# What's on the horizon for the treatment of solid tumours in 2019?

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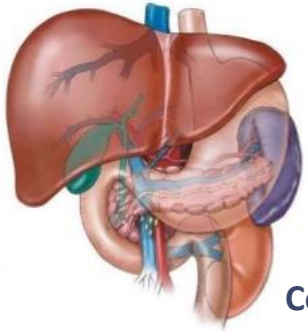
# Challenging GI cancers

**Hepatobiliary cancer**



**Gastric cancer**

**Colon cancer**

- Chemotherapy is SOC as first- and second-line treatment of GI cancer[1-3]
- A particular challenge is when cancers do not respond to SOC approaches
- An example is BTC, which is highly aggressive with poor prognosis and few treatment options following progression on gemcitabine-cisplatin chemotherapy[4]

BTC, biliary tract cancer; GI, gastrointestinal; SOC, standard of care.

1. Labianca R, et al. *Ann Oncol.* 2013;**24(Suppl 6)**:vi64–72; 2. Valle JW, et al. *Ann Oncol.* 2016;**27(Suppl 5)**:v28–37; 3. Smith EC, et al. *Ann Oncol.* 2016;**27(Suppl 5)**:v38–49; 4. Arkenau HT, et al. *Oncologist* 2018;**23**:1–11.

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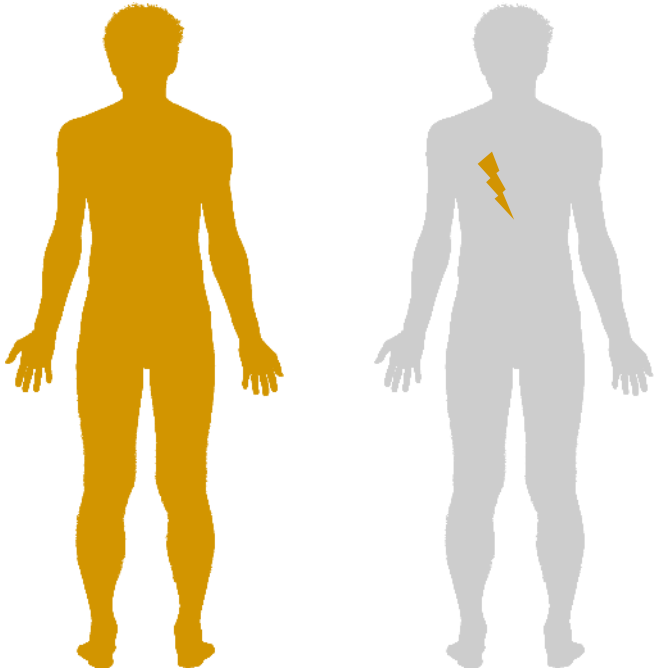
# There has been a move away from chemotherapy towards targeted treatment

Chemotherapy is a ‘One size fits all’ approach



Targeted therapy is based on the understanding of biologic and genetic drivers in specific tumour types

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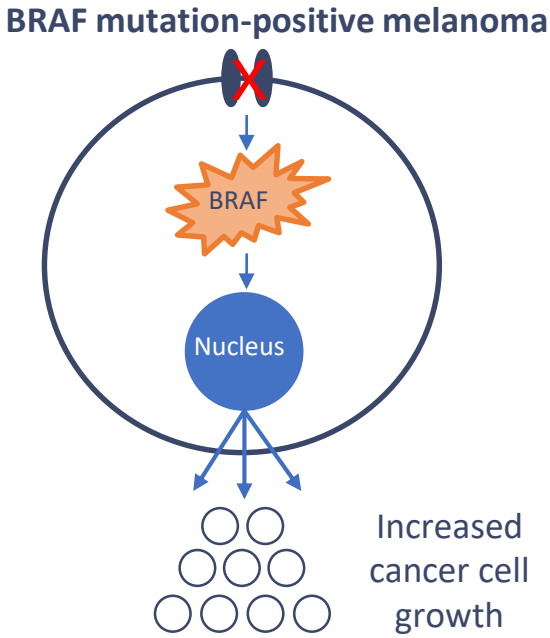
# Targeted treatments are improving long-term outcomes in solid tumours




- An example is the *BRAF*$^{V600E}$ mutation, which occurs in ~50% of melanomas[1]
- Targeted therapy with BRAF and MEK inhibitors has resulted in significant long-term treatment benefit in these patients[2]

V600E, a point mutation to the BRAF isoform at codon 600, where a valine is substituted for glutamate.

1. Ascierto PA, et al. *J Trans Med.* 2012;**10**:85; 2. Chen L, et al. *Mod Pathol.* 2018;**31**:24–38.

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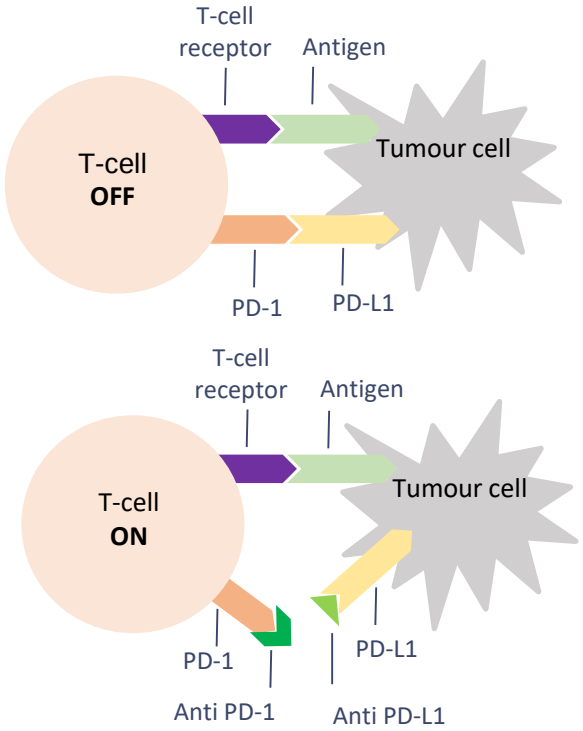
# Immunotherapy has become an established treatment for solid tumours[1]

- Mismatch repair pathways play a vital role in identifying mutations and guiding new treatment, e.g., PD-1 and PD-L1 immunotherapy[2]
- Pembrolizumab (PD-1 inhibitor) approved for mismatch repair deficiency/microsatellite instability-high refractory or metastatic solid tumours[3]
  - Durable responses in many solid tumours, e.g., melanoma, NSCLC, renal cell carcinoma and bladder cancer[2]
- PD-1/PD-L1 efficacy improved with combination therapy[4,5]




NSCLC; non-small cell lung cancer; programmed cell death protein 1; PD-1; programmed cell death ligand 1, PD-L1.

1. Kruger S, et al. *J Exp Clin Cancer Res.* 2019;**38**:268; 2. Zhao P, et al. *J Hematol Oncol.* 2019;**12**:54; 3. Lemery S, et al. *N Engl J Med.* 2017;**377**:1409–12; 4. Antonia SJ, et al. *Lancet Oncol.* 2016;**17**:883–95; 5. Larkin J, et al. *N Engl J Med.* 2015;**373**:23–34.

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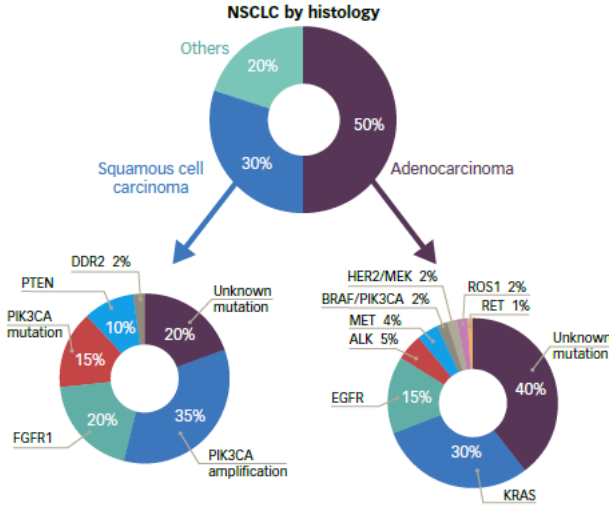
# Resistance is a major limitation of current therapies

Primary (intrinsic) and secondary (acquired) resistance to treatment with current therapies is still an issue




- An example of this is NSCLC, where gene mutations for receptor tyrosine kinases have been observed, e.g., the EGFR gene[2]
- This has led to the development of a number of new targeted therapies[2]

Image reproduced from Chan and Hughes, 2015.[1]
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.
1. Chan BA, et al. *Transl Lung Cancer Res.* 2015;**4**:36–54; 2. Schrank Z, et al. *Cancers* 2018;**10**:224.

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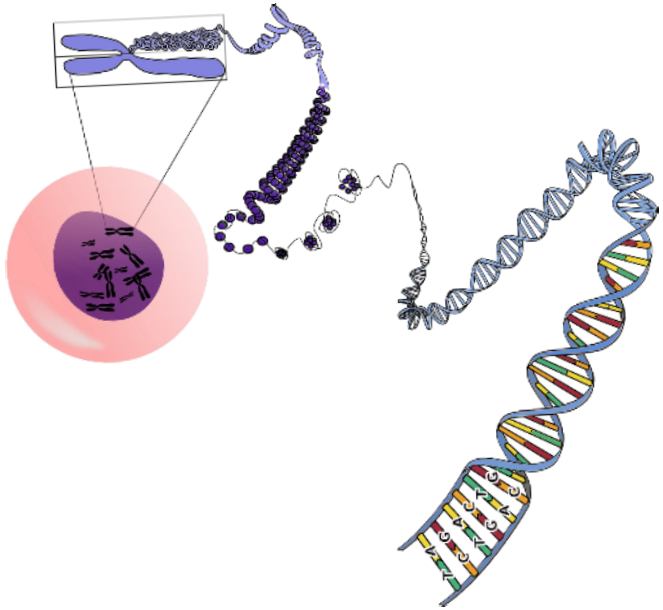
# Understanding tumour biology is key to developing new therapeutic approaches



Single gene mutations

Broader gene signatures*

**Guiding new therapeutic approaches for solid tumours**

*Immune gene signatures can predict a good response to treatment.
Image source: https://pixabay.com/vectors/genetics-chromosomes-rna-dna-156404/
DNA, deoxyribonucleic acid.
Lima ZS, et al. *J Hematol Oncol.* 2019;**12**:38.

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# The direction of future treatment strategies

Improvements in understanding of solid tumours means that, in many cases, cancer can be defined as a chronic disease[1]

- ✓ Greater understanding of the biology of solid tumours
- ✓ Tailoring future treatment to match disease profile
- ✓ Re-defining clinical trials to assess responses to treatment and mechanisms of resistance in order to guide future treatment decisions over the longer term

Pizzoli SFM, et al. *Cogent Psychol.* 2019;**6**:1577593.

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# Latest updates from ESMO 2019

- New data on targeting the *KRAS* mutation in solid tumours, e.g. colon cancer, lung cancer
- Updates on role of immunotherapies, in particular combinations, and how to overcome resistance to initial immunotherapy treatment

https://www.esmo.org/Conferences/ESMO-Congress-2019/Programme

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