Updates in Gastrointestinal (GI) Cancers

FLASCO Fall Session 2019

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MOFFITT CANCER CENTER

Objectives

1. Design a treatment plan for microsatellite instability high and BRAF mutant subtypes of colorectal cancer (CRC) based on emerging data

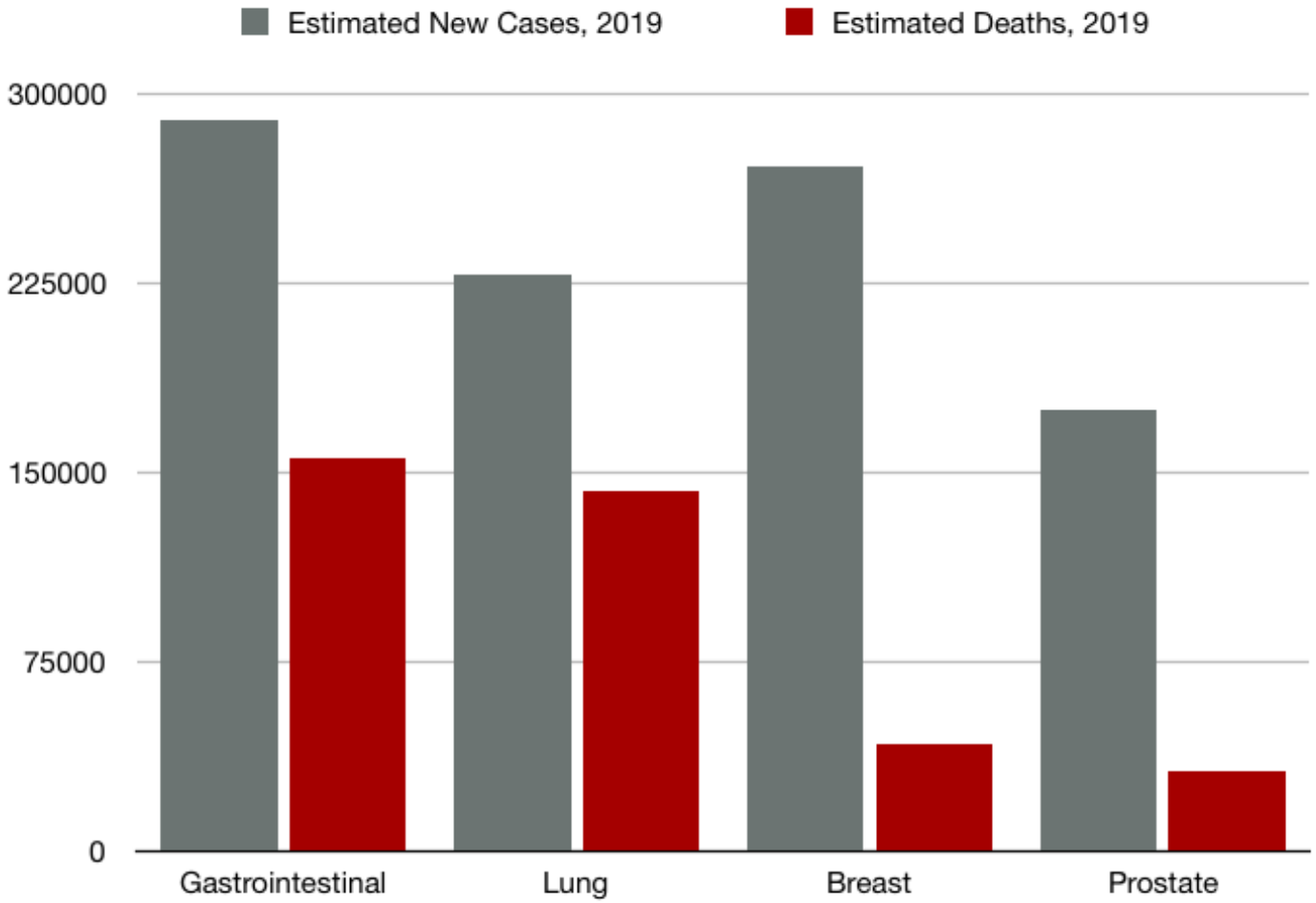
2. Highlight the recent strides made in the management of metastatic hepatocellular carcinoma (HCC)

3. Outline the latest therapies approved in gastric and gastroesophageal junction (G/GEJ) cancers including immunotherapy and trifluridine/tipiracil

4. Analyze new approaches in the management of resectable pancreatic cancer and BRCA mutated pancreatic cancer

GI Cancers – An Urgent Need

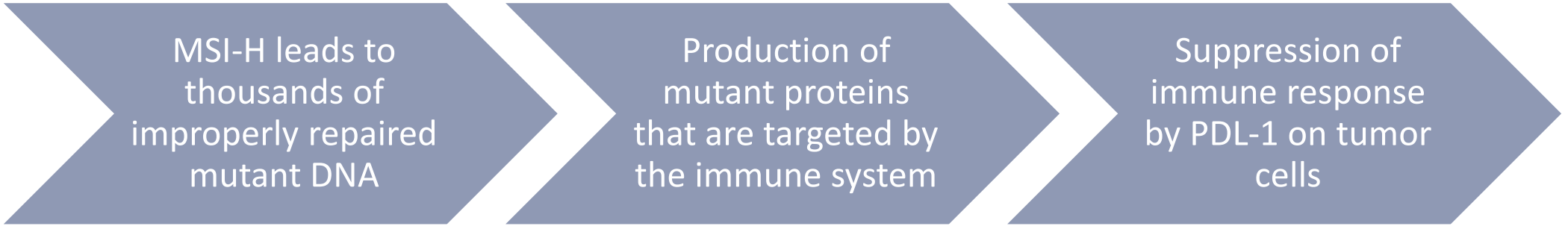
- Consists of cancers of the esophagus, stomach, liver, pancreas, small intestine, colon, rectum and anus
- Overall #1 cancers in incidence and mortality
- Rising incidence in age <50 - up from 6% in 1990 to 11% in 2013



Cancer Facts and Figures - available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2017-2019.pdf Accessed 10/2/2019.
SEER*Stat Database: available at https://seer.cancer.gov/explorer/ Accessed 10/2/2019.

Updates in CRC - MSI High Tumors

- Approximately 15% of colorectal cancers (CRC) display high level of microsatellite instability (MSI-H)
- Mutations affecting DNA mismatch repair genes: MLH1, MSH2, MSH6, PMS2
- Distinct histologic features
  - Mucin-rich, signet cell and medullary subtypes
  - **Active immune microenvironment as shown by an excess of tumor-infiltrating lymphocytes**



Gatalica Z, et al. Familial Cancer. 2016; 15:405–412.
Hewish M, et al. Nat. Rev. Clin. Oncol. 2010;7:197–208.

Pembrolizumab in MSI-H

	Le DT et al. (Keynote-016)	Le DT et al. (Keynote-164)
Prior therapy	Progression on ≥ 2 lines of therapy	Progression on ≥ 1 line of therapy
Number of Patients	28	63
Dose	10 mg/kg q3 weeks up to 2 years	200 mg q3 weeks up to 2 years
ORR (%)	40	32
Duration of resopnse	78% PFS at 5 months	41% PFS at 12 months

Pembrolizumab FDA approval in MSI-H mCRC: progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

Le DT et al. N Engl J Med 2015; 372:2509-2520.
Le DT et al. J Clin Oncol 2018; 36:15_suppl, 3514-3154.

ORR – objective response rate
mCRC – metastatic colorectal cancer

CheckMate-142 Study in MSI-H

	Nivolumab (N) Cohort	Previously treated Ipilimumab (I) + Nivolumab Cohort	First line Ipilimumab + Nivolumab Cohort
Prior therapy	Progression on ≥ 1 line of therapy	Progression on ≥ 1 line of therapy	No prior treatment
Number of Patients	74	119	45
Dose	N 3 mg/kg q2w	N 3 mg/kg + I 1 mg/kg q3w x 4 doses, then N 3 mg/kg q2w	N 3 mg/kg q2w + I 1 mg/kg q6w
ORR (%)	31.1	55	60
Duration of resopnse	PFS 50% at 12 months	PFS 71% at 12 months	83% at 12 months
Incidence of Grade 3 or 4 ADR (%)	20	33	16

Nivolumab FDA approval in MSI-H mCRC: progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan as a single agent or in combination with ipilimumab

Overman MJ et al. Lancet Oncol. 2017;18:1182-1191.
Overman MJ et al. Lancet Oncol. 2018;36:773-779.
Lenz JJ et al. *Annals of Oncology* 29 (Supplement 8): viii714–viii714, 2018.

ADR - adverse drug reaction

BRAF Mutations in CRC

- BRAF mutations occur in about 12% of CRC cases
  - More than 90% of these are V600E
  - Associated with poor differentiation, mucinous histology and microsatellite instability
- Poor outcomes - median OS <12 months
- BRAF inhibitor alone response - 2-5% ORR

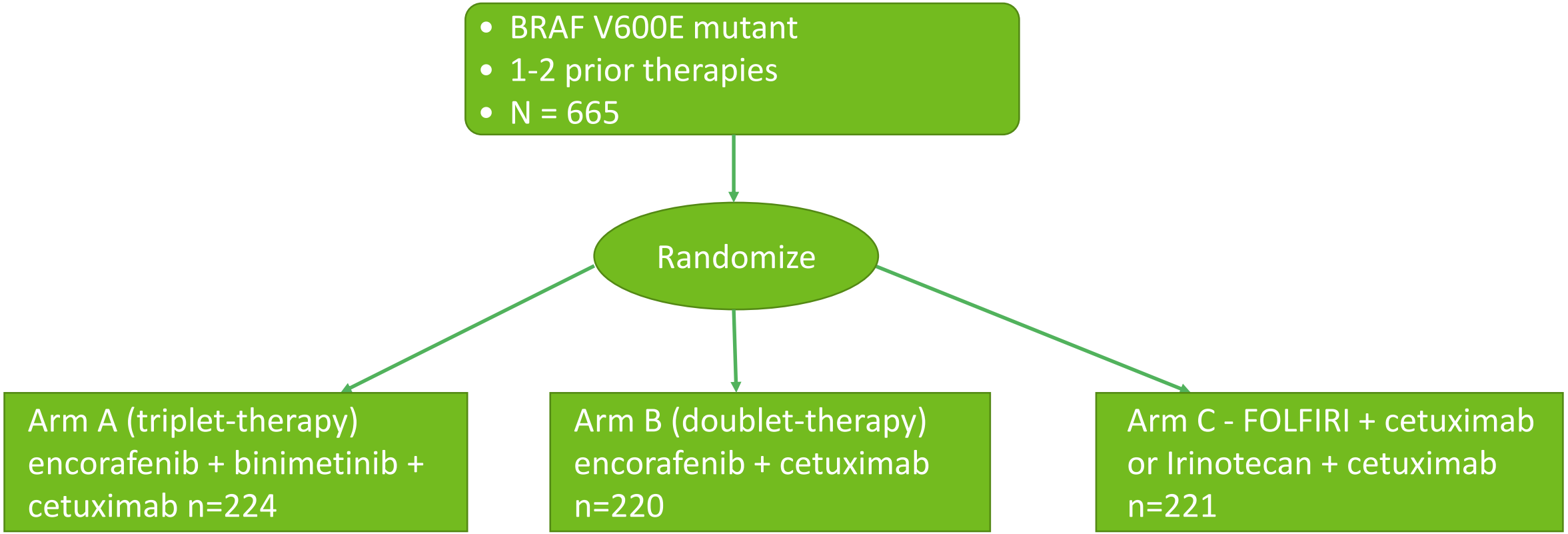
Venderbosch et al. Clinical Cancer Research. 2014;20(20):5322-5330.
Available at https://www.cbioportal.org. Accessed 9-27-2019.
Kopetz S et al. Journal of Clin Oncol. 2015;33(34):4032-4038.

Clinical Data in BRAF Mutant CRC

	ORR (%)	PFS (months)
Vemurafenib (n=21)	5	2.1
Dabrafenib + trametinib (n=43)	12	3.5
Encorafenib + cetuximab (n=52)	19.2	3.72
Vemurafenib + cetuximab + irinotecan (n=54)	16	4.3

Kopetz S et al. Journal of Clin Oncol. 2015;33(34):4032-4038.
Corcoran RB et al. J Clin Oncol 2015; 33:4023–4031.
Van Geel RMJM et al. Cancer Discov. 2017;7:610-9.
Tabernero J et al. J Clin Oncol 2016; 34:15_suppl,3544-3544.

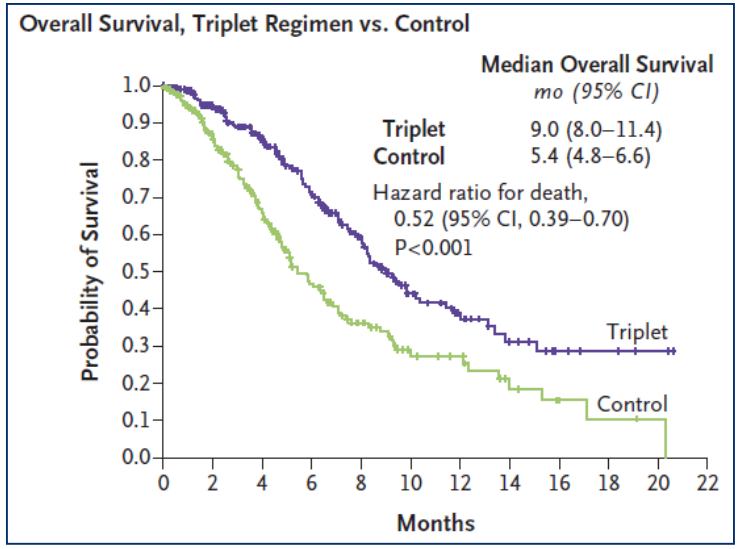
BEACON Trial – Study Design

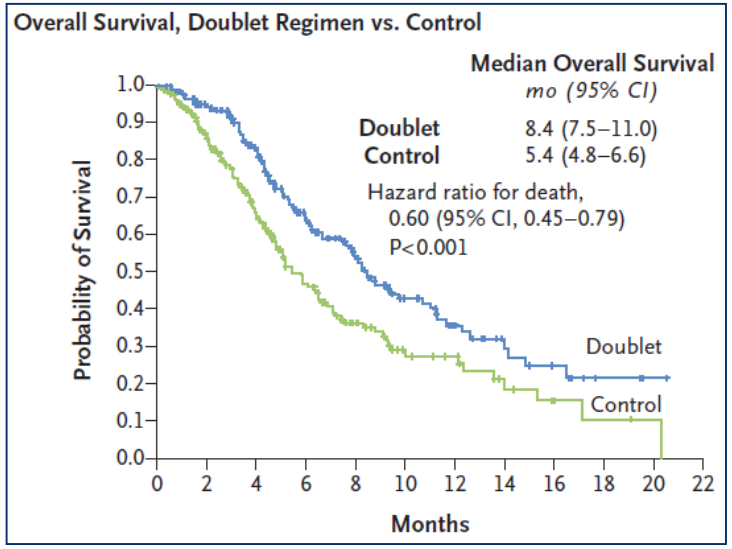


Dosing:
Encorafenib 300 mg daily
Binimetinib 45 mg bid
Cetuximab 400 mg/m2 loading dose then, 250 mg/m2 weekly

Kopetz S et al. New Eng J Med. 2019 Sept. DOI: 10.1056/NEJMoa1908075
Kopetz S et al. Annals of Oncology 30 (Supplement 4): iv137–iv151, 2019.

BEACON Trial - Outcomes





	Arm A (triplet), n=224	Arm B (doublet), n=221	Arm C (control), n=220
ORR, %	26	20	2
Median OS, mo	9	8.4	5.4
≥Grade 3 ADR, %	58	50	61

Treatment related adverse events:

More **GI side-effects** with **triplet-therapy** vs. doublet-therapy.

Headache, musculoskeletal pain, arthralgia, and myalgia occurred more frequently in the **doublet-therapy** group than in the triplet-therapy

Kopetz S et al. New Eng J Med. 2019 Oct. DOI: 10.1056/NEJMoa1908075.

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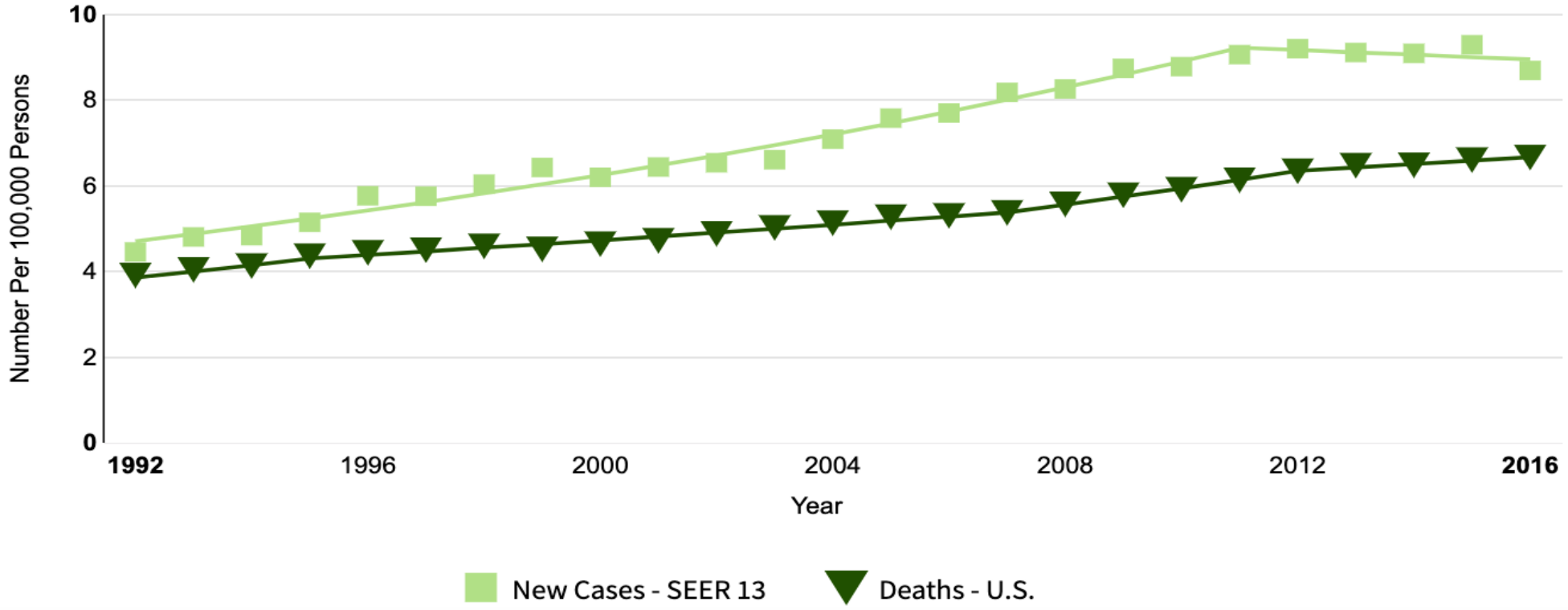
Hepatocellular Carcinoma – A Rising Trend

- New cases rising over the last decade on average 2% per year



HCC - New Cases and Deaths

SEER statistics. Liver and Intrahepatic Bile Duct Cancer. Available at https://seer.cancer.gov/statfacts/html/livibd.html. Accessed October 1, 2019.

HCC – hepatocellular carcinoma

Advanced HCC – Strides Made

NCCN 2017

Systemic Treatment Options

1. Sorafenib

NCCN 2019

Systemic Treatment Options

1. Sorafenib (first line and second line after lenvatinib)
2. Lenvatinib (first line)
3. Cabozantinib (second line)
4. Regorafenib (second line)
5. Ramucirumab (second line and AFP ≥400 ng/mL)
6. Pembrolizumab (second line)
7. Nivolumab (second line)

NCCN Guidelines. Hepatocelluar Carcinoma. Version 3.2019. Available at NCCN.org, Accessed 10/3/2019.

REFLECT Trial – Study Design

Global, phase 3, open-label, randomized, non-inferiority study design

- Unresectable HCC
- No prior therapy
- Child-Pugh Class A
- ECOG PS </= 1
- Adequate organ function
- N = 954

R

Lenvatinib 12 mg daily (weight ≥60 kg)
or Lenvatinib 8 mg (weight <60 kg)
n=478

Sorafenib 400 mg BID
n=476

Primary Endpoint – OS
Secondary Endpoint – PFS, ORR

Kudo et al. Lancet. 2018 Mar 24;391(10126):1163-1173.

ECOG PS – Eastern Cooperative Oncology Group Performance Status

REFLECT Trial – Outcomes

Efficacy	Lenvatinib	Sorafenib	Hazard Ratio
Median PFS, mo	7.4	3.7	0.64 (0.55–0.75), p<0.0001
Median OS, mo	13.6	12.3	0.92 (0.79–1.06)

Grade 3 or 4 ADR	Lenvatinib, %	Sorafenib, %
Hypertension	23	14
Palmar planter erythrodysaesthesia	3	11
Fatigue	4	4
Proteinuria	6	2
Diarrhea	4	4

Lenvatinib FDA approval: first-line treatment of unresectable hepatocellular carcinoma

Kudo et al. Lancet. 2018 Mar 24;391(10126):1163-1173.

TKI in Second Line HCC

Regorafenib (VEGF, PDGFR, RET etc.)

RESORCE study - regorafenib vs. placebo

- Child-Pugh Class A, previously tolerated at least sorafenib 400 mg daily
- Dose = 160 mg 3 weeks on 1 off

Results: Regorafenib improved median overall survival vs. placebo

- 10.6 months vs. 7.8 months, p<0.0001
- ADR: Hypertension, hand-foot syndrome and fatigue, increased LFT/bilirubin were common

Cabozantinib (CMET, PDGFR, VEGF, RET)

CELESTIAL study - cabozantinib vs. placebo

- Child-Pugh Class A, progressed on sorafenib
- Dose = 60 mg daily

Results: Cabozantinib improved median overall survival vs. placebo

- 10.2 months vs. 8.3 months, p=0.005
- ADR: hand-foot syndrome, hypertension, increased LFT, fatigue, diarrhea

Bruix, J et al. Lancet. 2017;389:56-66.
Abou-Alfa G, et al. N Engl J Med 2018; 379:54-63.

TKI – Tyrosine kinase inhibitor, LFT – Liver function test

Nivolumab CheckMate-040 Study

Non-randomized, open label, phase 1/2, dose-escalation and expansion study

- Progression or intolerance to sorafenib
- Child-Pugh Score 7 or less (Class A or B7)
- ECOG PS 0-1
- Dose: 3 mg/kg q 2 weeks

Results

- n=48 in dose escalation cohort, n=214 in expansion cohort
- Objective RR 20% in dose escalation cohort
- Objective RR 15% in expansion cohort

FDA granted accelerated approval in September 2017, based on median duration of response of 16.2 months

El-Khoueiry AB et al. Lancet. 2017 Jun 24;389(10088):2492-2502.

Pembrolizumab Keynote-224 Study

Non-randomized, open label, phase 2 study design

- Progression or intolerance to sorafenib
- Child-Pugh Class A
- ECOG PS 0-1
- Dose: 200 mg every 3 weeks

Results

- n=104
- Objective RR 16.3%
- Grade 3-4 ADR – 25%

At median follow up of 12.3 months, median duration of response was not reached

FDA granted accelerated approval in November 2018

Zhu AX et al. Lancet Oncol. 2018 Jul;19(7):940-952.

HCC Immunotherapy Recent Updates

Phase 3 CheckMate-459 study

- Randomized study, comparing nivolumab vs. sorafenib in first line setting
- Failed to meet primary endpoint of improved OS

Phase 3 Keynote-240 study

- Randomized study, comparing pembrolizumab vs. placebo in previously treated HCC
- Failed to meet primary endpoint of improved PFS+OS

BMS Press Release, June 24, 2019. Available at https://news.bms.com/press-release/bmy/bristol-myers-squibb-announces-results-checkmate-459-study-evaluating-opdivo-nivol Accessed, Sept 30th, 2019.
Yao T et al. Annals of Oncology (2019) 30 (suppl_5): v851-v934.
Finn R et al. J Clin Oncol 2019; 37:15_suppl,4004-4004.

Ramucirumab

Ramucirumab – monoclonal antibody inhibiting activation of VEGFR2

REACH trial - Ramucirumab vs. placebo, 2nd line, n=565

- Did not improve primary endpoint of OS
- Subgroup analysis showed potentially improved outcomes in AFP ≥ 400 ng/mL

REACH-2, randomized, placebo-controlled, 2nd line, and baseline AFP ≥ 400 ng/mL, Child-Pugh class A

- Median OS improved with ramucirumab vs. placebo, 8.5 vs. 7.3 months, [HR] 0·710 [95% CI 0·531–0·949]; p=0.0199

May 2019 - FDA approved ramucirumab in 2nd line HCC and AFP ≥ 400 ng/mL

Zhu AX et al. Lancet Oncol. 2015 Jul;16(7):859-70.
Zhu AX et al. Lancet Oncol. 2019 Feb;20(2):282-296.

AFP – Alpha feto-protein

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Recent Approvals G/GEJ Tumors

- Feb 2019 - trifluridine/ tipiracil FDA approved for advanced or metastatic gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, in third line setting

- May 2019 - Pembrolizumab FDA approved for advanced or metastatic esophageal **squamous cell carcinoma** (E-SCC) with CPS ≥ 10 in second line setting
  - 2017 – Pembrolizumab was previously approved for G/GEJ adenocarcinoma and CPS ≥ 1 in third line

Lonsurf [Package Insert]. Princeton, NJ; Taiho Oncology; February 2019.
Pembrolizumab [Package Insert]. Whitehouse Station, NJ. Merck and Co. Inc. September 2019.

TAGS Trial – Study Design

Randomized, double-blind, placebo-controlled study design

- G/GEJ Adenocarcinoma after at least 2 previous lines of therapy
- Adequate organ function
- N = 507
- Primary endpoint – overall survival

R 2:1

Trifluridine/Tipiracil (35 mg/m² BID on days 1–5 and 8–12) q28 days	Placebo

Shitara et al. Lancet Oncol. 2018 Nov;19(11):1437-1448.

TAGS Trial - Results

	Trifluridine/Tipiracil	Placebo	Hazard Ratio [CI]
Median PFS, mo	2	1.8	0·57 [0·47–0·70], p<0·0001
Median OS, mo	5.7	3.6	0.69 [0·56–0·85], p=0.00029

Most common grade 3-4 ADR with trifluridine/tipiracil

- Anemia (19%), neutropenia (25%), fatigue (7%) and decreased appetite (8%)

Shitara et al. Lancet Oncol. 2018 Nov;19(11):1437-1448.

Pembrolizumab for Esophageal SCC

	KN-181	KN-180
Subgroup	E-SCC, CPS ≥ 10	E-SCC, CPS ≥ 10
Prior therapy	Progression after 1st line therapy	Progression after 2 or more lines of therapy
Number of patients	85	35
ORR, %	22	20
Survival	Median OS 10.3 months	71% of responders alive at 6 months

May 2019 - FDA approved in second-line setting for esophageal SCC (E-SCC) and CPS ≥ 10

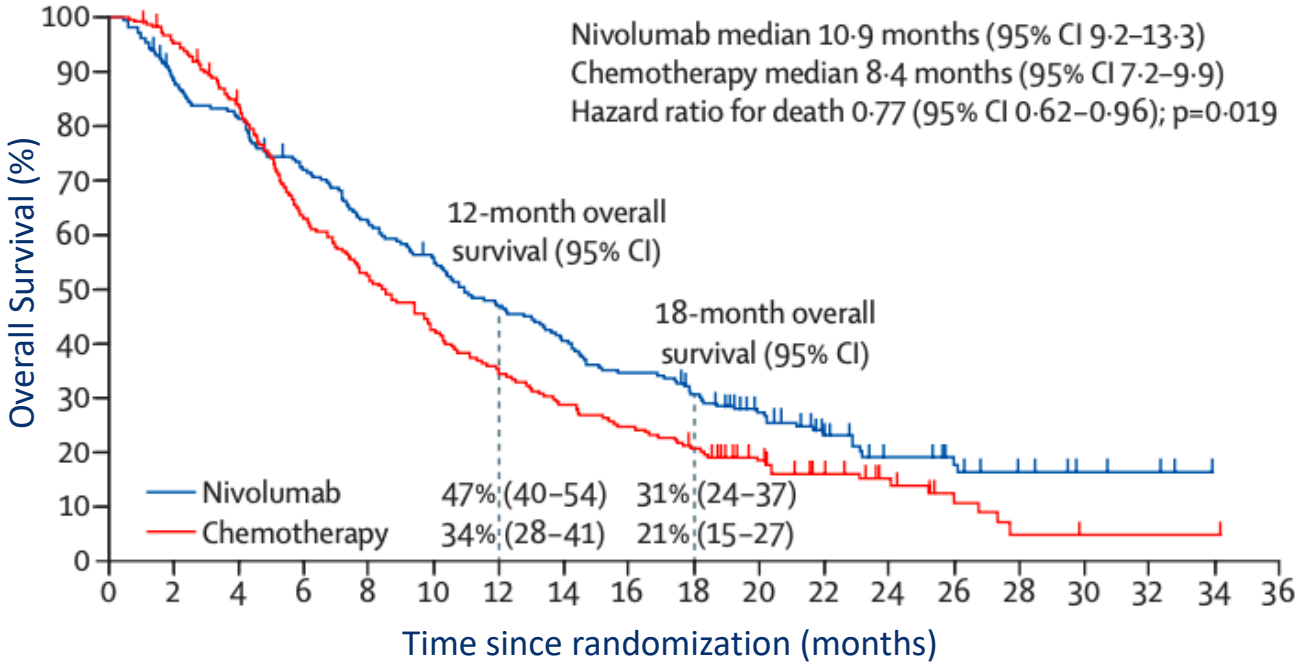
Shah M et al. JAMA Oncol. 2019;5(4):546-550.
Shah M et al. J Clin Oncol 2019; 37:15_suppl,4010-4010.

Nivolumab E-SCC – ATTRACTION-3 Trial

Phase 3, randomized, open label in patients with advanced E-SCC, progressed on one line of therapy

	Nivolumab	Investigator Choice
Number of patients	210	209
ORR, %	19	22
Survival*	10.9	8.4

*P=0.0019



96% of patient population was Asian → Global generalizability?

Kato K et al. Lancet Oncol. Oct 2019 Published Online. Available at https://doi.org/10.1016/ S1470-2045(19)30626-6. Accessed Oct 1, 2019.

Investigator choice chemotherapy: paclitaxel, irinotecan or docetaxel

Keynote-062 - First Line G/GEJ

Keynote-062 - randomized, phase 3 study, first-line G/GEJ adenocarcinoma tumors:

- 5-FU + platinum based chemo (C) vs.
- Pembrolizumab (P) monotherapy vs.
- P+C

P+ C did not meet primary endpoint for superiority vs. C

OS with P was non-inferior compared to C (10.6 months vs. 11.1 months)

Subgroups with CPS ≥ 10 or MSI-H had a greater response from immunotherapy

Tabernero et al. J Clin Oncol 37, 2019 (suppl; abstr LBA4007)

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Pancreatic Cancer

- Cure rate: 8%
- Moved from fourth leading cause of cancer-related death to third in 2016
    - Expected to become 2nd leading cause within the next decade
- Despite “curative” surgery less than 4% patients will survive 10 years or more

Pancreatic Cancer - Adjuvant Therapy

No significant advance in adjuvant treatment of pancreatic cancer in 30 years

- Best median OS has been around 28 months
- Gemcitabine +/- capecitabine was historical standard of care

This changed with the results from a phase III study comparing mFOLFIRINOX vs. gemcitabine

mFOLFIRINOX regimen:

- Oxaliplatin 85 mg/m2
- Leucovorin 400 mg/m2
- Irinotecan 150 mg/m2 (reduced from 185 mg/m2 after interim safety analysis)
- 5-FU 2400 mg/m2 CIVI over 46 hours
- No 5-FU bolus

Conroy T et al. N Engl J Med 2018; 379:2395-2406.

PRODIGE 24/CCTG PA.6 – Study Design

Multicenter, randomized, open-label, phase 3 trial conducted in France and Canada

- Pancreatic adenocarcinoma s/p R0 or R1 surgery
- Allowed up to 12 weeks of recovery from surgery
- Age 18-79; ECOG PS 0-1
- Randomized, open-label, multicenter study design
- Primary endpoint: disease free survival (DFS)

R

mFOLFIRINOX regimen every 14 days for 24 weeks
n=247

Gemcitabine 1000 mg/m2 on days 1, 8, 15 every 28 days for 24 weeks
n=246

Conroy T et al. N Engl J Med 2018; 379:2395-2406.

PRODIGE 24/CCTG PA.6 – Results

	mFOLFIRINOX	Gemcitabine	Hazard Ratio and CI
Median DFS, mo	21.6	12.8	0.58 (0.46–0.73), p<0.001
Median OS, mo	54.4	35	0.64 (0.48–0.86), p=0.003

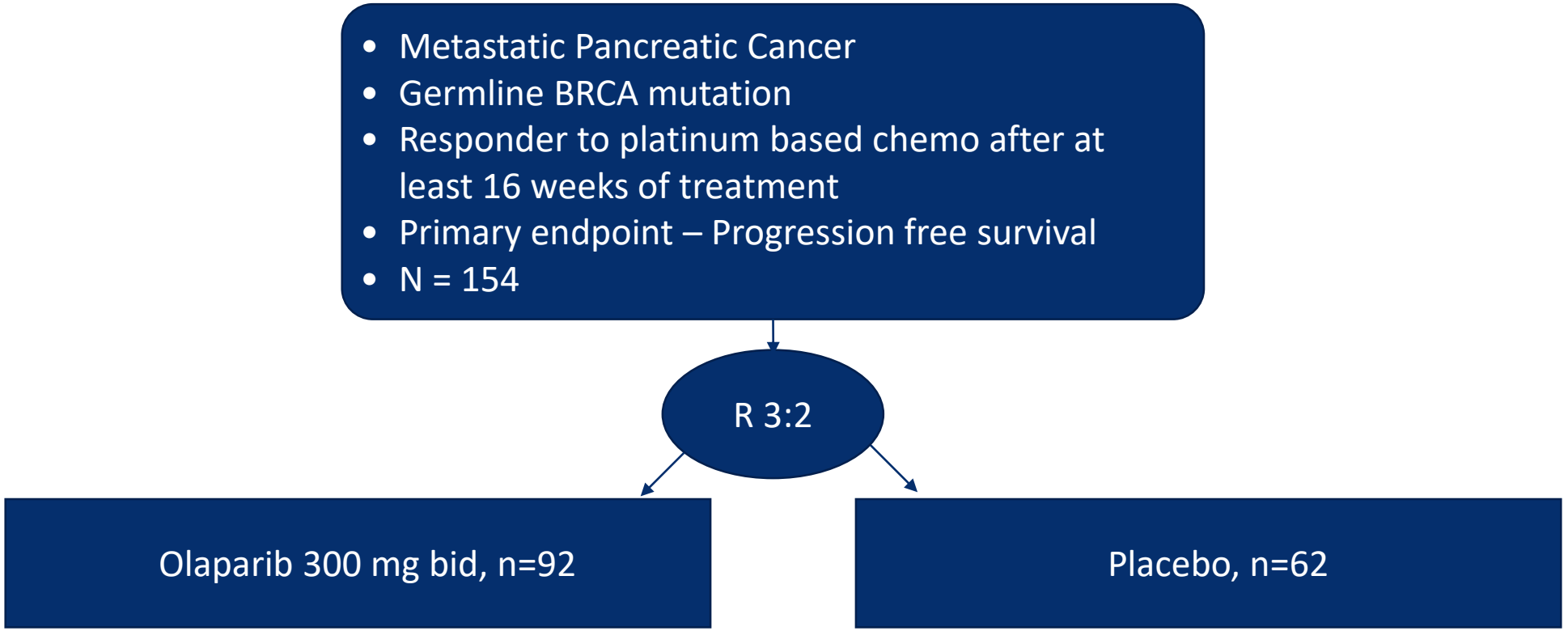
Grade 3 or 4 ADR	mFOLFIRINOX, %	Gemcitabine, %
Nausea/Vomiting	10.6	2
Fatigue	11	4.6
Diarrhea	18.6	3.7
Paresthesia/Sensory neuropathy	23	0
Thrombocytopenia	1.3	4.5
Neutropenia	28.4	26

mFOLFIRINOX – is now the new standard of care in adjuvant pancreatic cancer after R0 or R1 surgery

Conroy T et al. N Engl J Med 2018; 379:2395-2406.

POLO Study - Maintenance Olaparib

Global, randomized, double-blind, placebo-controlled, phase 3 trial



Golan T et al. N Engl J Med 2019; 381:317-327.

POLO Study Results

	Olaparib	Placebo	Hazard Ratio [CI]
Median PFS, mo	7.4	3.8	0·53 [0·35–0·82], p=0·004
Median OS, mo (interim analysis)	18.9	18.1	0.91 [0·56–1.46], p=0.68

- Most common grade 3-4 ADR: anemia (11%), fatigue (5%), decreased appetite (3%)
- No difference in health-related quality of life between 2 groups

Golan T et al. N Engl J Med 2019; 381:317-327.

Summary

1. Pembrolizumab, nivolumab and combination of nivolumab + ipilimumab are approved in MSI-H mCRC. Benefit appears to be of the highest magnitude with combination regimen.

2. BRAF mutated mCRC carries a poor prognosis. Recent studies indicate a combination of BRAF inhibitor, MEK inhibitor AND EGFR inhibitor improves ORR and OS vs. chemotherapy alone.

3. Several new options, including TKI, anti-VEGFR monoclonal antibody and immunotherapy, are now available in HCC compared to just a few years ago.

4. Trifluridine/tipiracil was recently approved in G/GEJ cancers in the third line setting. Pembrolizumab is now a second-line option in patients with E-SCC and CPS≥ 10.

5. mFOLFIRINOX is the new standard of care in adjuvant treatment of pancreatic cancer.

Questions?

Acknowledgements:

- FLASCO & Program Committee
- Moffitt GI Med-Onc and Pharmacy Team
- Our patients