

CS-7

Shortlisted for Oral Presentation

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A phase I trial of selective PI3K inhibitor taselisib (tas) plus palbociclib (palb) with and without endocrine therapy incorporating pharmacodynamic (PD) studies in patients (pts) with advanced cancers

Background

The phosphatidylinositol 3-kinase (PI3K) pathway is commonly mutated in cancer. Tas is a selective β -isoform-sparing PI3K inhibitor with improved therapeutic index compared to pan-PI3K inhibitors. Palb is a CDK4/6 inhibitor now standard of care in combination with endocrine therapy (ET) in hormone receptor positive breast cancer. Combination of Tas, Palb and ET is synergistic in preclinical models.

Methods

This investigator-initiated study investigated safety, pharmacokinetics (PK), PD and antitumor activity of Tas+Palb, with addition of ET in dose expansion. Pts were enrolled in 3+3 dose escalation design. Tas was given continuously or 3-weeks-on, 1-week-off (3/1), Palb was given on 3/1 schedule. PD studies included analyses of platelet-rich plasma (PRP) (n=20) and paired tumor biopsies (n=5). Serial circulating tumor DNA was monitored in pts with *PIK3CA* mutations.

Results

24 pts were treated, 22 with Tas+Palb, 2 with Tas+Palb+fulvestrant(ful); M/F 11/13, median lines prior therapy 4. Treatment was well tolerated with mainly G1-2 toxicities. Most frequent G3 toxicities were neutropenia (5/24), thrombocytopenia (5/24) and rash (5/24), with no G4/5 toxicities. At 3/1 schedule, no dose-limiting toxicities (DLTs) were observed for Palb 100mg + Tas 2mg (n=4), but 2 of 3 pts had DLTs (G3 mucositis, G3 hyperglycemia, G3 fatigue) at Tas 4mg. No DLTs were observed when Tas was given 2mg continuously with palb 125mg on 3/1 schedule (n=6), although pts experienced delayed neutrophil recovery. PK was linear and comparable with monotherapy. At 125mg Palb, significant decreases in pAKT and pGSK3 β in PRP confirmed PI3K target inhibition. Two pts with *PI3KCA* H1047R mutant breast cancers have ongoing RECIST partial response; 1 pt with *PI3KCA* E542K colorectal cancer had stable disease for 20 weeks.

Conclusions

Tas+Palb is well tolerated with evidence of PD and antitumor activity. Dose expansion including recruitment to triplet Tas+Palb+ful and Tas+Palb+letrozole is ongoing with continuous Tas 2mg QD, and Palb 100mg QD on 3/1 schedule, increasing to 125mg after cycle 1 in absence of myelosuppression.

CS-8

Shortlisted for Poster Award Presentation

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A Survey of the Behaviour and Barriers to Colorectal Cancer Screening in Non-Colorectal Cancer Survivors

Background

Understanding behaviours of cancer survivors is imperative as they are at risk of cancer recurrence or second cancers. Colorectal cancer (CRC) is the most common cancer in Singapore. We aim to determine attitudes and barriers of non-colorectal cancer survivors towards CRC screening.

Methods

We enrolled 150 non-colorectal cancer survivors. Data about CRC knowledge, motivators and barriers of screening were collected. Information on cancer history, family history and one's perceived health status were also obtained.

Results

Majority were survivors of breast (69.3%), prostate (7.3%), endometrial (4%), ovarian (4%), cervix (3.3%) and nasopharyngeal (3.3%) cancer. 63.3%, 61.3% and 55.3% of survivors respectively obtained high knowledge scores for CRC symptoms, screening tests and risk factors. Only 36.7% of survivors had previously received doctor's recommendation on CRC screening, and less than half (48%) had ever undergone CRC screening. Lack of symptoms (73.1%) and lack of doctor's recommendation (14.1%) were the most common barriers. Cancer survivors with higher education, higher household income, family history and those who perceived "great need" or "some need" were more likely to have undergone CRC screening (56.4% vs 30.6%, $p=0.003$; 62.2% vs 41.9%, $p=0.022$; 70.6% vs 45.1%, $p=0.048$; 70.8% vs 27.4%, $p<0.001$). Physician's recommendation (76.4% vs 31.6%, $p<0.001$) and high CRC symptom knowledge (55.8% vs 34.5%, $p=0.012$) were also associated with increased likelihood of screening. On multivariate analysis, physician's recommendation, higher household income and survivors' perceived need to undergo screening remained strong predictors for CRC screening ($p<0.001$; $p=0.036$; $p<0.001$).

Conclusion

Physician's recommendation for CRC screening has a positive impact on patients' behavior. Screening among cancer survivors can be improved by raising knowledge and awareness.

CS-14

Shortlisted for Poster Award Presentation

Raghav Sundar^{1,2}, Ana Custodio², Stan B. Kaye², Juanita Lopez²¹ Department of Haematology- Oncology, National University Health System² Institute of Cancer Research and The Royal Marsden Hospital, U.K.**Clinical outcome of patients with advanced biliary tract cancer in a dedicated Phase 1 unit**Background

Advanced biliary tract carcinomas (ABC) are malignancies with limited effective therapies for advanced disease. Anatomic factors often lead to liver dysfunction rendering patients unfit for clinical trials. There is little published evidence of outcomes of ABC patients participating in phase I clinical trials.

Methods

Patient characteristics and clinical outcomes of ABC patients treated at the Drug Development Unit, Royal Marsden Hospital, between 2002 and 2016, were captured and analysed from case and trial records.

Results

A total of 123 ABC patients were included in the study, of which 48 patients participated in 41 different phase I trials; 75 (61%) did not participate due to rapid disease progression or patient's choice. Of those that participated in at least one trial, 36 (75%) had cholangiocarcinoma, six (13%) had gallbladder carcinoma and six had ampullary carcinoma. Molecular characterisation of tumours using a targeted panel was conducted in 15 (31%), yielding several potentially actionable mutations including BRCA, PIK3CA, FGFR, AKT and PTEN loss. Of the 39 evaluable patients, there was one exceptional responder; a 52 year old male who had a partial response (PR) that was maintained for 1.5 years on a poly ADP-ribose polymerase (PARP) inhibitor study. Eighteen (46%) other patients achieved stable disease (SD) as their best response, with a clinical benefit rate at 4 months of 10%. Median progression free survival was 1.9 months (95% CI: 1.5 to 2.4) and median overall survival was 5.1 months (95% CI: 3.2 to 6.2). Treatment was generally well tolerated with grade 3 or 4 adverse events only observed in 8 patients (17 %) of which 6 were drug related and led to trial discontinuation in 1 (3%), with no toxicity related deaths.

Interpretation

Novel agents are required for the treatment of ABC, and is an area of unmet research need. Carefully selected patients have been found to tolerate experimental phase I clinical trials without excess toxicity.

CS-23Pei Yi Ong¹, Soo Chin Lee¹

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Spectrum of BRCA1 and BRCA2 mutation in breast and ovarian cancer patients tested at a cancer genetics clinic in SingaporeBackground

BRCA1/2 genes are key genes that cause hereditary breast and ovarian cancer. Understanding the prevalence and spectrum of BRCA1/2 mutations in breast and ovarian cancer patients may inform testing strategies.

Methods

We compared the characteristics, BRCA1/2 testing uptake, motivations and test results of breast or ovarian cancer patients counselled at our cancer genetics clinic from 2000 to August 2016.

Results

742 women with breast (n=615, 82.9%) or ovarian (n=127, 17.1%) cancer were counselled. Main referral reasons were young cancer <40 years, family history of breast cancer (or ovarian cancer for ovarian cancer patients), and family history of breast-ovarian cancer (30.2% vs 36.9% vs 15% and 11.8% vs 16.5% vs 44.9%) for breast and ovarian cancer patients respectively. Test uptake was significantly higher in ovarian than breast cancer patients (61.4% vs 41.1%, p=0.001). Main motivation for testing for breast and ovarian cancer patients was for screening and preventive surgery strategies (28.1%) and treatment (51.3%), respectively. 53/253 (20.9%) breast cancer patients tested had mutations in BRCA1 (32) and BRCA2 (21) genes. 25.6% (20/78) ovarian cancer patients tested had mutations in BRCA1 (13) and BRCA2 (7) genes. The probability of finding BRCA1/2 mutations in breast and ovarian cancer patients were 13.2% and 10% for young cancer, 35.8% and 20% for family history of breast cancer (or ovarian cancer), and 47.2% and 65% for family history of breast-ovarian cancer, respectively.

Conclusions

Ovarian cancer patients were more likely than breast cancer patients to undergo BRCA1/2 testing to aid therapeutic decisions. Family history of breast and ovarian cancer remains the key predictor for BRCA1/2 mutations in both breast and ovarian cancer patients.

CS-24

Pei Yi Ong, Jeffrey Jen Hui Low, David Shao Peng Tan, Yi Wan Lim, Khin Zarchi Aung, Joyce Biaw Theng Er, Soo-Chin Lee

Impact of PARP inhibitor expanded access program on the uptake of genetic testing in newly diagnosed or recurrent ovarian cancer patients in SingaporeBackground

Olaparib, a PARP inhibitor, has been approved for treatment of BRCA mutant metastatic ovarian cancer, and is available in Singapore through an expanded access program since April 2014.

Methods

We reviewed the demographic characteristics, genetic testing uptake, and test results of newly diagnosed or recurrent ovarian cancer patients seen at cancer genetics clinic before (2007 to March 2014) and after (April 2014 to May 2016) the PARP inhibitor access program.

Results

Before the program, only 5.4% (28/520) of newly diagnosed or recurrent ovarian cancer patients were referred, compared to 41.6% (89/214, $p=0.001$) after the program. There were no differences in ethnicity ($p=0.28$), family history risk category ($p=0.47$), stage ($p=0.67$) or age at cancer diagnosis ($p=0.14$) between patients counselled before and after the program. However, after the program, significantly more patients with serous ovarian adenocarcinoma were seen (60.7% vs 39.3%, $p=0.003$), and more patients undertook genetic testing (66.3% vs 39.3%, $p=0.18$). 39/59 (66.1%) patients tested after the program have relapsed disease and may potentially be treated with a PARP inhibitor if they carry deleterious BRCA1/2 mutation. Overall, 24/70 (34.3%) patients tested had deleterious mutations, 40% had variants of uncertain significance and 25.7% tested negative. Of the 24 patients with deleterious mutation, 50% had BRCA1, 29.2% had BRCA2, 12.5% had DNA mismatch repair gene, and 8.3% other ovarian cancer susceptibility gene mutations (BRIP1=1, RAD51C=1). Serous adenocarcinoma is the predominant histological subtype in BRCA1 and BRCA2 mutation carriers (83.3% and 71.4%).

Conclusions

Since the clinical availability of olaparib, referral of ovarian cancer patients for genetic counselling increased by almost 8-fold and uptake of testing almost doubled. BRCA1/2 remain the most common causative genes in ovarian cancer patients with suspected hereditary cancer syndrome.

CS-25

Shortlisted for Poster Award Presentation

Pei Yi Ong, Jeffrey Low, Philip lau, Mikael Hartman, Soo-Chin Lee

Uptake and outcome of multi-gene panel testing in women with breast, ovarian or uterine cancer counselled at a cancer genetics clinic in SingaporeBackground

Although most inherited breast, ovarian and uterine cancers are due to BRCA1/2 or mismatch repair gene mutations, there are other causative cancer susceptibility genes, which can now be sequenced in a multi-gene panel.

Methods

We reviewed the characteristics, genetic test motivations, uptake, and test results of women with breast, ovarian or uterine cancer offered multi-gene testing from July 2014 to August 2016.

Results

308 patients with primary breast (n=205), ovarian (n=85) or uterine cancer (n=18) were counselled, and 51.3% underwent testing. Primary suspected diagnosis was hereditary breast-ovarian, Lynch, Li-Fraumeni, and Cowden syndrome in 81.6%, 15.2%, 1.9% and 1.3% respectively. Test uptake was significantly higher in ovarian than breast and uterine cancer patients (69.4% vs 44.9% vs 38.9%, p=0.001). There were no differences in ethnicity (p=0.07), risk category (p=0.13) or age at cancer diagnosis (p=0.83) between patients counselled and tested. Main motivation for testing for breast, ovarian and uterine cancer patients was to plan screening and preventive surgery (38.0%), for treatment options (59.3%) and for knowledge (42.9%), respectively. 23/92 (25.0%), 16/59 (27.1%) and 3/7 (42.9%) of breast, ovarian and uterine cancer patients tested had deleterious mutations. 13/23 (57%) breast cancer mutation carriers had BRCA1 (5) and BRCA2 (8) mutations, 10/23 (43%) had mutations in other genes. One BRCA2 mutation carrier had an incidental RET pathogenic mutation. 12/16 (75%) ovarian cancer mutation carriers had BRCA1 (8) and BRCA2 (4) mutations, 4/16 (25%) had mutations in other ovarian cancer predisposition genes. All 3 uterine cancer mutation carriers had mismatch repair gene mutations.

Conclusions

Almost 50% breast cancer and 25% ovarian cancer mutation carriers had mutations in cancer predisposition genes other than BRCA1/2 and mismatch repair genes, highlighting the relevance of adopting multi-gene testing in the clinic.

CS-26

Wei-Peng Yong^{1,2}, Sun Young Rha³, Iain Bee-Huat Tan⁴, Su-Pin Choo^{2,4}, Nicholas Syn¹, Vivien Koh^{1,2}, Shi-Hui Tan^{1,2}, Jimmy So⁵, Asim Shabbir⁵, Chee-Seng Tan¹, Hyo Song Kim³, Min Kyu Jung³, Hyun Cheol Chung³, Matthew Chau-Hsien Ng⁴, David Tai⁴, Ming-Hui Lee⁶, Jeanie Wu⁶, Khay Guan Yeoh⁷, Patrick Boon Ooi Tan^{2,6}

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Microarray-based tumor molecular profiling to direct choice of cisplatin plus S-1 or oxaliplatin plus S-1 for advanced gastric cancer: A multicentre, prospective, proof-of-concept phase 2 trial

Platinum regimens are interchangeably used in the management of AGC. We previously developed a classification tool using gene expression signatures which successfully stratified gastric cancer cell lines and primary tumour samples according to their sensitivity to SOX or SP (Tan et al, Gastroenterology 2011). We now report the first prospective study to evaluate the feasibility and efficacy of using a genomic classifier to tailor treatment in this setting. Pts with histologically-confirmed locally-advanced, metastatic and recurrent GC were recruited from 3 centres in Singapore and South Korea. Tumours were analysed using the Affymetrix U133 Plus 2.0 array and results were used to classify pts as G1 (oxaliplatin-sensitive), G2 (cisplatin-sensitive) or G3 (status unclear). G1 and G2 pts were matched to SOX and SP regimens respectively, while G3 pts were assigned SOX. The primary endpoint was best overall response; secondary endpoints were turnaround time and biomarker analyses. Between 2 July 2010 and 2 Apr 2015, we screened 85 AGC pts. 74 pts received at least 1 cycle of treatment and were evaluable for analysis. Median turnaround time was 7 working days (IQR, 5–9). The misclassification rate was 6%. After an initial 30 pts in the G1 subgroup treated with SOX, subsequent pts (N = 13) classified as G1 received the SP regimen. The ORR were 44.8%, 8.3%, 26.7% and 55.6% for G1 SOX, G1 SP, G2 SP (N = 19), G3 SOX (N = 12) respectively; and was higher in G1 pts treated with SOX compared with SP (P = 0.033). Post hoc genomic reclassification based on Lei et al (Gastroenterology 2013) confirmed the utility of the metabolic subtype as a predictive marker of benefit from chemotherapy (log rank P value for PFS = 0.004). This bench-to-bedside effort establishes that molecular profiling to direct choice of conventional chemotherapy for AGC is possible within a reasonable timeframe. The clinical utility of our genomic classifiers are promising but warrant further investigation.

CS-27

Valerie Heong^{1,2}, Ong Pei Yi, Mathilda Lee, Lim Yi Wan, Lim Siew Eng, Jeffrey Low, Ilancheran Arun, Samuel Ow, Lee Soo Chin, David SP Tan

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Clinical outcomes in Asian patients (pts) with germline BRCA1/2-mutation associated ovarian, primary peritoneal or fallopian tube carcinoma (gBMOPFC): experience from an Asian cancer centre

Background

Improved prognosis and response rates to platinum-based chemotherapy are hallmarks of gBMOPFC. These features are attributed to homologous recombination mediated DNA repair defects. Unfortunately, there is limited published data on the prognosis and response rates to platinum chemotherapy in Asian pts with gBMOPFC. Here we report on the frequency and clinical outcomes of BMOPFC from an Asian cancer centre.

Methods

From 2014 – 2016, data was prospectively collected on pts with OPFCs referred to the cancer genetics clinic. Germline HRD related gene mutations were determined by next generation sequencing and deletion/duplication analysis. Progression free survival (PFS) and response rate (RR) to subsequent lines of chemotherapy in patients were assessed.

Results

Total of 88 Asian women with OPFCs underwent genetic testing. A germline pathogenic mutation in the DNA repair pathway was observed in 25% (22/88) of pts, of which 59% (n=13/22) were BRCA1 and 32% (n=7/22) were BRCA2 mutant, with 4.5% (1/22) in RAD51c and 4.5% (1/22) in BRIP1. 13% (11/88) harboured a variant of unknown significance (VUS) in the HRD pathway. One pt had a BRCA1 variant initially classified as a VUS but subsequently reclassified as a pathogenic mutation. All pts received platinum based chemotherapy as initial treatment. Median PFS for HRD compared to non- HRD pts following 1st line treatment was 22 vs 16 mths; p value ≤ 0.55 . BRCA1 gBMOPFC pts had a median PFS of 15 mths vs 21 mths for BRCA2 gBMOPFC; p value ≤ 0.77). 13.6% of pts with HRD related mutations compared to 26% of pts with non-HRD related mutations relapsed within 6 mths of initial therapy (p value < 0.067). Following disease relapse in BMOPFC pts, 2nd line RR to further platinum therapy was 56%

Conclusions

BRCA1/2 mutations are common in Asian pts. Asian pts with HRD mutations are less likely to relapse with platinum resistant disease. Differences in PFS reflective of other datasets in non-Asian patients

CS-34

Shortlisted for Oral Presentation

Matilda X Lee¹, Barr Kumarakulasinghe Nesaretnam¹, Chong Wan Qin¹, Tham Weng Keong Ivan², Ho Cho Hao Francis², Ooi Kiat Huat², Loh Kwok Seng Thomas³, Lim Chwee Meng³, Goh Boon Cher¹, Tan Chee Seng¹

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Induction chemotherapy with cisplatin and TS-1 in locally advanced nasopharyngeal carcinoma

Background

The standard treatment for locally advanced nasopharyngeal carcinoma (NPC) is concurrent chemoradiotherapy (CCRT). Role of induction chemotherapy followed by CCRT in NPC is not clearly established but may facilitate radiotherapy planning and reduce locoregional and distant failures. TPF has been investigated, but has many adverse effects. Platinum-5FU combination had been widely used and we investigate cisplatin/TS-1 as an induction chemotherapy regimen.

Methods

In the National University Hospital between 2009 and 2011, 23 patients with NPC who had Stage IVA or IVB disease had undergone induction chemotherapy with three cycles of cisplatin 70mg/m² and TS-1 (40mg for BSA<1.25m², 50mg for BSA 1.25 – 1.5m², and 60mg for BSA <1.5m²) followed by CCRT (70Gy of intensity-modulated radiation therapy with weekly cisplatin 40mg/m²). Primary end point was overall survival (OS) and secondary end points were progression free survival (PFS), rate of complete response (CR) and safety.

Results

At a median follow up of 66.9 months, the median overall survival has not been reached, while the median PFS is 61.4 months. No patient progressed during induction chemotherapy. 17 out of 23 patients received 3 cycles of cisplatin/TS-1 and more than or equal to 4 cycles of cisplatin during CCRT. Their 3 year failure free rate was 76.5% and 94.1% achieved complete response. The most frequently observed adverse effects associated with induction chemotherapy were fatigue, which occurred in 33.3% of those treated, and leucopenia which occurred in 25% (12.5% grade 3 leucopenia). Two patients (8.3%) had grade 3 febrile neutropenia and there were no deaths related to induction chemotherapy reported.

Conclusions

Induction chemotherapy with cisplatin/TS-1 yields comparable results to a recently published randomized trial and was better tolerated. Prospective randomized studies can be considered to further understand this combination in the setting of induction chemotherapy.

CS-35

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First-line chemotherapy for advanced gastric cancer: A Cochrane systematic review and meta-analysis

Background We did a meta-analysis with the Cochrane Collaboration to compare the efficacy and toxicity of several first-line chemotherapy regimens for HER2-negative, advanced gastric cancer.

Methods 60 randomised controlled trials, comprising a total of 11,698 patients, were included in the meta-analysis of OS.

Results

Based on 3 trials, chemotherapy improved OS compared to best supportive care (HR=0.37; 95%CI=0.24–0.55; n=184). 23 trials which compared combination chemotherapy to single-agent chemotherapy regimens demonstrated an OS advantage in favour of combinations (HR=0.84; 95%CI=0.79–0.89; n=4,447), but at the cost of increased toxicity. Prespecified comparisons further delineated:

- a. Overall, irinotecan-containing regimens improves OS compared to non-irinotecan-containing regimens (HR=0.88; 95%CI=0.81–0.96; n=2,090 from 10 trials). However, subgroup analysis revealed that irinotecan modestly improves OS when used to substitute another drug (HR=0.87; 95%CI=0.75–1.00; n=826 from 6 trials), but not when irinotecan was added to an active regimen (HR=0.88; 95%CI=0.76–1.03; n=500 from 3 trials).
- b. Docetaxel improves OS when added to a single-agent or two-drug combination (HR=0.80; 95%CI=0.71–0.91; n=1,466 from 4 trials), but not when docetaxel is used to substitute another drug (HR=1.05; 95%CI=0.87–1.27; n=479 from 3 trials).
- c. Capecitabine was neither superior to 5-FU in terms of OS (HR=0.94; 95%CI=0.79–1.11; n=732 from 5 trials) or toxicity.
- d. Oxaliplatin significantly improves OS when compared against the same regimen containing cisplatin (HR=0.81; 95%CI=0.67–0.98; n=1,105 from 5 trials).
- e. The addition of a fluoropyrimidine to taxane/platinum duplet does not significantly improve OS (HR=0.86; 95%CI=0.71–1.06; n=482 from 3 trials)
- f. The substitution of 5-FU by S-1 leads to a modest improvement in OS (HR=0.91; 95%CI=0.83–1.00; n=1,793 from 4 trials).

Conclusions

Pooled results concerning response rates, PFS and toxicity will be shared at the meeting.

CS-36

Shortlisted for Oral Presentation

Joan Choo¹, Yvonne Ang¹, Tong Shuk In², Rebecca Chua¹, Ednajoyn Ngo³, Rathi Mahendran⁴, Lim Siew Eng¹, Andrea Wong^{1,5}, Nesaretnam Barr Kumarakulasinghe¹, Anand Jeyasekheran^{1,5}, Tan Sing Huang¹, Huang Yi Qing¹, Ho Jingshan¹, Samuel Ow¹, Natalie Ngoi¹, Gloria Chan¹, Matilda Lee¹, Goh Boon Cher^{1,5}, Lee Soo Chin^{1,5}

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A randomized controlled study of a 12-week exercise intervention program versus observation in early stage breast cancer patients on the impact on mental health, quality of life and immune markers

Background

Breast cancer and its treatment can have lasting physical and psychological sequelae. Randomised controlled trials have demonstrated benefits of exercise, but mechanisms are unclear.

Methods

Resected stage I-III breast cancer patients are randomized 1:1 to a 12-week, 24-session personalised exercise program versus advice alone. Serial assessments and questionnaires are performed for 5 years. Primary endpoints are mental health and quality of life (QOL). Others include adherence, fitness, immune markers, serum telomere length and survival.

Results

44 of a planned 300 patients have been enrolled - 22 each to exercise (Arm A) and observation (Arm B). Median age was 55 (30-69). 75% had ER+, and 39%, 45% and 16% had stage I, II and III disease respectively. 64% received adjuvant chemotherapy and 61% radiotherapy. Both arms were similar in baseline characteristics, except for HER2 status (13.6% [Arm A] vs 45.4% [Arm B], $p=0.021$). Median duration of follow up was 10 months (1-22). For the entire cohort, breast cancer specific QOL scores were equal to the reference mean at baseline; scores improved at 3 and 6 months ($p=0.041$, $p=0.047$). 6-minute walk test scores improved from 387m (267-567) to 417m (309-504) and 402m (306-537) at 3 and 6 months respectively ($p=0.011$, $p=0.033$); the mean for healthy females is 494m (310-664). Scores did not differ between each arm. Compliance with assessments was high at baseline and 3 months (91%, 80%), but fell at 6 and 12 months (63%, 47%); 9 of 13 evaluable Arm A patients achieved $\geq 90\%$ adherence to the exercise program. 4 patients had recurrence - 1 on Arm A at 15 months, 3 on Arm B at 19, 6 and 0 months. Of these, 1 Arm B patient had HER2+ cancer.

Conclusion

QOL and fitness measures improve after definitive surgery and adjuvant treatment in patients enrolled into an exercise program. Significant decline in adherence to study procedures after 6 months highlights the difficulty of sustaining lifestyle modifications in patients.

CS-42

Shortlisted for Poster Award Presentation

Gloria Chan¹, Pei Yi Ong¹, Jeffrey JH Low¹, Hwai Loong Kong¹, Samuel GW Ow¹, David SP Tan^{1,2}, Yi Wan Lim¹, Siew Eng Lim¹, Soo-Chin Lee^{1,2}

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Multi-gene panel testing of patients with multiple primary malignancies suspected with hereditary cancer syndrome

Background

Developing multiple primary cancers is an indicator of underlying hereditary cancer predisposition, but there is a paucity of data regarding the characteristics and clinical genetic testing outcome of these patients.

Methods

We compared cancer index patients with 1 vs > 1 primary malignancy who underwent evaluation with multi-gene panels comprising up to 49 genes in a cancer genetics clinic in a tertiary cancer centre in Asia from 1998-2016.

Results

Among 1191 cancer index patients, 960 (80.6%), 205 (17.2%), and 26 (2.2%) respectively had 1, 2, and ≥ 3 primary malignancies. Among patients with > 1 primary cancers (n = 231), the most common cancer pairs were breast-breast (35.4%), breast-ovary (12.1%), endometrium-ovary (8.2%), colon-colon (2.4%) and, colon-endometrium (2.4%). The mean age at diagnosis of the first, second and third cancers were 46.0 (21 to 87), 52.1 (21 to 89) and 57.7 (41 to 83) respectively. The mean duration between first and second cancers is 6.0 years (0 to 32). The most commonly suspected syndromes in patients with 1 vs > 1 primary cancer were hereditary breast and ovarian cancer 63.8% vs 53.6%, Lynch 24.8% vs 31.1%, Li-Fraumeni syndromes 1.8% vs 1.7%, and others 9.3% vs 13.4% (p = 0.03). Patients with > 1 primary cancer were more likely to have > 20% a priori risk of suspected hereditary cancer syndrome (42.8% vs. 26.5%; p < 0.001). 504/1191 (42.3%) patients underwent gene testing, including 394/960 (41.0%) and 110/231 (47.6%) patients with 1 vs > 1 cancer. Deleterious mutations were more likely to be identified in patients with > 1 vs 1 cancer (34.5% vs. 25.8%; p = 0.073), with causative genes being BRCA1 38.5%, BRCA2 17.9%, MLH1/MSH2/MSH6 20.5%, TP53 7.7%, and others for patients with > 1 cancer.

Conclusions

Patients with > 1 primary cancer comprised one-fifth of patients evaluated at a cancer genetics clinic, and were more likely to be found with deleterious mutations than patients with only 1 cancer on multi-gene panel testing.

CS-48

Natalie YL Ngoi¹, Alvin SC Wong¹, Angela SL Pang¹, Nesaratnam Kumarakulasinghe¹, Yvonne LE Ang¹, Wan Qing Chong¹, Hon Lyn Tan¹, Joline SJ Lim¹, Jingshan Ho¹, Raghav Sundar¹, Gloria HJ Chan¹, Anand D Jeyasekharan^{1,2}, David SP Tan^{1,2}, Andrea LA Wong^{1,2}, Samuel GH Ow¹, Yi Qing Huang¹, Chee Seng Tan¹, Ross LK Soo^{1,2}, Yi Wan Lim¹, Wei Peng Yong¹, Soo Chin Lee^{1,2}, Boon Cher Goh^{1,2}

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Lower incidence of pazopanib-related DILI in Asian patients

Background

Pazopanib is a CYP3A4-metabolized, multi-targeted tyrosine kinase inhibitor, recognized in treatment of advanced renal cell carcinoma (RCC) and soft tissue sarcoma (STS). An idiosyncratic transaminitis exceeding 3x upper limit of normal (ULN) is reported in 20% of patients. On meta-analyses, risk factors include RCC, liver metastases and age, but not race. A discovery analysis suggests association between HLA-B*57:01 (Whites 5-8%; Chinese <1%) carriage and pazopanib-related alanine aminotransferase (ALT) elevation, raising the possibility of interethnic variability in drug-induced liver injury (DILI) from pazopanib treatment. We hypothesize that patients of Asian ethnicity have lower incidence of pazopanib-related DILI compared to reported data for Caucasians, and determined the incidence of this adverse event in our patient population.

Methods

Retrospective medical record review of patients receiving pazopanib monotherapy, at the National University Hospital Singapore, from 2006-2016 was conducted. Hepatotoxicity was defined as grade 2 or higher aspartate aminotransaminase (AST) or ALT elevation.

Results

109 patients received pazopanib. 97% were ethnically Asian (77%Chinese, 12%Malay, 6%Indian, 1%Filipino, 1%Myanmese). RCC(62%), STS(12%) and thyroid cancer(9%) were most common. 21% of patients had liver metastases. Grade 2 AST or ALT attributable to pazopanib occurred in 7.3% and 2.4% of patients respectively, all of whom were Chinese. Liver metastases or RCC were not associated with higher odds of DILI [OR 1.62 (95% CI 0.51-5.11, p = 0.41) and(OR 1.46 (95% CI 0.50-4.30, p =0.49), respectively]. Median PFS was 4.8 months (0.03 -100). Median time to onset of DILI was 6.6 weeks.

Conclusions

Lower incidence of DILI was observed in this mainly Asian cohort compared to reported data. Liver metastases or RCC did not increase odds of DILI. Further analysis of the HLA*B5701 genotype and other pharmacogenetic factors are warranted.

CS-49

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Pushing the limits of immune-related response: A case of “extreme pseudo-progression”?

Background

The advent of immune checkpoint targeted immunotherapy has seen a spectrum of immune-related phenomena in both tumor responses and toxicities. We describe a case of pseudo-progression that pushes the limits of immune-related response criteria and challenges the boundaries and definitions set by clinical trial protocols.

Methods

A single illustrative case from the medical oncology clinics of NCIS.

Results

A middle aged man with conventional clear cell renal cell carcinoma (RCC) had received multiple prior systemic treatments including vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs: pazopanib, sunitinib, axitinib) and mammalian target of rapamycin (MTOR) inhibitor (everolimus), as well as multiple surgeries (including nephrectomy) and radiotherapy treatments. He was eventually started on Nivolumab – an anti-programmed-death-receptor-1 (anti-PD1) monoclonal antibody approved for the treatment of advanced RCC. Clinical deterioration was observed soon after a 100mg dose of Nivolumab, with onset of acute renal failure and declining performance status. Radiologic progression was documented in multiple sites including worsening tumor infiltration of his residual kidney. The patient was on palliative treatment and visited by the home hospice-care team. Do-not-resuscitate (DNR) orders were established. Unexpectedly, the patient returned to the clinic 2 months after Nivolumab was given, and showed gradual improvement in clinical and biochemical parameters. An impressive response was seen in subsequent imaging. The patient is currently more than 6 months from receiving the single dose of Nivolumab and is doing well.

Conclusions

We continue to be bemused by the spectrum of immune-related phenomena seen in clinical practice. This single case of “extreme pseudo-progression” provokes us to re-examine our approach to immune-related response and clinical trial interpretation.

CS-53

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Precision oncology for advanced prostate cancer: where do we stand now?Background

Precision oncology, the utilization of next-generation sequencing (NGS) based genomic profiling of tumors to identify new treatment options at the point-of-care is rapidly changing therapeutic strategies and practices across cancer types. Here we report the potential use of NGS tumor profiling to guide treatment decision for advanced prostate cancer patients in Taiwan.

Methods

Genomic profiling using a comprehensive cancer panel covering 409 cancer-related genes and ultra-deep next-generation (defined as ≥ 800 X) targeted sequencing to analyze all coding regions of the tumor, we report on clinically relevant variants such as single nucleotide variants (SNVs) and small insertion/deletions (INDELs, defined as ≤ 15 nucleotides) detected in the tumor, copy number variations (CNVs). Subsequent integration of genomic aberrations into pathway analysis allows us to identify actionable targetable genomic alterations for treatment strategies among chemo-, and targeted therapies.

Results

In our series of case studies, we identified multiple recurrent targetable genomic alterations in advanced prostate cancers. The alterations include copy number gain of MET and CDK6 and loss of CDK12. These genomic alterations led to the aberration in the DNA repair pathway, and dysregulated MET signaling and cell cycle. Our study suggests alternative therapeutic options, including the use of PARP, MET and CDK4/6 inhibitors. The aforementioned therapeutic agents have been approved for other cancer types, namely ovarian cancer, lung cancer and breast cancer, respectively.

Conclusion

Targeting of the androgen receptor (AR) remains the primary therapeutic strategy in prostate cancer. Yet, most patients developed resistance, making it imperative to explore other therapeutic options. From our series of case studies in Taiwan, we have demonstrated the potential of comprehensive genomic profiling to explore alternative and new treatment options in advanced prostate cancer.

CS-54**Chun-Tsu Lee, Elaine Seah Zhu Hui, Chin Hin Ng****Clinical response and outcomes of patients after the use Azacitidine- a real life experience**Background

Treatment options for Myelodysplasia (MDS), and Myelodysplasia/Myeloproliferative Neoplasms (MDS/MPN) are mainly supportive care for elderly, chemotherapy followed by stem cell transplant for younger patients. Prognosis is dismal in patients with complex cytogenetics and monosomal karyotype. With the introduction of Azacitidine, a hypomethylating agent, treatment is allowed in the elderly and frail patients with MDS, MDS/MPN and even as salvage therapy in relapsed AML. Due to the heterogeneity of treatment response with Azacitidine, there is limited published data and real life experience to guide clinicians in choosing treatment options. Hence, we perform a retrospective cohort study to investigate the clinical response and outcome of patients after Azacitidine.

Methods

Pharmacy and medical records of consecutive patients treated with Azacitidine in NUH from 2011-2016 were reviewed.

Results

64 patients including 41(64.1%) AML, 15(23.4%) MDS and 8(12.5%) MDS/MPN were treated with Azacitidine. Their median age was 61.5 years (range 3-86 years). In 47(73.4%) cases, Azacitidine was used as first line treatment while 17 (26.6%) as salvage therapy. Hematologic improvement (HI) was noted in 11(27.5%), 2(13.3%), 1(12.5%) in AML, MDS and MDS/MPN groups and bone marrow blast clearance in 10(37%), 4 (50%) and 3(60%) respectively. Overall response (OR) including HI, CR and PR among patients with adverse complex cytogenetics and others was 8(66.7%) vs 15(35.7%), $p=0.056$. The OR between monosomal karyotype and others was 9 (64.3%) vs 14(35%), $p=0.056$. The median PFS was 11.4 months (95%CI 4.9-17.9) and 4.6 months (95%CI 0-9.3) in the AML and MDS/MPN groups. The mean PFS was 10.8 months (95%CI 2.3-19.5) in the MDS group.

Conclusion

The efficacy of Azacitidine in patients with adverse cytogenetic is encouraging. Azacitidine has impacted the way clinicians approach the treatment of MDS, MDS/MPN and relapsed AML and has given much hope to patients with these diseases.

CS-55

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Trends in MSI/MMR testing: An audit of referral patterns in NUH from 2015 to 2016Background

Since 2015, Mismatch Repair (MMR) status has been shown to have predictive value in patients with advanced solid tumours being considered for anti-programmed cell death protein-1 (PD-1) therapy. Clinicians are thus recommended to order MMR testing through MMR-immunohistochemistry (IHC) or microsatellite instability (MSI) polymerase chain reaction (PCR) fragment analysis testing in patients with Lynch syndrome associated tumors. We examine the trends of MMR testing and prevalence of high microsatellite instability (MSI-H) among solid tumours sent for MSI PCR testing in National University Hospital (NUH) Diagnostic Molecular Oncology Centre (DMOC) from 2015 to 2016.

Methods

All samples sent for MSI PCR testing in NUH from 2015 to 2016 were retrospectively retrieved from DMOC testing records. We gathered information on MMR status and cancer type and stage for each of the samples.

Results

We evaluated 464 samples sent for MSI PCR testing, of which 170 samples belonged to patients of NUH. The demand for MSI testing increased from 3-7 samples/month from January to April 2015, to 20-30 samples/month from May 2015. Of these 170 samples, colorectal cancer (125 of 170 patients, 73.5%), gastric cancer (16 of 170 patients, 9%), and biliary tract cancers (9 of 170 patients, 5.3 %) were most commonly tested. Prevalence of MSI-H was 4% (5 of 125 patients) in colorectal cancers, and 6.25% (1 of 16 patients) in gastric cancers. The former is lower than the estimated 5-15% in other studies, depending on colorectal cancer stage. There was a concomitant increased demand for MMR IHC testing, from 38 in 2015, to 127 in 2016.

Conclusions

The jump in demand for MMR testing coincided with the discovery that MMR-deficient/MSI-H tumors are more responsive to PD-1 blockade. The low MSI-H prevalence for colorectal cancers may be due to factors such as the site of origin. MSI-H is more frequent in right-sided compared with left-sided colon cancers. This warrants further analysis.

CS-56**Ley Fang Kua¹, Kousaku Mimura², Koji Kono^{2,3}, Wei Peng Yong^{1,3}**¹ *Department of Haematology- Oncology, National University Health System*² *Fukushima Medical University, Japan*³ *Cancer Science Institute of Singapore***Combination immunotherapy of peptide-based vaccine and immune-checkpoint blockade therapy for treatment of gastric cancer**Background

Peptide-based cancer vaccination, which elicits endogenous tumor-specific T-cell responses after administration of tumor associated antigen (TAA) epitope peptides, remains as an attractive cancer treatment due to its low toxicity shown in many clinical trials. However, despite the detection of vaccine-induced T-cell responses, these immune responses are rarely associated with anti-tumor effects of cancer vaccine. This may be due to the “masking” effect exerted by co-inhibitory receptors such as CTLA-4 and PD-1, widely known to play important roles in manipulating T cell responses. These have been proven to be effective targets in diseases whereby their up-regulation dampens antitumor immunity associated with T-cell “exhaustion” and reduced T-cell functionality. Therefore, in order to mediate or augment the anti-tumor effects of cancer vaccine, combination immunotherapy of peptide-based cancer vaccines and immune-checkpoint blockade therapies acts as a good candidate for cancer immunotherapy.

Methods and Results

In this study, patients were administered with a 5-peptide cocktail vaccine comprising of five HLA-A2402-restricted, TAA-epitope peptides from FOXM1, DEPDC1, KIF20A, URLC10 and VEGFR1. CTL responses specific to the vaccinated peptide were evaluated in vitro. Peptide-specific CTL clones were first generated from patients with positive CTL response towards KIF20A, and then subjected to immune-checkpoint blockade monoclonal antibodies (mAbs) specific for PD-1, PD-L1, Lag-3 and Tim-3. A significantly higher anti-tumor response was observed upon immune-checkpoint blockade therapy.

Conclusions

Apart from the CTLA-4 and PD-L1 lines of treatment, Lag-3 and Tim-3, which are equally important molecules that regulate immune responses, may also serve as new targets for therapeutic intervention. Work is in progress to further evaluate the ligand expression for Lag-3 and Tim-3.

CS-57

Shortlisted for Poster Award Presentation

Chee Cheng Ean^{1,2}, Tai Bee Choo²¹ Department of Haematology- Oncology, National University Health System² Saw Swee Hock School of Public Health**Clinical Outcome and Prognostic Factors for Patients Treated in a Phase I Study at the National University Cancer Institute, Singapore (NCIS)**Background

Patient selection for phase I trials in oncology is challenging. A typical inclusion criterion for phase I studies is 'life expectancy >3 months', however overall survival (OS) of patients with advanced solid malignancies are difficult to predict. In order to better select our patients for phase I trials, a retrospective study was conducted to assess outcomes and survival.

Methods

Patients in phase I studies completed between Oct. 2013 – Jan. 2016 at NCIS and had EMR available were reviewed. Patient characteristics and survival data were analysed.

Results

120 patients from 10 completed phase I studies were included. Median age was 44.5 years (range: 23-79). Baseline variables were: age >60 (56%), male (53%), ECOG 0-1 (98%), co-morbidities ≥ 2 (26%), no. of prior therapies ≥ 3 (65%), no. of metastatic sites ≥ 3 (40%). Univariate analysis revealed that albumin <35 g/L (HR: 3.23, 95% CI: 1.93 – 5.39, $p < 0.001$) and LDH >618 IU/L (HR: 2.28, 95% CI: 1.35 – 3.87, $p=0.002$) were highly significant negative prognosticators for OS. The number of metastatic sites (>2 sites) was also at the threshold of significance (HR: 1.59, 95% CI: 0.97 – 2.59, $p < 0.063$). Of the 66 patients with confirmed deaths, median OS was 5 months (range: 0-31 months) from time of enrollment in a phase I study.

Conclusion

Preliminary results indicate that objective clinical parameters such as albumin and LDH, may be used as markers of overall survival for patients in phase I clinical trials. Additional analyses including a multivariate analysis and prognostic score are planned to provide a tool to assist with the selection of patients for phase I studies.

CS-61

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Does MYD88 specimen matter? - A single centre experience on MYD88 mutation testing and its correlation with clinical diagnosis

Background and Aims

Differentiating between Waldenstrom macroglobulinemia/ lymphoplasmacytoid lymphoma (WM/ LPL) and other indolent B cell lymphomas may sometimes be challenging due to their overlapping clinical and pathological features and MYD88 mutational testing may have diagnostic utility in this setting. There is also limited data regarding feasibility of MYD88 testing outside of paraffin tissue specimens. We retrospectively reviewed our centre's experience following introduction of this test. Our study aimed to assess the utility of this test in correlation with final clinicopathologic diagnoses and sample types sent for analysis.

Methods

Retrospective review of records of samples sent for MYD88 testing was performed and correlation with clinical and pathologic findings was done to ensure the most accurate diagnosis and sub-classification.

Results

A total of 43 MYD88 mutation specimens were collected from 36 patients at time of diagnosis. These included blood (n=19), bone marrow aspirate (n=16) as well as cerebrospinal fluid (CSF) (n=2) and paraffin tissue (n=6). 35% of specimens (n=15) were MYD88 mutation positive, including 36%, 31%, 50% and 33% in blood, bone marrow aspirate, CSF and tissue biopsies respectively. Among the patients who had paired specimens (Blood and bone marrow/ tissue) (N=5), 3 had MYD88 being positive in tissue/ marrow but negative in paired blood specimens. MYD 88 mutation was detected in 67% of WM cases as compared to 26% of other B-Non Hodgkin lymphoma cases.

Conclusions

Our results confirm the feasibility for detecting MYD88 L265P mutation by peripheral blood as well as CSF and decalcified marrow trephine specimens. Paired specimen analyses however suggest that tissue samples may have a higher sensitivity for MYD88 detection. Our study also confirms the high prevalence of the MYD88 L265P mutation in Asian patients with WM/ LPL.