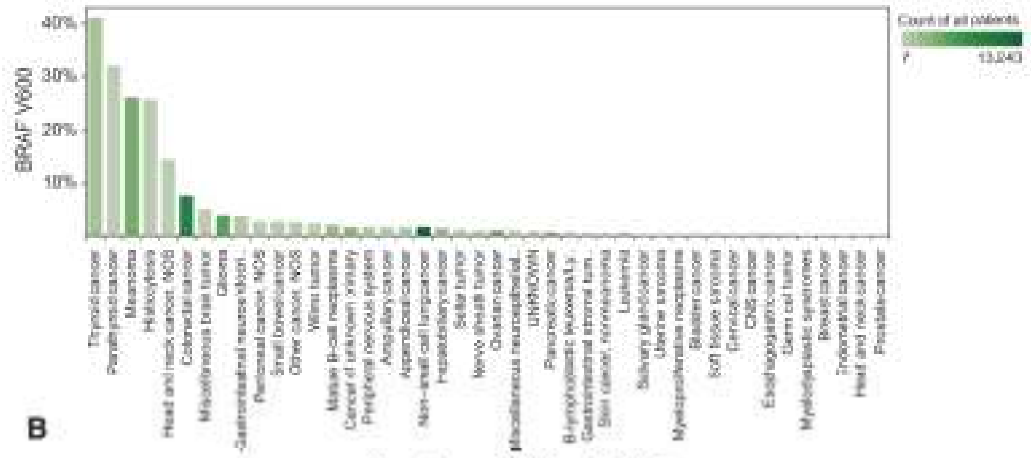
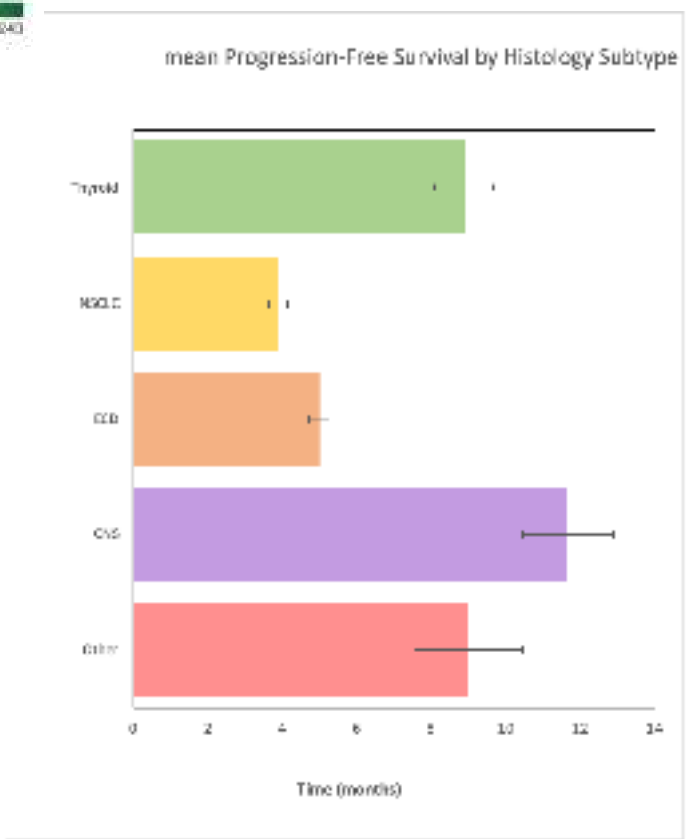
BRAF (/MEK) Inhibition in BRAF V600E



Drug/Combination	Nonmelanoma Indications (Date of FDA approval)
Dabrafenib plus trametinib	Metastatic NSCLC with BRAF V600E mutation (6/22/2017)
	Locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation and with no satisfactory locoregional treatment options (5/4/2018)
Vemurafenib alone	Treatment of patients with Erdheim-Chester disease with BRAF V600 mutation (7/6/2017)
Vemurafenib plus cobimetinib	No nonmelanoma indication
Encorafenib	In combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation (11/9/2020)
Encorafenib plus binimetinib	No nonmelanoma indication



Review of 178 pts

Adashek et al Mol Cancer Ther (2022) 21 (6): 871–878.
https://doi.org/10.1158/1535-7163.MCT-21-0950

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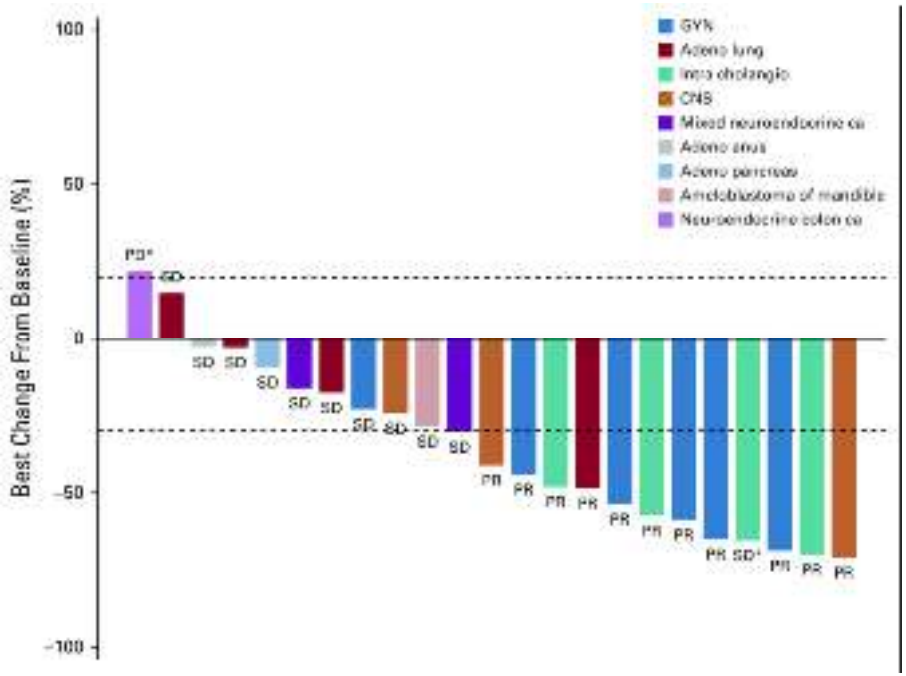
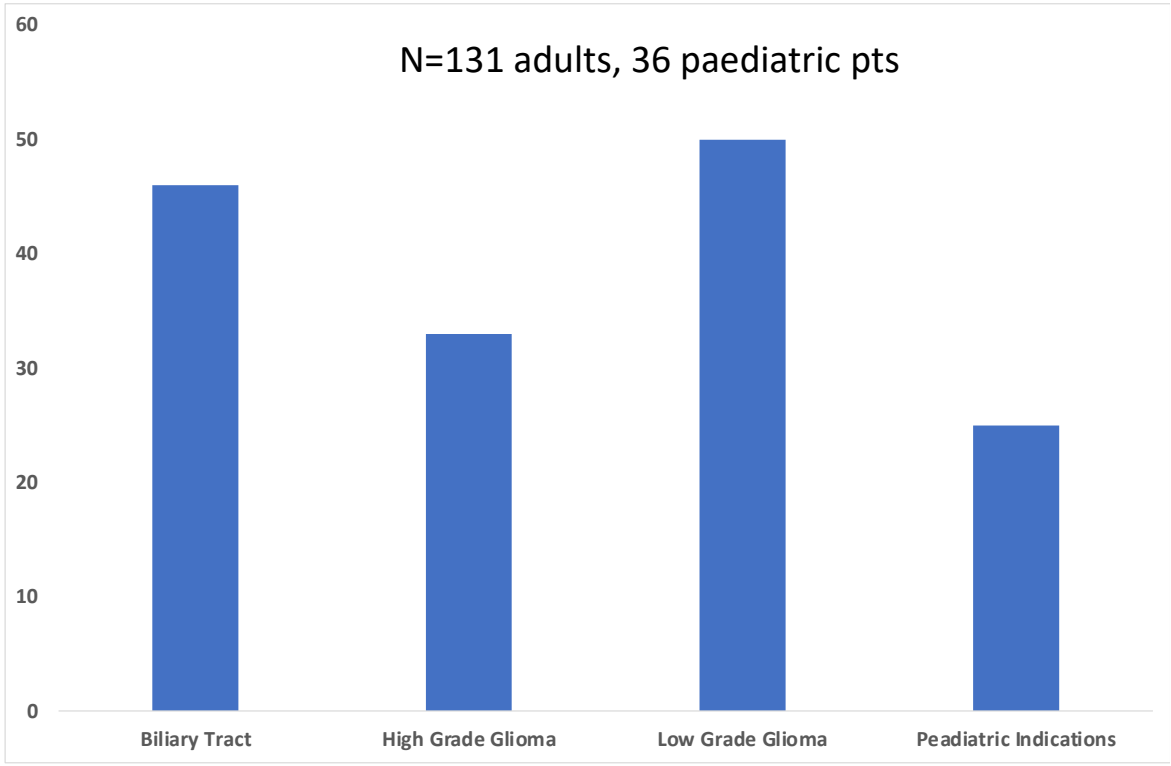
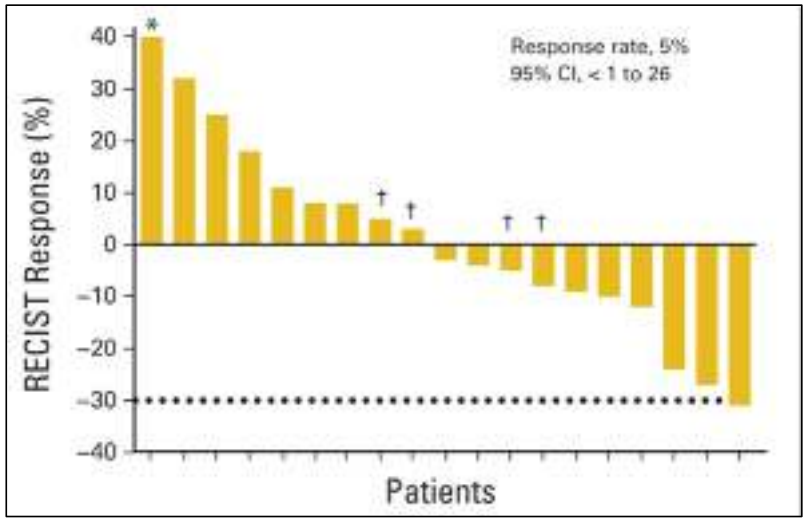


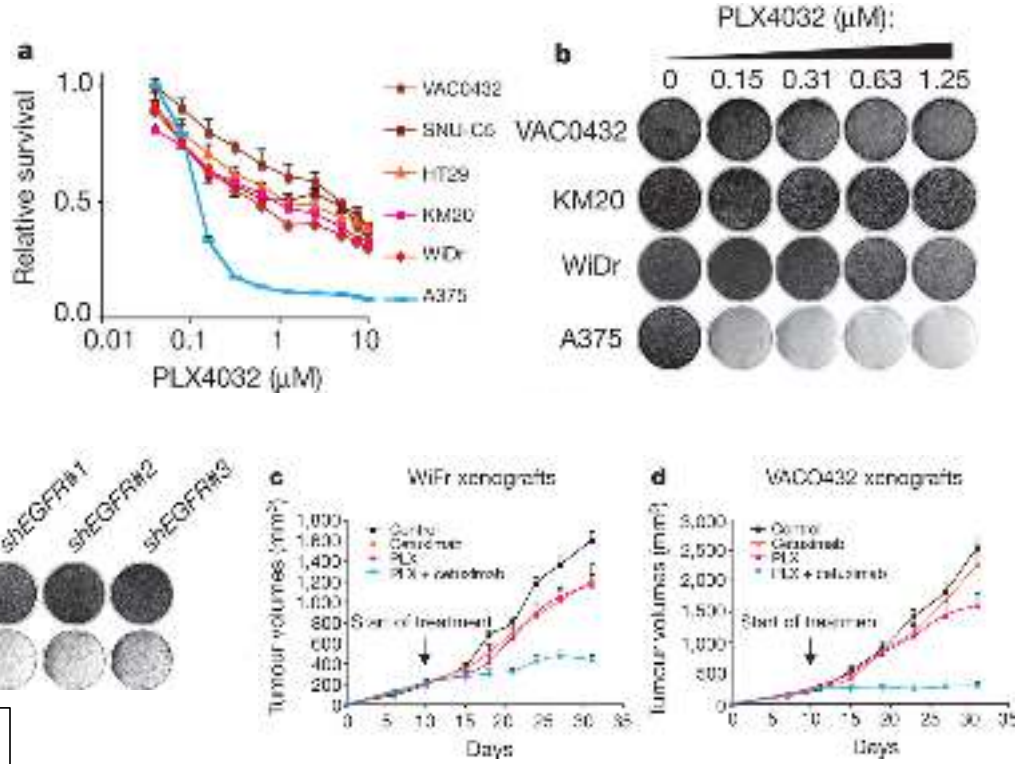


Salama et al J Clin Oncol. 2020 Nov 20;38(33):3895-3904.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid

BRAF (/MEK) Inhibition in BRAF V600E Colorectal Cancer





"Dabrafenib in combination with trametinib is not indicated for patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition"

Kopetz et al J Clin Oncol. 2015 Dec 1;33(34):4032-8. doi: 10.1200/JCO.2015.63.2497.

A Prahallad *et al. Nature* **000**, 1-5 (2012) doi:10.1038/nature10868

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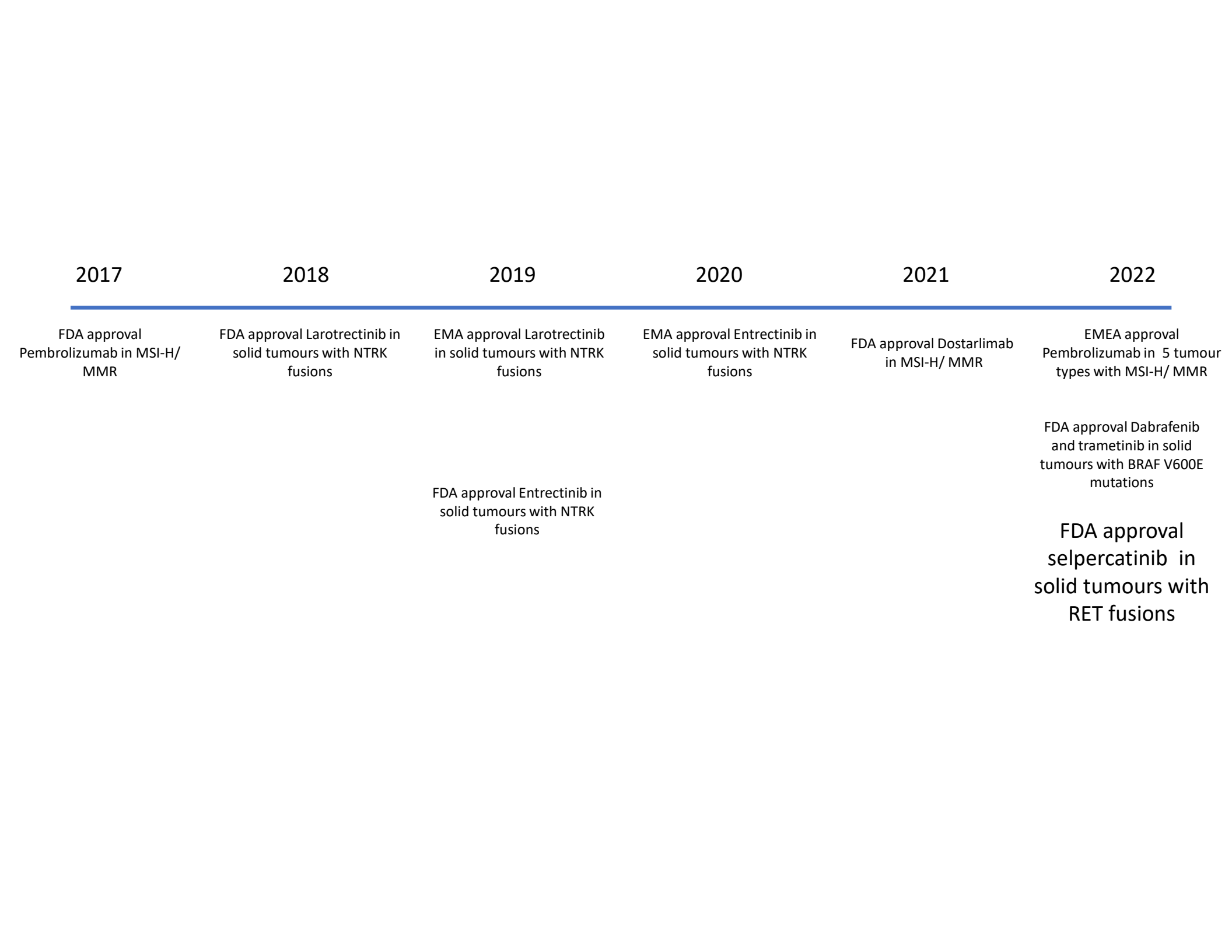
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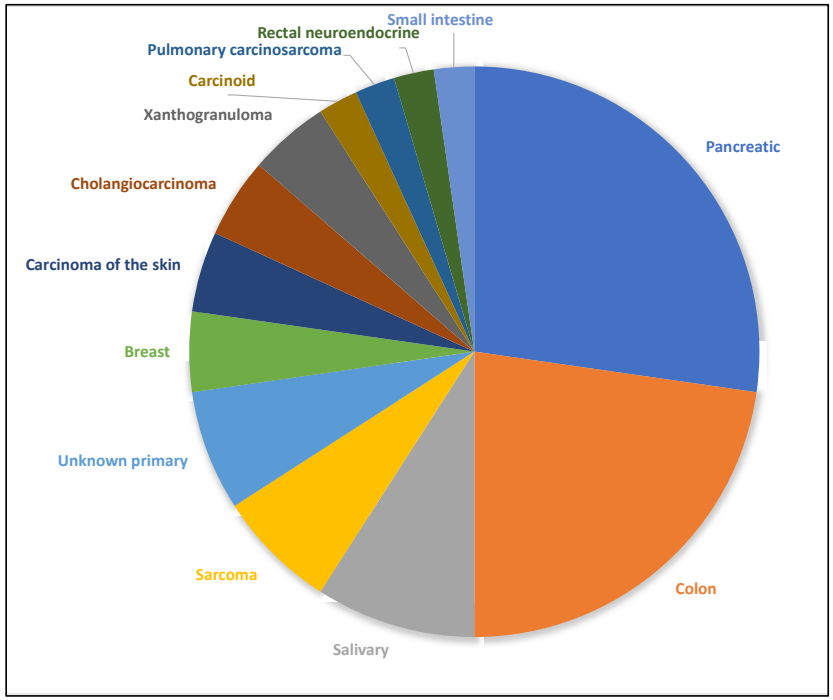
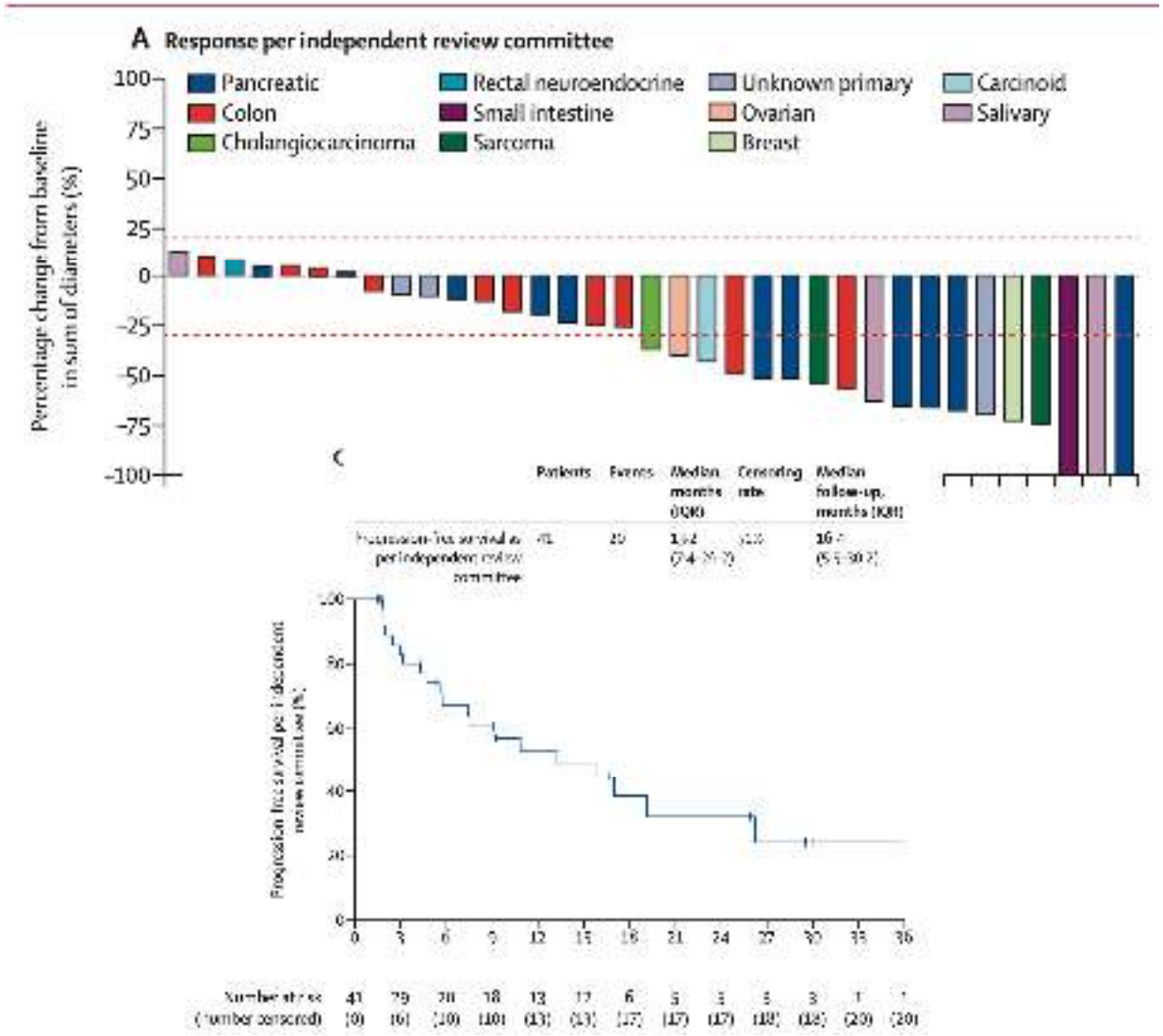
RET fusions

N= 46





Subbiah et al Lancet Oncol 2022; 23: 1261–73

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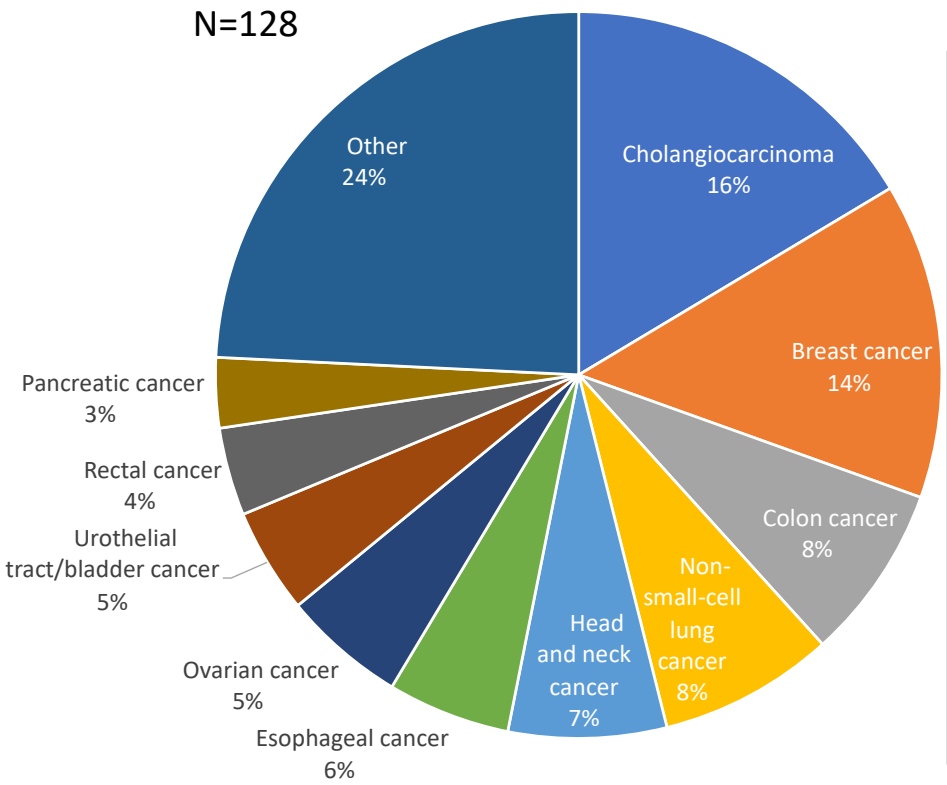
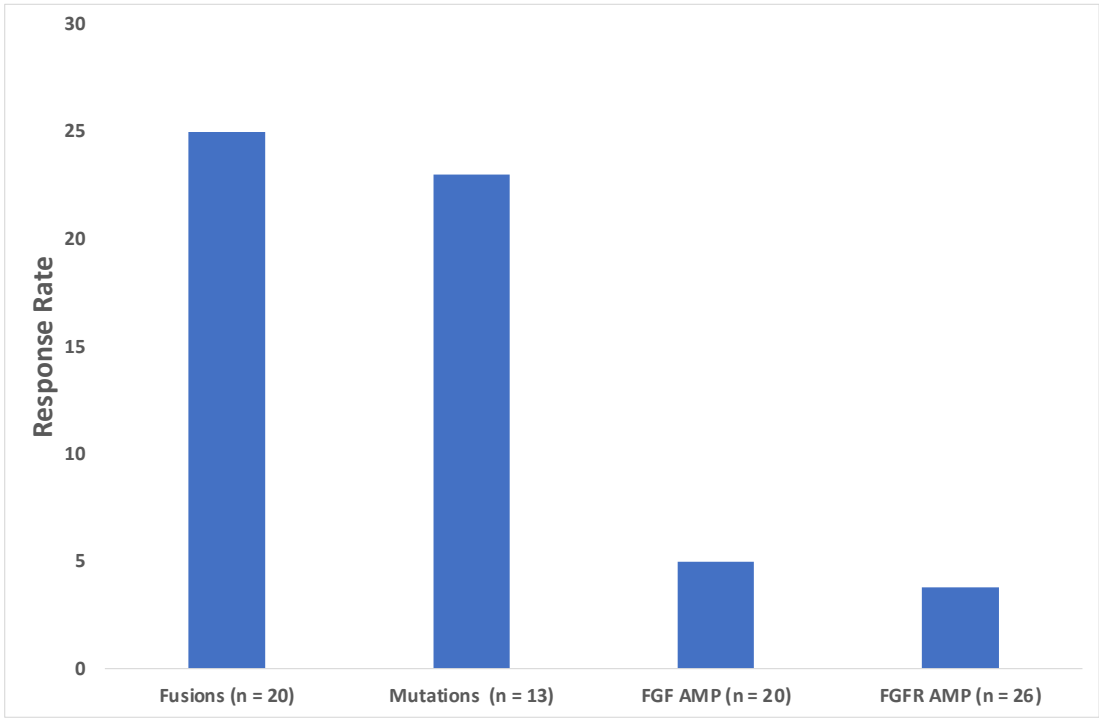
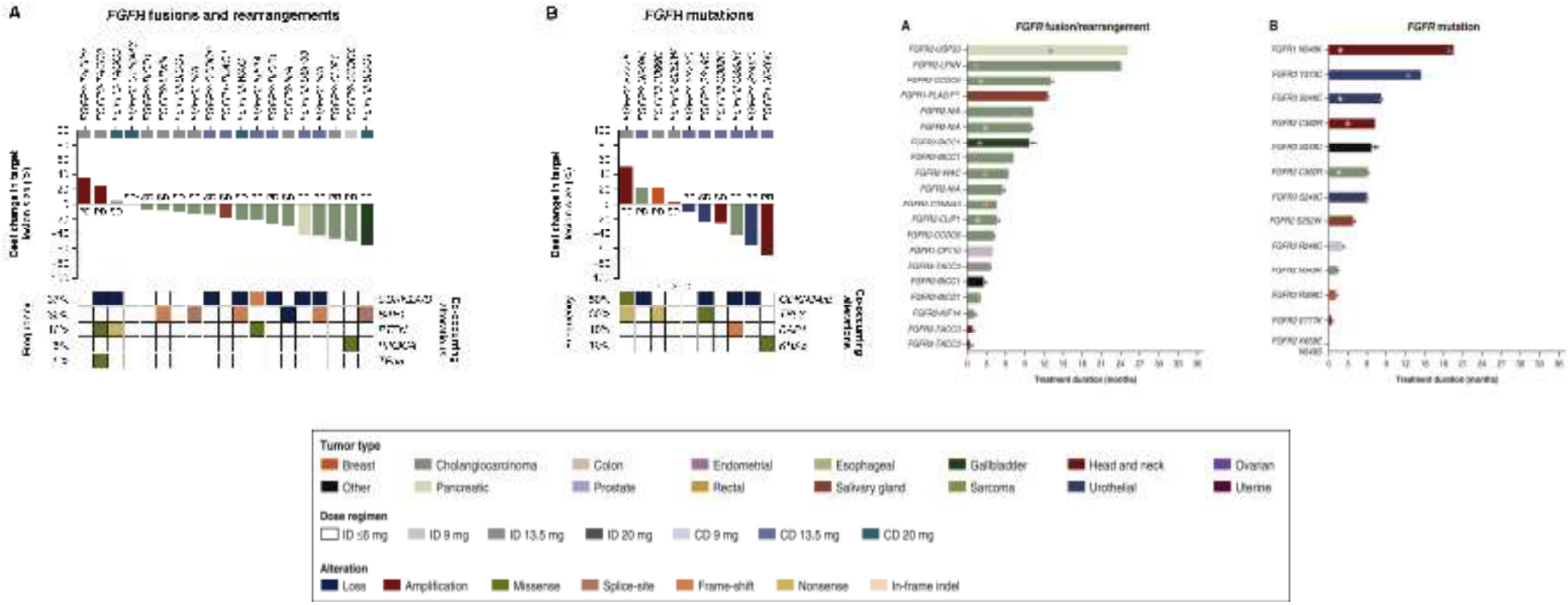
Whats next? FGF/FGFR abnormalities





Subbiah et al *Annals of Oncology* 2022 33522-533
DOI: (10.1016/j.annonc.2022.02.001)

FGF/FGFR abnormalities



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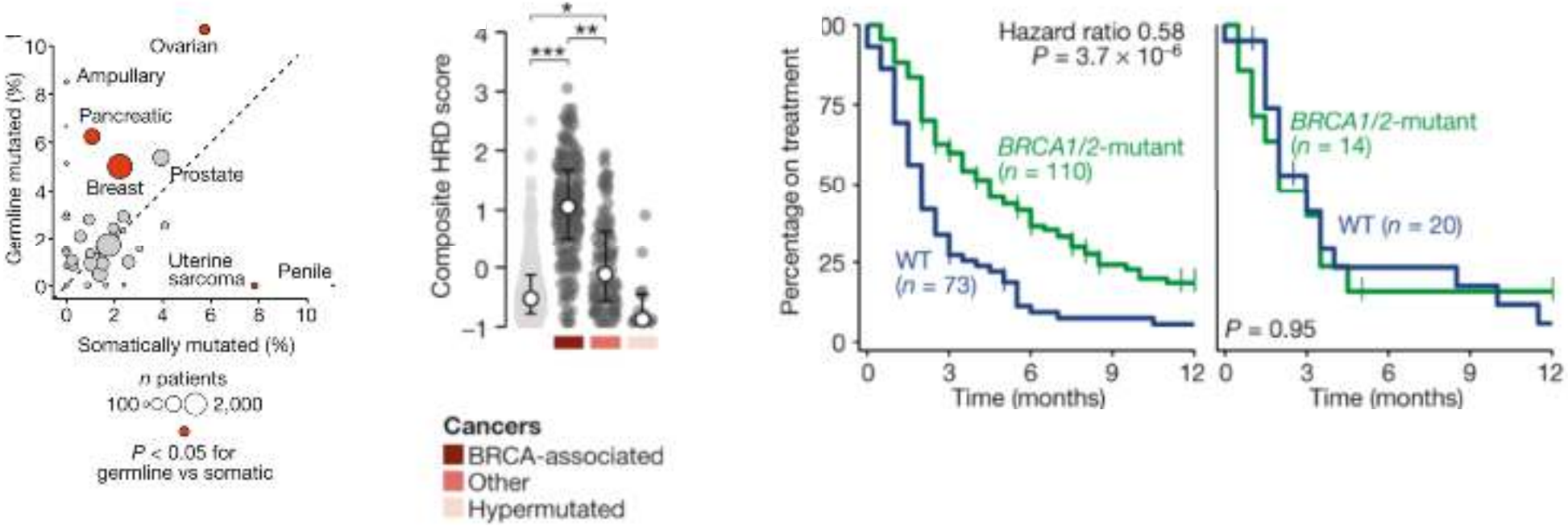
FGFR			?	

What Next? BRCA1/2



Jonsson er al. Nature. 2019 Jul;571(7766):576-579. doi: 10.1038/s41586-019-1382-1.

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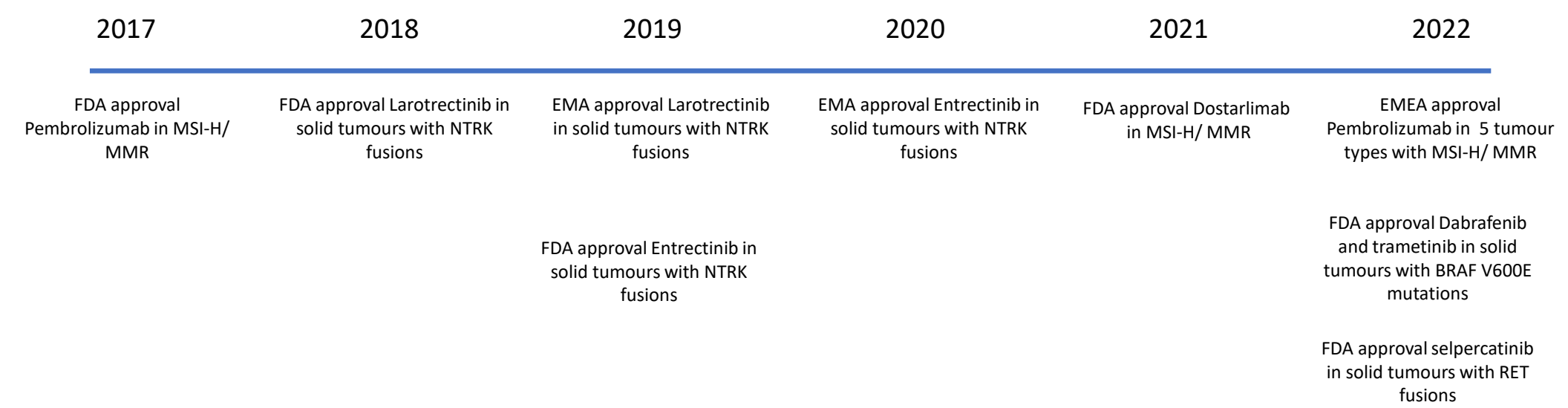
BRCA 1/2				

Successes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Summary

- Tumour profiling allowing development of histology agonist therapies
- Successful approvals
  - FDA
  - (EMA)
- Future opportunities
  - Fusions FGFR/NRG1
  - Mutations FGFR/KRAS/P53
  - DNA Damage response