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EPICS CONGRESS COVERAGE: ASCO 2021 – FOCUS ON GI

Thursday, January 21, 2021

FULL REPORT

FACULTY EXPERTS

Chair
Axel Grothey, MD

Dirk Arnold, MD, PhD

Cathy Eng, MD, FACP

David H. Ilson, MD, PhD

Scott Kopetz, MD, PhD

Fotios Loupakis, MD, PhD

Eric Van Cutsem, MD, PhD

Tanios Bekaii-Saab, MD, FACP

AGENDA

EPICS

Time EST	Topic	Speaker/ Moderator
10.00 – 10.05	Welcome and Introductions	Axel Grothey, MD
10.05 – 10.20	Colorectal Cancer – Chemotherapy and Targeted Therapy	Eric Van Cutsem, MD, PhD
10.20 – 10.40	Discussion	Moderator: Axel Grothey, MD
10.40 – 10.45	Colorectal Cancer – Chemotherapy and Targeted Therapy: Key Takeaways	Eric Van Cutsem, MD, PhD
10.45 – 11.00	Colorectal Cancer – Immunotherapy	Scott Kopetz, MD, PhD
11.00 – 11.20	Discussion	Moderator: Axel Grothey, MD
11.20 – 11.25	Colorectal Cancer – Immunotherapy: Key Takeaways	Scott Kopetz, MD, PhD
11.25 – 11.40	Hepatocellular Carcinoma	Tanios S. Bekaii-Saab, MD, FACP
11.40 – 12.00	Discussion	Moderator: Axel Grothey, MD
12.00 – 12.05	Hepatocellular Carcinoma – Key Takeaways	Tanios S. Bekaii-Saab, MD, FACP
12.05 – 12.10	*Break*	
12.10 – 12.25	Gastroesophageal Cancers	David Ilson, MD, PhD
12.25 – 12.45	Discussion	Moderator: Axel Grothey, MD
12.45 – 12.50	Gastroesophageal Cancers – Key Takeaways	David Ilson, MD, PhD
12.50 – 1.00	Pancreatic Cancer	Dirk Arnold, MD, PhD
1.00 – 1.20	Discussion	Moderator: Axel Grothey, MD
1.20 – 1.25	Pancreatic Cancer – Key Takeaways	Dirk Arnold, MD, PhD
1.25 – 1.30	Summary and Closing Remarks	Axel Grothey, MD

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Colorectal Cancer – Chemotherapy and Targeted Therapy

ERIC VAN CUTSEM, MD, PHD

ASCO GI Abstract 14: Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are noneligible for intensive therapy (TASCO1): Results of the final analysis on the overall survival. Eric Van Cutsem, et al

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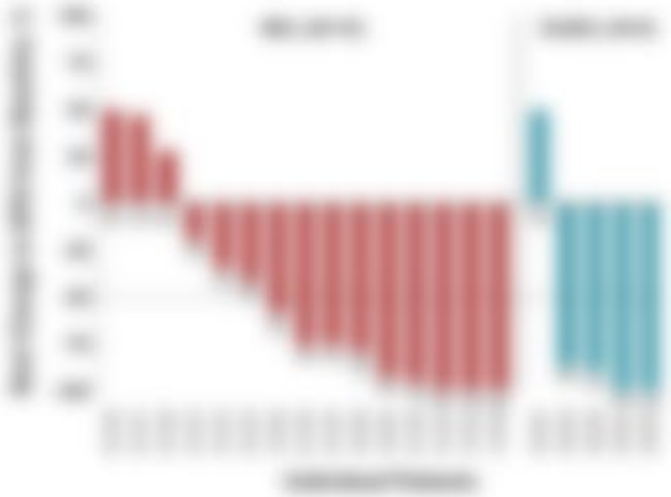
Background

> The results of the primary study analysis were reported earlier and demonstrated promising efficacy in terms of progression-



ASCO GI Abstract 115: Predicting resistance to first-line FOLFOX plus bevacizumab in metastatic colorectal cancer: Final results of the multicenter, international PERMAD trial. Thomas Seufferlein, et al

EPICS

Background

- Phase I dose-escalation study of VLS-101, a ROR1-targeting ADC, in patients with heavily pretreated MCL and DLBCL
- Primary objective was to refine estimates of MTD and recommended dosing regimen

Results

- 32 patients were enrolled, including 15 patients with MCL
- DLTs were G4 neutropenia and G3 diarrhea
- G4 neutropenia occurred in 28% of patients; G-CSF successfully ameliorated neutropenia
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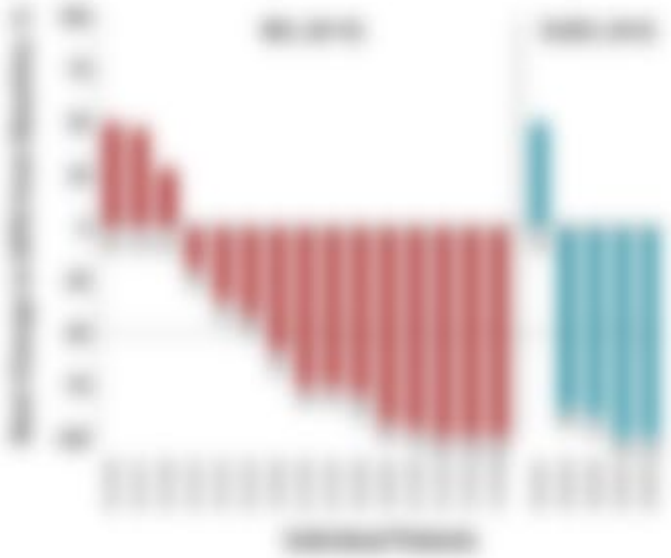

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI 85: PARADIGM study: A multicenter, randomized, phase III study of mFOLFOX6 plus panitumumab or bevacizumab as first-line treatment in patients with *RAS (KRAS/NRAS)* wild-type metastatic colorectal cancer. Takayuki Yoshino, et al

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ASCO GI Abstract TPS143: PULSE: A randomized phase II open label study of panitumumab rechallenge versus standard therapy after progression on anti-EGFR therapy in patients with *RAS* wild-type metastatic colorectal cancer (mCRC). John H. Strickler, et al

EPICS

Background

> Some studies have suggested clinical benefit from EGFR Ab rechallenge, but there is limited evidence that EGFR Ab

ASCO GI Abstract 37: Preliminary safety analysis of phase II open-label NIVACOR trial (GOIRC-03-2018) in patients with advanced colorectal cancer *RAS* or *BRAF* mutated. Angela Damato, et al

EPICS

Background

> NIVACOR is an open-label, multicentric, Italian phase II trial of 5-FU, leucovorin, oxaliplatin, irinotecan (FOLFOXIRI)–

ASCO GI Abstract TPS155: A phase Ib/II study of the polo-like kinase 1 (PLK1) inhibitor, onvansertib, in combination with FOLFIRI and bevacizumab for second-line treatment of patients with *KRAS*-mutated metastatic colorectal cancer (mCRC). Daniele H. Ahn, et al

EPICS

Background

ASCO GI Abstract TPS146: KRYSTAL-2: A phase I/II trial of adagrasib (MRTX849) in combination with TNO155 in patients with advanced solid tumors with *KRAS* G12C mutation. Joshua K. Sabari, et al.

EPICS

Background

- *KRAS* G12C tumor mutations occur in ~3%–4% of colorectal adenocarcinomas
- Adagrasib (MRTX849) is a specific small-molecule investigational inhibitor of KRAS G12C. Preliminary results from a phase I/II study of adagrasib demonstrated promising antitumor activity and tolerability across multiple KRAS G12C tumor types. TNO155 is a selective inhibitor of SHP2 with demonstrated inhibition of RTK signaling and significant antitumor activity in preclinical models
- Preclinical studies have shown that resistance to KRAS G12C inhibition may be mediated by SHP2-dependent feedback loops. The addition of TNO155 to adagrasib may augment antitumor activity and overcome resistance
- In KRAS G12C human tumor models, adagrasib combined with a SHP2 inhibitor demonstrated greater activity compared with each agent alone
- KRYSTAL-2 is a multicenter phase I/II study evaluating adagrasib and TNO155 in pts with advanced solid tumors harboring a KRAS G12C mutation

ASCO GI Abstract TPS153: MOUNTAINEER: open-label, phase II study of tucatinib combined with trastuzumab for HER2-positive metastatic colorectal cancer (SGNTUC-017, trial in progress). John H. Strickler, et al

EPICS

Background

- Human epidermal growth factor receptor 2 (*HER2*) amplification occurs in ~3%–5% of pts with mCRC
- Adagrasib (MRTX849) is a specific small-molecule investigational inhibitor of *KRAS G12C*. Preliminary results from a phase I/II study of adagrasib demonstrated promising antitumor activity and tolerability across multiple *KRAS G12C* tumor types. TNO155 is a selective inhibitor of SHP2 with demonstrated inhibition of RTK signaling and significant antitumor activity in preclinical models
- Preclinical studies have shown that resistance to *KRAS G12C* inhibition may be mediated by SHP2-dependent feedback loops. The addition of TNO155 to adagrasib may augment antitumor activity and overcome resistance
- In *KRAS G12C* human tumor models, adagrasib combined with a SHP2 inhibitor demonstrated greater activity compared with each agent alone
- KRYSTAL-2 is a multicenter phase I/II study evaluating adagrasib and TNO155 in pts with advanced solid tumors harboring a *KRAS G12C* mutation

ASCO GI Abstract TPS157: An open-label, phase II study of patritumab deruxtecan (HER3-DXd, U3-1402) in patients (pts) with previously treated advanced/metastatic colorectal cancer (CRC). Kanwal P. Raghav, et al

EPICS

Background

> Patritumab deruxtecan (HER3-DXd; U3-1402) is a novel, investigational antibody-drug conjugate (ADC) comprising an anti-

ASCO GI Abstract TPS154: FRESCO-2: A global phase III study of the efficacy and safety of fruquintinib in patients (pts) with metastatic colorectal cancer (mCRC). Arvind Dasari, et al

EPICS

Background

- Fruquintinib is a novel, highly selective, vascular endothelial growth factor receptor (VEGFR) TKI

KEY TAKEAWAYS: COLORECTAL CANCER – CHEMOTHERAPY AND TARGETED THERAPY (1/2)

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Chemotherapy

> TASCO1 data with optimized fluoropyrimidines in frontline demonstrate that the biology of the disease remains

KEY TAKEAWAYS: COLORECTAL CANCER – CHEMOTHERAPY AND TARGETED THERAPY (2/2)

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Biomarkers and Targeted Therapy (cont.)

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Colorectal Cancer – Immunotherapy

SCOTT KOPETZ, MD, PHD

ASCO GI Abstract 6: KEYNOTE-177: Phase III randomized study of pembrolizumab versus chemotherapy for microsatellite instability-high advanced colorectal cancer. Kai-Keen Shiu, et al

EPICS

Background

> KEYNOTE-177 (NCT02563002) evaluated the antitumor activity of pembrolizumab (pembro) vs chemotherapy ±

ASCO GI Abstract 58: Subgroup analyses of patients (pts) with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) treated with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line (1L) therapy: Two-year clinical update. Heinz-Josef Lenz, et al

EPICS

Background

> In the phase II CheckMate 142 trial, NIVO + low-dose IPI had robust, durable clinical benefit and was well tolerated as first-

ASCO GI Abstract 61: Tissue and plasma tumor mutation burden (TMB) as predictive biomarkers in the CO.26 trial of durvalumab + tremelimumab (D+T) versus best supportive care (BSC) in metastatic colorectal cancer (mCRC). Jonathan M. Loree, et al

EPICS

Background

> Pembrolizumab was recently granted tissue-agnostic US Food and Drug Administration (FDA) accelerated approval for

ASCO GI Abstract 9: Safety and efficacy of anti–PD-1 antibody dostarlimab in patients (pts) with mismatch repair-deficient (dMMR) solid cancers: Results from GARNET study. Thierry Andre, et

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ASCO GI Abstract 8: NRG-GI002: A phase II clinical trial platform using total neoadjuvant therapy (TNT) in locally-advanced rectal cancer (LARC)—Pembrolizumab experimental arm (EA) primary results. Osama E. Rahma, et al

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ASCO GI Abstract 94: LEAP-005: A phase II multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—Results from the colorectal cancer cohort. Carlos Gomez-Roca, et al

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ASCO GI Abstract 79: Phase II trial of bintrafusp alfa in patients with metastatic MSI-H cancers following progression on immunotherapy. Van K. Morris, et al

EPICS

Background

> MSI-H tumors are characterized by dMMR, high TMB, and exceptional antitumor responses to immunotherapy. While

Background

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Results

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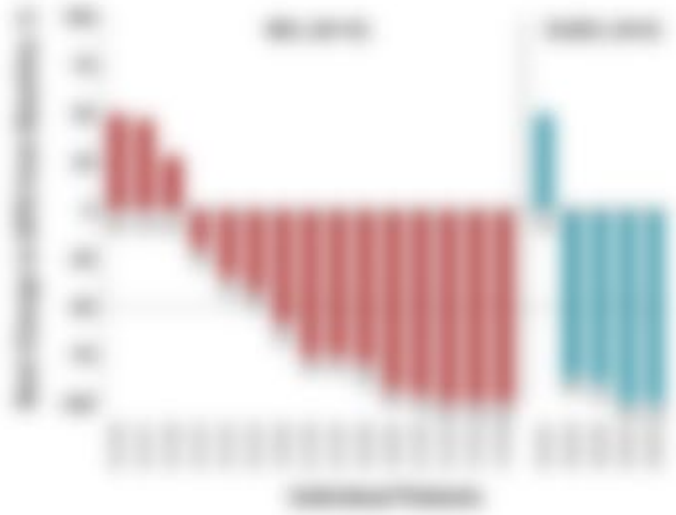

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 77: Phase II study of pembrolizumab plus capecitabine and bevacizumab in microsatellite stable (MSS) metastatic colorectal cancer (mCRC): Interim analysis. Andrea G. Bocobo, et al

EPICS

Background

> MSS mCRC rarely responds to pembrolizumab monotherapy, but capecitabine and bevacizumab may induce immune-

ASCO GI Abstract 80: Interim analysis of the AVETUXIRI Trial: Avelumab combined with cetuximab and irinotecan for treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC)—A proof of concept, open-label, nonrandomized phase IIa study. Marc Van Den Eynde, et al

EPICS

Background

> Immune checkpoint inhibitors have demonstrated poor efficacy in MSS mCRC. Previous research indicates that cetuximab

ASCO GI Abstract 7: Phase II study of ipilimumab, nivolumab, and panitumumab in patients with *KRAS/NRAS/BRAF* wild-type (WT) microsatellite stable (MSS) metastatic colorectal cancer (mCRC). Michael S. Lee, et al

EPICS

Background

> Preclinical data show that anti-EGFR therapy causes a tumor-specific adaptive immune response and immunogenic

ASCO GI Abstract 82: Phase Ib/II open-label, randomized evaluation of efficacy and safety of atezolizumab plus isatuximab versus regorafenib in MORPHEUS-colorectal cancer. Jayesh Desai, et al

EPICS

Background

> The MORPHEUS platform consists of multiple global, open-label, randomized phase Ib/II trials designed to identify early

KEY TAKEAWAYS: COLORECTAL CANCER – IMMUNOTHERAPY (1/2)

EPICS

MSI-H mCRC

> PD-1 inhibitors have changed the SOC in MSI-H pts, vs chemotherapy

KEY TAKEAWAYS: COLORECTAL CANCER – IMMUNOTHERAPY (2/2)

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Rectal Cancer

> Data from the NRG-GI002 study have shown that pembrolizumab in addition to chemoradiotherapy does not appear to be

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Hepatocellular Carcinoma

TANIOS S. BEKAII-SAAB, MD, FACP

ASCO GI Abstract 267: IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). Richard S. Finn, et al

EPICS

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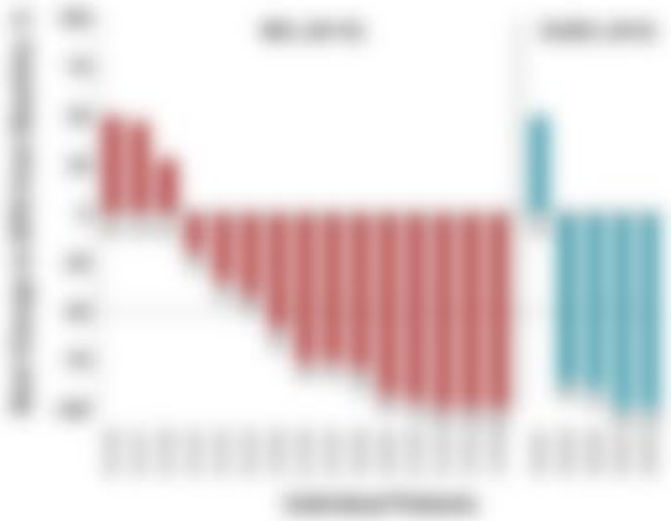

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 294: DEDUCTIVE: A study of tivozanib in combination with durvalumab in subjects with untreated advanced hepatocellular carcinoma—Phase Ib results. Renuka V. Iyer, et al

EPICS

Background

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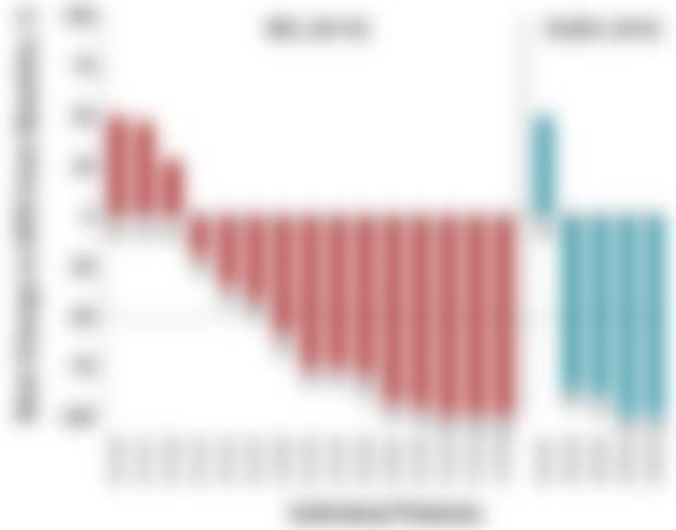

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 268: Pembrolizumab (pembro) vs placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (aHCC) previously treated with sorafenib: Updated data from the randomized, phase III KEYNOTE-240 study. Philippe Merle, et al

EPICS

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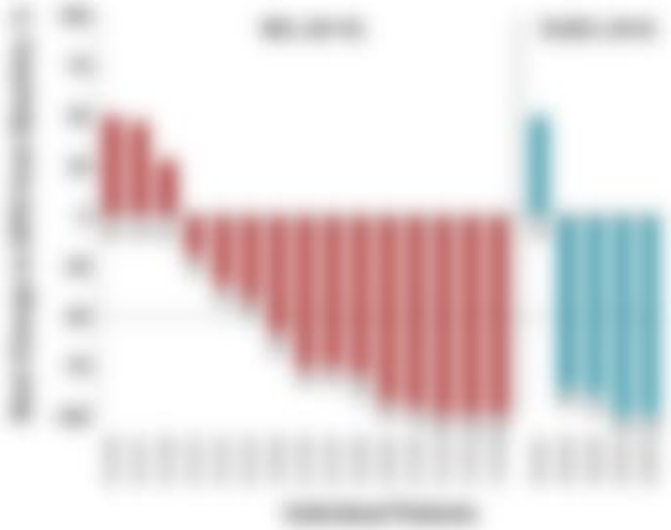

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 297: Pembrolizumab (pembro) monotherapy for previously untreated advanced hepatocellular carcinoma (HCC): Phase II KEYNOTE-224 study. Jean-Luc Van Laethem, et al

EPICS

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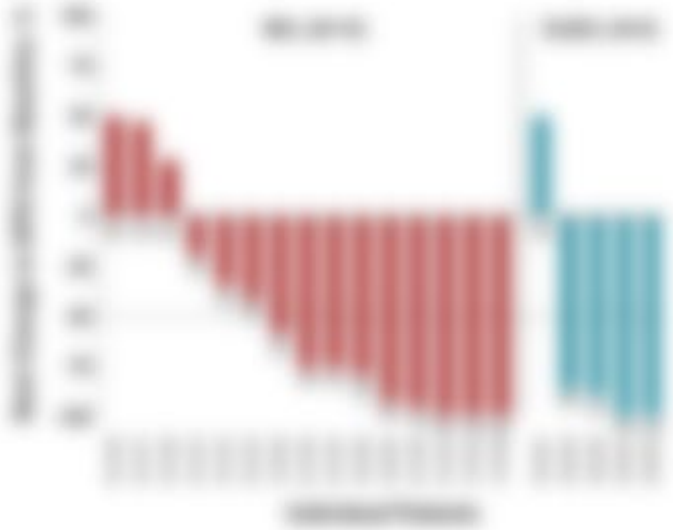

Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 269: Nivolumab (NIVO) plus ipilimumab (IPI) combination therapy in patients (Pts) with advanced hepatocellular carcinoma (aHCC): Long-term results from CheckMate 040.

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ASCO GI Abstract 270: TACTICS: Final overall survival (OS) data from a randomized, open label, multicenter, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients (pts) with hepatocellular carcinoma (HCC). Masatoshi Kudo, et al

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ASCO GI Abstract TPS358: A phase II study of atezolizumab (ATEZO) and bevacizumab (Bev) in combination with Y90 TARE in patients (Pts) with hepatocellular carcinoma (HCC). Aiwu R. He, et al

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ASCO GI Abstract TPS349: A phase III, double-blind, randomized study of nivolumab (NIVO) and ipilimumab (IPI), nivo monotherapy or placebo plus transarterial chemoembolization (TACE) in patients with intermediate-stage hepatocellular carcinoma (HCC). Bruno Sangro, et al

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KEY TAKEAWAYS: HEPATOCELLULAR CARCINOMA

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> Frontline atezolizumab + bevacizumab combination is the SOC for the majority of pts, with

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Gastroesophageal Cancers

DAVID ILSON, MD, PHD

ASCO GI LBA 160: Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT). Zev A. Wainberg, et al

EPICS

Background

> Bemarituzumab (bema) selectively binds to fibroblast growth factor (FGFR)2b. The FIGHT study is a global, randomized, double-blind,

ASCO GI Abstract 299: Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study. Funda Meric-Bernstam, et al

EPICS

Background

> Standard second-line chemotherapy yields ORRs <10%, and median OS of these pts is <6 months. HER2 overexpression/

ASCO GI Abstract 168: Health-related quality of life (HRQoL) of pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase III KEYNOTE-590 study. Wasat Mansoor, et al

EPICS

Background

> In the phase III KEYNOTE-590 study, pembrolizumab (pembro) + chemotherapy (chemo) provided statistically significant

ASCO GI Abstract 167: Checkmate 577: Health-related quality of life (HRQoL) in a randomized, double-blind phase III study of nivolumab (NIVO) versus placebo (PBO) as adjuvant treatment in patients (pts) with resected esophageal or gastroesophageal junction cancer (EC/GEJC). Eric Van Cutsem, et al

EPICS

Background

> NIVO is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in disease-free

ASCO GI Abstract 162: Impact of preoperative therapy for locally advanced thoracic esophageal cancer on the risk of perioperative complications: Results from multicenter phase III trial JCOG 1109. Kazuo Koyanagi, et al

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Background

> Authors conducted a randomized, 3-arm phase III trial comparing cisplatin + 5-FU (CF) vs docetaxel + CF (DCF) vs radiation

ASCO GI Abstract 159: Confirmed three-year RFS and OS of the randomized trial of adjuvant S-1 versus S-1 plus docetaxel after curative resection of pStage III gastric cancer (JACCRO GC-07). Kazuhiro Yoshida, et al

EPICS

Background

> JACCRO GC-07 is a randomized controlled trial to explore postoperative S-1–docetaxel compared with S-1 alone after D2

KEY TAKEAWAYS: GASTROESOPHAGEAL CANCERS (1/2)

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Immunotherapy

> It is important to distinguish adenocarcinoma from squamous cell carcinoma. The role of PD-L1 positivity as a predictive

KEY TAKEAWAYS: GASTROESOPHAGEAL CANCERS (2/2)

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Chemotherapy Use in US

> Triplet docetaxel, oxaliplatin, leucovorin, 5-FU (FLOT) is recommended in the preoperative setting, and would only be

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Pancreatic Cancer

DIRK ARNOLD, MD, PHD

ASCO GI Abstract 406: Randomized multicenter phase II/III study with adjuvant gemcitabine versus neoadjuvant/adjuvant FOLFIRINOX in resectable pancreatic cancer: The NEPAFOX trial. Salah-Eddin Al-Batran, et al

EPICS

Background

> The outcome for pancreatic cancer remains poor. Few pts can be assigned to surgery, and 80% of resected pts experience

ASCO GI Abstract 413: Phase II randomized, double-blind study of mFOLFIRINOX plus ramucirumab versus mFOLFIRINOX plus placebo in advanced pancreatic cancer patients (HCRN GI14-198). Walid L. Shaib, et al

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Background

> VEGFA/VEGFR2 signaling plays an important role in inducing invasion and migration of pancreatic adenocarcinoma (PCA)

ASCO GI Abstract TPS448: A phase III trial of tumor-treating fields with nab-paclitaxel and gemcitabine for front-line treatment of locally-advanced pancreatic adenocarcinoma (LAPC): PANOVA-3. Vincent J. Picozzi, et al

EPICS

Background

ASCO GI Abstract 378: Overall survival from the phase 3 POLO trial: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. Talia Golan, et al

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Background

> POLO is the first phase III trial to evaluate maintenance therapy with the poly(ADP-ribose) polymerase inhibitor (PARPi)

ASCO GI Abstract TPS447: Randomized phase II trial of olaparib + pembrolizumab versus olaparib alone as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1 or BRCA2 (gBRCA1/2+) mutations: SWOG S2001. Vincent Chung, et al

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Background

> Olaparib was approved in 2019 as maintenance therapy for g*BRCA1/2*-positive metastatic pancreatic cancer (mPDA) pts.

ASCO GI Abstract 404: ARC-8: Phase 1/1b study to evaluate safety and tolerability of AB680 + chemotherapy + zimberelimab (AB122) in patients with treatment-naive metastatic pancreatic adenocarcinoma. G.A. Manji, et al

EPICS

Background

> AB680, a potent, selective small-molecule inhibitor of soluble and membrane-bound CD73, targets a major pathway of

Background

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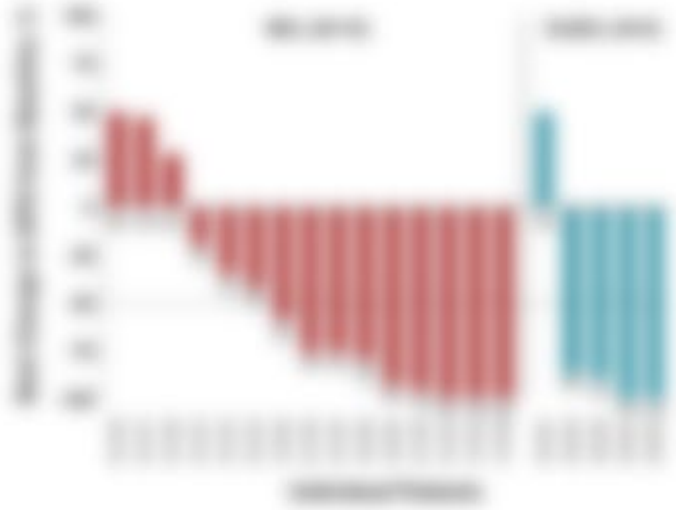


Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 411: Predictive value of plasma tumor mutation burden (TMB) in the CCTG PA.7 trial: Gemcitabine (GEM) and nab-paclitaxel (Nab-P) vs. GEM, nab-P, durvalumab (D) and tremelimumab (T) as first line therapy in metastatic pancreatic ductal adenocarcinoma (mPDAC). Daniel J. Renouf, et al

EPICS

Background

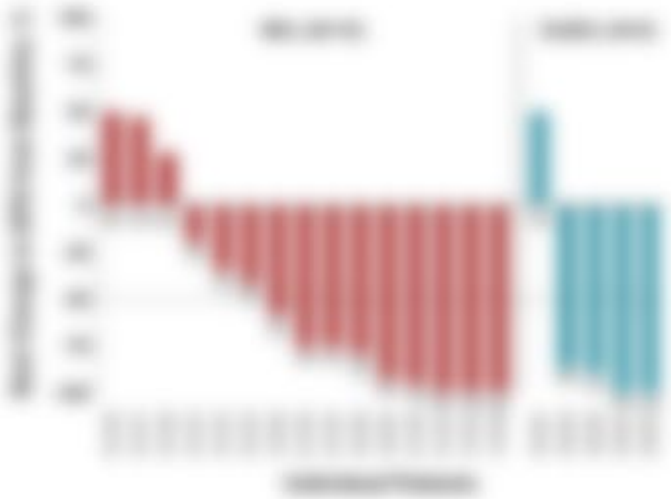
> PA.7 evaluated whether combining PD-L1 and CTLA-4 inhibition with GEM and *nab*-P increases efficacy as first-line therapy

Background

- Phase I dose-escalation study of VLS-101, a ROR1-targeting ADC, in patients with heavily pretreated MCL and DLBCL
- Primary objective was to refine estimates of MTD and recommended dosing regimen

Results

- 32 patients were enrolled, including 15 patients with MCL
- DLTs were G4 neutropenia and G3 diarrhea
- G4 neutropenia occurred in 28% of patients; G-CSF successfully ameliorated neutropenia
- On-study reversible G3 neuropathy occurred in 9% of patients; no G4 neuropathy occurred
- ORR was 47% (3 CR, 4 PR) for MCL cohort and 80% (2 CR, 2 PR) for DLBCL cohort
- 8 responding patients have ongoing responses ranging from 23 weeks to 58 weeks



Key takeaways: VLS-101 demonstrated a manageable and predictable safety profile and encouraging efficacy, with durable responses in advanced MCL and DLBCL. Experts mentioned neuropathy as a potential concern and the need to identify the best histologies in which to test this agent.

ASCO GI Abstract 423: Serial cell-free DNA (cfDNA) sampling in advanced pancreatic ductal adenocarcinoma (PDAC) patients may predict therapeutic outcome. Gehan Botrus, et al.

EPICS

Background

- Advanced PDAC remains a deadly disease, with a 5-year survival rate <10%. cfDNA-based next-generation sequencing

ASCO GI Abstract 400: Impact of pancreatic enzyme replacement therapy (PERT) on clinical outcomes in nonresected pancreatic cancer (PC): Initial results. Vincent J. Picozzi, et al

EPICS

Background

- Current NCCN guidelines recommend PERT use in PC pts with symptoms of exocrine pancreatic insufficiency (EPI).

KEY TAKEAWAYS: PANCREATIC CANCER

EPICS

Olaparib Maintenance

> There are 2 views on the clinical relevance of the POLO trial data

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