Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Emerging Data on the Treatment of Metastatic Colorectal Cancer — Axel Grothey, MD

Select Publications

Le DT et al. **PD-1 blockade in tumors with mismatch-repair deficiency.** *N Engl J Med* 2015;372(26):2509-20.

Le DT et al. **PD-1 blockade in tumors with mismatch repair deficiency.** *Proc ASCO* 2015;**Abstract LBA100**.

Ng K et al. **Vitamin D status and survival of metastatic colorectal cancer patients: Results from CALGB/SWOG 80405 (Alliance).** *Proc ASCO* 2015;**Abstract 3503**.

Siena S et al. **Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): The HERACLES trial.** *Proc ASCO* 2015;**Abstract 3508**.

Tabernero J et al. **Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study.** *Lancet Oncol* 2015;16(5):499-508.

Van Cutsem E et al. **Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer.** ESMO World Congress on Gastrointestinal Cancers 2015;**Abstract LBA-05**.

Van Cutsem E et al. **TAS-102 vs placebo (PBO) in patients (pts) ≥65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the RECOURSE trial.** *Proc ASCO* 2015;**Abstract 3595**.

Emerging Data on the Treatment of Metastatic Colorectal Cancer

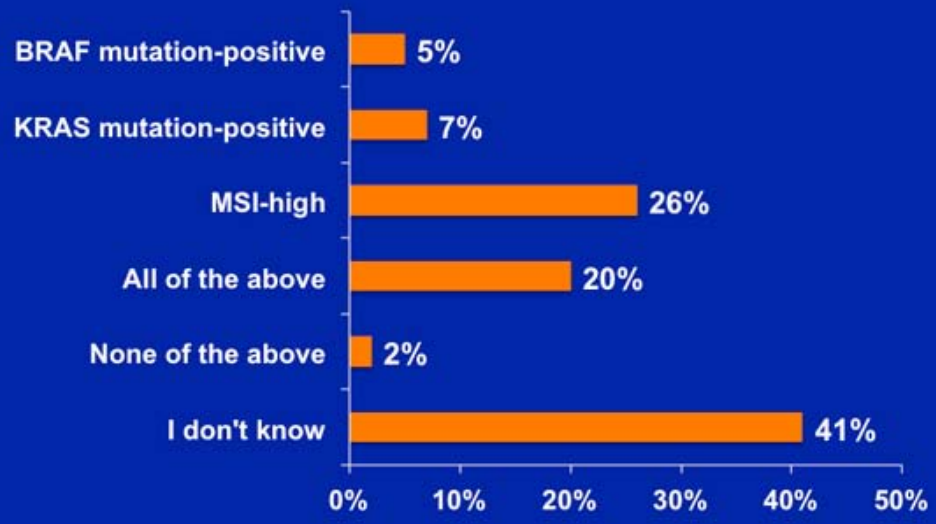
Axel Grothey, MD
Professor of Oncology
Department of Medical Oncology
Mayo Clinic
Rochester, Minnesota

Disclosures

Advisory Committee	Amgen Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Celgene Corporation, Genentech BioOncology, Lilly
Contracted Research	Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Eisai Inc, Genentech BioOncology, Lilly, Merck, Sanofi

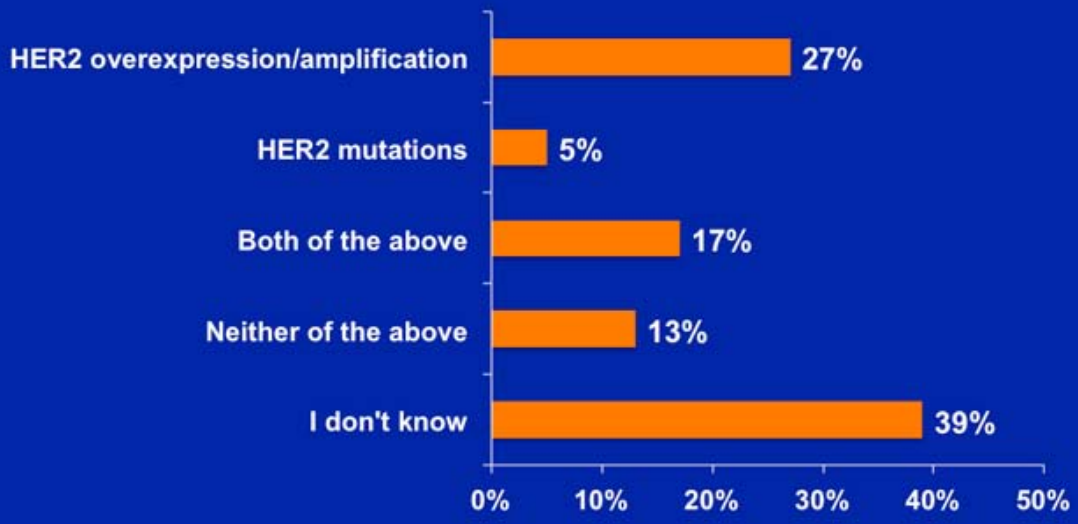
AUDIENCE POLL

Which of the following subsets of patients with metastatic colorectal cancer (mCRC) have been shown to experience clinical benefit from an anti-PD-1 antibody?



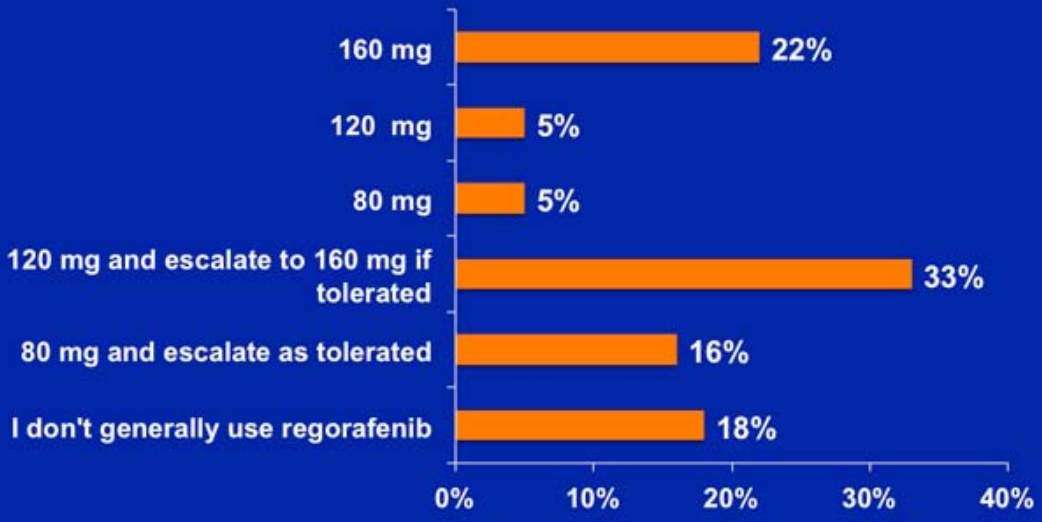
AUDIENCE POLL

Patients with mCRC and which of the following tumor alterations have been shown to derive benefit from anti-HER2 therapy?



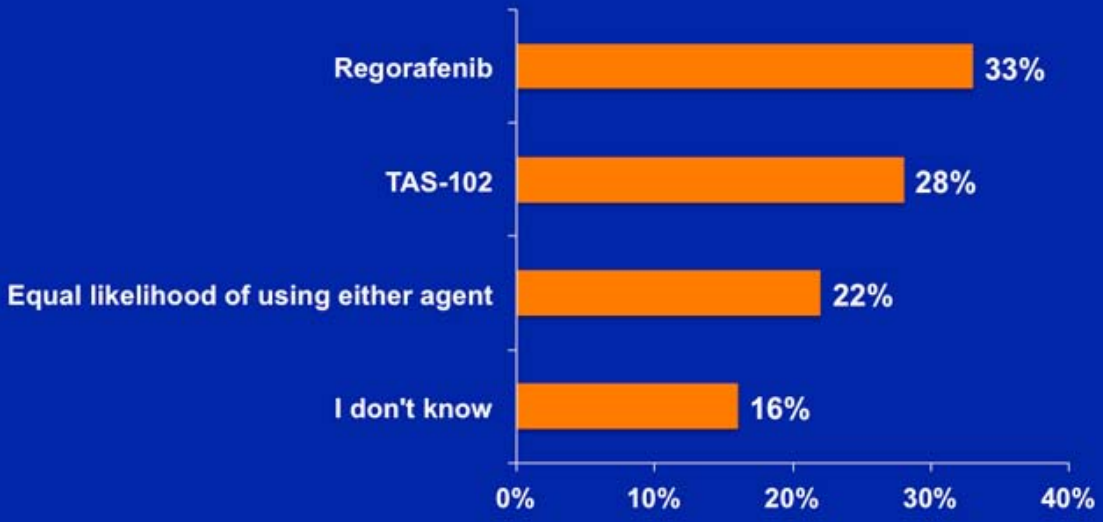
AUDIENCE POLL

In general, for a younger otherwise healthy patient with mCRC, which starting dose of regorafenib would you use (daily for 21 days of every 28-day cycle)?



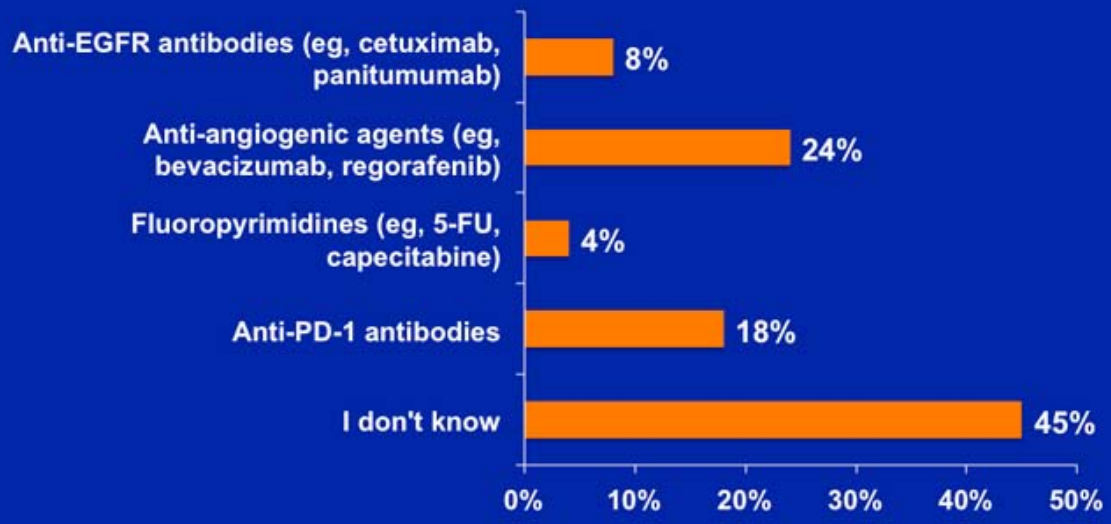
AUDIENCE POLL

In general, which agent would you most likely use first for a patient who has received multiple prior treatments for mCRC?



AUDIENCE POLL

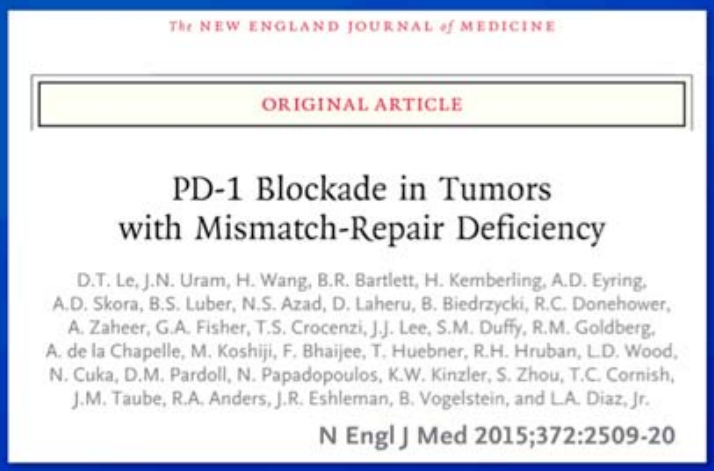
In patients with mCRC, central tumor necrosis observed radiologically in association with clinical benefit has been reported with…



PD-1 Blockade in Tumors with Mismatch Repair Deficiency

Le DT et al.

Proc ASCO 2015;Abstract LBA100.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

N Engl J Med 2015;372:2509-20

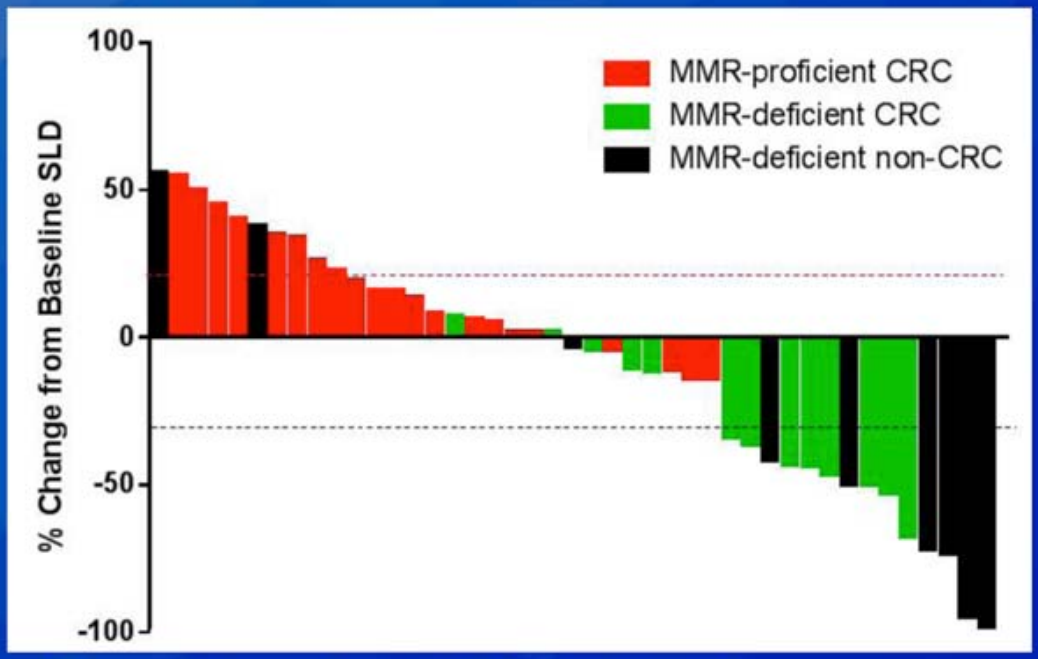
Study Design

Colorectal Cancers		Non-Colorectal Cancers
Cohort A **Deficient in Mismatch Repair (n=25)**	Cohort B **Proficient in Mismatch Repair (n=25)**	Cohort C **Deficient in Mismatch Repair (n=21)**

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Primary endpoint: immune-related 20-week PFS rate and response rate
- Mismatch repair testing using standard PCR-based test for detection of microsatellite instability

Le DT et al. *Proc ASCO* 2015;Abstract LBA100; *N Engl J Med* 2015;372(26):2509-20.

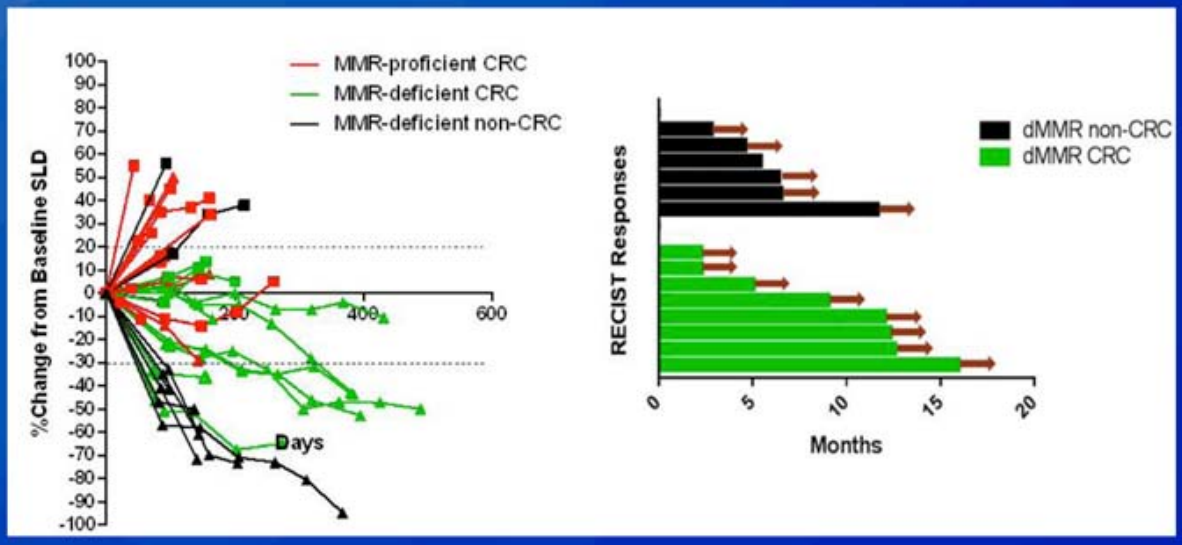
Tumor Response by MMR Status



SLD = sum of longest diameters; MMR = mismatch repair

Le DT et al. *Proc ASCO* 2015;Abstract LBA100; *N Engl J Med* 2015;372(26):2509-20.

Duration of Response



Le DT et al. *Proc ASCO* 2015;Abstract LBA100; *N Engl J Med* 2015;372(26):2509-20.

Conclusions

Critical finding(s): Cancers characterized by microsatellite instability (MSI-H), ie, mismatch repair deficient, hypermutated cancers, have a high chance of benefiting from single-agent PD-1/PD-L1 antibody therapy, even in a later-line setting.

Clinical implication(s): Testing for mismatch repair deficiency (MMR-D/MSI-H) should become standard in patients with colorectal cancers because it can identify a subgroup of about 5% of patients with metastatic disease who can benefit from immune checkpoint inhibitors.

Research relevance: Various clinical trials have been initiated to further test the efficacy of PD-1/ PD-L1 antibodies as single agents or in combination with other therapies in MSI-H cancers.

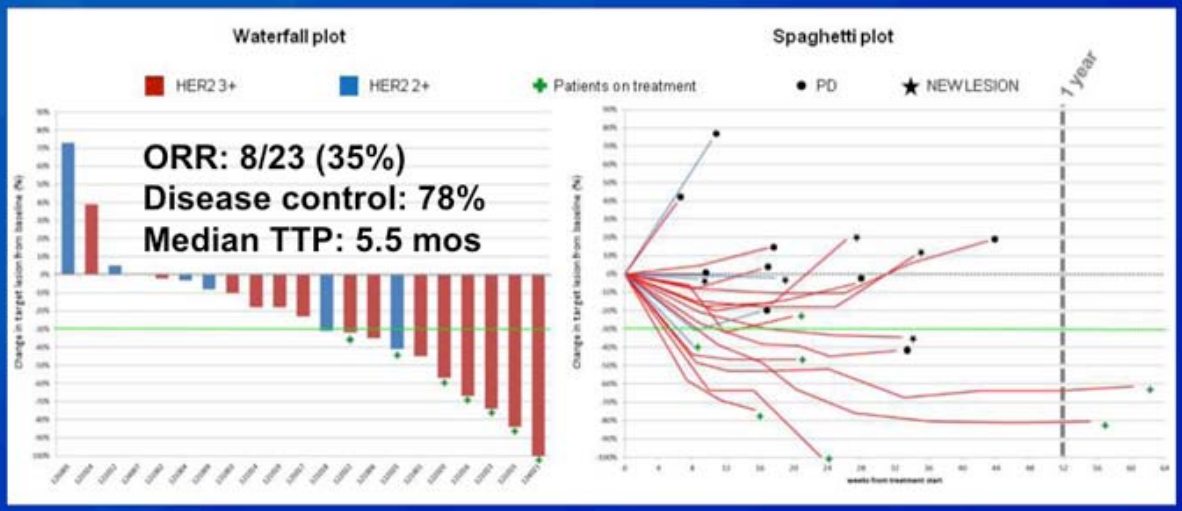
Trastuzumab and Lapatinib in HER2-Amplified Metastatic Colorectal Cancer Patients (mCRC): The HERACLES Trial

Siena S et al.

Proc ASCO 2015;Abstract 3508.

Response by HER2 IHC Score

- N = 23 mCRC progressing after fluoropyrimidines, oxaliplatin, irinotecan, cetuximab or panitumumab
- Median prior regimens: 5 (range: 3-8)
- HER2-positive (IHC3+ OR 2+ and FISH+)



HER2-amplified rate in KRAS wildtype mCRC: ~5%

Siena S et al. *Proc ASCO* 2015;Abstract 3508.

Conclusions

Critical finding(s): Patients with colorectal cancer refractory to EGFR mAbs that shows HER2 overexpression by IHC/FISH have a remarkable response and disease control rate with a combination of trastuzumab and lapatinib.

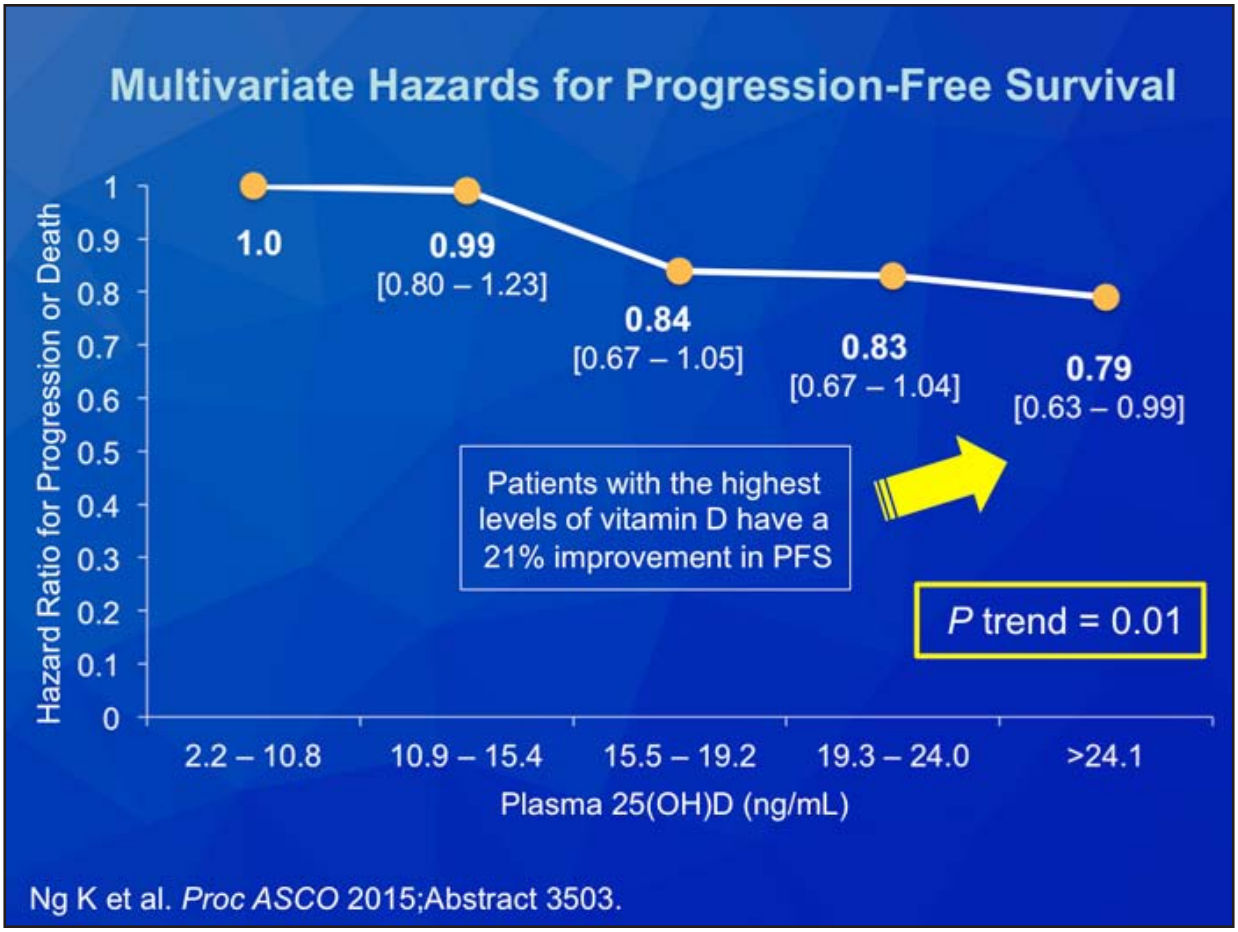
Clinical implication(s): Once these data have been validated, testing for HER2 overexpression could identify a subgroup of patients with CRC who benefit from HER2-targeted agents.

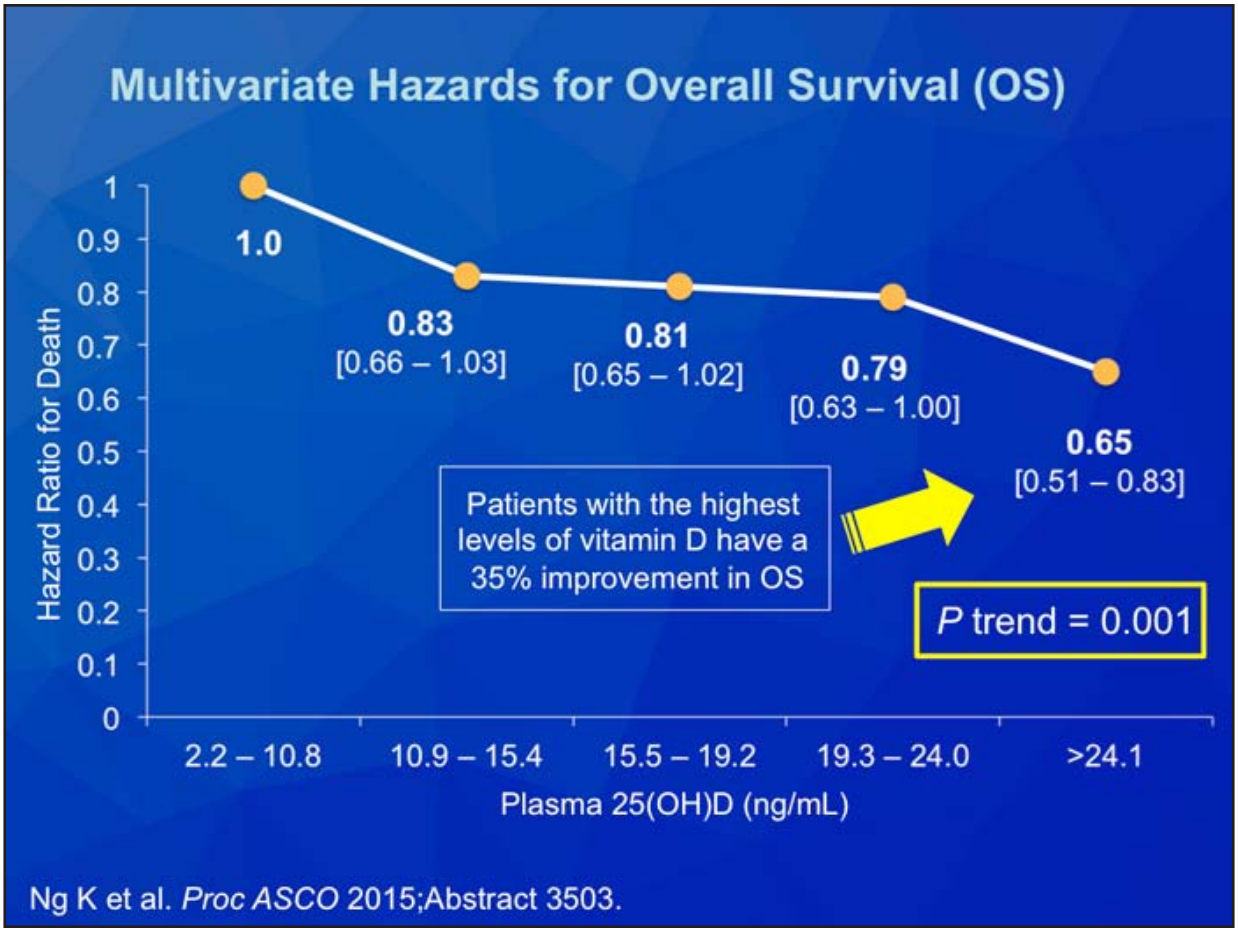
Research relevance: Several studies to validate the initial findings are underway. HER2 overexpression could emerge as a negative predictive marker for EGFR mAbs beyond RAS/RAF mutations.

Vitamin D Status and Survival of Metastatic Colorectal Cancer Patients: Results from CALGB/SWOG 80405 (Alliance)

Ng K et al.

Proc ASCO 2015;Abstract 3503.


Multivariate Hazards for Progression-Free Survival
Hazard Ratio for Progression or Death
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.0
0.99
[0.80 – 1.23]
0.84
[0.67 – 1.05]
0.83
[0.67 – 1.04]
0.79
[0.63 – 0.99]
Patients with the highest levels of vitamin D have a 21% improvement in PFS
P trend = 0.01
2.2 – 10.8
10.9 – 15.4
15.5 – 19.2
19.3 – 24.0
>24.1
Plasma 25(OH)D (ng/mL)
Ng K et al. Proc ASCO 2015;Abstract 3503.


Multivariate Hazards for Overall Survival (OS)
Hazard Ratio for Death
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1.0
0.83
[0.66 – 1.03]
0.81
[0.65 – 1.02]
0.79
[0.63 – 1.00]
0.65
[0.51 – 0.83]
Patients with the highest levels of vitamin D have a 35% improvement in OS
P trend = 0.001
2.2 – 10.8
10.9 – 15.4
15.5 – 19.2
19.3 – 24.0
>24.1
Plasma 25(OH)D (ng/mL)
Ng K et al. Proc ASCO 2015;Abstract 3503.

Conclusions

Critical finding(s): In a large Phase III trial in first-line CRC, patients with the highest level of plasma vitamin D have a 21% improvement in PFS and a 35% improvement in OS compared to patients with the lowest vitamin D levels. This trend was confirmed in multivariate analysis.

Clinical implication(s): It is still not clear if vitamin D per se is able to improve outcomes in malignancies or if vitamin D plasma levels are an expression of the overall health status of a patient. Based on these data, however, testing for vitamin D levels and substitution if very low levels are seen could be considered reasonable.

Research relevance: Studies that investigate the interventional use of vitamin D and its effect on outcome in CRC and other malignancies are ongoing.

Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study

Josep Tabernero, Takayuki Yoshino, Allen Lee Cohn, Radka Obermannova, Gyorgy Bodoky, Rocio Garcia-Carbonero, Tudor-Eliade Ciuleanu, David C Portnoy, Eric Van Cutsem, Axel Grothey, Jana Prausová, Pilar Garcia-Alfonso, Kentaro Yamazaki, Philip R Clingan, Sara Lonardi, Tae Won Kim, Lorinda Simms, Shao-Chun Chang, Federico Nasroulah, and the RAISE Study Investigators

Lancet Oncol 2015; 16: 499–508

Survival Analyses

Endpoint	Ramucirumab (n = 536)	Placebo (n = 536)	Hazard ratio	*p*-value
Overall survival	13.3 mo	11.7 mo	0.84	0.022
Progression-free survival	5.7 mo	4.5 mo	0.79	0.0005

Tabernero J et al. *Lancet Oncol* 2015;16:499-508.

Conclusions

Critical finding(s): The human VEGFR2 antibody ramucirumab leads to moderate gains in PFS and OS in patients with mCRC pretreated with a bevacizumab-containing regimen when added to a FOLFIRI backbone in the second line.

Clinical implication(s): The data confirm the efficacy of continued VEGF inhibition beyond first-line progression. Ramucirumab is the third VEGF inhibitor approved in this setting after bevacizumab and ziv-aflibercept. No clear advantage of ramucirumab over the other VEGF inhibitors can be seen for clinical practice.

Conclusions

Research relevance: The RAISE data support the concept that resistance to VEGF inhibitors follows a different time pattern than resistance to chemotherapy. Further continuation of VEGF inhibition into third-line therapy is currently being investigated in the BOND-3 trial.

Results from the Large, Open-Label Phase 3b CONSIGN Study of Regorafenib in Patients with Previously Treated Metastatic Colorectal Cancer

Van Cutsem E et al.

ESMO World Congress on Gastrointestinal Cancers 2015;Abstract LBA-05.

CONSIGN Efficacy and Safety

- Prospective, single-arm study in 188 sites in 25 countries
- N = 2,872 patients with mCRC who progressed after standard therapies
  - 96% received ≥2 prior regimens for metastatic disease
- Estimated median PFS: 2.7 months
  - KRAS wild type: 2.8 months
  - KRAS mutant: 2.5 months

Adverse events	Treatment-emergent drug-related	Treatment-emergent
Grade ≥3	57%	80%
Hypertension	15%	17%
Hand-foot skin reaction	14%	14%
Fatigue	13%	18%
Diarrhea	5%	6%
Hypophosphatemia	5%	7%
Serious AEs	9%	44%
AEs leading to discontinuation	9%	25%

Van Cutsem E et al. ESMO World Congress on GI Cancers 2015;Abstract LBA-05.

Conclusions

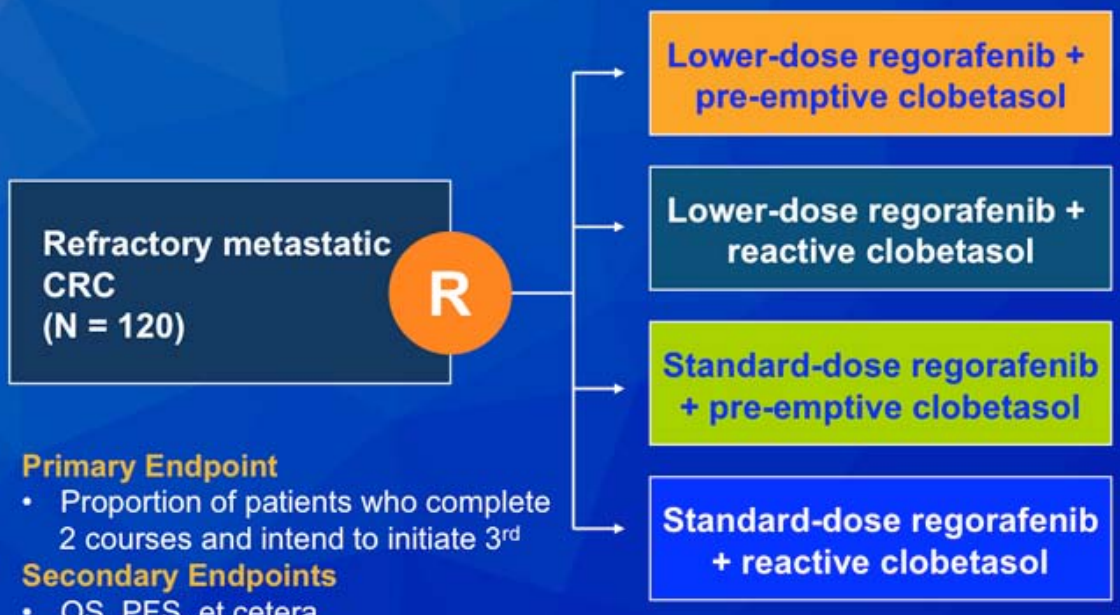
Critical finding(s): The use of regorafenib in an expanded access program with almost 3,000 patients confirms the safety and efficacy data obtained in the pivotal Phase III CORRECT study that led to the approval of regorafenib in CRC.

Clinical implication(s): The study confirms that hand-foot skin reaction, fatigue and hypertension are the most critical side effects associated with regorafenib. These side effects emerge early, commonly within the first cycle, and require proactive management and short follow-up intervals in the initial treatment phase.

Conclusions

Research relevance: The data from the expanded access program confirm key safety and efficacy data from the prior Phase III trial, thus confirming that such single-arm cohort studies can be used to obtain valuable clinical information in a less selected patient population compared to randomized trials.

Regorafenib Dose Optimization Study (ReDOS): Randomized Phase II Study of Lower- versus Standard-Dose Regorafenib in Refractory mCRC



Primary Endpoint
- Proportion of patients who complete 2 courses and intend to initiate 3rd

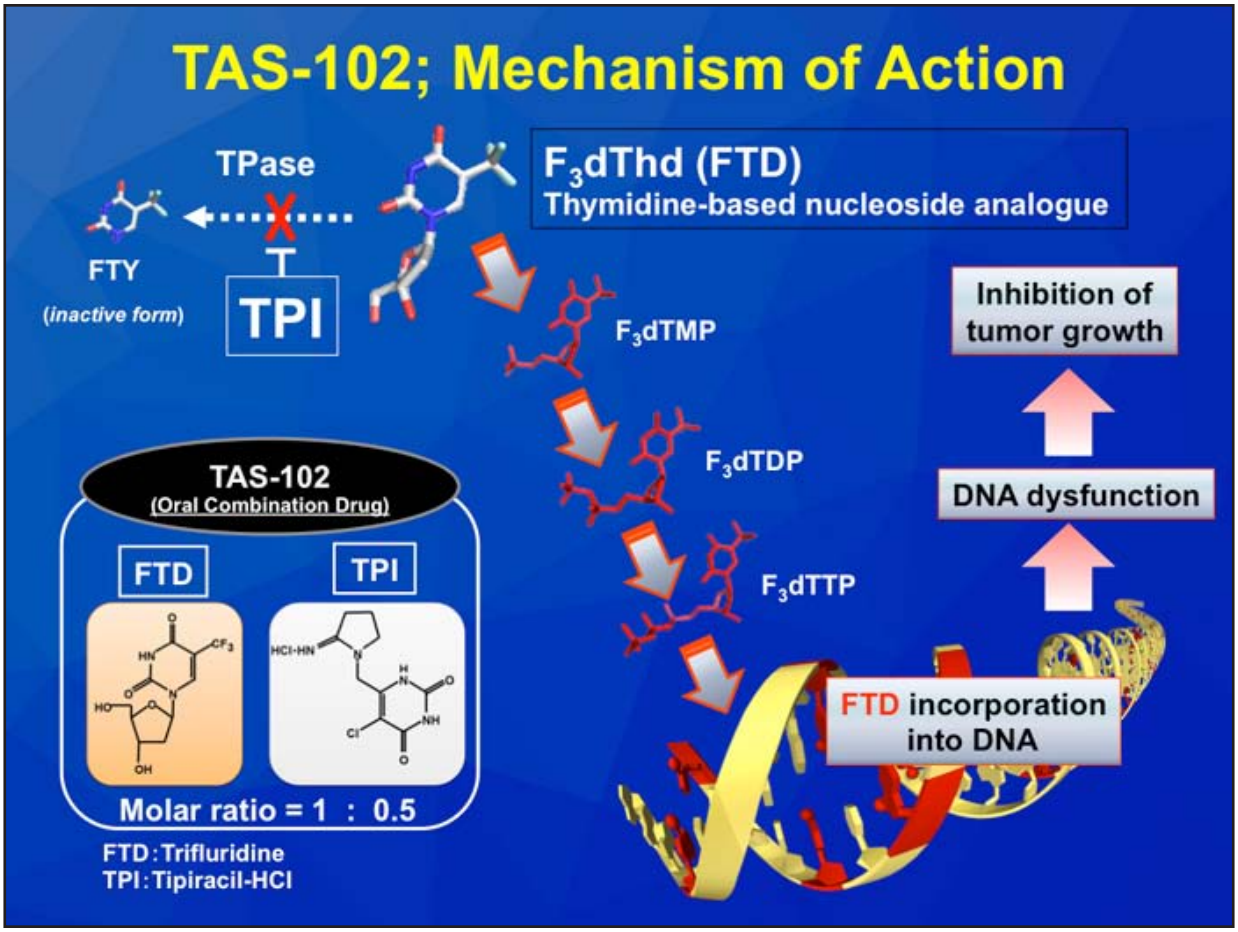
Secondary Endpoints
- OS, PFS, et cetera

Clinicaltrials.gov, April 2015 (NCT02368886)

TAS-102 vs Placebo (PBO) in Patients (pts) ≥65 years (y) with Metastatic Colorectal Cancer (mCRC): An Age-Based Analysis of the RECOURSE Trial

Van Cutsem E et al.

Proc ASCO 2015;Abstract 3595.



Overall and Progression-Free Survival: <65, ≥65, <70 and ≥70 Years: TAS-102 (TAS) vs Placebo (PI)

	Age <65 Years		Age ≥65 Years		Age <70 Years		Age ≥70 Years	
	TAS N = 300	PI N = 148	TAS N = 234	PI N = 118	TAS N = 406	PI N = 210	TAS N = 128	PI N = 56
Median OS	**7.1 mo**	**5.7 mo**	**7.0 mo**	**4.6 mo**	**7.1 mo**	**5.3 mo**	**7.0 mo**	**4.7 mo**
Hazard ratio	0.74		0.62		0.70		0.65	
p-value	0.013		0.0002		0.0003		0.023	
Median PFS	**1.9**	**1.7**	**2.1**	**1.8**	**1.9**	**1.7**	**2.5**	**1.8**
Hazard ratio	0.52		0.41		0.49		0.44	
p-value	<0.0001		<0.0001		<0.0001		<0.0001	

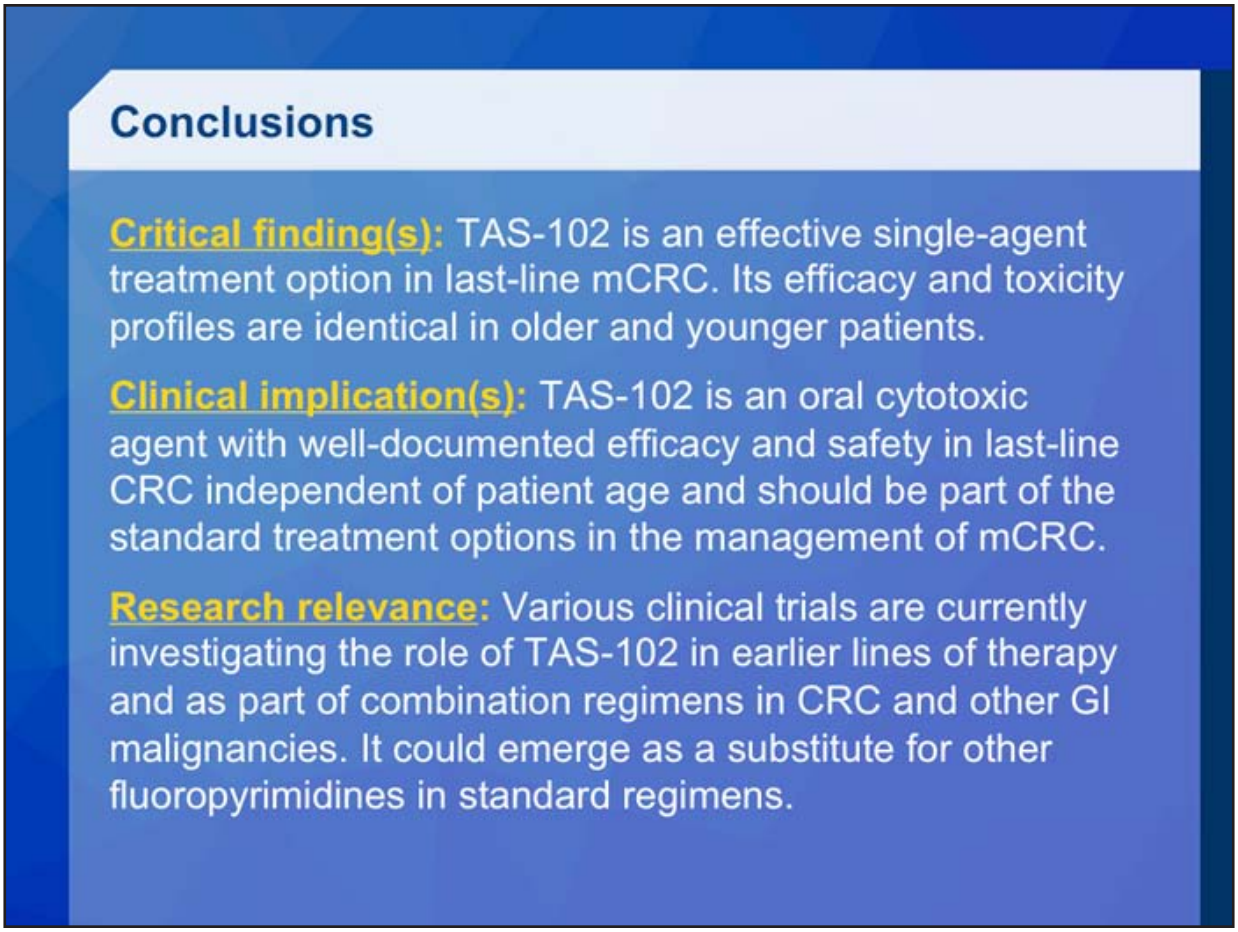
Van Cutsem E et al. *Proc ASCO* 2015;Abstract 3595.

RECOURSE: Adverse Events by Age

	TAS-102, < 65 y (n=299)	TAS-102, ≥ 65 y (n=234)	TAS-102, ≥ 75 y (n=36)
Overall AEs, %	98.0	98.7	100
Treatment-related AEs, %	83.6	88.5	91.7
≥ Grade 3 AEs, %	65.2	74.8	75.0
Severe AEs, %	28.8	30.8	33.3
Anemia, %*	23.4	41.9	44.4
Neutropenia, %*	25.8	32.5	33.3
Decreased platelets, %*	9.0	21.4	11.1
Decreased appetite, %*	23.7	29.9	22.2

*Treatment-related.

Van Cutsem E et al. *Proc ASCO* 2015;Abstract 3595.


Conclusions
Critical finding(s): TAS-102 is an effective single-agent treatment option in last-line mCRC. Its efficacy and toxicity profiles are identical in older and younger patients.
Clinical implication(s): TAS-102 is an oral cytotoxic agent with well-documented efficacy and safety in last-line CRC independent of patient age and should be part of the standard treatment options in the management of mCRC.
Research relevance: Various clinical trials are currently investigating the role of TAS-102 in earlier lines of therapy and as part of combination regimens in CRC and other GI malignancies. It could emerge as a substitute for other fluoropyrimidines in standard regimens.