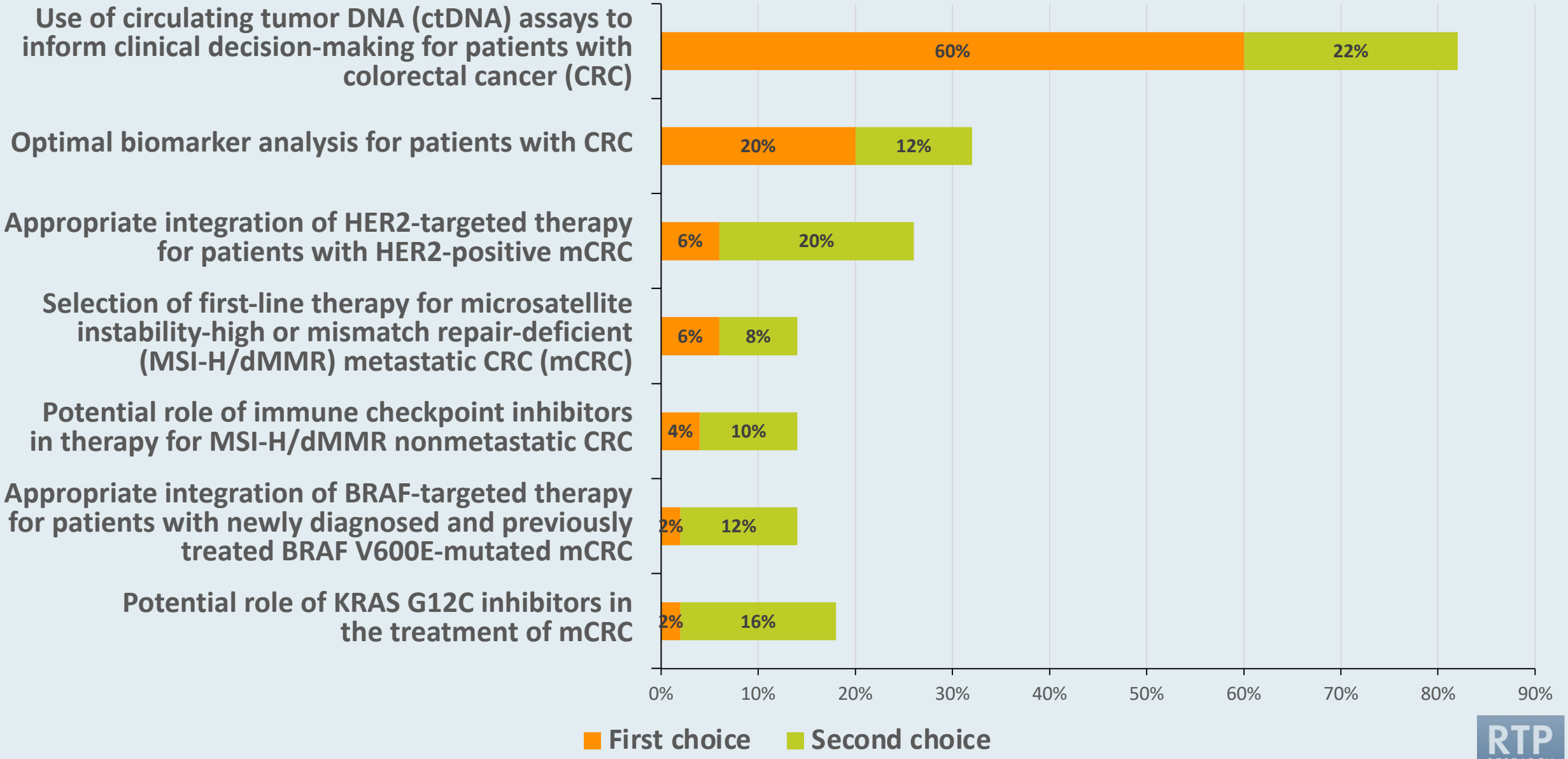
Survey of General Medical Oncologists: January 10 – January 16, 2025

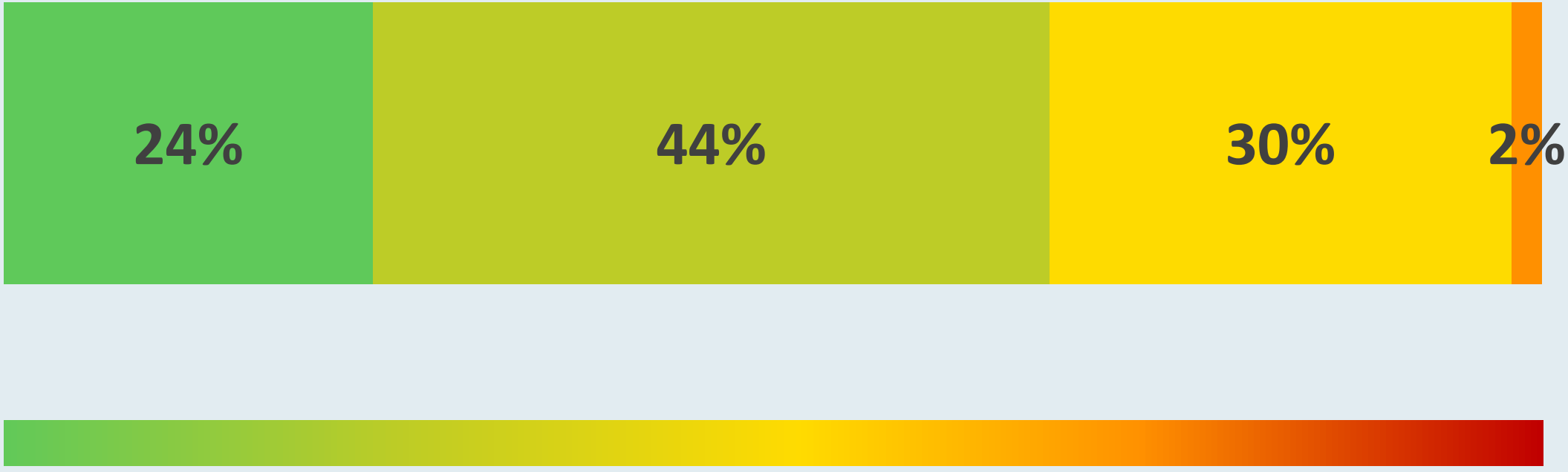
Results available on iPads and Zoom chat room

RTP
RESEARCH
TO PRACTICE

Topics of Interest for Future CME Programs



How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to optimal biomarker analysis for patients with CRC?



RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about optimal biomarker analysis for patients with CRC

- Need to understand BRAF testing in setting of MSH promoter methylation and relevance of genetic testing in this setting
- Will pts with HER2+ mCRC respond to EGFR inhibitors? Previous answer was no, now I'm not so sure
- I am informed enough. But I could still use your help on this topic. Do you have a systemic treatment strategy based on various markers?
- Would you use Nivo/ipi first line?
- Combination immunotherapy I feel comfortable. Question that I struggle with is combination of checkpoint chemotherapy in MSI-H pt population, especially who have high tumor burden, where I may be concerned about checkpoint flare. In curative setting, stage 3 colon cancer, any role of just doing checkpoint inhibitor and avoiding surgery if CR? When to stop checkpoint inhibitor with mCRC in CR. Role of circulating DNA to guide when to stop checkpoint inhibitor in MSI-H CRC
- Which patient should get which third-line agent for mCRC? Who is best treated with fruquintinib?
- What are actionable biomarkers in CRC?
- What biomarker tests impact first-line treatment?

Questions from general medical oncologists about optimal biomarker analysis for patients with CRC (continued)

- What is the role of liquid bx in relapse disease?
- Sequencing in BRAF mutation-positive patient, start with FOLFIRINOX plus bev and then EC versus now EC plus FOLFOX?
- Front-line therapy of choice for metastatic CRC MSI high. Duration of therapy if NED
- Clinical application of ctDNA if positive and negative scans
- What do you do for a patient who is on surveillance and has rising CEA without evidence of recurrence of staging scans?
- Pt with mCRC has progression of disease on imaging on FOLFOX but ctDNA is negative and ctDNA was positive prior to starting FOLFOX
- For a patient who is claudin 18 positive, would you consider new agents off label?
- Use of ctDNA for decision-making in Stage 2 and 3 colon cancer
- Many patients with CRC have PIK3A mutations as the sole mutation. Is this targeted in CRC with PIK3 inhibitors?
- I use Tempus for essentially all my patients. If there is no ERBB2 amplification seen, do I still need to have HER2 by IHC?
- NGS-based testing (liquid and tissue) for early stages 1, 2, is this routinely done?

Questions from general medical oncologists about optimal biomarker analysis for patients with CRC (continued)

- I try to get broad NGS panel, IHC and MSI. Sometimes insurance denies broad NGS and then will have to resort to testing RAS/HER2/MSI alone. Do investigators have a preference as to which method they use?
- In addition to RAS, BRAF, HER2, RET, PD-L1, MMR, TMB, NTRK, are there any emerging biomarkers? Claudin 18.2 (but I think that's mostly for eso/GEJ)? POLE testing?
- Which targets are highest priority?
- Pt with wild-type RAS and positive HER2, 2 situations:
  - HER2 2+, FISH-positive
  - HER amplified on NGS

  1L treatment in each of these scenarios
- When deciding to offer adjuvant therapy to stage 2/3 patients, how do you factor in the molecular profile? Eg, when I have an otherwise average risk stage 2 patient who is mKRAS or mBRAF or HER2 amplified, will that influence your decision to offer treatment vs observation?
- What about toxicities in patients who received BRAF V600E-directed therapy in front line?
- What is the first-line treatment recommended for patients with multiple mutations present such as HER2, MSI high? How should we expect to find patterns of mutations in terms of any being mutually exclusive?

RTP RESEARCH TO PRACTICE

Questions from general medical oncologists about optimal biomarker analysis for patients with CRC (continued)

- What is the high-quality evidence in regard to treatment for HER2 altered advanced CRC?
- Have there been any studies confirming the survival benefit for closely following guidelines?
- Role of biomarker evaluations at progression and what methodology should be used, liquid vs tissue
- Different/best ways to detect biomarkers — tissue, blood, etc
- Any upcoming biomarkers that will have impact on treatment in both nonmetastatic and metastatic CRC?
- 78 y/o male with oligometastatic colon cancer, EGFR/KRAS negative, HER2 mutated, post Rt upper lobectomy on adjuvant/palliative FOLFOX + panitumumab. Would you use HER2 targeted therapy in the first or second line?
- Would you recommend occasionally checking GUARDANT360® or similar test during the treatment for met colon cancer?
- What to do about KRAS G12V mutation in CRC
- Should we be adding trastuzumab to first-line therapy for HER2 over-expressed CRC? Why wait for second line?
- Biomarker based therapy
- Would you recommend running tumor mutational analysis at every possible relapse?

RTP RESEARCH TO PRACTICE

Questions from general medical oncologists about optimal biomarker analysis for patients with CRC (continued)

- How do we sequence therapies optimally using sidedness, RAS, HER2 status?
- 1. What is the optimal approach for testing biomarkers, especially if there's limited tissue block, any top 4-5 biomarkers you recommend to prioritize in this scenario?
  2. Is it acceptable to send NGS from blood (liquid biopsy) if ctDNA is positive? If yes, do we know if that has good correlation with the tissue biopsy NGS?
  3. Any noticeable differences in testing biomarkers from primary tumor vs from a metastatic site (like liver or lung)?
- HER2 positivity definition, any difference in upper GI tract and colorectal?
- Right now, I check in NGS panel — MSI-H, MMR status, KRAS and NRAS including KRASG12C, BRAFV600E, HER2 by IHC and FISH, NTRK, RET alterations — are there any markers that are significant other than the ones mentioned above? I see lot of APC mutations — are there any targets in development for it? Also, I have a patient with STK11 on genetic testing, are there any targeted therapies in development for it?
- Do you recommend biopsy in progression for biomarkers re-analysis?
- How often should ctDNA be checked in the adjuvant setting?
- Is there any utility in repeating testing over the course of the disease?

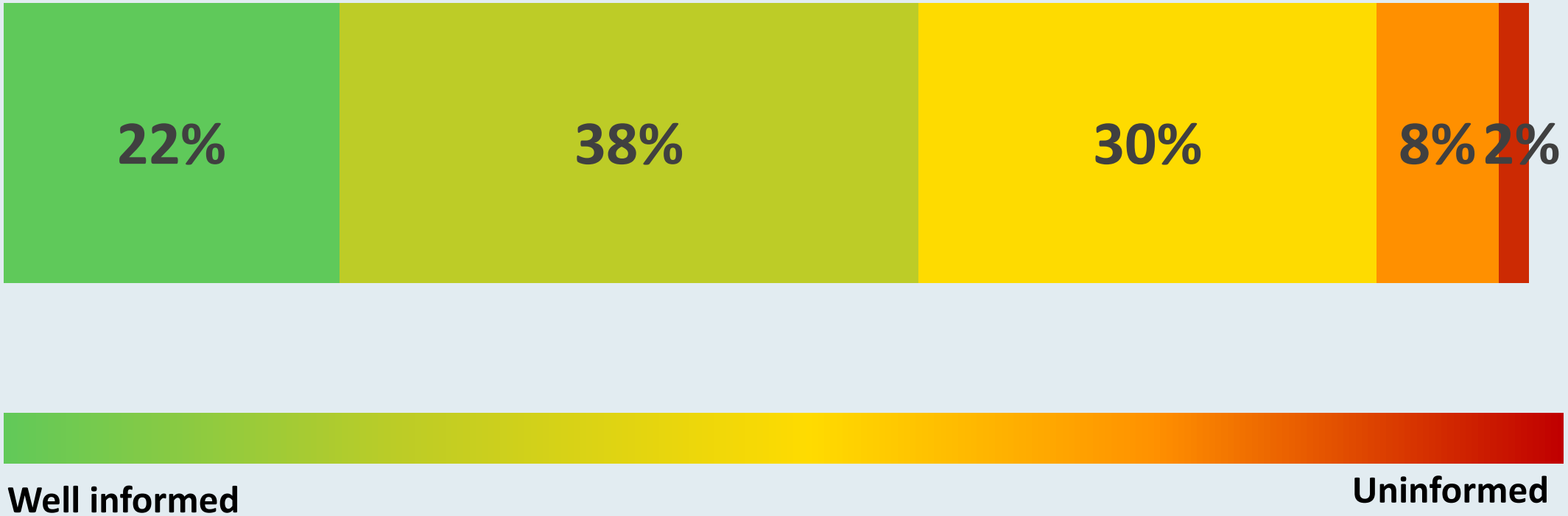
RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about optimal biomarker analysis for patients with CRC (continued)

- When should we repeat biomarker during adjuvant, metastatic setting?
- In first-line treatment of oligometastatic colon cancer with liver mets, with RAS mutation, is FOLFIRINOX plus beva optimal first-line Tx than FOLFOX plus beva?
- Biomarker analysis pretty standard at diagnosis, but when do you recommend repeating NGS, if at all, at progression?
- 50-year-old male with M1 (distant nodal) CRC, received chemo, definitive RT and surgery for curative intent. KRAS WT. Now recurrence and PD on capecitabine, bevacizumab, FOLFOX cetuximab. FOLFIRI. Remains asymptomatic low disease burden. Would investigators ever consider re using EGFR targeted agent if it has been a while since pt received and he remains KRAS WT? (Other biomarkers neg pMMR HER2 neg)
- What's the minimum biomarkers to test for?
- Besides NGS are there any new techniques we should be using to check for biomarkers?
- I have a patient that is RIGHT SIDED (sigmoid) colon cancer with metastatic disease on first-line FOLFOX bevacizumab. KRAS wt. Is FOLFIRI bevacizumab or panitumumab a better second line?

RTP
RESEARCH TO PRACTICE

How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC?



RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC

- Is there a role of combining immunotherapy with chemotherapy in patients with high burden of visceral metastatic disease?
- Would you use ipi-nivo in the 1L setting for mCRC pts, dMMR/MSI-H, if approved? How to decide over pembrolizumab monotherapy?
- Please discuss: Nivolumab + ipilimumab vs chemotherapy as first- and second-line treatment for MSI-H/dMMR mCRC and nonmetastatic CRC patients. Looking for some case studies
- How long would you continue immunotherapy? 2 years?
- I feel very comfortable with rectal ca and checkpoint inhibitor data. That question is not well answered in which selected pt population you can avoid surgery, if treated with neoadjuvant checkpoint inhibitor, esp Stage 3 colon cancer. Role of checkpoint in adjuvant setting, with or without chemotherapy
- Is there a role for combining chemotherapy with immunotherapy?
- Use of IO therapy and which IO therapy
- What is the optimal treatment for MSI-H neoadjuvant therapy?
- When to use nivo plus ipi vs nivo only
- Immunotherapy of choice?
- Integration in the first line and continuation through the lines

Questions from general medical oncologists about the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC (continued)

- Do you ever consider neoadjuvant immune therapy for patients with MSI-H colon cancer?
- Would you consider IO without chemo as adjuvant therapy in ctDNA-positive stage II or stage III CRC?
- For a patient who is also TMB-H, how to choose between pembro vs nivo/ipi?
- A 52-yo male with rectal cancer, MSI-H, and positive lymph nodes on PET/CT. What would be the recommended regimen of CPIs and duration of treatment?
- A common scenario is sometimes older patients who have high-risk stage 3 CRC who are MSI-H. If not candidates for FOLFOX or even if they are, would you use immunotherapy outside of a trial without chemotherapy? I did this recently with a 90-year-old pt with stage 3c colon cancer
- A 65yo WM with T3N1 colon cancer. MSI high. Outside of clinical trials, do I still offer FOLFOX? Or you prefer ctDNA to guide treatment?
- Role of immunotherapy for MSI-H/dMMR in stage 3?
- Had a patient with localized cecal cancer, clinically appeared to be stage III. dMMR. Surgeon was not sure about getting clear margins, as the tumor was opposed/possibly involving peritoneum locally. There are several IO neoadjuvant trials, ended up starting pembrolizumab with plan to reevaluate after 3 cycles, currently on C2. Questions: Optimal neoadjuvant treatment single vs double IO, duration pre surgery, whether IO should be continued after surgery?

RTP RESEARCH TO PRACTICE

Questions from general medical oncologists about the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC (continued)

- 84yo F ECOG 3 with MSI high metastatic colon cancer treated with ipi nivo followed by nivolumab for 6 months with minimal response/stable disease. She declined IV chemotherapy. Changed to capecitabine and 2 months later scans showed complete response. I suspect delayed response to immunotherapy, but as she is doing well on capecitabine, she continues on that for now. Would investigators switch back to maintenance immunotherapy or maybe add it on with capecitabine?
- Optimal IO therapy?
- T3 N1 or N2 colon ca, MSI-H BRAF hypermethylated, optimal treatment
- NCCN recommends adjuvant IO for rectal cancer and also in the setting of metastatic colorectal cancer. Are we poised to recommend IO for adjuvant colon as well? Is there a reason we would approach colon cancer differently than rectal cancer when it comes to chemotherapy and immunotherapy?
- Explain about KRAS inhibitors in colon cancer, is adagrasib superior to sotorasib combination?
- What is the available data in how to guide whether we should consider first-line dual IO vs single IO with or without chemo?
- What is the high-quality evidence for neoadjuvant treatment of MSI-H rectal carcinoma — I recall the one *NEJM*/ASCO discussion but there doesn't seem to be much

Questions from general medical oncologists about the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC (continued)

- Would you recommend IO instead of traditional FOLFOX for resected stage 3 MSI high CRC?
- Use as neoadjuvant or perioperative regimens?
- What to induce immunogenicity for I/O use in non-MSI-high tumors
- Is there any role of adjuvant CPI in nonmetastatic CRC who are ineligible for chemo?
- I never add chemo to ICI in front-line metastatic MSI-H cancer and have had immense success with pembrolizumab with patients NED off therapy for many years. It is like magic! Because of that, I never give adjuvant chemotherapy to stage 3 MSI-I CRC but prefer to wait until they are metastatic. Is it wrong to do that?
  PS: None of the stage 3 patients has progressed in the past 3 years.
- What is the best initial treatment for nonmetastatic MSI-high colon cancer?
- What are data on adjuvant immunotherapy in MSI-H/dMMR in early-stage colorectal cancer?
- When will immune therapy be standard adjuvant therapy for stage 3 disease? Does it matter if you are MSI-high due to genetic vs somatic (methylation) in treating the patient?
- How to sequence therapy after immunotherapy?
- Do you recommend immune check inhibitors adjuvant therapy over chemo in stage 2 CRC and add ICI to FOLFOX or CAPOX in stage 3?

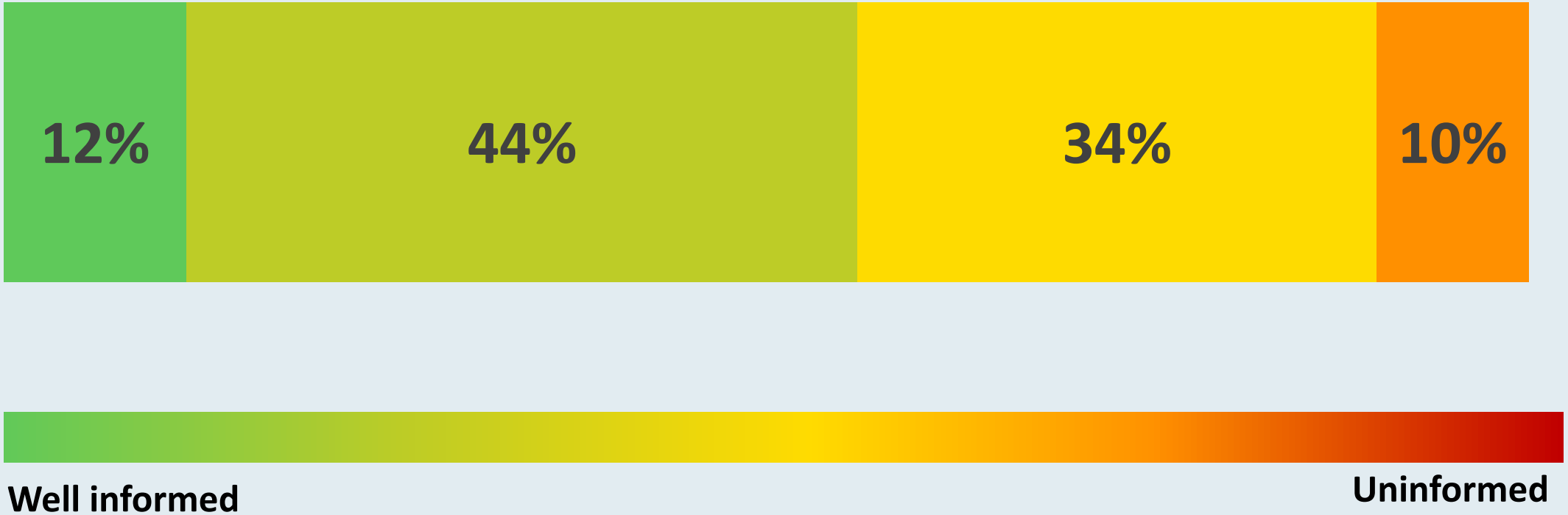
Questions from general medical oncologists about the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC (continued)

- Are there MSI-H met colon cancer patients that may benefit from chemo-immuno (say FOLFOX/Pembro) or double IO in front line?
- Any role of perioperative immunotherapy in such patients, extrapolating from the rectal cancer data space?
- Should we offer neoadjuvant immunotherapy for locally advanced colon cancer?
- 50-year-old patient with stage IIIA MSI-H CRC with ctDNA positive, what is most appropriate adjuvant treatment, role of checkpoint inhibitors in adjuvant therapy?
- Would you recommend adjuvant IO to stage 2 or 3 CRC, with or without chemo?
- Any role for Pembro or Nivo?
- Is MSI high by itself a good reason to start patients on IO based therapy?
- When to use PD-1 in neoadjuvant setting and adjuvant setting?
- In case of complete response to first-line ICI, can I omit therapy with it?
- For colon, not rectal, cancer, what role if any does neoadjuvant checkpoint inhibitor play?
- What would investigators recommend for stage II high risk patient with dMMR? What if they are elderly with neuropathy but T4 disease, would you ever consider immuno?

Questions from general medical oncologists about the potential role of immune checkpoint inhibitors in therapy for MSI-H/dMMR nonmetastatic CRC (continued)

- **What's the best first-line immune regimen?**
- **In a patient with MSI-H colon cancer in the adjuvant setting, can immunotherapy alone be used instead of chemo as adjuvant therapy?**
- **If treated with ICI, can you use in metastatic setting?**

How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to the use of ctDNA assays to inform clinical decision-making for patients with CRC?



RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the use of ctDNA assays to inform clinical decision-making for patients with CRC

- How to better define/assess role of ctDNA in patients with stage 2 and stage 3 colon cancer
- How does this assist with practical decisions, beyond recurrence monitoring? Are these being used to assist adjuvant therapy decisions, particularly in stage III colon ca, or perhaps the length or intensity of adjuvant therapy?
- It is also based on the topic above. I have a patient in 2L mCRC, finished Neoadj treatment. Went through surgery. Planning on adj therapy shortly. Treatment choices and options? Patient is 62, male, ECOG 1
- How often do you use ctDNA to stop chemo?
- The challenge I have is that in my clinical practice at VA, ctDNA requires authorization and can be considered in a pt with Stage 2 colon cancer, where adjuvant chemotherapy is being potentially considered. Routine monitoring with ctDNA is not done. I have seen pts from community practice with Signatera™ being done every 4 months and that is not available to me, nor do I see how it adds to value-based medicine. Also, ctDNA is not likely to be elevated with pts with lung mets. Also, role of ctDNA after metastectomy surveillance, or using that to give adjuvant therapy after metastectomy
- When can ctDNA replace imaging studies in determining a patient's response to therapy?
- When and how to use ctDNA in treatment of CRC

RTP RESEARCH TO PRACTICE

Questions from general medical oncologists about the use of ctDNA assays to inform clinical decision-making for patients with CRC (continued)

- Where and when, outside of stage II cancer, should ctDNA be used if at all?
- Why test stage 3 patients with ctDNA if no clinical trial available?
- Differentiate between use of tests such as Signatera and Guardant360
- Picking the right candidate for the test to avoid pitfalls?
- I have a patient with resected stage IV (hepatectomy for isolated liver met). What is the role of ctDNA in surveillance for this patient?
- What would be role of ctDNA in management of stage III colon ca?
- Given the mixed data regarding longitudinal ctDNA testing, what is your preferred approach?
- A 52 yo male with colon cancer, MSI-H and liver mets, would you use ctDNA to make decisions about duration of therapy?
- Do you think it should be standard of care to withhold chemotherapy in standard risk stage 2a CRC who have a postoperative negative ctDNA test?
- A 54-year-old man with T3N2 colon cancer s/p 6 months of capecitabine chemo. ctDNA was positive at the initiation of chemo. It was negative during and right after chemo. About 6 months later, the Signatera showed ctDNA 0.6%. Repeated the test in 6 weeks and 3 months were about the same. No increase. CT, PET and MRI of the liver were all unremarkable. What does this low value of ctDNA mean?

RTP RESEARCH TO PRACTICE

Questions from general medical oncologists about the use of ctDNA assays to inform clinical decision-making for patients with CRC (continued)

- How often to check for MRD, in advanced stages? Every 3 months?
- Are there any clinically meaningful differences/false neg-pos between tumor guided vs non-tumor guided ctDNA tests?
- ctDNA can help determine whether adj tx can be stopped at 3 months or extended to 6 months. However, for patients that develop ctDNA positive on surveillance after adj therapy, is there any evidence to support doing anything other than more frequent scans/endoscopy?
- How to best utilize?
- Except for stage 2 CRC, still struggling with optimal use of ctDNA
- If you are using ctDNA in surveillance, how much does CEA and imaging add? Can we omit CEA and imaging or are we just adding additional testing?
- When can we let go adjuvant treatment in Stage II-III colon cancer based on ctDNA result? How often should we monitor?
- What predictive data do we have to begin using ctDNA regularly in the clinic?
- What is the high-quality evidence to use these assays in regard to Stage II adjuvant therapy? Doesn't seem to be much
- Is ctDNA ready for prime time to guide the de-escalation of adjuvant treatment for stage 3 CRC?

RTP
RESEARCH TO PRACTICE

Questions from general medical oncologists about the use of ctDNA assays to inform clinical decision-making for patients with CRC (continued)

- ctDNA positivity treatment recommendations if imaging is negative?
- Is it valid? Other tumor types
- Should one change chemo if ctDNA is persistently positive or rising in adjuvant setting?
- I know it is recommended not to use negative ctDNA to de-escalate therapy, but it is really tempting and I have done it for low-risk stage 3 disease. How strongly would you recommend against it?
- Is there any proven reason to check for ctDNA?
- How often do you test ctDNA in surveillance stage? Do you use ctDNA in metastatic colon cancer to determine treatment break?
- Other than stage II disease, where is the utility for ctDNA?
- Is this NCCN guideline based?
- Newer data from studies in *JAMA Onc* suggests ctDNA may not be as helpful as previously thought in clinical decision-making and may even have false-negative test results. What is your opinion on the future application of ctDNA?
- Utility of ctDNA in organ preservation/nonsurgical management of rectal cancer after TNT

Questions from general medical oncologists about the use of ctDNA assays to inform clinical decision-making for patients with CRC (continued)

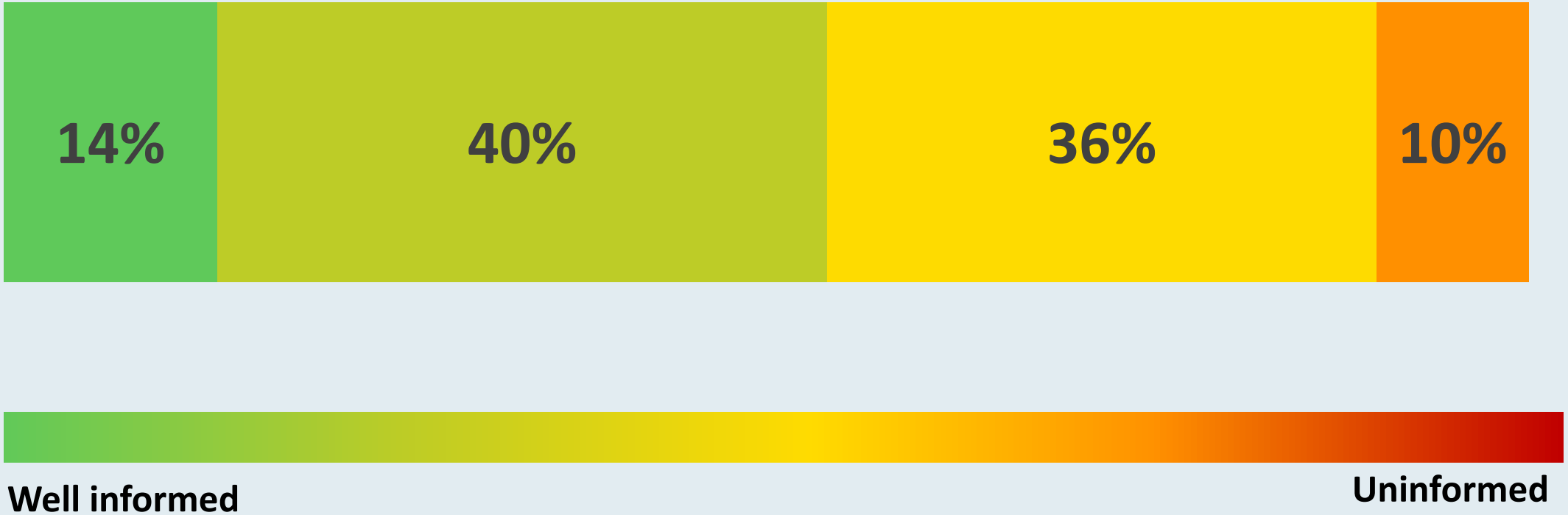
- 65 y/o M with Stage III colon cancer has positive ctDNA after surgery, then has adjuvant therapy with 5-FU and oxaliplatin, subsequent ctDNA negative after 3 months and onwards of adjuvant therapy.
  Surveillance scans after 3, 6 months & 12 months of adjuvant therapy NED but ctDNA starts becoming positive at 12 month period. Repeat in 2 months shows mild increase in ctDNA levels.
  What would you recommend as ideal management in this situation? Wait and watch for metastatic lesions to appear on scans? Or start treatment based on positive ctDNA?
- Are we allowed to omit chemo for stage III colon cancer patient who has negative tumor-informed ctDNA test after surgery?
- I have a patient 50 yr old with a Stage II colon ca, recurrence in peritoneum initially detected on ctDNA analysis before imaging, treated initially with FOLFOX + bevacizumab with excellent response, followed by HIPEC and adjuvant FOLFOX to complete 6 months therapy. 3 months after completion, ? peritoneal disease on CT, ctDNA positive at low levels, genetic testing VUS SMARCA4. She has KRAS G12V mutation on next-gen sequencing. Is FOLFIRI + bevacizumab best next option?
- Off protocol, would you use ctDNA to decide on adjuvant chemo in stage 3 CRC?

RTP
RESEARCH TO PRACTICE

Questions from general medical oncologists about the use of ctDNA assays to inform clinical decision-making for patients with CRC (continued)

- How often to image positive ctDNA pt?
- The main question in my mind is what is the optimal timing and clinical scenarios where one could order ctDNA?
- What is the role of ctDNA in stage III colon cancer?
- Patient with resected colorectal liver mets after adjuvant Tx for resected colon cancer, after resection of liver mets, we need further systemic Tx or not?
- Outside of ongoing trials, how does ctDNA result change adjuvant decision-making, if at all?
- 43-year-old female stage II colon cancer and clinically obstructing, close margin. She was unsure about chemo. We drew ctDNA as it could be influential esp if positive. Would investigators ever use ctDNA off trial in stage II?
- Is it ready for prime time to de-escalate therapy?
- I still do not know what to do with ctDNA that is positive but scans are negative in CRC. If ctDNA is positive, what should we do when scans are negative? I don't see the utility of using this test until we know when we should treat based on it
- If a patient is stage IIa with MULTIPLE high risk features, would you offer adjuvant treatment even if ctDNA was negative?

How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to the appropriate integration of BRAF-targeted therapy for patients with newly diagnosed and previously treated BRAF V600E-mutated mCRC?



RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the appropriate integration of BRAF-targeted therapy for patients with newly diagnosed and previously treated BRAF V600E-mutated mCRC

- Can BRAF targeted therapy be combined with chemotherapy in patients with high burden of visceral metastatic disease?
- If a pt with progression on 1L mFOLFOX6/cetuximab/encorafenib, what's the optimal 2L therapy?
- AE associated with encorafenib and cetuximab in BRAF V600E mCRC patients. Any further updates on the BEACON CRC study?
- Would you use Enco/bini first line?
- Would like to know more about use of BRAF/EGFR combination along with VEGF inhibitor.
- Use of BRAF inhibitors with chemotherapy, or in the first line, or adjuvant?
- What is the role of BRAF-targeted therapy as initial treatment rather than salvage therapy after failure with FOLFOX or FOLFIRI?
- What line of therapy to use BRAF targeted treatments?
- What line of therapy should BRAF inhibition be used?
  What are the optimal agents?
- Sequence EC later versus up front with the new FDA approval?
- Change in practice based on recent FDA approval?

RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the appropriate integration of BRAF-targeted therapy for patients with newly diagnosed and previously treated BRAF V600E-mutated mCRC (continued)

- Using it in relapsed BRAF ... need toxicity management education
- 85 F with metastatic colon ca (de novo) with liver mets. She has MSI-H disease and BRAF mutation. She progressed on first-line pembrolizumab. How would you dose BRAF/MEK inhibitor in an 85-year-old?
- Would you consider adding cetuximab with encorafenib to FOLFIRI in BRAF V600E who has progressed on FOLFOX initially?
- With the newest FDA approval, do you prefer to use BRAF agents in 1L or 2L?
- Discuss the sequence of therapy for patients with BRAF mutated disease
- Are patients with BRAF V600E mutations who also are MSI-H more likely to respond to BRAF inhibitor therapy?
- For young and healthy patients with stage IV mCRC, do we give FOLFOX + Bev or FOLFIRINOX + Bev?
- How to sequence these targeted therapies?
- Would you use BRAF targeted therapy as initial therapy for BRAF V600E mutated mCRC? Or would this be reserved for the second line following the usual FOLFOX/FOLFIRI +/- EGFR/bev regimens?

Questions from general medical oncologists about the appropriate integration of BRAF-targeted therapy for patients with newly diagnosed and previously treated BRAF V600E-mutated mCRC (continued)

- When to use BRAF targeting
- Have the results of the BREAKWATER trial changed your first-line treatment?
- Toxicity concerns
- What is the available data for how to incorporate BRAF targeted therapy particularly if BRAF mutation in context of MSI-H? Is this the same mechanism as Lynch related MSI-H?
- Has survival benefit been demonstrated with this strategy?
- Is there any role for continuing BRAF inhibitor beyond progression?
- Use in first-line combinations or maintenance therapy prior to progression?
- Is it whack-a-mole?
- Should BRAF therapy be utilized in earlier lines?
- Is BRAF V600E mutation as poorly prognostic in L sided as in R sided colon cancer?
- For metastatic disease how do you sequence therapies?
- How do you overcome hyperthermia while using a BRAF inhibitor?
- In CRC why do we block the receptor and BRAF vs in melanoma we block BRAF and MEK?
- What to use for first- and second-line BRAF-positive colon cancer?

RTP
RESEARCH TO PRACTICE

Questions from general medical oncologists about the appropriate integration of BRAF-targeted therapy for patients with newly diagnosed and previously treated BRAF V600E-mutated mCRC (continued)

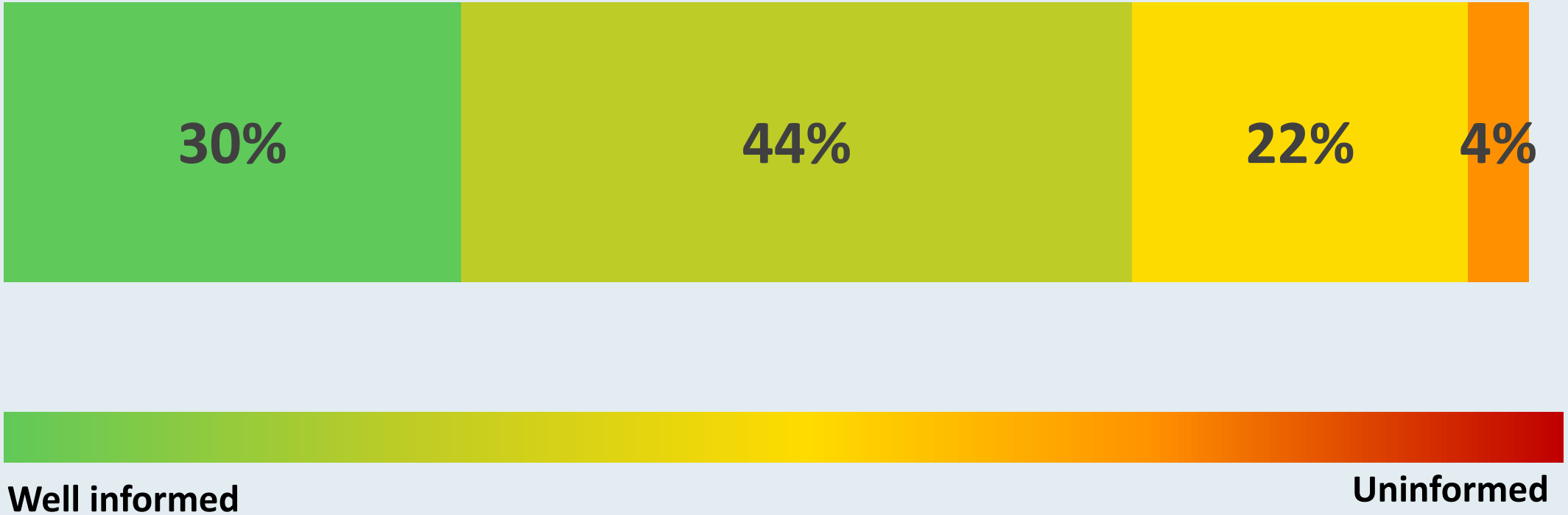
- Would you add targeted therapy to all eligible patients on FOLFOX and FOLFOXIRI?
- Optimal front-line strategy for BRAF mutated colon cancer. Does sidedness matter?
- What would be the ideal line of therapy in which we would introduce BRAF inhibitor therapy? Second line or even in some cases first line?
  Would this be acceptable as a first-line systemic therapy approach for recurrent disease in a 70 y/o M who has had FOLFOX previously for Stage III colon cancer 12 months ago and has residual neuropathy from that therapy and wishes to avoid 5-FU again?
- Should we add BEACON CRC regimen into chemo backbone now without OS data?
- I want to know more about toxicity of integrating chemo with targeted therapy in first-line management of BRAF mutation metastatic CRC
- Encora plus anti-EGFR antibody without chemo in first line for PS2 patients
- If MSI is also high what tx is preferred in first line vs second line?
- When do you use BRAF targeted therapy in the first line?
- In case of BRAF aggressive mutation, first line with FOLFIRINOX better than FOLFOX if no access to encorafenib?

RTP
RESEARCH TO PRACTICE

Questions from general medical oncologists about the appropriate integration of BRAF-targeted therapy for patients with newly diagnosed and previously treated BRAF V600E-mutated mCRC (continued)

- DPD testing used to be a send-out for us. Sometimes took too long to come back! Now I'm house but I'm curious in community how often this is checked?
- Are we ready to bring targeted therapy to first line?
- Any opportunities to pair BRAF with immunotherapy in this place?
- BRAF targeted treatment in right-sided colon cancer in second-line metastatic?

How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to the selection of first-line therapy for MSI-H/dMMR mCRC?



RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the selection of first-line therapy for MSI-H/dMMR mCRC

- Are there any studies going on combining nivolumab with relatlimab as a first-line therapy in patients with MSI-H colon cancer, in the hopes of gaining the same efficacy while decreasing the side effects?
- For a pt with progression on 1L mFOLFOX6/cetuximab/encorafenib, what's the optimal 2L therapy?
- When do you use Nivo/ipi first line?
- In which clinical scenario would I pick single agent vs doublet checkpoint? Timing when to stop? Surveillance with ctDNA while on checkpoint inhibitor?
- Should immunotherapy be combined with chemotherapy as initial treatment?
- Use of pembrolizumab vs nivolumab/ipilimumab
- Should one or two drugs be used?
  Is there any role for dual IO after failure of single-agent IO?
- Up-front nivo plus ipi vs nivo?
- In which situations would you do monotherapy?
- Integration in the first line?

RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the selection of first-line therapy for MSI-H/dMMR mCRC (continued)

- 85 F with metastatic colon ca (de novo) with liver mets. She has MSI-H disease and BRAF mutation. Would you treat her first line with immune therapy or anti-BRAF therapy?
- Pt with low burden disease, would you consider single or dual IO therapy?
- For a patient who is also TMB-H, how to choose between pembro vs nivo/ipi?
- I would want a discussion of combination immunotherapy or combination immuno-chemotherapy
- How do you determine whether to use dual checkpoint inhibitors vs single IO?
- I have several older patients that I treat with single-agent pembrolizumab. What is the front-line therapy for a younger patient? When patients fail single-agent PD-L1 treatment, can the patient be salvaged by adding anti-CTLA-4?
- With so many new agents, which to choose for first line?
- Have not treated mCRC with IO recently. Is there a preference between single vs double IO strategies?
- Ipi nivo vs pembro monotherapy for MSI-high mCRC?
- Best IO choices?
- For first line, optimal treatment chemo + IO or ipi + nivo?

Questions from general medical oncologists about the selection of first-line therapy for MSI-H/dMMR mCRC (continued)

- A Crohn's patient with a hx of fistulae currently well controlled on biologicals — would you try IO therapy? What can the gastroenterologist do to help enable this? Any pearls to share?
- Is nivo/ipi better compared to pembrolizumab alone?
- When to use single vs dual IO first line?
- Is there any difference between checkpoint inhibitors in this context?
- Is there any efficacy difference between the currently available options?
- Monotherapy vs combination with CTLA-4i or chemotherapy?
- Rechallenge/continue treatment with toxicity (in patients with no other treatment options)?
- Is there a benefit to combination chemo/IO in this setting vs IO alone?
  Ipi/Nivo vs pembrolizumab, which is preferred?
- Ipi/Nivo or just Nivo?
- What is your experience with immunotherapy in patients with liver mets?
- Single agent vs dual blockage? Is there a way to determine if there are some patients who need one vs others that need both CTLA-4 and PD-L1 blockage?
- Which one to use, ipi/nivo or pembrolizumab, as first line

RTP
RESEARCH
TO PRACTICE

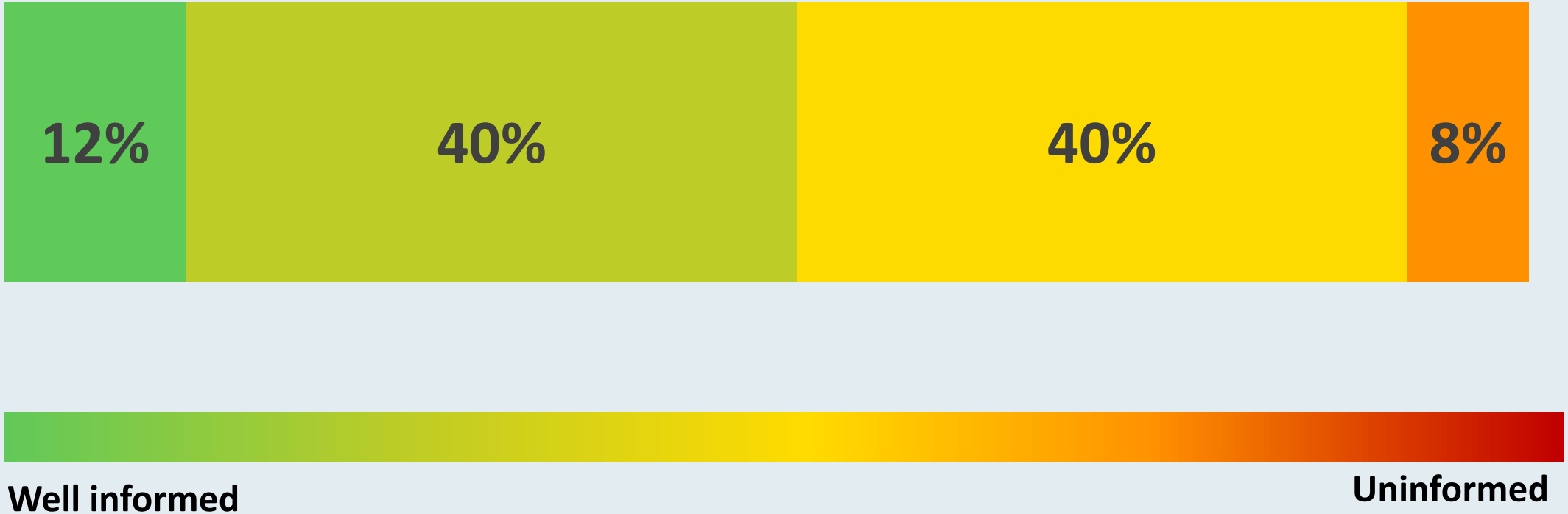
Questions from general medical oncologists about the selection of first-line therapy for MSI-H/dMMR mCRC (continued)

- In what group of patients would you add chemo (FOLFOX) to single-agent pembrolizumab in first-line metastatic colorectal cancer?
- Any role for salvage immunotherapy options in patients that have progressed after prior immunotherapy?
- Any difference with the addition of chemotherapy with immunotherapy, especially for a younger, fit patient with high-volume disease, similar to a debulking/induction approach, followed by maintenance immunotherapy approach?
- Dual immunotherapy vs single PD-1 inhibitor
- When to use Nivo + ipi vs pembro single agent?
- Single agent Pembro vs combination IO
- Any role for combined Ipi with Nivo?
- What IO therapy is preferred?
- When would you use ipi nivo?
- If patient progresses on first-line immunotherapy, what is the appropriate second-line Tx?
- What patients would be better served with ipi/nivo, then pembro for 1L MSI-H?

Questions from general medical oncologists about the selection of first-line therapy for MSI-H/dMMR mCRC (continued)

- HER2-positive colon cancer sent to me for second opinion. Received T-DXd before trastuzumab/tucatinib. Would you ever consider trastuzumab/tucatinib, or what would be the next line?
- Should we use combo therapy vs single agent?
- I'm not sure what drugs to use in this space. Any role for dual immunotherapy, or should we move back to standard chemotherapy (FOLFOX, FOLFIRI)?
- If immunotherapy is not an option, what is the best choice?

How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to the appropriate integration of HER2-targeted therapy for patients with HER2-positive mCRC?



Questions from general medical oncologists about the appropriate integration of HER2-targeted therapy for patients with HER2-positive mCRC

- What are the long-term outcomes of treatment with a tucatinib-trastuzumab based regimen?
- HER2 3+ or 2+, which is more relevant? T-DXd based on tumor-agnostic approval, or tucatinib-trastuzumab, which is likely more effective? Will these pts respond to EGFR inhibitors?
- Discussion around treatment integration of HER2-targeted agents and sequencing of HER2 agents
- What line do you use T-DXd?
- Like in breast cancer, can metastasis be heterogeneous? That means a separate site of met may be HER2/neu-positive when the primary is negative. Or the emergence of HER2/neu-positivity as we see the pattern in breast cancer, resulting in a need for multiple biopsy and testing. HER2/neu mutation testing and recommendation. Is there data, just like in esophageal ca, with a combination of checkpoint, trastuzumab and chemotherapy if PD-L1 over 1% and HER2/neu-positive?
- Why does tucatinib play such a prominent role in treating these patients?
- Which product to use — trastuzumab vs pertuzumab vs trastuzumab deruxtecan
- How common is HER2 disease? What is the optimal testing?
- When to test and when to add?

RTP
RESEARCH TO PRACTICE

Questions from general medical oncologists about the appropriate integration of HER2-targeted therapy for patients with HER2-positive mCRC (continued)

- What testing for HER2 status?
- Which line to start the treatment with HER2 meds and which agents?
- 90yo F with HER2-positive metastatic colon cancer: Would you consider first-line anti-HER2 therapy for this patient?
- Is there any role of HER2-directed therapy in pts with HER2 mutation without overexpression?
- For patients with ILD and other contraindications to T-DXd, would you prefer trastuzumab in 1L?
- 67 yo with stage 3 colon cancer and HER2 positive, what is the role of adding anti-HER2 treatment as adjuvant therapy?
  What would be the sequence of using trastuzumab deruxtecan?
  Is there any role for trastuzumab deruxtecan in HER2-low colon cancer?
- What is the optimal anti-HER2 therapy and would you use it in second or third line?
- I usually use oxaliplatin-based chemo as the first line, and tucatinib/trastuzumab as the second-line therapy. When it fails, do you recommend T-DXd or FOLFIRI?
- Can these agents be used even for HER2 low? Like breast cancer?

RTP
RESEARCH TO PRACTICE

Questions from general medical oncologists about the appropriate integration of HER2-targeted therapy for patients with HER2-positive mCRC (continued)

- Newly diagnosed HER2 IHC-positive mCRC with brain mets — use T-DXd as initial therapy due to CNS activity?
- Best combo and sequencing?
- Role of just HP in HER2-positive CRC?
- How effective is T-DXd when administered after trastuzumab/tucatinib?
- Is it in third line?
- What data do we have to incorporate into the first line and what is the hierarchy among other possible mutations present?
- What is the frequency of such patients in a community-based population?
- Will you incorporate HER2-directed therapy in the front-line setting?
- T-DXd prior to or after tucatinib, other potential ADCs
- What about HER2 low?
- Should HER2 targeted therapy be combined with chemo up front?
- Is it appropriate to target HER2 in high-risk stage 3 adjuvant therapy and front line in stage IV?
- Which anti-HER2 therapy is preferred?

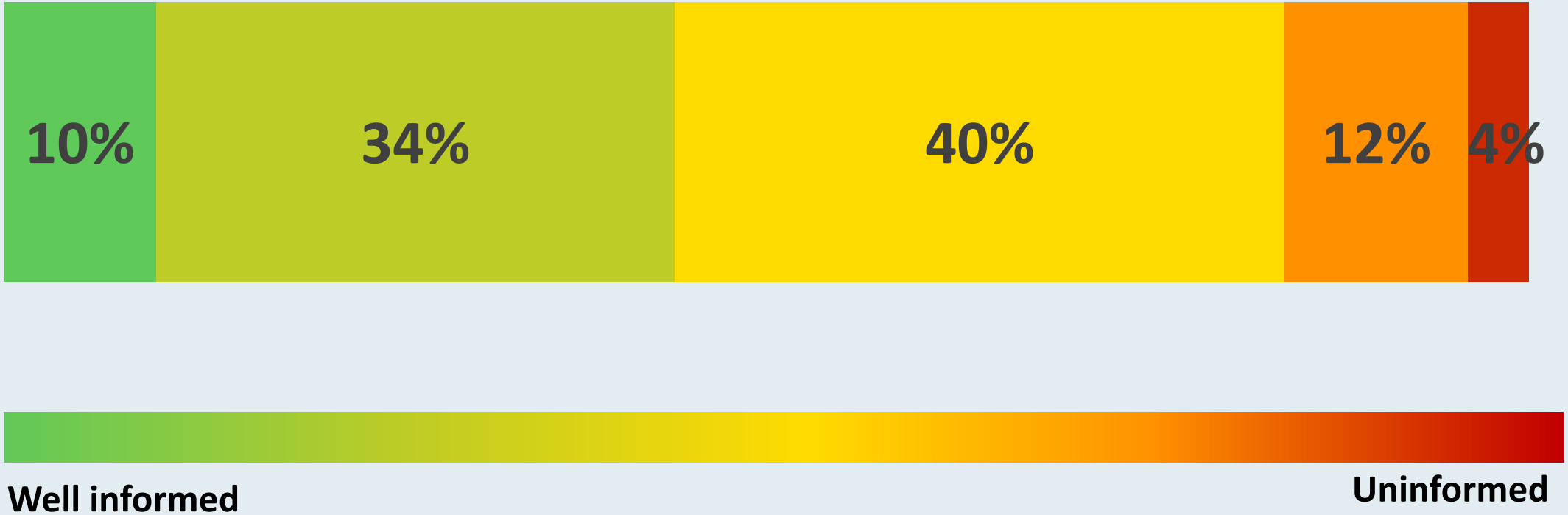
Questions from general medical oncologists about the appropriate integration of HER2-targeted therapy for patients with HER2-positive mCRC (continued)

- How do you sequence anti-HER2 treatment and other mutations such as KRAS, BRAF?
- Why are we treating this sequentially vs combined therapy?
- What line to use trastuzumab and T-DM1. Trastuzumab deruxtecan is second line I am assuming
- Do you see adding of trastuzumab deruxtecan to FOLFOX in first-line metastatic colorectal cancer? How is the tolerability issue you expect?
- Optimal front-line HER2 directed therapy in mCRC. Any roles for HER2 testing/anti-HER2 therapies in the adjuvant setting?
- 60 y/o F with non-ischemic cardiomyopathy and LVEF 35% with metastatic colon cancer, s/p first-line therapy with CapeOX and then capecitabine maintenance, has disease progression after 12 months. What HER2 agent, if any, would you select for this patient given the cardiac comorbidities?
- How to sequence the treatment T-DXd after MOUNTAINEER?
- In a patient with KRAS mutation and HER positive, is T-DXd still an option?
- First-line therapy in HER2-positive mCRC?
- Which is preferred, first-line tucatinib or trastuzumab deruxtecan?

Questions from general medical oncologists about the appropriate integration of HER2-targeted therapy for patients with HER2-positive mCRC (continued)

- I always get confused on the main difference pathologically for interpretation of HER2 results. When it comes to breast cancer and other types of cancers?
- What is the standard of care in first-line metastatic disease?
- FOLFOX plus trastuzumab in this setting?
- What line of therapy would you use T-DXd?
- Starting HER2 second line or beyond?
- Is there a best sequence of therapy?
- Will there be any role for HER2 targeted adjuvant treatment in the nonmetastatic setting?

How comfortable and/or familiar are you with the published datasets, available guidelines, investigator perspectives and ongoing research pertaining to the potential role of KRAS G12C inhibitors in the treatment of mCRC?



RTP
RESEARCH
TO PRACTICE

Questions from general medical oncologists about the potential role of KRAS G12C inhibitors in the treatment of mCRC

- What are the long-term outcomes of treatment with KRAS G12C inhibitors?
- Can we incorporate these into the 1L setting, rather than waiting for 2L/relapse?
- Use of adagrasib with cetuximab in patients with KRAS G12C. I recall having read an *NEJM* article but with inconclusive data. Any further thoughts?
- What line would you use adagrasib?
- How to choose between sotorasib vs adagrasib.
  Challenge is that the majority of CRC are non-KRAS G12C, and need for pan-RAS inhibitor with or without chemo or other targeted partners
- Should drugs such as adagrasib be incorporated into first-line therapy?
- Which KRAS inhibitors to use and when?
- What line of treatment should KRAS G12C be used?
  What are the expected outcomes?
- When to test and add adagrasib?
- Which anti-EGFR agent do you use with a KRAS G12C inhibitor?
- Never used so need guidance on the right patients indicated

RTP RESEARCH TO PRACTICE

Questions from general medical oncologists about the potential role of KRAS G12C inhibitors in the treatment of mCRC (continued)

- 34-year-old mCRC has progressed on FOLFOX, FOLFIRI with bev. Has KRAS G12C mutation. How do you choose between divarasib, sotorasib, and adagrasib? What are the commonest side effects of these as monotherapy or in combination with EGFR inhibitors?
- Would you consider KRAS directed therapy in front line?
- What are the biggest barriers to pan-RAS inhibitors in 1L?
- How can we compare the different KRAS G12C inhibitors?
- Which is your preferred agent to target KRAS G12C, and would you use in second or third line?
- I have not yet seen a pt with G12C mutation. Should G12C inhibitor be used as the second line or can it be combined with chemo as the first line?
- Have expertise with lung cancer, but not with KRAS targeted therapy for mCRC. Are these approved? Both?
- KRAS G12C mCRC: FOLFOX/FOLFIRI +/- EGFR/bev up front, or would you use KRAS G12C drug +/- EGFR as up-front therapy?
- Best utility of KRAS targeting?
- How do you choose between sotorasib and adagrasib? Please compare the efficacy and toxicity

Questions from general medical oncologists about the potential role of KRAS G12C inhibitors in the treatment of mCRC (continued)

- Do we need tissue biopsy or just liquid to detect this mutation? Do we need to test at each progression, or is this mutation present de novo in most cases?
- What is the most updated data in terms of how to incorporate KRAS-targeted agents, and which is the soonest line to start?
- What is the toxicity of agents used in this scenario?
- Is there any role in combining a KRAS G12C inhibitor with traditional chemo?
- Development of TKIs and potential combinations
- Is there hope for better agents? Is it highly pathogenic or is it a cofactor?
- Is this an acquired mutation that should be checked at each progression?
- I have not had the opportunity to use it. Is it effective as a single agent or in combination?
- Use instead of chemo or after chemo?
- Are there trials for other KRAS mutations?
- Why are we using this pathway as a single agent in the second line? Why not in combination with first-line therapy or why not use it with BRAF meds or EGFR antibodies?
- Would you add adagrasib to FOLFOX for patients with KRAS G12C mutated metastatic CRC?
- Where are G12C inhibitors best positioned in this space?

Questions from general medical oncologists about the potential role of KRAS G12C inhibitors in the treatment of mCRC (continued)

- 1. How do you manage the common toxicities of KRAS inhibitors?
  2. What is the best line to use these agents? Second line?
- Which G12C agent to use?
- I heard the data, but haven't had a chance to use KRAS G12C inhibitors in combination with cetuximab or panitumumab. How to manage side effects with the combination?
- First line; second-line therapy in this population?
- At what line of treatment would you use sotorasib?
- There are 2 studies using 2 separate KRAS G12C inhibitors — which one would you recommend?
- Can we use adagrasib plus cetuximab in the first-line setting?
- What line of therapy would you use a KRAS G12C and EGFR mAb combination?
- Please describe when targeted therapy is used for KRAS G12C — what line and can this mutation be acquired?
- What is the best sequence of therapy?
- Should KRAS G12C inhibitors be used front line alone in low performance status mCRC patients?
- How effective are KRAS inhibitors in patients with significant disease?

RTP
RESEARCH TO PRACTICE

Impediments or Barriers to the Delivery of High-Quality Care

- Ability to get ctDNA testing done on a timely basis
- TIME! Time to review all this data and keep up!
- Treating medical complexities with advanced stage CRC and the potential side effects from treatments along with comorbidities, knowing the survival outcomes, has been a challenge
- Insurance
- Education and fast pace of oncology. Historically drug reps would flood practitioner and update us, now we need to rely on FDA announcement, a clinical meeting, or an email. NCCN guidelines are a good resource. Also in colorectal cancer, the testing of biomarkers is not ongoing and there is no need for repeat biopsy to assess for emergent mutation. Fair amount of colon cancer pts are RAS mutation, HER neg, BRAF neg, microsatellite stable, and no other mutation. I feel this group has limited treatment options. Also, not all systems allow routine testing of ctDNA. In the midst of treatment, and therapeutics, value-based medicine cannot be overlooked. We have drugs like regorafenib, not an easy drug to tolerate and has suboptimal efficacy.
- The need to deintensify therapy for elderly frail patients. Is bolus FU best avoided? Is oxaliplatin toxicity prohibitive?
- Lack of knowledge and newer data, which is difficult to keep up with

Impediments or Barriers to the Delivery of High-Quality Care (Continued)

- Lack of third-line therapy for pts with MSS and no target
- Patient volume
- Insurance approval
- Applying ctDNA results into action
- Understanding data and learning how to dose, monitor and handle side effects from new targeted therapy agents
- Utilization of ctDNA along with imaging
- Difficulty in interpreting positive longitudinal ctDNA without demonstrable disease radiographically
- The lack of definitive studies to make grounded recommendations, especially with multiple mutations present
- Lack of good effective options for third line and beyond
- Insurance coverage and access to care
- Lack of biomarker testing, lack of referral for clinical trials
- Trying to keep up with newer data

Impediments or Barriers to the Delivery of High-Quality Care (Continued)

- Access to care. In resource-challenged managed care in California (the majority of community patients), sometimes difficult to get appropriate NGS/molecular testing and/or access to targeted therapies. Even if approved, high copays and lack of assistance programs mean patients cannot afford targeted therapies
- Knowledge of all new data and trials, hard to keep up
- Insurance denials
- Management of the side effects of treatment
- Insurance issues
- Difficult to keep up with all the changes in the community as a generalist
- Are there any additional, emerging biomarkers helpful for mCRC management with actionable alterations more frequent than HER2 aberrations?
- It is really difficult to keep up with the ever-changing landscape of CRC treatment
- Oligometastatic disease that may benefit from a liver transplant
- Insurance approval for small-benefit, high-cost medications
- Staying up to date with the latest publications
- Knowledge about appropriate targeting of HER2

Impediments or Barriers to the Delivery of High-Quality Care (Continued)

- Insurance denial
- Mixed response in first- and second-line treatment and whether to continue with treatment or move on to the next line
- When to stop treatment or give drug holidays for patients with well controlled stage IV CRC?
- Lack of therapy options after 3 lines of treatment
- Side effects and tolerability
- Reimbursement challenges are definitely difficult
- Lack of resources, lack of patient access to care, underserved population with a huge need for social support and wide variety of social services
- Insurance preauthorization
- I always have problems when a new year starts — I have patients on chemo with bevacizumab or cetuximab or panitumumab or targeted therapy for many months or even more than a year and if the patient changes the insurance, I am not sure why the new insurance takes a lot of time in approving the regimen the patient has been getting for a long time, and it's frustrating to see it again and again delaying care for the patients
- Delays in getting NGS results

Impediments or Barriers to the Delivery of High-Quality Care (Continued)

- Poor efficacy with third line and beyond
- The most challenging scenarios are patients who are extremely young in age once they progress past the first line of therapy. I would like to hear more opinions from experts to guide the treatment selection approach
- Difficulty obtaining sufficient tissue for testing of KRAS G12C
- Access to some drugs
- Lack of effective therapies for patients who are KRAS mutated without driver mutation, after 1L therapy
- For oligometastatic disease — one site. In liver, surgery requests up-front chemo before resection. Sometimes liver lesion no longer detectable
- Cost containment
- Insurance approval of drugs. Also convincing patients to take certain drugs over others
- Difficulty with obtaining biomarkers quickly