Role of Targeted Therapy in GI cancers

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Objective

- Understanding the concept of targeted therapy.
- Current statistics of GI cancer.
- Discuss in detail about targeted therapy in various GI cancers.

Targeted Therapy

What is targeted therapy?

- If we use the analogy of pesticides: empiric therapy would be “Raid” while targeted therapy is the “Roach Hotel”

Dr. David Gandara

- A “Smart” bomb versus a “Cluster” **Bomb.**

Dr Naveen Murray

- It is a type of cancer treatment that targets the proteins, genes or tissue environment that control how cancer cells grow, divide, and spread.
- This uses the drugs that inhibit a more specific target in cells.
- Limit damage to healthy cells
- The first targeted therapy was tamoxifen approved in 1970s for breast cancer
- There are two main groups of targeted therapy drugs
  - Monoclonal antibodies
  - Small molecule inhibitors

Monoclonal antibodies

- Synthetic versions of natural antibodies (that help to fight infections).
- They lock onto a protein on the surface of cells or surrounding tissues to affect how cancer cells grow and survive.

Type	How they work	Examples
Angiogenesis inhibitors	• Reduce the blood supply to tumor to slow or stop its growth. • Target various proteins linked with growth of new blood vessels and stop them from working	• Bevacizumab • Cetuximab
HER2- targeted agents	• High level of HER2 cause cancer cells to grow uncontrollably • These targeted agents destroy HER2 positive cancer cells or reduce their ability to grow or divide.	• Transtuzumab • Pertuzumab
Anti-CD20 monoclonal antibodies	• These drugs target a protein called CD20 found in some B-cell leukemia and non-Hodgkin lymphomas	• Rituximab • Obinutuzumab

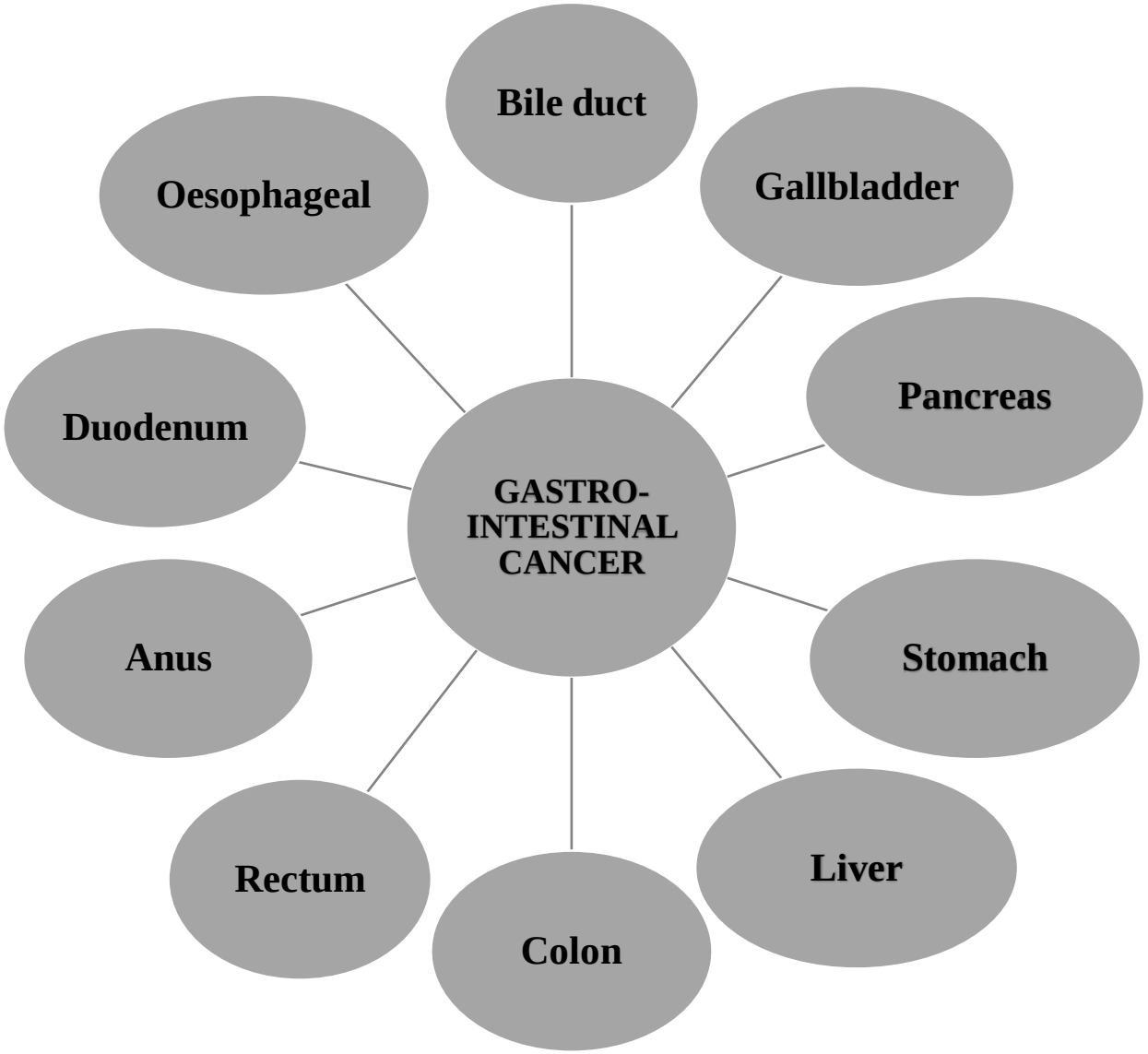
Small molecule inhibitors

- Small drugs to get inside cancer cells and block certain proteins that tell cancer cells to grow.

Type	How they work	Examples
TKIs	• Blocks proteins tyrosine kinases that sends signal to cancer cells to grow, multiply and spread. • Without this signal cancer cells may die.	• Erlotinib • Sunitinib • Imatinib • Dasatinib • Larotrectinib
mTOR inhibitors	• Block mammalian target of rapamycin (mTOR), a protein that tells cancer cells to grow and spread.	• Everolimus
PARP inhibitors	• Blocks poly (ADP-ribose) polymerase (PARP), a protein that repairs damaged DNA in cancer cells.	• Olaparib
CDK inhibitors	• Blocks cyclin-dependent kinase (CDK) from sending signal to cancer cell to grow, multiply and spread. • Without this signal cancer cells may die.	• Palbociclib • Ribociclib • Abemaciclib

GI cancer statistics

Types of different GI cancer



World GI cancer Statistics

GI Cancer is the 5th most common cancer worldwide.

It is the 4th most common cancer in Men.

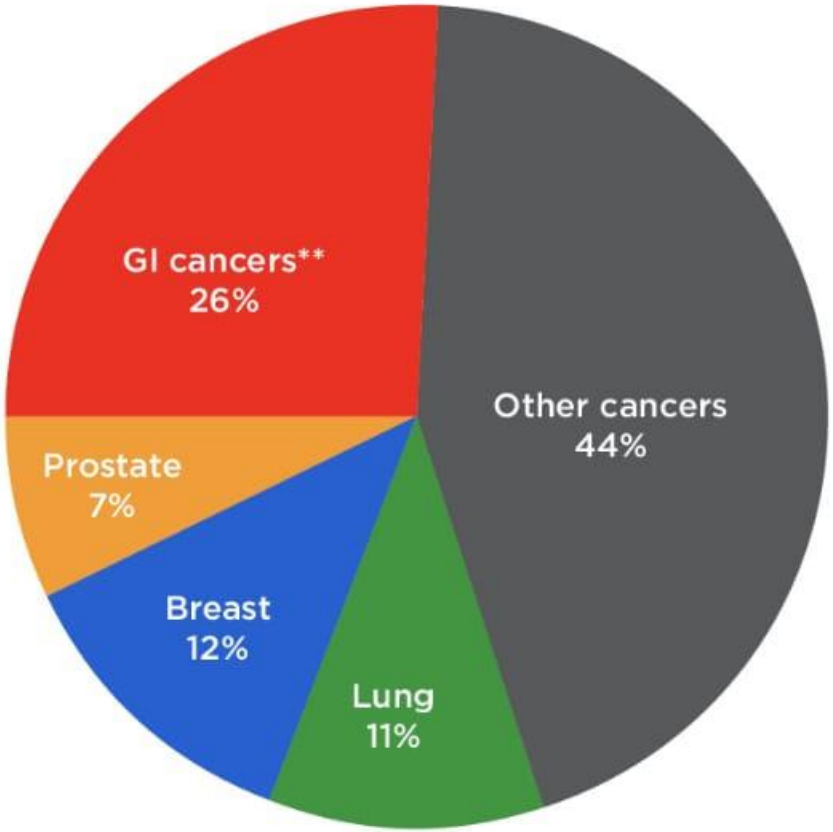
It is the 7th most common cancer in women.

GI cancer contributes 26 % of all cancers in the World.

GI cancer contributes 50.8 % of all cancers in the India.

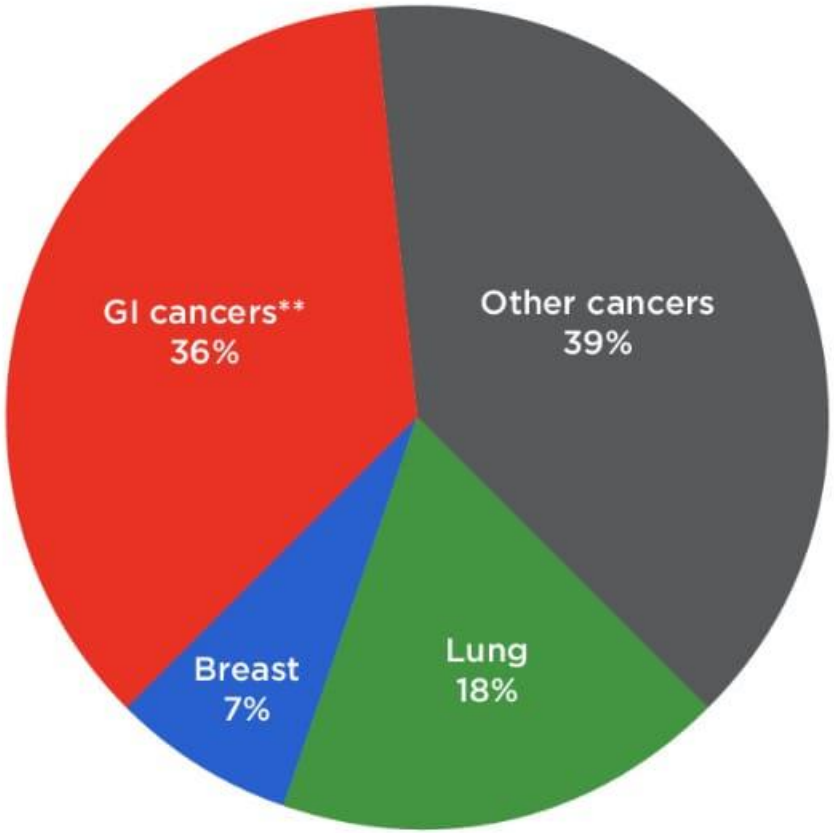
Common GI cancers: global incidence and mortality[6]

Cancer incidence in 2020*



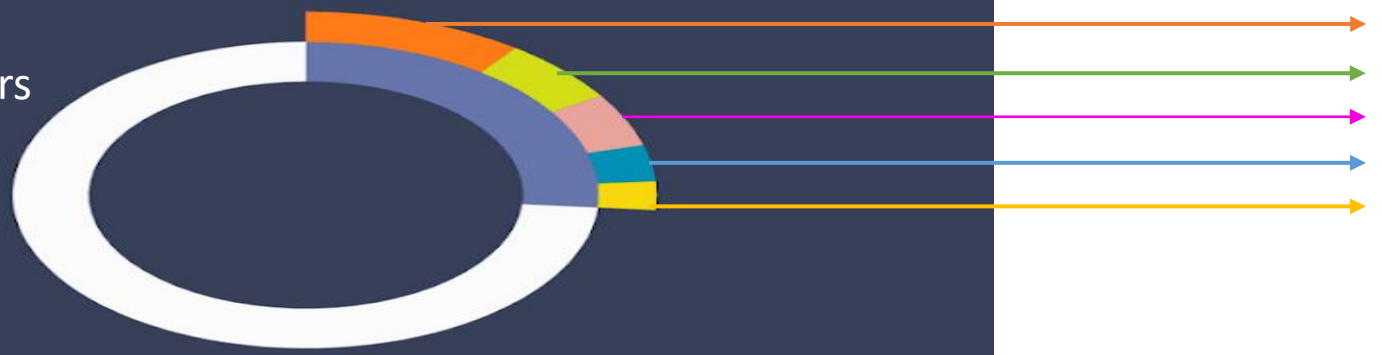
5,026,242 patients were diagnosed with the most common GI cancers

Cancer deaths in 2020*



3,544,225 people died from the most common GI cancers

Globally, gastrointestinal cancers (GI) are responsible for 1 in 4 cancer cases and 1 in 3 cancer deaths



Incidence
4.8 million cancer cases

Mortality
3.4 million cancer deaths

Source: Cancer Today, https://gco.iarc.fr

In India

DOI:10.31557/APJCP.2022.23.2.409
Descriptive Epidemiology of Gastrointestinal Cancers in India

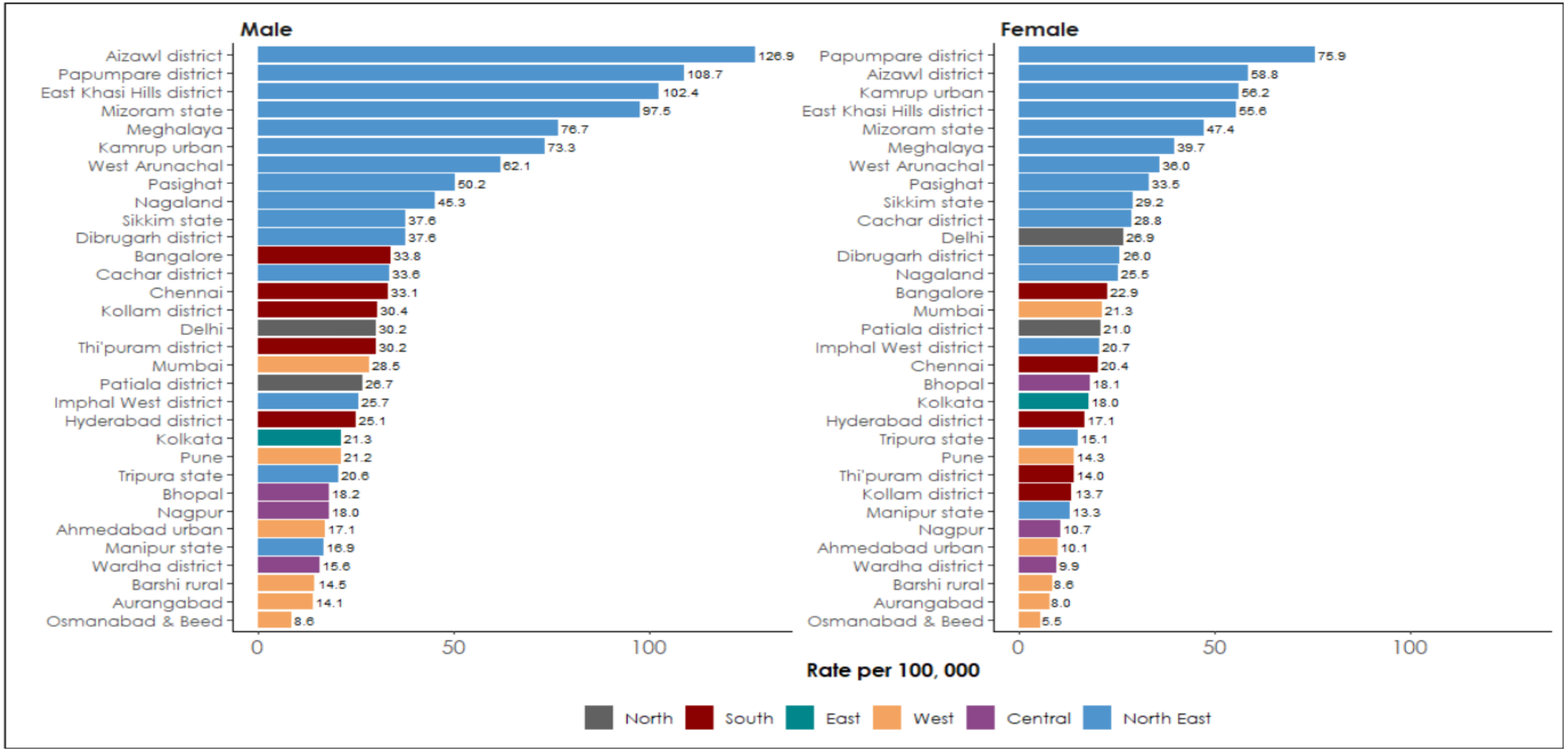


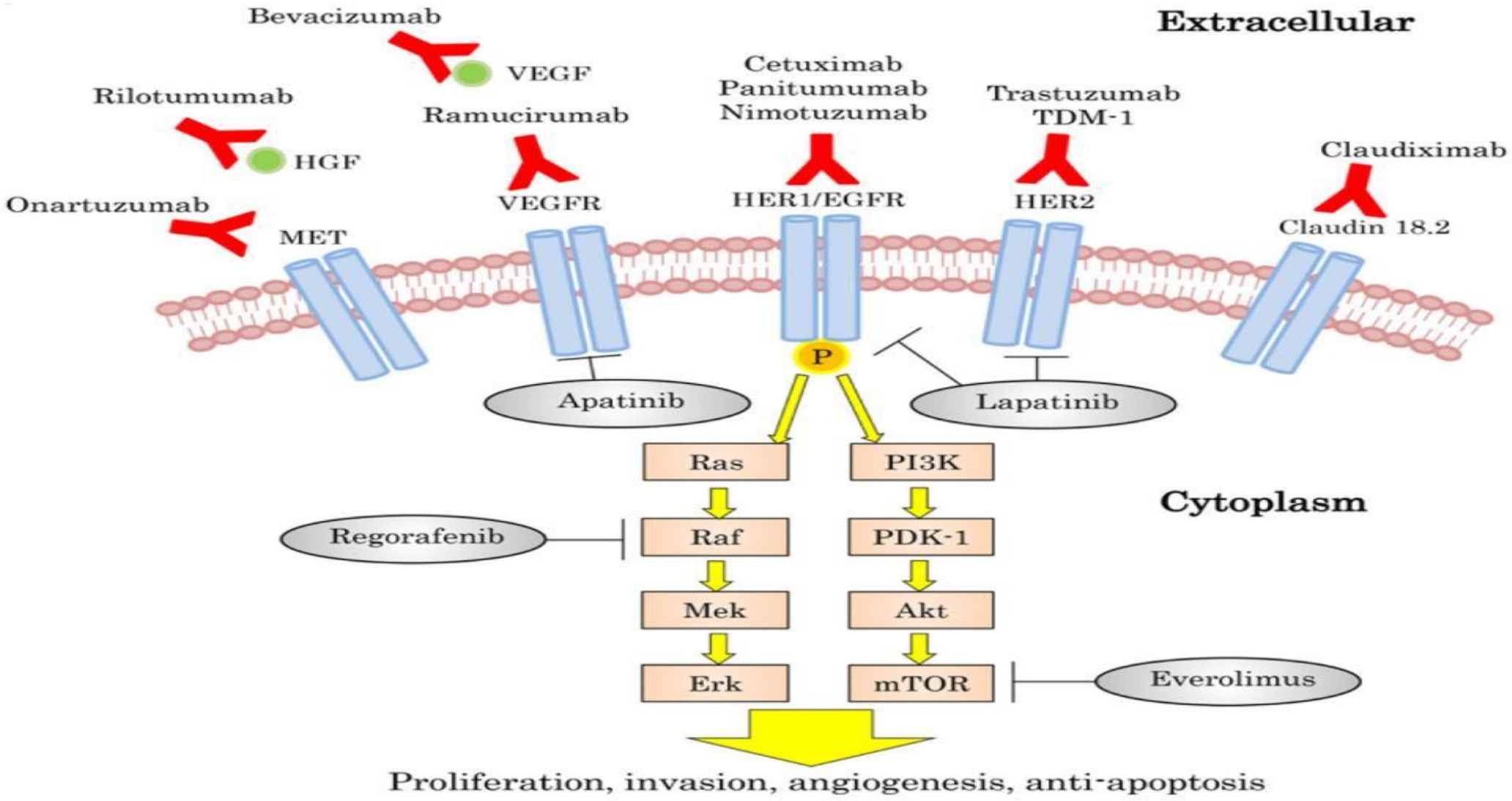
Figure 1. Comparison of Age-Adjusted Incidence Rates (AARs) of GI Cancers for 28 Population-Based Cancer Registries according to regions in India

Targeted therapy in various GI cancers

Treatment of GI cancers

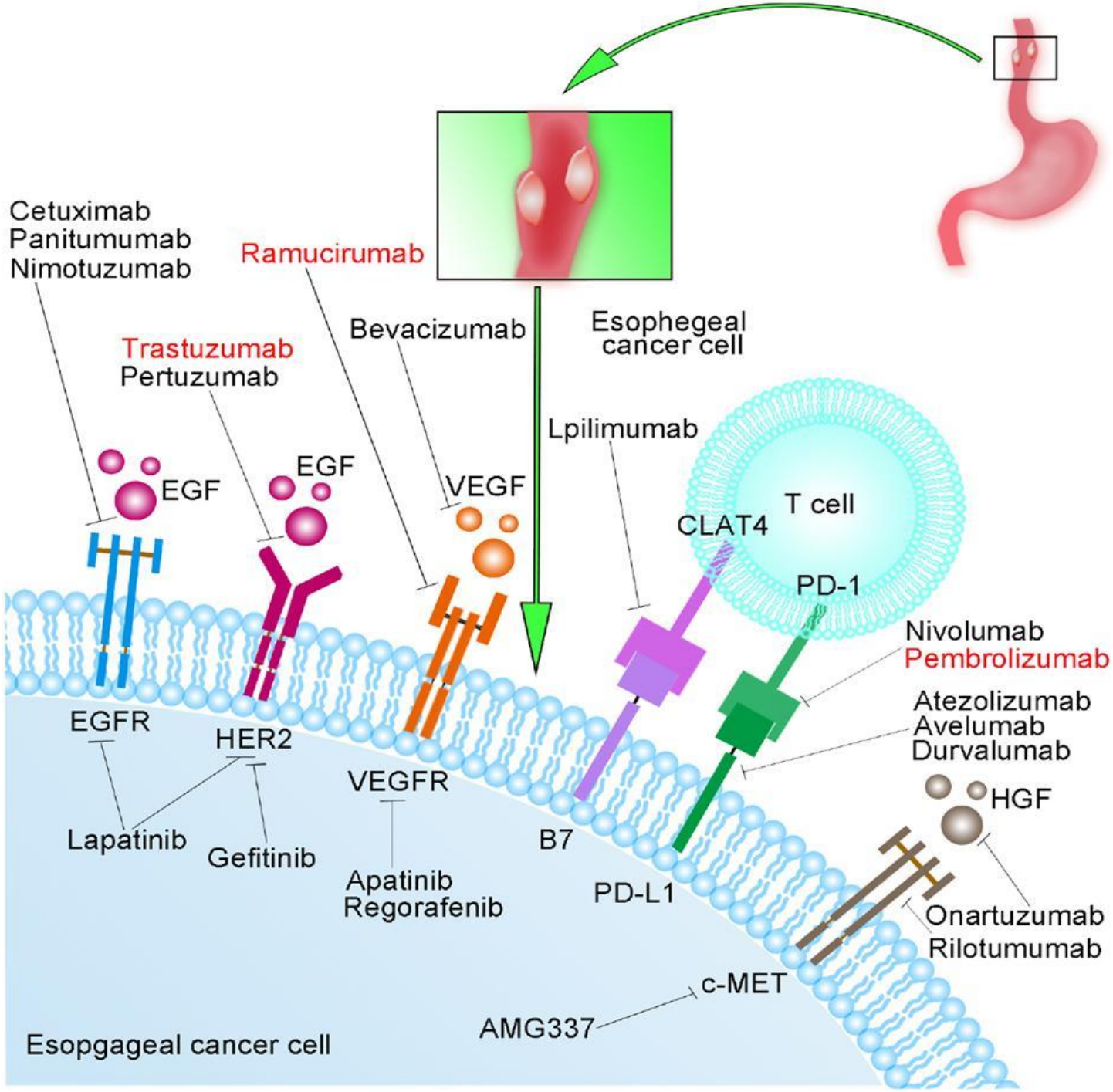
- In early stage
  - Surgery
  - Chemotherapy
  - Radiation Therapy
- In advanced and metastatic stage
  - Chemotherapy
  - Targeted Therapy
  - Immunotherapy

Mechanism of Targeted therapy in GI Cancers



Targeted Therapy in Oesophageal and Gastric Cancers

- Her2 Inhibitor
- PD-L1 Inhibitor
- VEGF Inhibitor
- TRK Inhibitors
- IDH 1 Inhibitor
- FGFR 1-3 Kinase Inhibitor



HER2 Inhibitor

- High level of HER2 cause cancer cells to grow uncontrollably.
- These targeted agents destroy HER2 positive cancer cells or reduce their ability to grow or divide.
- A man-made version of immune system protein
- **Transtuzumab**
  - Monoclonal antibodies
  - Helps to improve in objective RR, PFS and OS
  - Loading dose 8mg/kg and subsequent dose is 6mg/kg IV over 90 minutes 3 weekly
  - Lower infusion related toxicity but It sometime causes heart damage leading to the heart muscles becoming weak

HER2 Inhibitor

- **Transtuzumab deruxtecan**
  - Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate
  - Consists of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor.
  - 6.4 mg per kilogram of body weight every 3 weeks

  - Other Her2neu inhibitors: Pertuzumab, Lapatinib, T-DM1

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Lancet; Aug 20, 2010

- Patients with gastric or gastro-oesophageal junction cancer with Her2neu+
- Chemotherapy: capecitabine/5Fu plus cisplatin 3 weekly X 6 cycles with/without IV trastuzumab
- N=584.
- Median OS was 13·8 months (95% CI) in trastuzumab plus chemotherapy compared with 11·1 months in chemotherapy alone
- Hazard ratio 0·74; 95% CI 0·60–0·91; p=0·0046
- No significant difference in gr ¾ toxicities in between arms

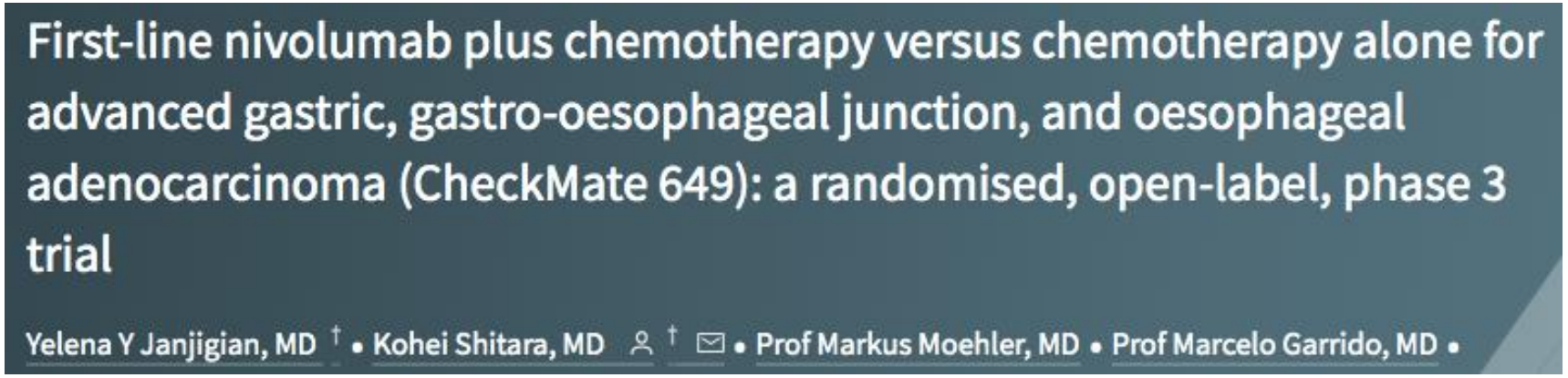
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

Kohei Shitara, M.D., Yung-Jue Bang, M.D., Ph.D., Satoru Iwasa, M.D., Ph.D., Naotoshi Sugimoto, M.D., Ph.D., Min-Hee Ryu, M.D., Ph.D., Daisuke Sakai, M.D., Ph.D.,

NEJM; June 18, 2020

- Phase 2
- HER2+ gastric or GEJ adenocarcinoma progressed on atleast 2 lines inc. trastuzumab
- Trastuzumab deruxtecan vs physician's choice of chemotherapy (Irinotecan/Paclitaxel)
- An objective response in 51% of the patients in the trastuzumab deruxtecan group vs 14% in physician's choice group ($P<0.001$).
- OS benefit with trastuzumab deruxtecan than with chemotherapy (median, 12.5 vs. 8.4 months; hazard ratio for death, 0.59; 95% CI, 0.39 to 0.88; $P=0.01$)
- A total of 12 patients had trastuzumab deruxtecan–related interstitial lung disease or pneumonitis (grade 1 or 2 in 9 patients and grade 3 or 4 in 3). 1 reported death.
- Cytopenias also more common



Lancet; June 5, 2021

- Previously untreated, unresectable, non-HER2-positive gastric, GEJ, or oesophageal adenocarcinoma, regardless of PD-L1 expression
- 1:1 nivolumab plus chemotherapy (CapOX 3 weekly or FOLFOX every 2 weeks) or chemotherapy alone
- N= 1581
- Nivolumab+chemotherapy: OS 13.1 vs 11.1 months (hazard ratio [HR] 0·71 [98·4% CI 0·59–0·86]; p<0·0001) and PFS benefit 7.7 vs 6 months (HR 0·68 [98 % CI 0·56–0·81]; p<0·0001) vs chemotherapy alone in patients with a PD-L1 CPS of >/=5
- No sig. diff in adverse events in between arms

CheckMate 648: similar results for SCC

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

Jong-Mu Sun, MD • Lin Shen, MD • Prof Manish A Shah, MD • Peter Enzinger, MD • Prof Antoine Adenis, MD •

Lancet; Aug 28, 2021

- Previously untreated, unresectable, Seiwert type 1 GEJ, or oesophageal primary, regardless of PD-L1 expression
- 1:1) to intravenous pembrolizumab 200 mg or placebo, plus 5-fluorouracil and cisplatin (chemotherapy), once every 3 weeks for up to 35 cycles
- N= 749
- SCC and PD-L1 CPS > 10: Pembrolizumab plus chemotherapy was superior to placebo plus chemotherapy (median 13·9 months vs 8·8 months; hazard ratio 0·57 [95% CI 0·43–0·75]; p<0·0001)
- Oesophageal squamous cell carcinoma (12·6 months vs 9·8 months; 0·72 [0·60–0·88]; p=0·0006); PFS 6.3 vs 5.8
- PD-L1 CPS of 10 or more (13·5 months vs 9·4 months; 0·62 [0·49–0·78]; p<0·0001); PFS 7·5 months vs 5·5 months
- All randomised patients (12·4 months vs 9·8 months; 0·73 [0·62–0·86]; p<0·0001); PFS 6·3 months vs 5·8 months
- Sig. Grade 3 toxicity in both arms. 72% vs 68%

VEGF Inhibitor

- **Ramucirumab**
  - It blocks to VGEF and stops signal to the body to make more blood vessels
  - It can be used along and combination with the chemo drug paclitaxel.
  - Single agent dose is 8mg/Kg IV over 60 minutes 2 weekly
  - In combination Ramucirumab dose is 8mg/Kg and Paclitaxel 80mg/m2 IV weekly.
  - Infusion related reactions >10%

Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial

Hansjochen Wilke, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka, Naotoshi Sugimoto, Oleg Lipatov,

Lancet; Sep 17, 2014

- Advanced gastric or GEJ adenocarcinoma and disease progression on or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline)
- 1:1 Ramucirumab 8 mg/kg or placebo intravenously on days 1 and 15, plus paclitaxel 80 mg/m2 intravenously on days 1, 8, and 15 of a 28-day cycle
- N= 665
- OS benefit in ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (median 9·6 months [95% CI 8·5–10·8] vs 7·4 months [95% CI 6·3–8·4], hazard ratio 0·807 [95% CI 0·678–0·962]; p=0·017)

TRK Inhibitor

- **<u>Entrectinib and Larotrectinib</u>**
  - Kinase Inhibitor
  - These drugs used to treat esophageal cancer with an NTRK gene fusion
  - These are oral drugs
  - Doses (Orally once daily)
    - BSA .91 to 1.10m2 - 400mg
    - BSA 1.11 to 1.50m2 – 500mg
    - BSA greater than 1.50m2 – 600 mg
  - Can cause hepatotoxicity and confusion

Targeted Therapy in Cholangiocarcinoma

IDH 1 Inhibitor

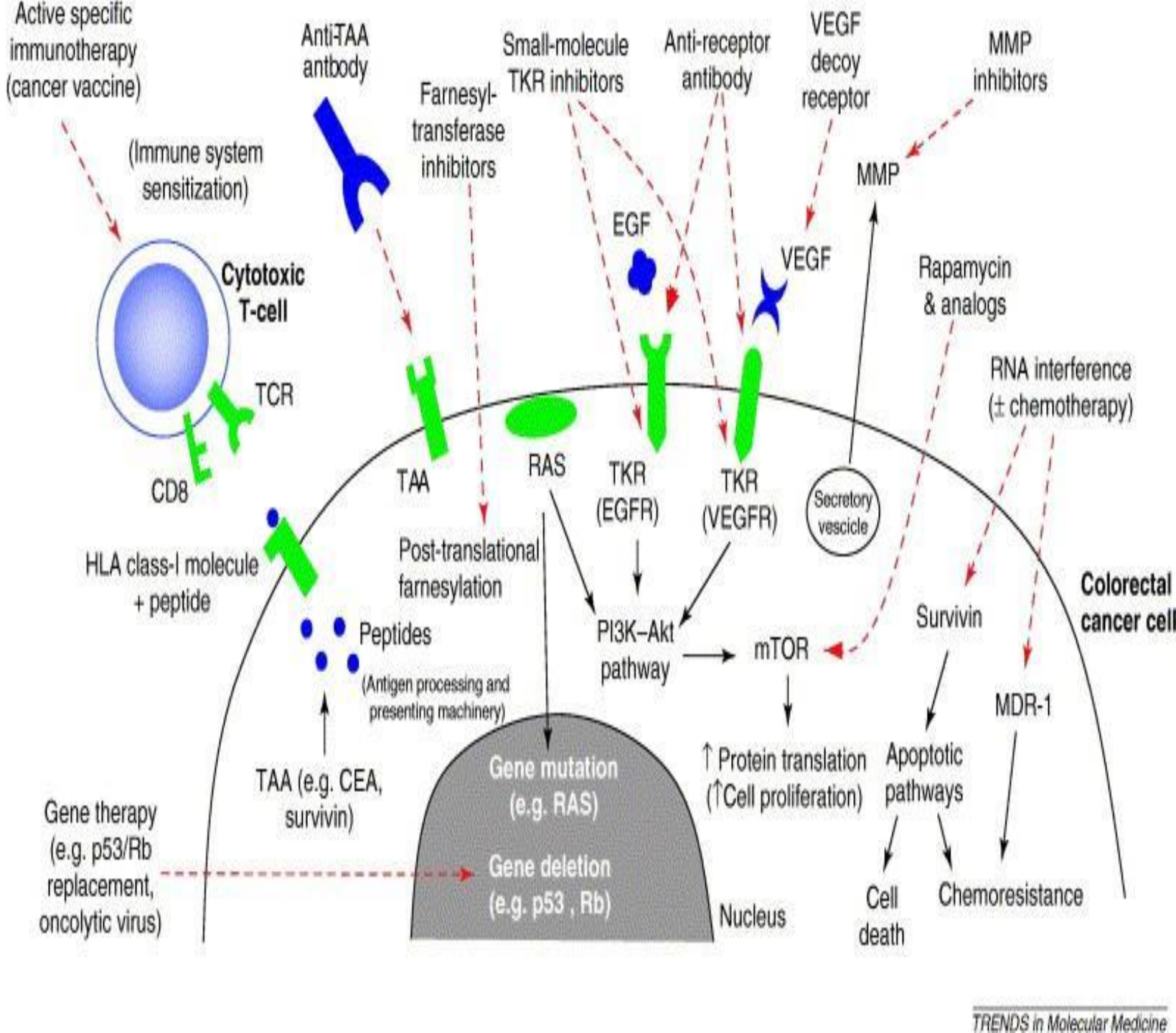
- **Ivosidenib (TIBSOVO)**
  - TIBSOVO is the first and only targeted therapy approved for patients with previously treated IDH1-mutated cholangiocarcinoma.
  - 500 mg orally once daily
  - TIBSOVO demonstrated an impressive, acceptable safety profile significant benefit in PFS
  - Adverse reactions (≥15%) in patients

FGFR 1-3 Kinase Inhibitor

- **Infigratinib**
  - Oral tyrosine kinase inhibitor in previously treated advanced CCA
  - 125 mg orally for 21 days and one week off/ 28 days cycle
  - overall response rate for the drug was 23%
  - progression-free survival was 7.3 months.
  - Common side effect of the drug is hyperphosphatemia in 77% patients.
- **Pemazyre**
  - The new kinase inhibitor, developed by Incyte, blocks fibroblast growth factor receptor(FGFR) types 1, 2 and 3
  - PEMAZYRE is available in 3 strengths to enable dose modifications as needed—13 .5 mg, 9 mg, & 4 .5 mg
  - dose13.5 mg oral, OD, 3 weekly cycle (14 days on and 7 days off)
  - Common side effect of drug is Hyperphosphatemia ≥20%
  - Serious adverse reactions in ≥2% of patients

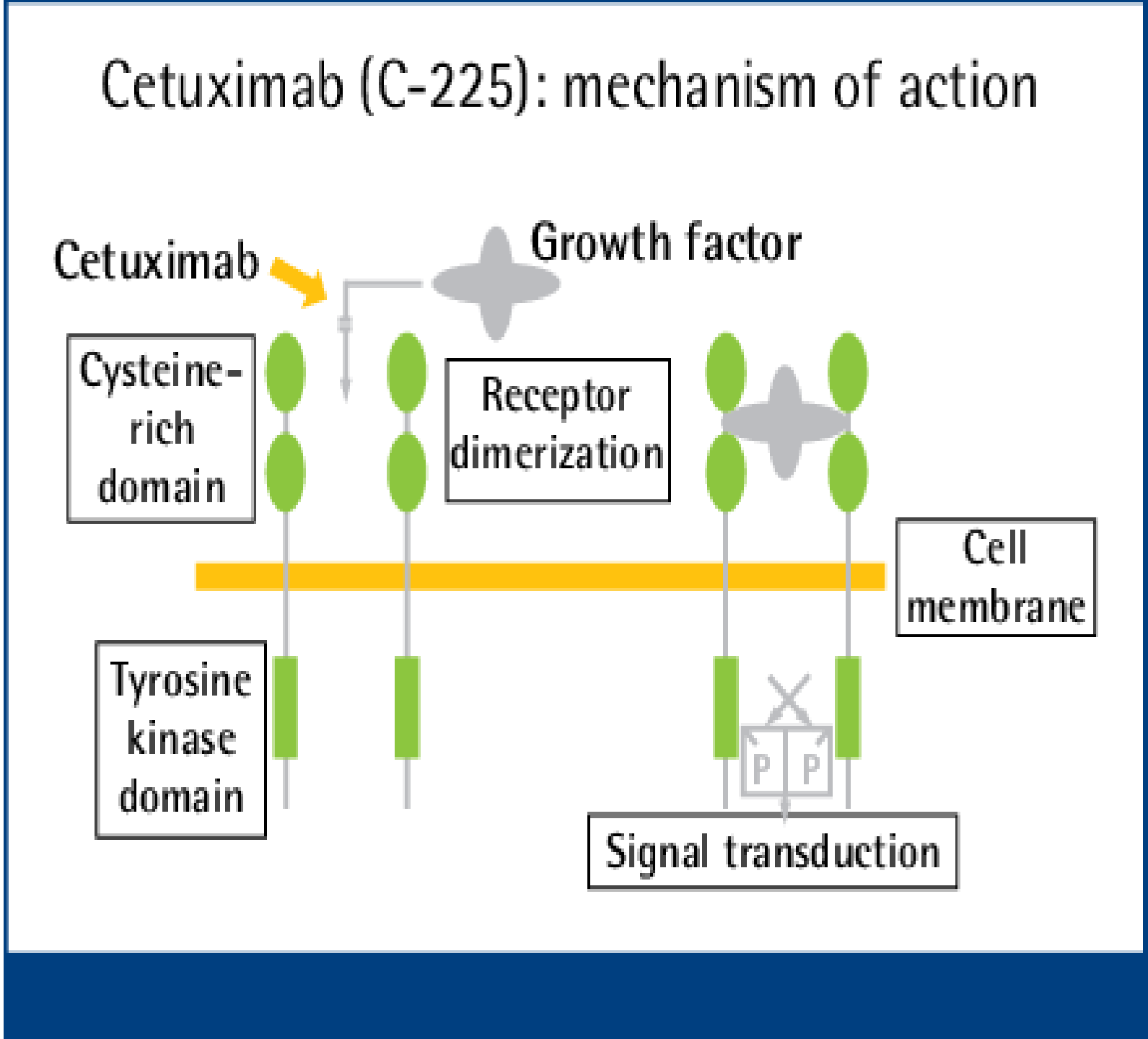
Targeted Therapy in Colorectal Cancer

- EGFR Inhibitor
- VEGF Inhibitor
- Tyrosinase Kinase Inhibitor



EGFR Inhibitor

- **<u>Cetuximab</u>**
  - Chimeric antibody
  - Precise MOA unknown, cause EGFR inhibition
  - Has nearly 10-fold higher affinity to EGFR than other ligands
  - 400 mg/m2 IV 1st infusion given over 2 hours, then 250 mg/m2 weekly or 500mg/m2 IV every 2 weeks
  - In fusional related toxicity more



ORIGINAL ARTICLE

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Eric Van Cutsem, M.D., Ph.D., Claus-Henning Köhne, M.D., Erika Hitre, M.D., Ph.D., Jerzy Zaluski, M.D., Chung-Rong Chang Chien, M.D., Anatoly Makhson, M.D., Ph.D.,

Lancet; April 2, 2009

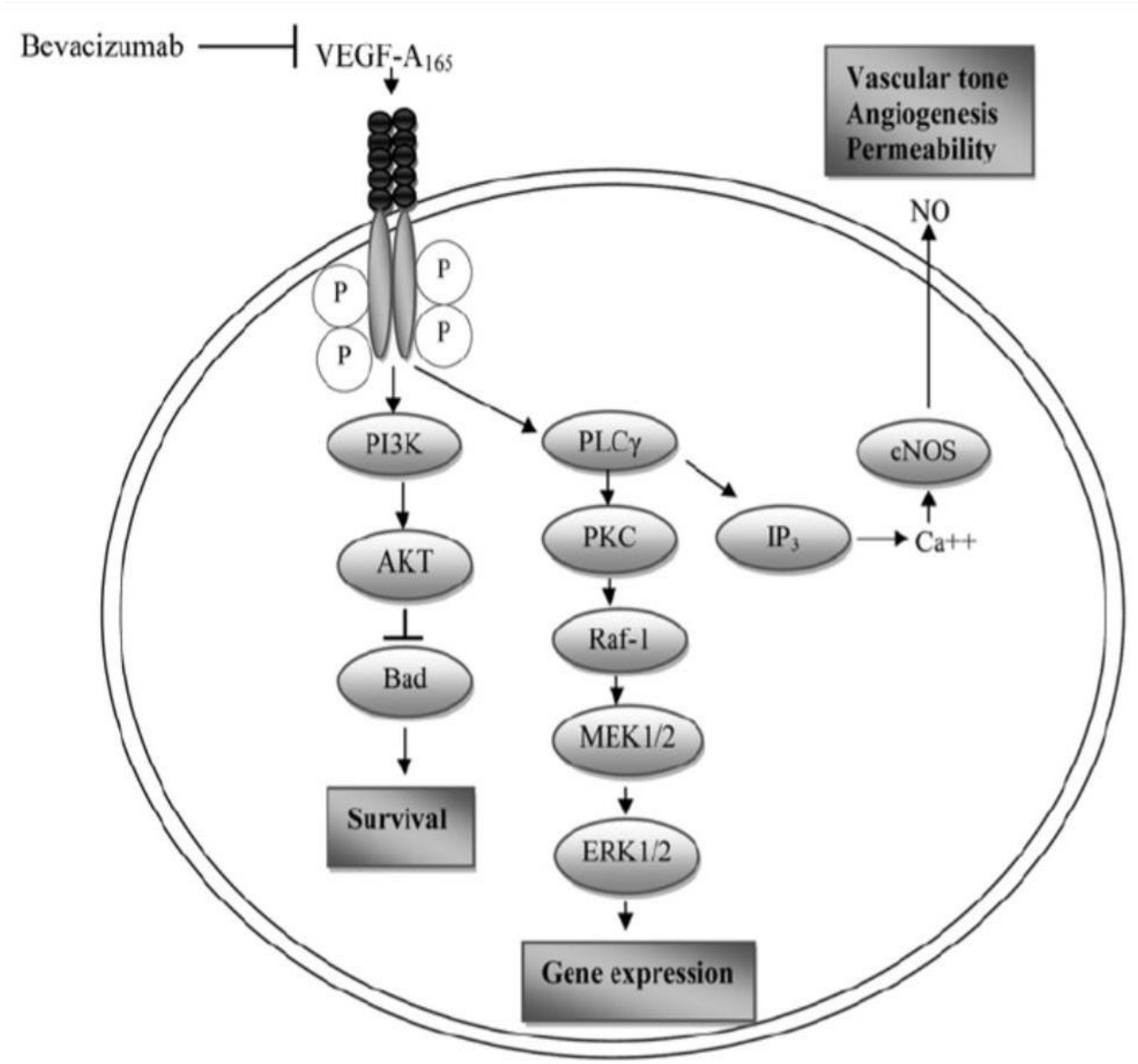
- N=998
- 1:1 cetuximab plus FOLFIRI vs FOLFIRI alone.
- The HR for PFS in the cetuximab–FOLFIRI group as compared with the FOLFIRI group was 0.85 (95% confidence interval [CI], 0.72 to 0.99; P=0.048)
- No difference in OS between the groups (hazard ratio, 0.93; 95% CI, 0.81 to 1.07; P=0.31).
- There was a significant interaction between treatment group and KRAS mutation status for tumor response (P=0.03) but not for progression-free survival (P=0.07) or overall survival (P=0.44).
- The hazard ratio for progression-free survival among patients with wild-type–KRAS tumors was 0.68 (95% CI, 0.50 to 0.94), in favor of the cetuximab–FOLFIRI group
- The benefit of cetuximab was limited to patients with KRAS wild-type tumors

- **Panitumumab**
  - Fully humanized antibody
  - 40-fold affinity to EGFR
  - 6mg/kg IV over 60 minutes every 2 weeks
  - Lower infusion related toxicity

ASPECCT STUDY (2014) Panitumumab vs Cetuximab
Median OS 10.4 months vs 10 months
Similar Toxicity profile but lesser infusion reaction 3% vs 14%

VEGF Inhibitor

- **<u>Bevacizumab</u>**
  - Combination with bolus-IFL: 5 mg/kg IV over 60 to 90 minutes2 weekly
  - Combination with FOLFOX4: 10 mg/kg IV over 60 to 90 minutes 2 weekly
  - In combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy regimen in patients who have progressed on a first-line bevacizumab-containing regimen: 5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks
  - Common side effects: High blood pressure, Protein in urine, Nosebleeds, Rectal bleeding, Back pain, Headache, Taste change, Dry skin



Bevacizumab in Combination With Oxaliplatin-Based Chemotherapy As First-Line Therapy in Metastatic Colorectal Cancer: A Randomized Phase III Study

Leonard B. Saltz , Stephen Clarke , Eduardo Díaz-Rubio , Werner Scheithauer , Arie Figer , Ralph

JCO; September 21, 2016

- Patients with MCRC were randomly assigned, in a 2 × 2 factorial design, to XELOX versus FOLFOX-4, and then to bevacizumab versus placebo.
- N=1,401
- Median PFS was 9.4 months in the bevacizumab group vs 8.0 months in the placebo group (hazard ratio [HR], 0.83; 97.5% CI, 0.72 to 0.95; P = .0023)
- Median OSwas 21.3 months in the bevacizumab group and 19.9 months in the placebo group (HR, 0.89; 97.5% CI, 0.76 to 1.03; P = .077).
- Response rates were similar in both arms.
- The toxicity profile of bevacizumab was consistent with that documented in previous trials

Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial

Andrea Sartore-Bianchi, Filippo Pietrantonio, Sara Lonardi, Benedetta Mussolin, Francesco Rua,

Nature; August 1, 2022

- EGFR monoclonal antibodies are approved for the treatment of RAS wild-type (WT) metastatic colorectal cancer (mCRC), but the emergence of resistance mutations restricts their efficacy.
- RAS, BRAF and EGFR mutant alleles, which appear in circulating tumor DNA (ctDNA) during EGFR blockade, decline upon therapy withdrawal.
- The primary endpoint was objective response rate. Secondary endpoints were progression-free survival, overall survival, safety and tolerability of this strategy.
- ctDNA-based screening of 52 patients, 16 (31%) carried at least one mutation conferring resistance to anti-EGFR therapy and were excluded.
- 27 enrolled patients, eight (30%) achieved partial response and 17 (63%) disease control, including two unconfirmed responses.
- These clinical results favorably compare with standard third-line treatments and show that interventional liquid biopsies can be effectively and safely exploited in a timely manner to guide anti-EGFR rechallenge therapy with panitumumab in patients with mCRC.

Proximal Colon vs Distal Colon

- Metastatic LCC exhibit longer survival compared with RCC
- LCC benefits more from Cetuximab treatment than RCC
- Advanced LCC shows a higher sensitivity to Bevacizumab treatment compared with advanced RCC
- Separated pathways dominate progression to relapse in RCC and LCC
- Comparison of survival between RCC and LCC undefined

Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials

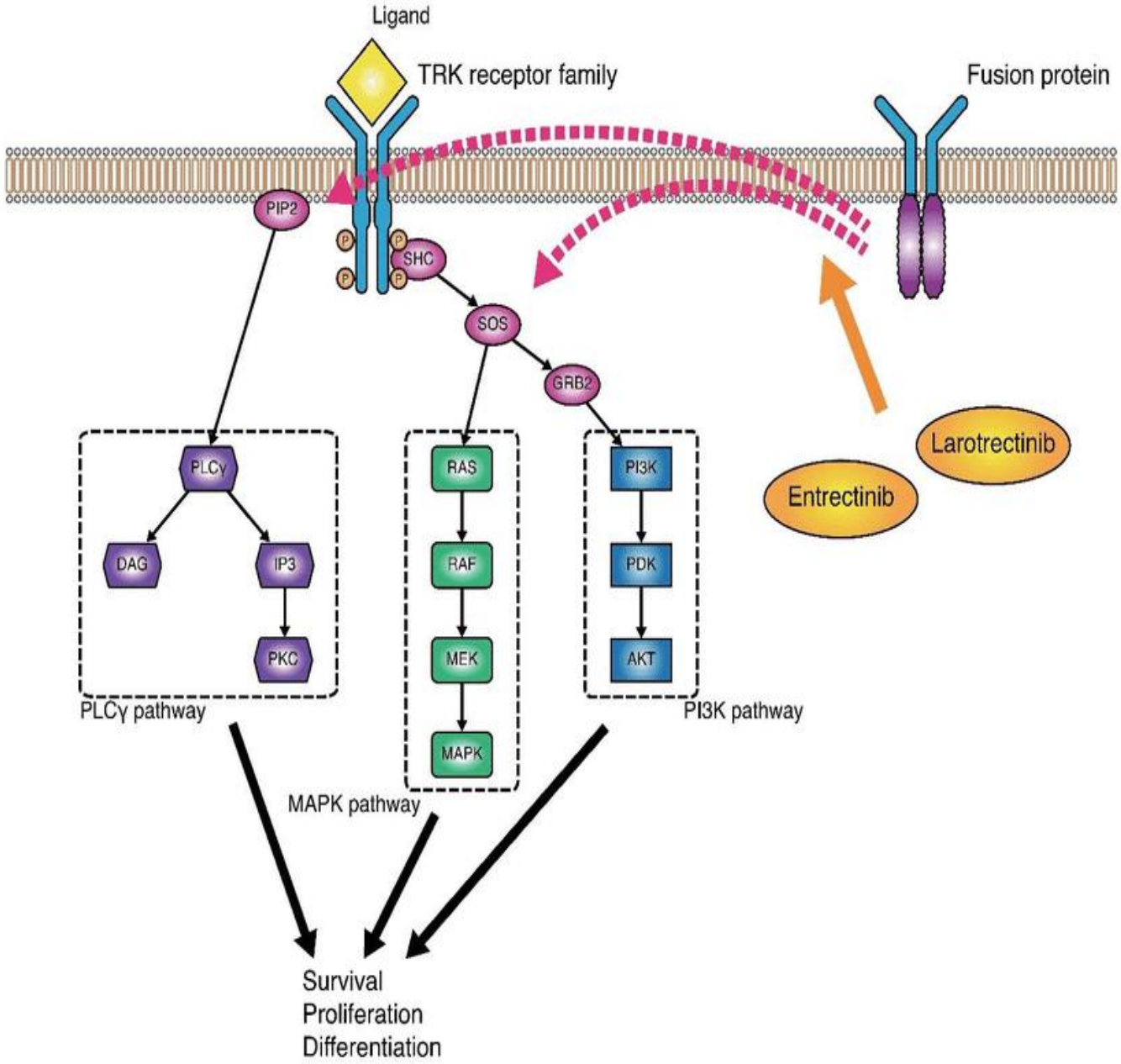
D Arnold [1], B Lueza [2], J-Y Douillard [3], M Peeters [4], H-J Lenz [5], A Venook [6], V Heinemann [7],

Annals of Oncology; August 1, 2017

- Retrospective analysis, prognostic and predictive influence of the localization of the primary tumour in patients with unresectable RAS wt mCRC included in six randomized trials
- Primary tumour location and RAS mutation status were available for 2159 of the 5760 patients, 515 right-sided and 1644 left-sided.
- A significantly worse prognosis was observed for patients with right-sided tumours compared with those with left-sided tumours in both the pooled control and experimental arms for OS [HRs = 2.03 (95% CI: 1.69-2.42) and 1.38 (1.17-1.63), respectively], PFS [HRs = 1.59 (1.34-1.88) and 1.25 (1.06-1.47)], and ORR [ORs = 0.38 (0.28-0.50) and 0.56 (0.43-0.73)].
- In terms of a predictive effect, a significant benefit for chemotherapy plus EGFR antibody therapy was observed in patients with left-sided tumours [HRs = 0.75 (0.67-0.84) and 0.78 (0.70-0.87) for OS and PFS, respectively] compared with no significant benefit for those with right-sided tumours [HRs = 1.12 (0.87-1.45) and 1.12 (0.87-1.44) for OS and PFS, respectively;
- P value for interaction <0.001 and 0.002, respectively]. For ORR, there was a trend (P value for interaction = 0.07) towards a greater benefit for chemotherapy plus EGFR antibody therapy in the patients with left-sided tumours [OR = 2.12 (1.77-2.55)] compared with those with right-sided tumours [OR = 1.47 (0.94-2.29)]

TRK Inhibitor

- **<u>Larotrectinib and entrectinib</u>**
- larotrectinib :-
  - Dose 100 mg oral 2 BD 1st reduction 75 mg oral 2 BD 2nd reduction 50 mg oral BD
  - Common side effects : nausea, vomiting, diarrhea, constipation, cough; dizziness; tiredness; or abnormal liver function tests.
- Entrectinib :-
  - 600 mg Oral OD
  - Common side effects : Pain in stomach, numbness, nausea, vomiting, diarrhea, constipation, cough; dizziness; tiredness, confusion, itching and skin rashes



Targeted Oncology
https://doi.org/10.1007/s11523-021-00815-4

ORIGINAL RESEARCH ARTICLE

TRK Fusion Cancer: Patient Characteristics and Survival Analysis in the Real-World Setting

Lyudmila Bazhenova[1] · Andrew Lokker[2] · Jeremy Snider[2] · Emily Castellanos[2] · Virginia Fisher[3] · Marc Fellous[4] · Shivani Nanda[4] · Jihong Zong[4] · Karen Keating[4] · Xiaolong Jiao[4]

Accepted: 3 February 2021

Abstract

Background Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in various tumor types. While *NTRK* gene fusions are predictive of benefit from tropomyosin receptor kinase inhibitors regardless of tumor type, the prognostic significance of *NTRK* gene fusions in a pan-tumor setting remains unclear.

Objective This study evaluated the characteristics and prognosis of tropomyosin receptor kinase fusion cancer in the real-world setting.

Patients and Methods This retrospective study used a de-identified clinico-genomic database and included patients with cancer who had comprehensive genomic profiling between January 2011 and July 2018. Patients were classified as having cancer with *NTRK* gene fusions or *NTRK* wild-type genes. Patients were matched with a 1:4 ratio (*NTRK* fusion:*NTRK* wild-type) using the Mahalanobis distance method on demographic and clinical characteristics, including age and Eastern Cooperative Oncology Group performance status. Descriptive analysis of clinical and molecular characteristics was conducted. Kaplan–Meier estimator and Cox regression were used for overall survival analysis.

Results Median overall survival was 12.5 months (95% confidence interval 9.5–not estimable) and 16.5 months (95% confidence interval 12.5–22.5) in the *NTRK* gene fusion ($n = 27$) and *NTRK* wild-type cohorts ($n = 107$), respectively (hazard ratio 1.44; 95% confidence interval 0.61–3.37; $p = 0.648$). Co-occurrence of select targetable biomarkers including *ALK, BRAF, ERBB2, EGFR, ROS1,* and *KRAS* was lower in cancers with *NTRK* gene fusions than in *NTRK* wild-type cancers.

Conclusions Although the hazard ratio for overall survival suggested a higher risk of death for patients with *NTRK* gene fusions, the difference was not statistically significant. Co-occurrence of *NTRK* gene fusions and other actionable biomarkers was uncommon.

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DOI: 10.1002/cam4.4561

RESEARCH ARTICLE

Cancer Medicine Open Access WILEY

NTRK fusion positive colorectal cancer is a unique subset of CRC with high TMB and microsatellite instability

Hui Wang[1] | **Zhi-Wei Li**[2] | **Qiuxiang Ou**[3] | **Xue Wu**[3] | **Misako Nagasaka**[4] | **Yang Shao**[3,5] | **Sai-Hong Ignatius Ou**[6] | **Yu Yang**[7]

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Abstract

TRK fusions are rare but targetable mutations which occur across a wide variety of cancer types. We report the prevalence of approximately 0.7% for *NTRK*-positive colorectal cancer (CRC) by genetically profiling 2519 colonic and rectal tumors. The aberrations of *APC* and *TP53* frequently co-occurred with *NTRK* gene fusions, whereas *RAS/BRAF* oncogenic alterations and *NTRK* fusions were almost always mutually exclusive. *NTRK*-driven colorectal cancer patients demonstrated increased TMB (median = 53 mut/MB, 95% CI: 36.8–68.0 mut/MB), high microsatellite instability, and an enrichment for *POLE/POLD1* mutations when compared to molecularly unstratified colorectal cancer population. These data shed light on possible future approach of multimodality treatment regimen including TRK-targeted therapy and immune checkpoint inhibitor therapy in *NTRK*-positive CRCs.

KEYWORDS

colorectal cancer, gene fusions, microsatellite instability, NTRK, *POLE/POLD1*, tumor mutation burden

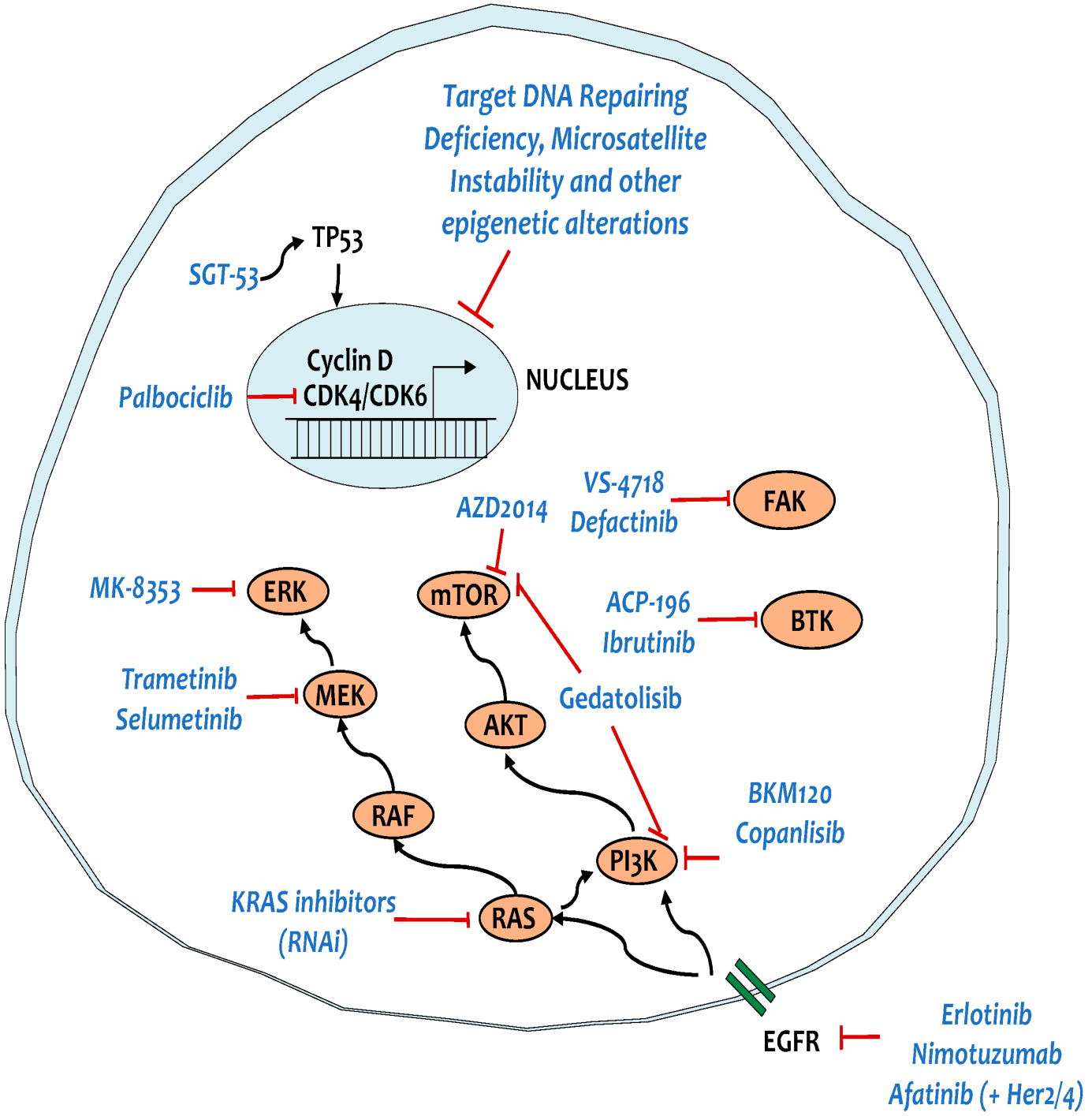
Key study findings with targeted therapies in colon cancer

Targeted Therapy Drug	Results
Bevacizumab (Avastin)	• OS of bevacizumab plus IFL compared with IFL alone (20.3 vs 15.6 months; P <.001). • PFS of bevacizumab plus IFL compared with IFL alone (10.6 vs 6.2 months; P <.001)
Cetuximab (Erbitux)	• Median time to disease progression comparing cetuximab plus an irinotecan-based regimen with cetuximab alone (4.1 vs 1.5 months; P <.001).
Panitumumab (Vectibix)	• 46% reduction in the relative risk of progression was observed in patients receiving panitumumab compared with those receiving best supportive care (HR, 0.54; 95% CI, 0.44-0.66).
Ramucirumab (Cyramza)	• For patients receiving ramucirumab plus FOLFIRI, median OS duration was 13.3 months, while patients receiving FOLFIRI alone had a median OS duration of 11.7 months (P = .0219).
Ziv-aflibercept (Zaltrap)	• OS was longer in patients receiving ziv-aflibercept plus FOLFIRI compared with patients receiving placebo plus FOLFIRI (13.80 vs 11.93 months; P = .0008). • The difference in median PFS also favored the ziv-aflibercept plus FOLFIRI compared with placebo plus FOLFIRI (6.80 vs 4.53 months; P <.0001).
Regorafenib (Stivarga)	• OS was longer in the regorafenib arm than in the placebo arm (6.4 vs 5.0 months; P = .0052). • PFS was also longer in the regorafenib arm: 1.9 months versus 1.7 months in the placebo arm (P <.0001).

HR indicates hazard ratio; IFL, irinotecan/fluorouracil/levoleucovorin regimen; OS, overall survival; PFS, progression-free survival.

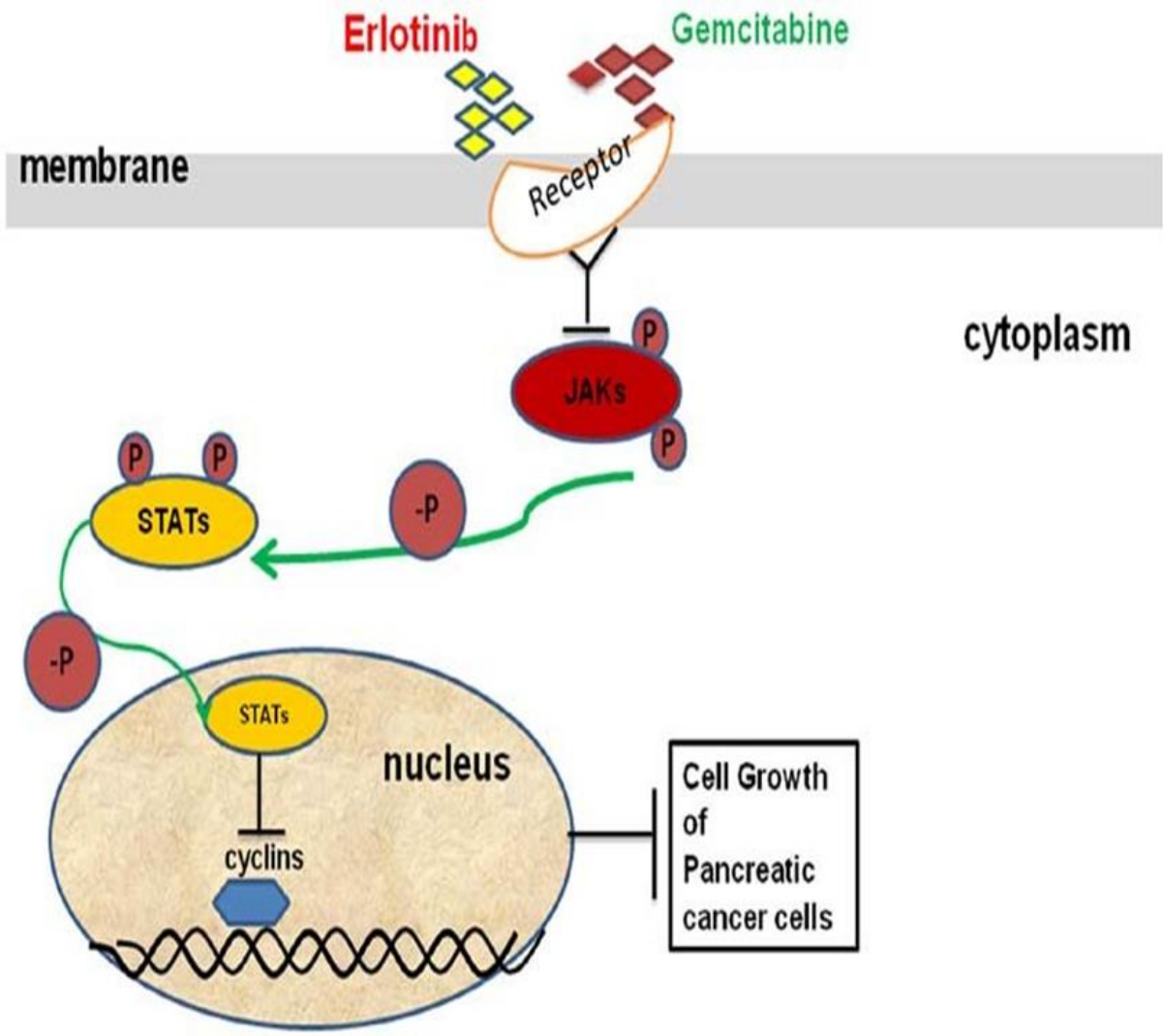
Targeted Therapy in Pancreatic Cancer

- EGFR Inhibitor
- PARP Inhibitor
- TRK Inhibitors
- VEGF Inhibitors



Erlotinib- EGFR Inhibitor

- It targets a protein on cancer cells called EGFR
- Combination with the chemotherapy gemcitabine is approved for use in advanced pancreatic adenocarcinoma.
- Dose 100 mg OD
- Common side effects of erlotinib include acne-like skin rash, diarrhea, nausea, appetite loss and fatigue.



PARP Inhibitor

- Blocks poly (ADP-ribose) polymerase (PARP), a protein that repairs damaged DNA in cancer cells.
- **Olaparib**
  - Combination with platinum-containing chemotherapy extend the PFS 1st line treatment.
  - Germline mutations of BRCA (BRCA1 or BRCA2)
  - Dose300 mg BD daily dose reduction if AE 1st 250 mg BD and 2nd 200mg BD
  - Common side effects of Olaparib include lowered blood cell count, nausea, vomiting, diarrhea, fatigue, upper respiratory tract infection and joint or muscle pain.

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Molecular Cancer

REVIEW Open Access

PARP inhibitors in pancreatic cancer: molecular mechanisms and clinical applications

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Abstract

Pancreatic cancer is a highly lethal disease with a poor prognosis, and existing therapies offer only limited effectiveness. Mutation gene sequencing has shown several gene associations that may account for its carcinogenesis, revealing a promising research direction. Poly (ADP-ribose) polymerase (PARP) inhibitors target tumor cells with a homologous recombination repair (HRR) deficiency based on the concept of synthetic lethality. The most prominent target gene is BRCA, in which mutations were first identified in breast cancer and ovarian cancer. PARP inhibitors can trap the PARP-1 protein at a single-stranded break/DNA lesion and disrupt its catalytic cycle, ultimately leading to replication fork progression and consequent double-strand breaks. For tumor cells with BRCA mutations, HRR loss would result in cell death. Pancreatic cancer has also been reported to have a strong relationship with BRCA gene mutations, which indicates that pancreatic cancer patients may benefit from PARP inhibitors. Several clinical trials are being conducted and have begun to yield results. For example, the POLO (Pancreatic Cancer Olaparib Ongoing) trial has demonstrated that the median progression-free survival was observably longer in the olaparib group than in the placebo group. However, PARP inhibitor resistance has partially precluded their use in clinical applications, and the major mechanism underlying this resistance is the restoration of HRR. Therefore, determining how to use PARP inhibitors in more clinical applications and how to avoid adverse effects, as well as prognosis and treatment response biomarkers, require additional research. This review elaborates on future prospects for the application of PARP inhibitors in pancreatic cancer.

Keywords: PARP inhibitor, Pancreatic cancer, BRCA, Synthetic lethality, Homologous recombination repair, Chemotherapy resistance, Biomarkers

Introduction

Pancreatic cancer is a highly fatal disease with a poor prognosis. The 5-year survival rate is a mere 9%, and the incidence has steadily increased worldwide over the past 3 decades. Moreover, it is the fourth leading cause of cancer death in both males and females of all ages in the USA [1, 2]. Surgical resection is considered the only potentially curative therapy; however, only 20% of the patients diagnosed with pancreatic cancer are candidates for initial resection. Because pancreatic cancer is often asymptomatic at the early stage, the disease has typically already progressed to an advanced stage at the time of diagnosis [3, 4]. Unfortunately, even after surgical resection, most patients eventually experience recurrence [5], and they receive limited benefit from and often become resistant to chemotherapy and radiotherapy. Thus, the current state of pancreatic cancer is a grim picture, and novel drug strategies are urgently needed. It has been well acknowledged that pancreatic cancer has many different molecular subgroups with unique biological characteristics, which is partially responsible for the poor effectiveness and drug resistance observed for existing treatments [6]. Therefore, it is essential to identify the molecular mechanism of different subsets of patients

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TRK Inhibitor

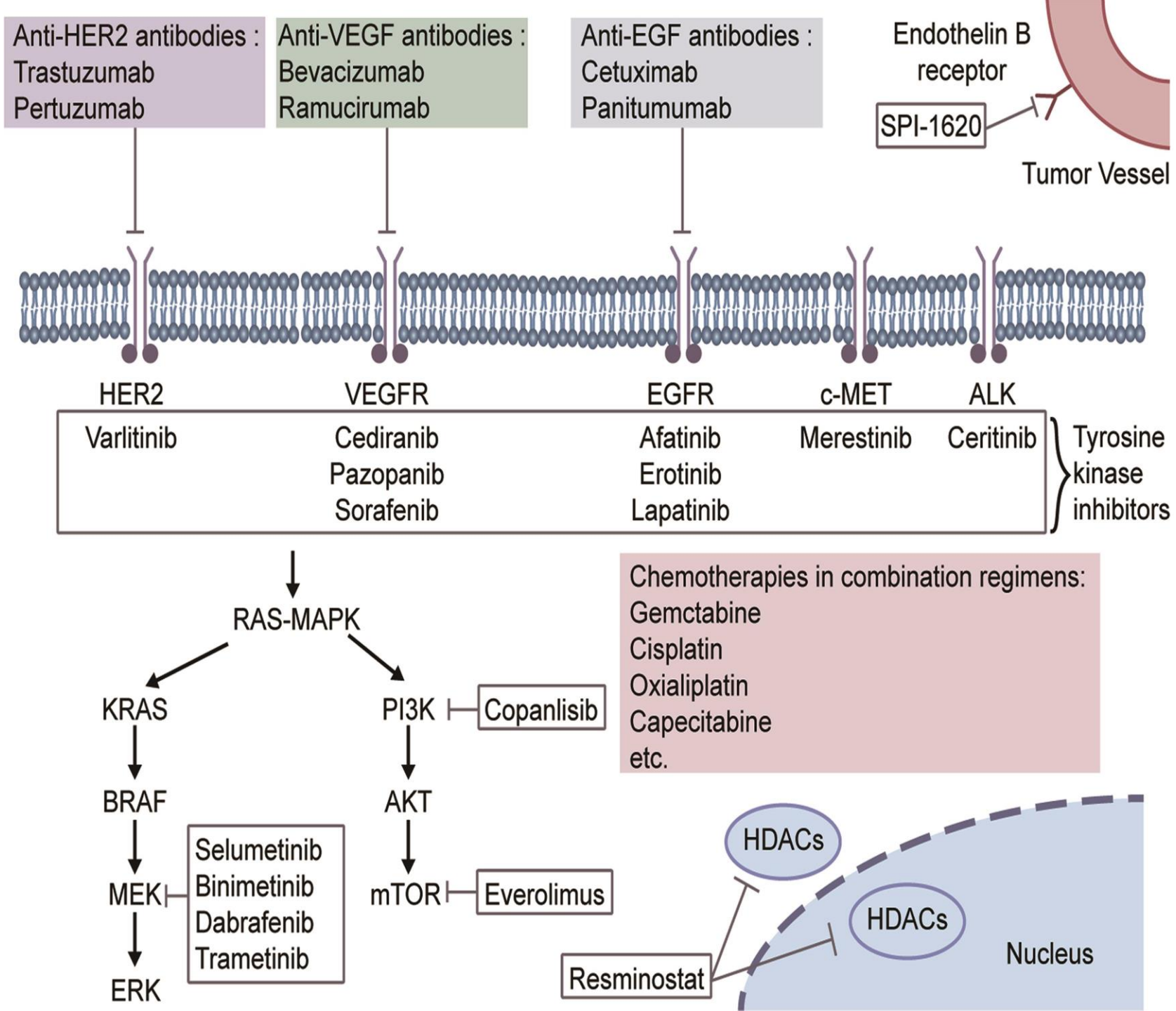
- It is very rare only in 0.5% patients
- **Vitrakvi and REK**
  - Vitrakvi (larotrectinib) 100 mg orally BD daily dose 1st reduction 75 mg orally BD daily 2nd reduction50 mg orally BD daily 3rd reduction 100 mg orally Daily.
  - ROZLYTREK (entrectinib) 600 mg orally OD, 1st dose reduction 400 mg OD, 2nddose reduction 200 mg OD
  - Common side effects of these treatments include fatigue, vomiting, constipation, dizziness, diarrhea and nausea

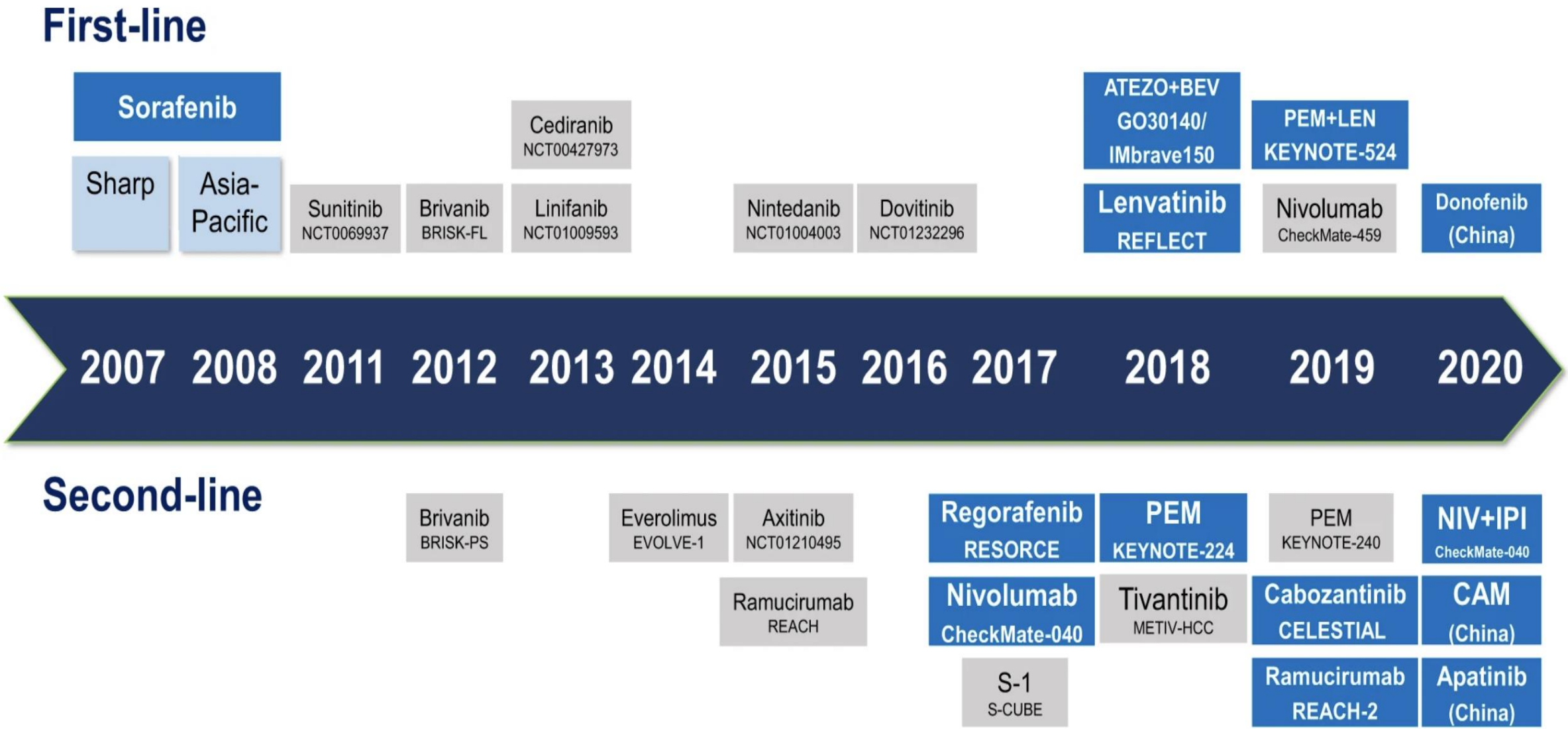
VEGF inhibitors

- 7% of pancreatic tumors are neuroendocrine tumors.
- **Sutent and Afinitor**
  - Taken as a daily pill
  - Sutent (sunitinib 37.5 mg) and Afinitor (everolimus 10 mg)
  - Common side effects of Sutent include lowered blood cell counts, diarrhea, upset stomach, nausea, vomiting, mouth sores, loss of appetite, fatigue and congestive heart failure.
  - Common side effects of Afinitor include lowered blood cell counts, fatigue, nausea, diarrhea, cough, mouth sores, high blood sugar and pneumonitis (inflamed lung tissue).

Targeted Therapy in Hepatocellular Carcinoma

- VEGF Inhibitors
- EGFR Inhibitor
- Her2-Positive Inhibitor
- C-MET
- ALK





Overview of the targeted agents approved for HCC. ATEZO atezolizumab, BEV bevacizumab, CAM camrelizumab, LEN lenvatinib, PEM pembrolizumab, NIV nivolumab, IPI ipilimumab

- Sorafenib and Lenvatinib most commonly used TKIs in HCC.
- Lenvatinib non inferior to Sorafenib in terms of OS. Improved ORR and PFS
- Atezolizumab+Bevacizumab shows improved outcomes compared to sorafenib alone hence new first line SOC. (IMbrave150)
- Refractory setting: regorafenib, cabozantenib and ramucirumab (in pts. with baseline AFP> 400ng/dl)

Conclusion

- Due to evolution of understanding of various targets which help in propagation of cancer there is a serge for development of various targeted treatments in cancer.
- There is some success of such agents in colorectal cancers thus tailoring the treatment to a personalized management.
- Some progress in the management of Gastric and GE cancers.
- However, the transition from bench to bedside is in progress with various bottlenecks including robust R & D infrastructure.
- Financial toxicity versus survival benefits needs to be kept in mind .

Thank You