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Review Article

Awardee Summary of 2023 Taiwan Oncology Society Clinical Research Award Recipient: Persistent Endeavors on Research of Digestive Cancers for Three Decades

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Abstract

Objective: Digestive cancers account for five of the top ten cancer-related deaths in Taiwan. Our team has made persistent endeavors in translational research and clinical trials of digestive cancers for almost three decades. **Data Sources and Study Selection:** We enrolled relevant translational and clinical studies for digestive cancers published by our groups in the past three decades. **Results:** First, we developed a unique weekly 24-h infusion of high-dose 5-fluorouracil (5-FU) and leucovorin regimen (HDFL) in 1992. HDFL exhibits satisfactory single-agent activity, minimal myelosuppression, and mild toxicity. A variety of HDFL-based doublet combinations (such as cisplatin-HDFL, oxaliplatin-HDFL, and paclitaxel-HDFL) have become cornerstone regimens for three decades for the treatment of gastric cancers, with high efficacy and manageable toxicity at our hospital. Second, we have made persistent efforts in translational research and clinical trials on early-stage gastric mucosa-associated lymphoid tissue lymphomas (MALTomas), gastric diffuse large B-cell lymphomas, colorectal cancers (CRCs), pancreatic cancers, and immuno-oncology. Third, on behalf of the Taiwan Oncology Society, we participated in and published the Pan-Asian adapted European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for locally advanced and metastatic CRC, gastric, and esophageal cancers, and the consensus meeting on tumor-agnostic indications of microsatellite instability-high (MSI-H) and NTRK. **Conclusion:** In the future, our team will make persistent endeavors in research on digestive cancers for immunotherapy and precision medicine to further improve treatment outcomes.

Keywords: Colorectal cancer, digestive cancers, gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma, high-dose 5-fluorouracil (5-FU) and leucovorin, pancreatic ductal adenocarcinoma

Introduction

Digestive cancers account for five of the top ten cancer-related deaths in Taiwan. Our team has made persistent endeavors in

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translational research and clinical trials of digestive cancers for almost three decades.

HDFL-Based Combinations in the Treatment of Gastric Cancers (GCs)

First, we developed a unique high-dose 5-fluorouracil (5-FU) and leucovorin (HDFL) regimen (weekly 24-h infusion of high-dose 5-FU 2000–2600 mg/m^2 and leucovorin 300 mg/m^2) with satisfactory single-agent activity, minimal myelosuppression, and mild toxicity. To overcome central venous portable pump blockage by calcite, a slightly lower dose of leucovorin (300 mg/m^2), instead of the initial 500 mg/m^2, has been used in Taiwan.[1,2] This regimen was found to be not only highly effective for colorectal cancer (CRC) and GC but also associated with surprisingly low treatment-related toxicity.[2-4]

The HDFL regimen has been successfully used to treat patients with advanced GC, with a response rate of 48% (95% confidence interval [CI], 32%–72%).[4,5] The low-myelosuppressive nature of HDFL has made it ideal for patients with GC presenting with a poor general condition[4] or even with acute DIC (disseminated intravascular coagulation).[5,6]

The half-life of 5-FU in the serum is very short, ranging from 8 to 14 min. The steady-state serum concentration (Css) of 5-FU (approximately 7.5 μM) by 24-h high-dose 5-FU (2000–2600 mg/m^2) infusion was much lower than the serum concentration (approximately 420 μM) of 5-FU (370-500 mg/m^2) by bolus injection. Moreover, due to a probable physiological "bone marrow barrier," the concentration of 5-FU in bone marrow is about one-third to one-fifth of that in serum during low Css achieved by infusional 5-FU.[7] In contrast, the physiological "bone marrow barrier" does not exist during high concentrations of 5-FU achieved by bolus injection, and the concentration of 5-FU in bone marrow is about the same as that in serum.

First, a possible mechanism for the satisfactory anti-cancer efficacy of HDFL has been elucidated. Prolonged exposure of GC cells to low concentrations of 5-FU for 24 h and enhanced thymidylate synthase (TS) inhibition, thereby increases the cytotoxicity of 5-FU.[8] HDFL has been prospectively studied at our hospital for the treatment of patients with advanced GC. This enabled us to explore the possibility that the expression of TS, the target enzyme of 5-FU, is related to the drug sensitivity of GC to HDFL monotherapy. We reported that 2 of the 16 patients (12.5%) with high expression of TS and 13 of the 14 patients (92.9%) with low expression of TS responded to chemotherapy ($P < 0.001$).[9] High expression of TS is associated with the drug resistance of GC to HDFL monotherapy.[9]

Furthermore, a possible mechanism for the low myelotoxicity of HDFL has been reported.[10]

The HDFL regimen has been repeatedly demonstrated to cause minimal myelosuppression[2-5] and is, therefore, an ideal component for combination chemotherapy with other cytotoxic agents against GC. Various HDFL-based combinations with high efficacy and manageable toxicity have become cornerstone regimens. All HDFL-based doublets (e.g. cisplatin-, oxaliplatin-, and paclitaxel-HDFL) are well tolerated and have a respectable objective tumor response of 52%–61%.[11-14] The median overall survival (OS) of intent-to-treat patients is 10–11.4 months.[11-14]

Everolimus (RAD001, Afinitor) is a rapamycin derivative that specifically inhibits the mammalian target of rapamycin, a potential target agent in the treatment of GC. We demonstrated the chemosensitizing effects and sustained G1-S cell cycle arrest by low-dose RAD001 and 5-FU in human GC cells. We initiated and conducted an investigator-initiated multi-center phase II study of low-dose everolimus plus cisplatin-HDFL for the first-line treatment of AGC has also been completed in Taiwan with a respectable median progression-free survival of 6.9 (95% CI, 4.9–8.4) months, and without any additional toxicities.[15]

We also initiated and conducted an investigator-initiated multi-center phase II study of weekly cetuximab plus weekly cisplatin and HDFL combination regimen as an effective first-line treatment for patients with metastatic GC (mGC).[16] Besides, we conducted a phase II study of weekly vinorelbine plus HDFL doublet regimen as an effective first-line treatment for patients with metastatic breast cancer.[17]

HDFL-based regimens require the insertion of a totally implantable venous port (Port A) for ambulatory outpatient care. We identified the predictors of bloodstream infection (BSI) associated with a permanently implantable venous port in patients.[18] Solid cancer, who were prospectively observed for the occurrence of Port-A-associated BSI (PABSI), defined as BSI without other identifiable infection foci. The PABSI risk score was calculated using the Cox proportional hazards model. The PABSI risk score can assist in identifying patients with high-risk solid cancer and may assist in designing future preventive strategies.[18] Later, we reported that chlorhexidine for the prevention of BSI was associated with totally implantable venous ports in patients with solid cancers.[19]

In summary, from 1992 to 2023, HDFL-based doublet combinations have been constantly and widely used in the routine first-line treatment of mGC for three decades.

Helicobacter Pylori Eradication Therapy on Early-stage Gastric Mucosa-associated Lymphoid Tissue Lymphomas and Gastric Diffuse Large B-cell Lymphomas

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma (MALToma) is the most common type of lymphoma. Most gastric MALTomas are characterized by their association with *Helicobacter pylori* (HP) infection and are cured with first-line HP eradication (HPE) therapy.

The t (11;18)(q21;q21) translocation is a specific marker for HP-independent low-grade MALToma. We previously reported that the nuclear expression of BCL10 or nuclear factor kappa B (NF-κB) helps predict the HP-independent status of low-grade gastric MALTomas with or without t (11;18) (q21;q21).[20]

An explorative study evaluates the efficacy of HPE therapy on early-stage gastric diffuse large B-cell lymphomas (DLBCLs) without features of MALT, the pure (*de novo*) DLBCLs, in comparison with its efficacy on high-grade transformed gastric MALTomas, the DLBCL (MALT). In total, 68.8% (11/16) of patients with pure (*de novo*) DLBCL and 56.3% (18/32) of patients with DLBCL (MALT) achieved complete pathological remission (pCR) after HPE therapy. Our data revealed that HPE therapy was effective for the treatment of early-stage HP-positive gastric DLBCL.[21]

We showed that HP-positive gastric "pure" DLBCL may respond to HPE therapy. To draw a closer biological link to HP, HP-positive tumors were further examined for CagA expression in lymphoma cells. Compared to CagA-negative cases ($n = 16$), CagA-positive cases ($n = 27$) were associated with high phosphorylated SHP-2 expression ($P = 0.016$) and better 5-year event-free survival (EFS) (85.2% vs. 46.3%, $P = 0.002$) and OS (88.9% vs. 52.9%, $P = 0.003$). HP-related gastric "pure" DLBCL may be a distinct tumor entity, which is less aggressive, and responds better to conventional chemotherapy.[22] We reported that the direct contact of HP and B cells results in CagA translocation into the latter and that the translocated CagA regulates intracellular signaling pathways.[23] Further, our results indicate that CagA protein expression is biologically relevant and is associated with the activation of its downstream signals in HP-dependent gastric MALToma.[24]

First-line antibiotic treatment for eradicating HP infection is effective in HP-positive low-grade gastric MALToma; however, its role in HP-negative cases is uncertain. In this exploratory retrospective study, we assessed the outcomes and potential predictive biomarkers of 25 patients with HP-negative localized gastric MALToma who received first-line HPE therapy. We observed an antibiotic response in 9 (36.0%) of 25 patients.[25] Nuclear BCL10 expression was significantly higher in antibiotic-unresponsive tumors than in antibiotic-responsive tumors (14/16 [87.5%] vs. 1/9 [11.1%]; $P = 0.001$). Although the role of first-line HPE in the treatment of "HP-negative" gastric MALToma remains uncertain, we suggest that a proportion of "HP-negative" gastric MALTomas remain antibiotic-responsive and can be treated with HPE.[25]

Translational Research and Clinical Studies in Colorectal Cancers

Identifying better regimens for currently available chemotherapy would be beneficial to KRAS-mutant metastatic CRC (mCRC) because they have fewer treatment options than patients with *KRAS* wild-type mCRC. First, our *in vitro* studies revealed that the *KRAS* mutation is a predictor of oxaliplatin sensitivity in colon cancer cells.[26] We found that oxaliplatin-based chemotherapy might provide longer progression-free survival (PFS) in KRAS-mutant mCRC.[27] We reported that oxaliplatin-based chemotherapy is more beneficial with significantly longer OS in *KRAS* mutants than in patients with *KRAS* wild-type mCRC.[28]

We have joined a randomized, double-blind, placebo-controlled, phase 3 trial (CONCUR trial) of regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated mCRC (CONCUR).[29] This phase 3 trial is the second (in addition to CORRECT trial) to show an OS benefit with regorafenib compared with placebo in patients with treatment-refractory mCRC, substantiating the role of regorafenib as an important treatment option for patients whose disease has progressed after standard treatments.[29] We and all CORRELATE Taiwan colleagues reported the real-world evidence of the safety and effectiveness of regorafenib in Taiwanese patients with mCRC of a prospective, observational study (CORRELATE study).[30] The safety and effectiveness of regorafenib in this real-world study were generally consistent with the known efficacy and safety profile in Asian patients in clinical trials.[30]

We reported that the primary tumor site (tumor sidedness) is a useful predictor of cetuximab efficacy in third-line or salvage treatment of *KRAS* wild-type (exon 2 non-mutant) mCRC in a nationwide cohort study.[31] Our findings demonstrate that a left-sided primary tumor site is a useful predictor of improved cetuximab efficacy in third-line or salvage treatment of *KRAS* wild-type (exon 2 nonmutant) mCRC.[31]

We reported that the *BRAF* mutation may have different prognostic implications in early- and late-stage CRC.[32] We found that *BRAF* mutations were significantly associated with CpG island methylator phenotype (CIMP)-positive ($P < 0.001$) and microsatellite instability-high status ($P = 0.0013$) in patients with early-stage CRC. Conversely, *BRAF* mutation was significantly associated with CIMP positivity ($P = 0.0015$) and right-sided colon cancer ($P = 0.014$) in patients with late-stage CRC.[32] We also reported that more frequent *BRAF* mutations in early-onset CRC (under the age of 30) in Taiwan and their association with distinct clinicopathological and molecular features and poor clinical outcomes.[33]

Among the 450 CRC specimens with successfully determined CIMP status at our institution between 2005 and 2013, 74 (16.4%) had CIMP-high CRC. Our data revealed that the presence of CIMP independently predicts poor OS in patients with stage IV CRC.[34]

CIMP represents a carcinogenesis pathway. The association among CIMP CRC, molecular features, and risk factors in East Asian populations has not yet been extensively studied. We have reported that CIMP-high CRC in 14.3% of patients younger than 50 years (young CRC) is significantly higher in

East Asian (including Taiwan) patients than in about 5.0% of Caucasian patients.[34] Further, our data suggest a significant association between body mass index ≧ of 27.5 kg/m^2 and CIMP-high CRC in patients younger than 50 years in a Taiwanese cohort.[35] These data may pave for the very first step of potential cancer prevention for CRC by lifestyle changes in Taiwan.

Many studies have revealed that the BRAF V600E mutation is one of the worst prognostic factors for mCRC. Previously, we demonstrated a significant prognostic role in late-stage BRAF V600E mutant CRC, but not in early-stage tumors.[32] Thus, we hypothesized that immune contextures in the tumor microenvironment of BRAF V600E mutant CRC have prognostic implications in CRC. We enrolled 54 patients with untreated, metastatic microsatellite-stable (MSS) BRAF V600E-mutated CRC and analyzed the expression of immune-related genes. Our data revealed that many complement genes were associated with patient survival outcomes. We developed a complement score and compared it with that of BRAF V600E-mutated CRC with complement score. Our data showed that high complement scores were associated with significantly shorter PFS and OS.[36] We also found that complement score was significantly correlated with C4d (a surrogate marker of complement activation) density by immunohistochemical staining, which validated our RNA analysis data, as well as M2 macrophage signatures.[36] The fact that M2 macrophages are recognized as tumor-promoting may be one of the reasons why tumors with high complement scores are associated with poor survival.

Translational Research and Clinical Studies in Pancreatic Cancers

We reported the association of MDM2 expression with shorter PFS and OS in patients with advanced pancreatic cancer treated with gemcitabine-based chemotherapy.[37] We reported the patients' series in heavily pretreated patients with pancreatic adenocarcinoma, low-dose nab-paclitaxel-based chemotherapy was fairly tolerable with modest efficacy.[38]

We previously demonstrated that nuclear BCL10 translocation participates in the inactivation of NF-κB in breast cancer and lymphoma cell lines. Furthermore, we demonstrated that nuclear BCL10 translocation is clinically significant in advanced and metastatic pancreatic ductal adenocarcinoma (PDAC).[39] Inhibition of BCL10 differentially blocked cell cycle progression in PDAC cell lines. Arrest at the G1 phase was noted in wild-type *KRAS* cell lines, and arrest at the G2/M phase was noted in mutant *KRAS* cell lines. In a PANC-1-xenograft mouse model, inhibition of BCL10 expression attenuated PDAC tumor growth. In clinical samples, nuclear BCL10 expression was closely associated with nuclear NF-κB expression ($P < 0.001$), and patients with nuclear BCL10 expression had worse median OS than those without nuclear BCL10 expression (6.90 months vs. 9.53 months, $P = 0.019$). In summary, nuclear BCL10 translocation activates NF-κB signaling and contributes to tumor progression and poor prognosis in advanced/metastatic PDAC.[39]

Translational Research and Clinical Studies on Immuno-Oncology of Digestive Cancers

Colorectal cancers

Immunotherapy with immune checkpoint inhibitors (ICIs), such as anti-programmed death 1 (PD-1) antibodies, has led to breakthroughs in the treatment of patients with microsatellite instability-high (MSI-H) mCRC. However, MSI-H accounts for only 1.8%–4.0% of all patients with mCRC. To date, several phase III clinical trials have failed to demonstrate the efficacy of immunotherapy with a single ICI in patients with MSS mCRC; therefore, novel strategies are required.

Increases in the expression of major histocompatibility complex (MHC) class I, namely human leukocyte antigen class I, enhance the efficacy of cytotoxic T cells, which implies a higher response rate to ICIs. Our study revealed that the expression of MHC class I, PD-1, and PD-L1 significantly increased after chemotherapy and targeted therapy from the samples of real-world patients with *de novo* mCRC.[40] We had shown that among chemotherapy agents, particularly SN-38, the active metabolite of irinotecan significantly stimulated the expression of stimulatory MHC class I alleles and also the subsequent immunogenic cell death.[40] Further, our study revealed that bortezomib, a proteasome inhibitor, may successfully restore STAT1 expression and subsequently enhance the downstream expression of MHC class I.[41] We hypothesize that both bortezomib and irinotecan might increase the MHC class I expression[40,41] and thus probably potentiate the efficacy of ICIs for the innovative treatment of mCRC.

Pancreatic ductal adenocarcinoma

Although ICIs have limited efficacy in the treatment of PDAC, we reported the "negative" prognostic implications of splenomegaly in nivolumab-treated advanced or recurrent PDAC.[42] A total of 45 patients were identified. Biweekly nivolumab was administered as monotherapy ($n = 5$) or in combination with chemotherapy or targeted therapy ($n = 40$). Among 31 evaluable patients, the response and disease control rates were 7% and 36%, respectively. The median baseline splenic volume was 267 (110–674) mL. Patients with spleens ≥267 mL had significantly shorter median OS (1.9 months; 95% CI, 1.0–2.7) than those with smaller spleens (8.2 months; 95% CI, 5.6–10.8; $P = 0.003$). In a multivariate analysis, a spleen volume of <267 mL remained an independent favorable prognostic factor for OS.[42]

Gastric cancer

We report the first case of a patient with pMMR (mismatch repair-proficient) and MSS GC who exhibited a partial response to salvage anti-PD-1 therapy with pembrolizumab.[43] We also reported durable response to PD-1 blockade in a

patient with mGC with mismatch repair deficiency (dMMR) and MSI.[44] We have joined a randomized, double-blind, placebo-controlled, phase 3 trial (ATTRACTION-2) using nivolumab in patients with advanced GC or gastroesophageal junction cancer (GEJC) refractory to, or intolerant of, at least two previous chemotherapy regimens.[45] Median OS was 5.26 (95% CI, 4.60–6.37) and 4.14 (3.42–4.86) months in the nivolumab and placebo groups, respectively (hazard ratio 0.63; 95% CI, 0.51–0.78; $P < 0.0001$). In this phase 3 study, the survival benefits indicated that nivolumab may be a new treatment option for heavily pretreated patients with advanced GC or GEJC.[45]

Pan-Asian Adapted European Society for Medical Oncology Clinical Practice Guidelines, on Behalf of the Taiwan Oncology Society

On behalf of the Taiwan Oncology Society (TOS), we participated in and published the Pan-Asian adapted European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for mCRC,[46] GC,[47] esophageal cancer,[48] and locally advanced CRC.[49]

To focus on what we have learned from both MSI/dMMR biomarkers in predicting the efficacy of anti-PD-1)/PD-ligand 1 immunotherapy, and the neurotrophic tyrosine receptor kinase gene fusions in predicting the efficacy of inhibitors of the tropomyosin receptor kinase proteins across a range of solid tumor types.[50] We, on behalf of TOS, joined and published the JSCO-ESMO-ASCO-JSMO-TOS: International expert consensus recommendations for "tumor-agnostic" indications in patients with solid tumors with microsatellite instability or NTRK fusions.[50]

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Conflicts of interest

There are no conflicts of interest.

References

1. Yeh KH. Studies on the Drug Treatment of Gastric Cancers – With Emphasis on the High-Dose 5-Fluorouracil-based Chemotherapy and the Mechanisms of Drug Resistance of Gastric Cancer. Ph.D. Dissertation, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taiwan, ROC, Granted in May; 1998.
2. Yeh KH, Cheng AL. An alternative method to overcome central venous portable external infusion pump blockage in patients receiving weekly 24-hour high-dose fluorouracil and leucovorin. J Clin Oncol 1994;12:875-6.
3. Yeh KH, Cheng AL, Lin MT, Hong RL, Hsu CH, Lin JF, *et al*. A phase II study of weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin (HDFL) in the treatment of recurrent or metastatic colorectal cancers. Anticancer Res 1997;17:3867-71.
4. Hsu CH, Yeh KH, Chen LT, Liu JM, Jan CM, Lin JT, *et al.* Weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of advanced gastric cancers. An effective and low-toxic regimen for patients with poor general condition. Oncology 1997;54:275-80.
5. Yeh KH, Cheng AL. Gastric cancer associated with acute disseminated intravascular coagulation: Successful initial treatment with weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin. Br J Haematol 1998;100:769-72.
6. Huang TC, Yeh KH, Cheng AL, Hsu CH. Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. Anticancer Res 2008;28:1293-7.
7. Ho YF, Lu WC, Chen RR, Cheng AL, Yeh KH. Phase I, pharmacokinetic, and bone marrow drug-level studies of tri-monthly 48-h infusion of high-dose 5-fluorouracil and leucovorin in patients with metastatic colorectal cancers. Anticancer Drugs 2011;22:290-8.
8. Yeh KH, Yeh SH, Hsu CH, Wang TM, Ma IF, Cheng AL. Prolonged and enhanced suppression of thymidylate synthase by weekly 24-h infusion of high-dose 5-fluorouracil. Br J Cancer 2000;83:1510-5.
9. Yeh KH, Shun CT, Chen CL, Lin JT, Lee WJ, Lee PH, *et al.* High expression of thymidylate synthase is associated with the drug resistance of gastric carcinoma to high dose 5-fluorouracil-based systemic chemotherapy. Cancer 1998;82:1626-31.
10. Yeh KH, Yeh SH, Chang YS, Cheng AL. Minimal toxicity to myeloid progenitor cells of weekly 24-hr infusion of high-dose 5-fluorouracil: Direct evidence from colony forming unit-granulocyte and monocyte (CFU-GM) clonogenic assay. Pharmacol Toxicol 2000;86:122-4.
11. Yeh KH, Hsu CH, Lin JF, Lu YS, Li HT, Huang CL, *et al.* Prolonged survival in a pilot study of sequential non-cross-resistant chemotherapy using weekly 24-hour infusion of cisplatin, high-dose 5-fluorouracil and leucovorin (P-HDFL) followed by weekly docetaxel and irinotecan (DI) for recurrent or metastatic gastric cancer. Proc Am Soc Clin Oncol 2003; 22:306 (abstract 1229).
12. Chao Y, Yeh KH, Chang CJ, Chen LT, Chao TY, Wu MF, *et al.* Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer. Br J Cancer 2004;91:453-8.
13. Yeh KH, Lu YS, Hsu CH, Lin JF, Hsu C, Kuo SH, *et al.* Phase II study of weekly paclitaxel and 24-hour infusion of high-dose 5-fluorouracil and leucovorin in the treatment of recurrent or metastatic gastric cancer. Oncology 2005;69:88-95.
14. Yeh KH, Hsu CH, Lu YS, Hsu C, Kuo SH, Huang CL, *et al.* Phase II study of sequential non-cross-resistant chemotherapy using weekly 24-hour infusion of cisplatin, high-dose 5-fluorouracil and leucovorin (P-HDFL) followed by weekly docetaxel and irinotecan (DI) for recurrent or metastatic gastric cancer: An interim analysis. J Clin Oncol (Suppl) 2006;24(18S):(abstract 14063).
15. Shen YC, Li CP, Yen CJ, Hsu C, Lin YL, Lin ZZ, *et al.* Phase II multicentered study of low-dose everolimus plus cisplatin and weekly 24-hour infusion of high-dose 5-fluorouracil and leucovorin as first-line treatment for patients with advanced gastric cancer. Oncology 2014;87:104-13.
16. Yeh KH, Hsu CH, Hsu C, Lin CH, Shen YC, Wu SL, *et al.* Phase II study of cetuximab plus weekly cisplatin and 24-hour infusion of high-dose 5-fluorouracil and leucovorin for the first-line treatment of advanced gastric cancer. J Clin Oncol (Suppl) 2009;27(15S):(abstract 4567).
17. Yeh KH, Lu YS, Hsu CH, Lin JF, Chao HJ, Huang TC, *et al.* Phase II study of weekly vinorelbine and 24-h infusion of high-dose 5-fluorouracil plus leucovorin as first-line treatment of advanced breast cancer. Br J Cancer 2005;92:1013-8.
18. Chen IC, Hsu C, Chen YC, Chien SF, Kao HF, Chang SY, *et al.* Predictors of bloodstream infection associated with permanently implantable venous port in solid cancer patients. Ann Oncol 2013;24:463-8.
19. Kao HF, Chen IC, Hsu C, Chang SY, Chien SF, Chen YC, *et al.* Chlorhexidine for the prevention of bloodstream infection associated with totally implantable venous ports in patients with solid cancers. Support Care Cancer 2014;22:1189-97.
20. Yeh KH, Kuo SH, Chen LT, Mao TL, Doong SL, Wu MS, *et al.* Nuclear expression of BCL10 or nuclear factor kappa B helps predict *Helicobacter pylori*-independent status of low-grade gastric mucosa-associated lymphoid tissue lymphomas with or without t (11;18)(q21;q21). Blood 2005;106:1037-41.
21. Kuo SH, Yeh KH, Wu MS, Lin CW, Hsu PN, Wang HP, *et al.* *Helicobacter pylori* eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large B-cell lymphomas.

Blood 2012;119:4838-44.
22. Kuo SH, Yeh KH, Chen LT, Lin CW, Hsu PN, Hsu C, *et al. Helicobacter pylori*-related diffuse large B-cell lymphoma of the stomach: A distinct entity with lower aggressiveness and higher chemosensitivity. Blood Cancer J 2014;4:e220.
23. Kuo SH, Chen LT, Lin CW, Wu MS, Hsu PN, Tsai HJ, *et al.* Detection of the *Helicobacter pylori* CagA protein in gastric mucosa-associated lymphoid tissue lymphoma cells: Clinical and biological significance. Blood Cancer J 2013;3:e125.
24. Kuo SH, Yeh KH, Chen LT, Lin CW, Hsu PN, Wu MS, *et al. Helicobacter pylori* CagA translocation is closely associated with the expression of CagA-signaling molecules in low-grade gastric mucosa-associated lymphoid tissue lymphoma. Am J Surg Pathol 2015;39:761-6.
25. Kuo SH, Yeh KH, Wu MS, Lin CW, Wei MF, Liou JM, *et al.* First-line antibiotic therapy in *Helicobacter pylori*-negative low-grade gastric mucosa-associated lymphoid tissue lymphoma. Sci Rep 2017;7:14333.
26. Lin YL, Liau JY, Yu SC, Ou DL, Lin LI, Tseng LH, *et al.* KRAS mutation is a predictor of oxaliplatin sensitivity in colon cancer cells. PLoS One 2012;7:e50701.
27. Lin YL, Liau JY, Yu SC, Tseng LH, Lin LI, Liang JT, *et al.* Oxaliplatin-based chemotherapy might provide longer progression-free survival in KRAS mutant metastatic colorectal cancer. Transl Oncol 2013;6:363-9.
28. Lin YL, Liang YH, Tsai JH, Liau JY, Liang JT, Lin BR, *et al.* Oxaliplatin-based chemotherapy is more beneficial in KRAS mutant than in KRAS wild-type metastatic colorectal cancer patients. PLoS One 2014;9:e86789.
29. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, *et al.* Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2015;16:619-29.
30. Yeh KH, Yang TS, Hsu TC, Tzu-Liang Chen W, Chen HH, Teng HW, *et al.* Real-world evidence of the safety and effectiveness of regorafenib in Taiwanese patients with metastatic colorectal cancer: CORRELATE Taiwan. J Formos Med Assoc 2021;120:2023-31.
31. Chen KH, Shao YY, Chen HM, Lin YL, Lin ZZ, Lai MS, *et al.* Primary tumor site is a useful predictor of cetuximab efficacy in the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: A nationwide cohort study. BMC Cancer 2016;16:327.
32. Chen KH, Lin YL, Liau JY, Tsai JH, Tseng LH, Lin LI, *et al.* BRAF mutation may have different prognostic implications in early- and late-stage colorectal cancer. Med Oncol 2016;33:39.
33. Tsai JH, Liau JY, Lin YL, Tseng LH, Lin LI, Yeh KH, *et al.* Frequent BRAF mutation in early-onset colorectal cancer in Taiwan: Association with distinct clinicopathological and molecular features and poor clinical outcome. J Clin Pathol 2016;69:319-25.
34. Chen KH, Lin LI, Tseng LH, Lin YL, Liau JY, Tsai JH, *et al.* CpG Island methylator phenotype may predict poor overall survival of patients with stage IV colorectal cancer. Oncology 2019;96:156-63.
35. Chen KH, Lin LI, Yuan CT, Tseng LH, Chao YL, Liang YH, *et al.* Association between risk factors, molecular features and CpG island methylator phenotype colorectal cancer among different age groups in a Taiwanese cohort. Br J Cancer 2021;125:48-54.
36. Chen KH, Hsu CL, Su YL, Yuan CT, Lin LI, Tsai JH, *et al.* Novel prognostic implications of complement activation in the tumour microenvironment for de novo metastatic BRAF V600E mutant colorectal cancer. Br J Cancer 2023;128:102-11.
37. Yang SH, Lee JC, Guo JC, Kuo SH, Tien YW, Kuo TC, *et al.* Association of MDM2 expression with shorter progression-free survival and overall survival in patients with advanced pancreatic cancer treated with gemcitabine-based chemotherapy. PLoS One 2017;12:e0180628.
38. Yang SH, Guo JC, Hsu C, Kuo SH, Tien YW, Cheng AL, *et al.* Low-dose nab-paclitaxel-based combination chemotherapy in heavily pretreated pancreatic cancer patients. J Formos Med Assoc 2020;119:97-105.
39. Kuo SH, Yang SH, Wei MF, Lee HW, Tien YW, Cheng AL, *et al.* Contribution of nuclear BCL10 expression to tumor progression and poor prognosis of advanced and/or metastatic pancreatic ductal adenocarcinoma by activating NF-κB-related signaling. Cancer Cell Int 2021;21:436.
40. Liang YH, Tsai JH, Cheng YM, Chan KY, Hsu WL, Lee CC, *et al.* Chemotherapy agents stimulate dendritic cells against human colon cancer cells through upregulation of the transporter associated with antigen processing. Sci Rep 2021;11:9080.
41. Liang YH, Chen KH, Tsai JH, Cheng YM, Lee CC, Kao CH, *et al.* Proteasome inhibitors restore the STAT1 pathway and enhance the expression of MHC class I on human colon cancer cells. J Biomed Sci 2021;28:75.
42. Yang SH, Lu LC, Kao HF, Chen BB, Kuo TC, Kuo SH, *et al.* Negative prognostic implications of splenomegaly in nivolumab-treated advanced or recurrent pancreatic adenocarcinoma. Oncoimmunology 2021;10:1973710.
43. Chen KH, Yuan CT, Tseng LH, Shun CT, Yeh KH. Case report: Mismatch repair proficiency and microsatellite stability in gastric cancer may not predict programmed death-1 blockade resistance. J Hematol Oncol 2016;9:29.
44. Wu TH, Hsiue EH, Yuan CT, Tseng LH, Lin CC, Yeh KH. Durable response to programmed death-1 (PD-1) blockade in a metastatic gastric cancer patient with mismatch repair deficiency and microsatellite instability. J Cancer Res Pract 2017;4:72-5.
45. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, *et al.* Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:2461-71.
46. Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu RH, *et al.* Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: A JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018;29:44-70.
47. Muro K, Van Cutsem E, Narita Y, Pentheroudakis G, Baba E, Li J, *et al.* Pan-Asian adapted ESMO clinical practice guidelines for the management of patients with metastatic gastric cancer: A JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol 2019;30:19-33.
48. Muro K, Lordick F, Tsushima T, Pentheroudakis G, Baba E, Lu Z, *et al.* Pan-Asian adapted ESMO clinical practice guidelines for the management of patients with metastatic oesophageal cancer: A JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol 2019;30:34-43.
49. Yoshino T, Argilés G, Oki E, Martinelli E, Taniguchi H, Arnold D, *et al.* Pan-Asian adapted ESMO clinical practice guidelines for the diagnosis treatment and follow-up of patients with localised colon cancer. Ann Oncol 2021;32:1496-510.
50. Yoshino T, Pentheroudakis G, Mishima S, Overman MJ, Yeh KH, Baba E, *et al.* JSCO-ESMO-ASCO-JSMO-TOS: International expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or NTRK fusions. Ann Oncol 2020;31:861-72.