CAMO 2020 VIRTUAL ANNUAL GENERAL MEETING & ABSTRACT PRESENTATIONS

Thursday, June 11, 2020 | Jeudi le 11 juin 2020
Via Zoom

Co-chair: Dr. Erin Powell
Co-chair: Dr. Jonathan Loree

2020
CAMO Virtual AGM & Oral Abstract Presentations

Thursday, June 11 2020 / jeudi le 11 juin 2020 (all times in EST)

10h30 – 11h00 **CAMO Annual General Meeting / Réunion d'affaires annuelle de l'ACOM (members only/membres seulement)**

11h00 – 13h15 **CAMO Oral Presentations/Présentations de résumés**
Objectives
At the end of the session, participants will be able to:
1. Describe recent research findings in the field of Medical Oncology.
2. Describe interesting cases in the field of Medical Oncology.

- **1100-1110: Myuran Thana**: REAL-WORLD UTILIZATION AND SAFETY OF IPILIMUMAB PLUS NIVOLUMAB (I+N) IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS: RESULTS FROM THE CANADIAN KIDNEY CANCER INFORMATION SYSTEM (CKCIS)
- **1112-1122: Daniel Breadner**: EXPLOITATION OF TREATMENT INDUCED TUMOR LYSIS TO ENHANCE SENSITIVITY OF CTDNA ANALYSIS: A FIRST-IN-HUMAN PILOT STUDY
- **1124-1134: Sulaiman Al Saadi**: SAFETY OF CYCLES OF CHEMOTHERAPY WITH PLATINUM-PEMETREXED ADMINISTERED WITH NEUTROPHILS OF 1.0 TO 1.49 VS 1.5 OR GREATER
- **1136-1146: Ryan Holstead**: IMMUNE-RELATED ADVERSE EVENTS IN THE EMERGENCY DEPARTMENT: ANALYSIS OF FREQUENCIES AND MANAGEMENT AT KINGSTON GENERAL HOSPITAL
- **1148-1158: Andrea Fung**: A REAL WORLD COMPARISON OF CISPLATIN VERSUS CETUXIMAB USED CONCURRENTLY WITH RADIATION IN THE TREATMENT OF LOCALLY ADVANCED OROPHARYNGEAL CARCINOMA: UPDATED RESULTS
- **1200-1210: Adam Fundytus**: TRENDS IN THE CANADIAN MEDICAL ONCOLOGY WORKFORCE AND TRAINEES 1990-2019
- **1212-1222: Atul Batra**: ELIGIBILITY OF REAL-WORLD PATIENTS WITH STAGE II/III COLORECTAL CANCER (CRC) IN ADJUVANT CHEMOTHERAPY (AC) TRIALS
- **1224-1234: Maisam Makarem**: POPULATION-BASED ROS1 TESTING IN ADVANCED NSCLC
- **1236-1246: Marya Hussain**: NEOADJUVANT SYSTEMIC THERAPY UTILIZATION AND OUTCOMES IN BREAST CANCER
- **1248-1258: Erica Tsang**: EARLY ONSET PANCREATIC DUCTAL ADENOCARCINOMAS ARE CHARACTERIZED BY A DISTINCT MUTATIONAL LANDSCAPE
- **1300-1310: Ellen Cusano**: IMPACT OF VALUE FRAMEWORKS ON THE MAGNITUDE OF CLINICAL BENEFIT: EVALUATING A DECADE OF RANDOMIZED TRIALS FOR SYSTEMIC THERAPY IN SOLID MALIGNANCIES

REAL-WORLD UTILIZATION AND SAFETY OF IPILIMUMAB PLUS NIVOLUMAB (I+N) IN METASTATIC RENAL CELL CARCINOMA (MRCC) PATIENTS: RESULTS FROM THE CANADIAN KIDNEY CANCER INFORMATION SYSTEM (CKCIS)

Myuran Thana[1], Naveen S. Basappa[2], Sunita Ghosh[2], Christian K. Kollmannsberger[3], Daniel Y.C. Heng[4], Aaron R. Hansen[5], Jeffery Graham[6], Denis Soulières[7], M. Neil Reaume[8], Aly-Khan A. Lalani[9], Vincent Castonguay[10], Georg J. Bjarnason[11], François Patenaude[12], Rodney H. Breau[13], Frédéric Pouliot[10], Anil Kapoor[14], Lori A. Wood[1].

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OBJECTIVE

To determine the amount and tolerability of I+N, including discontinuation rates, reasons for discontinuation, and outcomes for treatment-naive mRCC patients in the CKCis database.

METHODS

Patients in CKCis who received first-line I+N were included. The number of doses of I+N, number of patients who received maintenance single-agent nivolumab and duration of maintenance nivolumab were identified. Reasons for treatment discontinuation, including details of toxicities, were determined. Efficacy outcomes include overall response rate (ORR), time to treatment failure (TTF), progression-free survival (PFS), and overall survival (OS).

RESULTS

The cohort includes 196 patients; 12% on a clinical trial. Median follow-up was 10.4 months. Median age was 63 yrs; 71% had clear cell histology; IMDC good risk 13%, intermediate 54%, and poor 33%. All 4 I+N doses were received by 91 patients (46%), of which 76 (84%) received maintenance nivolumab. 105 patients (54%) received less than 4 doses of I+N, of which 38 (36%) received maintenance nivolumab. 76 patients (39%) are still on treatment. The median time on maintenance nivolumab was 4.6 months. 67 toxicity events occurred, the most common being colitis (49%), pneumonitis (19%), and hepatitis (10%), with no toxicity-related deaths. 21% of patients discontinued therapy due to toxicity. ORR was 34% (4.3% complete). Median TTF was 4.1 months, PFS was 11.4 months. Median OS was not reached (41 events to date). 34% of patients received second-line treatment, sunitinib the most common.

CONCLUSION

In this real-world cohort, the majority of mRCC patients did not receive all 4 doses of I+N, contrasting with clinical trial reporting, yet many of these patients still received maintenance nivolumab. 21% of pts discontinued treatment due to toxicity. Further data will be presented, including outcomes stratified by the number of cycles of I+N received.

EXPLOITATION OF TREATMENT INDUCED TUMOR LYSIS TO ENHANCE SENSITIVITY OF CTDNA ANALYSIS: A FIRST-IN-HUMAN PILOT STUDY

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OBJECTIVE

Limitations in sensitivity, remains a barrier to circulating tumour DNA (ctDNA) replacing tissue-based testing. There is a paucity of data regarding the optimal time to measure ctDNA, specifically the dynamics of ctDNA levels in the hours to days following a new and effective treatment. We hypothesize that chemotherapy or radiation will yield an increased abundance of ctDNA in plasma by inducing tumor lysis, allowing for the detection of genetic alterations that were occult in baseline testing.

METHODS

Two prospective cohorts of twenty patients (pts) with stage III/IV NSCLC were enrolled. Cohort 1 (C1) contained patients starting the first cycle of platinum doublet chemoradiation (C1a, n=10) or the first cycle of platinum doublet cytotoxic chemotherapy ± immunotherapy (C1b, n=10). Cohort 2 (C2) contained patients receiving palliative radiation. Consenting patients provided two baseline samples. In C1, subsequent samples were collected 2-3, 4-6, 18-72 and 42-96 hours post initiation of chemotherapy. Pts in C2 had samples collected immediately prior to radiotherapy fractions 2, 3, and 4. Samples were analyzed for ctDNA using the 36-gene amplicon-based NGS Inivata InVisionFirst®-Lung assay.

RESULTS

Complete results were available for the first 28 of 40 enrolled pts, C1a – 8 pts, C1b – 8 pts, C2 – 12 pts. Detectable ctDNA was present at baseline in 21 pts (75%), 4 additional pts (14.3%) had detectable ctDNA in post treatment samples (C1a - 2pts, C1b - 1pt, C2 - 1pt). Three of the patients with detectable ctDNA at baseline (10.7%) had new genetic alterations detected in post treatment samples. A total of 7/28 pts (25%) had new genetic alterations detected in the post treatment samples. Mutant molecule numbers increased with treatment in 19 of 25 (76%) pts with detectable ctDNA, C1 - 11 of 15 pts (73.3%) and C2 - 8 of 10 pts (80%). ctDNA levels peaked a median of 2.2 hours (interquartile range (IQR): 1.5 – 2.9 hours) after the initiation of chemotherapy and a median of 1 day (IQR: 1-2 days) after radiation was commenced. The percentage increase in ctDNA levels was a median of 39.3% (IQR: -20.5 to +112.8%) in C1, with median increases of 22.0% and 39.3% in C1a and C1b, respectively. C2 had a median increase of 81.9% (IQR: 0 to +161.5%).

CONCLUSION

ctDNA levels increase in the hours to days after starting a new treatment. ctDNA testing in the acute post treatment phase can yield results that were not evident in pretreatment testing. Application of this principle could improve ctDNA utility as an alternate to tissue-based testing and/or improve sensitivity for the detection of treatment-resistant clones.

SAFETY OF CYCLES OF CHEMOTHERAPY WITH PLATINUM-PEMETREXED ADMINISTERED WITH NEUTROPHILS OF 1.0 TO 1.49 VS 1.5 OR GREATER

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BACKGROUND

The Canadian product monograph for pemetrexed states that treatment should only be administered once the absolute neutrophil count (ANC) is ≥ 1.5, but at our centre patients are routinely treated provided ANC is ≥ 1.0.

OBJECTIVES

To evaluate the risk of febrile neutropenia (FN) in patients with pre-treatment ANC <1.5 compared to pre-treatment ANC >=1.5, who received platinum-pemetrexed chemotherapy.

METHODS

With institutional research ethics board approval, a retrospective chart review of the medical records of patients who received first-line platinum-pemetrexed between 1 January 2014 and 30 June 2018 was performed. Data collected included baseline demographics, rates of hospitalization and FN, and overall survival. Univariate and multivariate analyses to determine factors associated with FN and survival were performed

RESULTS

Of 466 patients, 459 had pre-treatment ANC levels available for all cycles. Baseline characteristics: median age 66, females 50 %, carboplatin 60% / cisplatin 40 %, mesothelioma 6% / NSCLC 94 %. 74 patients received at least one cycle with ANC 1.0-1.49. There was a total of 20 FN events in 1656 cycles (1.21 %, 95 % CI 0.61-1.81). There was no significant difference in FN between patients who received chemotherapy with pretreatment neutrophil <1.5 compared to those with pre-treatment neutrophil >= 1.5. (0.97% vs 1.22% respectively, P= 0.92, which remained non-significant in multivariate analysis controlling for platinum type and age, P=0.88). Median overall survival was 14 months for the whole cohort, but median overall survival was significantly higher in patients with pretreatment neutrophil <1.5 compared to pretreatment neutrophil >=1.5% (21 months vs 12 months respectively, P= 0.0066). This retrospective study did not find a significant difference in the risk of FN in patients with pre-treatment ANC <1.5 compared to pre-treatment neutrophil >=1.5, who received platinum and pemetrexed.

IMMUNE-RELATED ADVERSE EVENTS IN THE EMERGENCY DEPARTMENT: ANALYSIS OF FREQUENCIES AND MANAGEMENT AT KINGSTON GENERAL HOSPITAL

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OBJECTIVES
Immune-related adverse events (iRAEs) are known complications of immune checkpoint inhibitors (ICIs) with significant variation on the presenting symptoms. Early identification and management lead to improved morbidity and mortality. There is limited research on the identification and management of iRAEs in the emergency department (ED).

METHODS
We performed a single center retrospective chart review of all patients (pts) treated with ICIs in 2018 and 2019. Patients were stratified by site of primary malignancy and all diagnoses of iRAEs were recorded. For all patients who presented to the ED following administration of an ICI, we assessed whether the presenting symptoms were eventually diagnosed as an iRAE. We assessed disposition, time to initiation of corticosteroids and outcomes in these patients.

RESULTS
From 2018-2019, 351 evaluable pts were treated with an ICI, the majority for melanoma (30.8%), and lung cancer (49.0%). In 2018, an iRAE of any grade was diagnosed in 47 pts (26.9%) and in 2019, 68 pts (25.4%). 59 (33.9%) pts had at least one presentation to the ED in 2018, 9 of who presented with symptoms due to a new iRAE and in 2019 there were 74 (27.7%) presentations, 8 new iRAEs. New iRAE diagnoses were broad, patient had received ICI for a median 2 cycles (interquartile range 1-3), majority were grade 3 or higher (12/17, 70.6%), two with grade 5 toxicity. Thirteen (76.5%) were admitted to the hospital during initial presentation or at follow-up, four required ICU care within 30 days. All patients required immunosuppressive therapy, and only 3 were later rechallenged with ICI therapy. Of the 13 patients who were admitted to the hospital, median time to first dose of corticosteroid was 30.5 hours (interquartile range 16-43 hours)

CONCLUSION
We found that a notable proportion of iRAEs have their first presentation at the ED at our center. A standardized approach at the time of presentation may lead to improved identification and management of these patients.

A REAL WORLD COMPARISON OF CISPLATIN VERSUS CETUXIMAB USED CONCURRENTLY WITH RADIATION IN THE TREATMENT OF LOCALLY ADVANCED OROPHARYNGEAL CARCINOMA: UPDATED RESULTS

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OBJECTIVE

In clinical practice, patients may be ineligible for cisplatin due to age, performance status or comorbidities, and real world evidence is needed to help guide management of these patients who are not well represented in randomized trials. This population-based study compares the efficacy of cisplatin versus cetuximab with concurrent radiation as definitive treatment in oropharyngeal carcinoma (OPC) patients utilizing real-world data.

METHODS

A retrospective analysis of stage III-IVB (AJCC 6th edition) OPC patients treated with cisplatin plus radiation (cis-RT) or cetuximab plus radiation (cetux-RT) between 2006-2016 at two tertiary cancer centres in Alberta was completed. Median overall survival (mOS) and disease-free survival (mDFS) were compared between treatment groups using the Kaplan-Meier method. Multivariable analysis with a Cox proportional hazards model was completed.

RESULTS

546 OPC patients were identified: 431 (78.9%) received cis-RT and 115 (21.1%) cetux-RT. Median age was 58, with 86% male, 30% never smokers, and 72% with HPV-positive disease. Patients who received cis-RT were younger than those treated with cetux-RT, and had a larger proportion of patients with a lower Charlson comorbidity index (CCI). Patients treated with cetux-RT were more likely to develop a recurrence after treatment compared to cis-RT (25% vs. 15%, P=0.01). mOS was longer in patients treated with cis-RT compared to cetux-RT regardless of HPV status, with mOS 32 vs. 16.5 months in HPV-negative patients (p=0.003) and mOS 51 vs. 35 months in HPV-positive patients (p<0.001). On multivariable analysis, current smoking, HPV-negative status, higher CCI and T-stage also independently predicted for worse OS and DFS. Treatment with cetux-RT was predictive of worse DFS (HR 2.15, P<0.001) and OS (HR 1.96, P=0.003) on multivariable analysis compared to cis-RT.

CONCLUSIONS

Real-world patients treated with cis-RT tended to be younger with less comorbidities. Consistent with results from recent randomized studies, we showed better survival outcomes with cis-RT compared to cetux-RT in a real-world population.

TRENDS IN THE CANADIAN MEDICAL ONCOLOGY WORKFORCE AND TRAINEES 1990-2019

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INTRODUCTION

Canadian cancer incidence rates have steadily risen over the last three decades, but it is unclear whether the medical oncology workforce has kept pace. The objective of this study is to characterize the national trends in the medical oncology workforce and trainees between 1990 and 2019, and explore their relationship to cancer incidence as a surrogate demand marker.

METHODS

We utilized publicly available databases from the Canadian Medical Association (CMA) subspecialty reports (1994-2019) in conjunction with records from the Canadian Institute of Health Information (CIHI) database (1990-2018) to estimate the number, age and gender demographics, and regional distribution of medical oncologists (MOs) in practice in Canada. Cancer incidence by province were obtained from Statistics Canada from 1990 to 2016, except for Quebec where only 1990-2010 data was available. Cancer incidence for all provinces among adult cancer patients were projected to 2019 using age-period-cohort modeling using Canadian population statistics from Statistics Canada. Annual cancer incidence to MO provider ratios were generated to estimate the demand for, and supply of, medical oncology services. In addition, 1990-2019 Canadian Post MD Education Registry (CAPER) data was used to characterize MO in-training programs.

RESULTS

Between 1990 and 2019, the annual number of cancer cases in adults rose from 102,780 cases to 218,574 cases (113%), while the number of MOs increased from 88 to 625 over the same timeframe representing a 610% increase. Cancer incidence to MO provider ratio dropped from 1,168 cases/MO in 1990 to 350 cases/MO in 2019. Overall, the Canadian MO workforce is aging with an average age of 39.3 in 1990 compared with 48.0 in 2018. In 1990, only 6% of MO providers were ≥ 50 years old and none were over 65 years old, compared with 42% and 11%, respectively, in 2018. Nationally, the MO workforce has nearly reached gender parity with 53% male in 2019 versus 76% in 1990. Trends in Canadian MO trainees have largely mirrored those in practice with a 341% increase in the annual trainee cohort from 27 in 1990 to 119 in 2019. In 1990, 80.6% of trainees were male compared with 42.9% in 2019. Although Ontario contains largest proportion of MOs (38% in 2019) and MO trainees (45%), these proportions have fallen over time relative to Quebec, Western Canada, and Atlantic Canada.

CONCLUSION

The MO workforce has shown considerable growth, and the ratio of incident cancer cases to MOs has fallen, in all regions across Canada between 1990-2019. In addition, with higher proportions of MO providers nearing retirement age, those exiting the workforce may influence future workforce trends. Our study is limited because it does not take into consideration the increasing number and complexity of systemic therapies or referral patterns for new and existing cancer patients. Therefore, continued monitoring of human resource levels in medical oncology and cancer incidence data are crucial to ensure training programs continue to meet future demands in cancer care.

ELIGIBILITY OF REAL-WORLD PATIENTS WITH STAGE II/III COLORECTAL CANCER (CRC) IN ADJUVANT CHEMOTHERAPY (AC) TRIALS

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OBJECTIVE

The results of AC trials in stage II/III CRC are often generalized to real-world patients. However, clinical trials have stringent inclusion and exclusion criteria, which can potentially lead to poor generalizability of results and slow accrual. This study was conducted to determine the proportion of real-world patients with stage II/ III CRC who would be eligible for AC trials based on common eligibility criteria and to compare the outcomes in eligible and ineligible patients.

METHODS

We identified all patients diagnosed with stage II/III CRC in 2004-2015 from the Alberta Cancer Registry. Patients meeting any one of the following criteria were considered ineligible: age >75 years, anemia, comorbid conditions (heart disease, uncontrolled diabetes, kidney disease, liver disease) and history of a prior malignancy or immunosuppression. Logistic regression was used to describe the likelihood of receiving AC and Cox regression models were constructed to determine overall survival (OS).

RESULTS

A total of 7841 patients with stage II/III CRC were identified, of whom 52% were men and median age at diagnosis was 71 years (IQR: 61-79 years). Approximately 59% patients were deemed trial-ineligible and the most common reasons for ineligibility were advanced age (36%), renal dysfunction (27%), and cardiac disease (17%), respectively. In the real-world, 54% of eligible patients received AC as compared to 23% of ineligible patients [odds ratio 3.89, 95% confidence interval (CI) 3.53-4.28, P< 0.0001]. The 5-year OS of trial-ineligible patients who received AC was significantly better than those treated with surgery alone (Table 1).

CONCLUSIONS

Majority of real-world patients with stage II/ III CRC are unable to participate in AC trials due to strict exclusion criteria, but a fair proportion of these patients still derive some benefit from AC. The eligibility criteria of AC trials in CRC should be broadened to be more representative of real-world patients.

Table 1: Survival of eligible and ineligible patients.

Group	5-year OS	Hazard Ratio	95% CI	P-value
Ineligible and received AC	56.3%	--	--	--
Ineligible and did not receive AC	74.4%	0.48	0.42-0.54	<0.001
Eligible	83.1%	0.54	0.48-0.61	<0.001

POPULATION-BASED ROS1 TESTING IN ADVANCED NSCLC

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BACKGROUND: ROS1 gene rearrangements are found in 1-2% of all non-small cell lung cancer (NSCLC) and reflex testing is recommended in all patients at diagnosis, but public funding is unavailable. This study models the most efficient ROS1 diagnostic testing strategy to maximize detection of true positive (TP) cases while minimizing costs and turnaround time (TAT).

METHODS

A decision model was developed for population-based ROS1 diagnostic testing from a Canadian (Ontario) public healthcare system perspective. Eight diagnostic strategies examined the use of immunohistochemistry (IHC) and next generation sequencing (NGS) compared with fluorescence in-situ hybridization (FISH, gold standard) in a molecular or clinician-selected (never smokers) setting using blood- versus tissue-based testing. Model inputs were obtained from existing literature and expert opinion. Direct testing costs and TAT were from the Ontario public perspective (University Health Network, Cancer Care Ontario).

RESULTS

Reflex testing with IHC and subsequent FISH confirmation identified a high proportion of TP within a relatively short TAT. IHC screening saves 233 CAD per case versus upfront FISH, and, among all testing strategies, captured the highest proportion of TP cases (88% vs 92% for FISH). NGS was the most costly reflex strategy, with a greater proportion of missed TP, and long TAT. Clinician-initiated strategies had the longest time to result. One-way sensitivity analysis demonstrated that cost estimates are most sensitive to specificity of the IHC assay.

CONCLUSION

ROS1 IHC screening with FISH confirmation offered the least costly strategy but still allowed a high proportion of TP to be detected with the shortest TAT. Clinician-initiated testing significantly lengthens TAT, and selecting for never smokers misses a large proportion of TP patients who would benefit from targeted therapy.

NEOADJUVANT SYSTEMIC THERAPY UTILIZATION AND OUTCOMES IN BREAST CANCER

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OBJECTIVE

This study identified changes in breast cancer (BC) neoadjuvant therapy (NT) utilisation trends and patient outcomes over time in Alberta.

METHODS

BC patients treated with NT in Alberta from 2008-2016 were identified from electronic medical records. Provincial cancer registry data was used to determine NT utilization. Kaplan-Meier curves with log-rank tests were used to analyze recurrence-free survival (RFS) and overall survival (OS). Detailed analysis was performed on a subset of patients to identify rates and factors associated with pathologic response (complete response (pCR), partial response (pPR) or no response (pNR)).

RESULTS

1866 patients were identified, with 455 patients included in the detailed subset. NT utilization steadily increased from 2008 to 2016 (Table 1), most prominently in the HER2 positive subtype. Rates of response varied by receptor subtype (Table 2). RFS did not differ by receptor subtype after NT (p = 0.096) but was significantly higher after pCR (Figure 1). Amongst patients with pNR after NT, hormone-receptor positive (HR+) patients had higher RFS than other groups (p = 0.002). OS for patients treated from 2008-2011 was similar to those treated in 2012 or later (p = 0.20). OS for HR+ BC was longer than HER-2 positive or triple-negative BC (p < 0.001).

CONCLUSIONS

NT utilization is increasing for early stage BC, especially for HER2 positive disease. Our results confirm previously reported pCR rates with NT in a real-world setting. Based on our results, we plan to create a predictive model estimating the relationship between variables known prior to starting NT and pathologic response. In the future, such a model (supplemented with imaging or other data, such as circulating tumour DNA) could be used to evaluate a patient's candidacy for neo-adjuvant chemotherapy.

Table 1. Proportion of BC patients receiving NT, by receptor subtype.

| Year	HR Positive	HER2 Positive*	Triple Negative	Total
2008	3.8%	5.4%	7.4%	5.0%
2009	4.3%	1.3%	5.5%	4.8%
2010	7.9%	12.7%	4.1%	7.7%
2011	8.6%	14.2%	6.8%	8.5%
2012	9.9%	18.2%	8.4%	10.5%
2013	11.1%	17.7%	8.7%	11.6%
2014	12.4%	19.5%	15.6%	14.2%
2015	12.2%	14.5%	13.0%	13.5%
2016	12.9%	17.4%	13.3%	14.4%

*HER-2 testing was not reported routinely during 2008 and 2009 resulting in lower proportions of HER-2 positive patients.

Table 2. Proportion of BC patients receiving NT achieving pNR, pPR or pCR at time of surgery (n = 455).
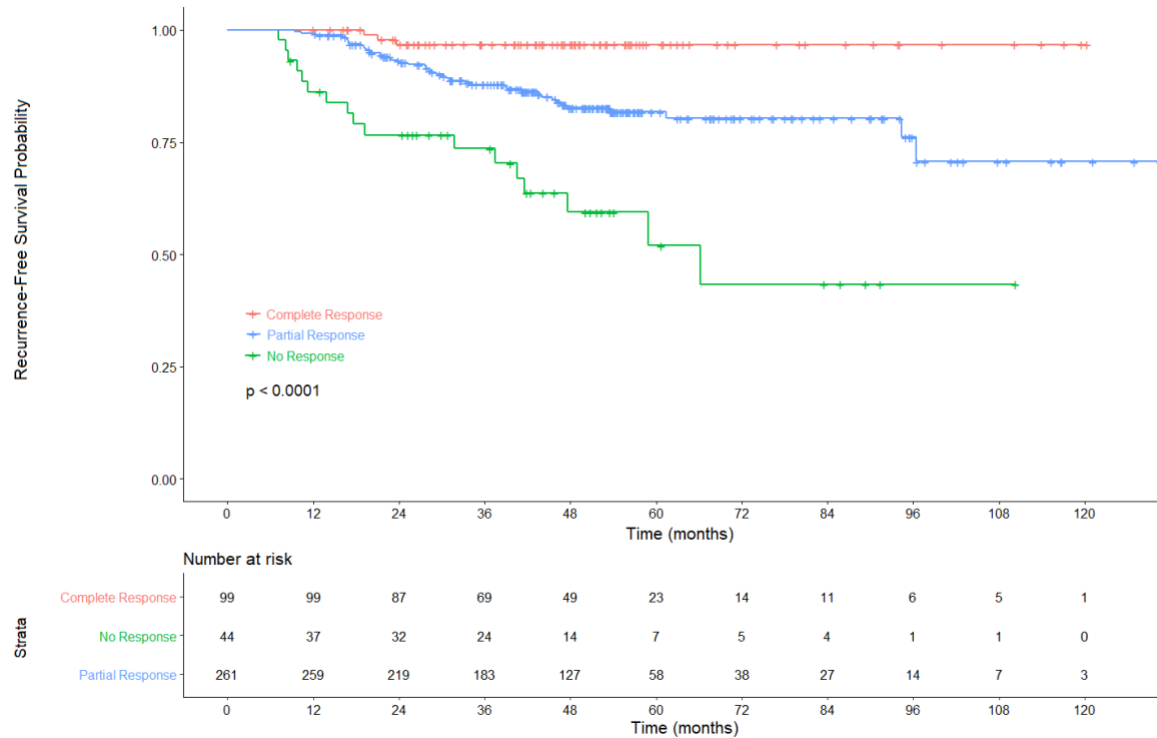
Receptor Status	No Response (pNR)	Partial Response (pPR)	Complete Response (pCR)
HR Positive	13.7%	74.8%	11.5%
HER2 Positive + HR Positive	3.7%	58.5%	37.8%
HER2 Positive + HR Negative	5.9%	35.3%	58.8%
Triple Negative	12.9%	51.6%	35.5%

Figure 1. RFS for BC patients by (A) Receptor Subtype and (B) Pathologic Response to NT.
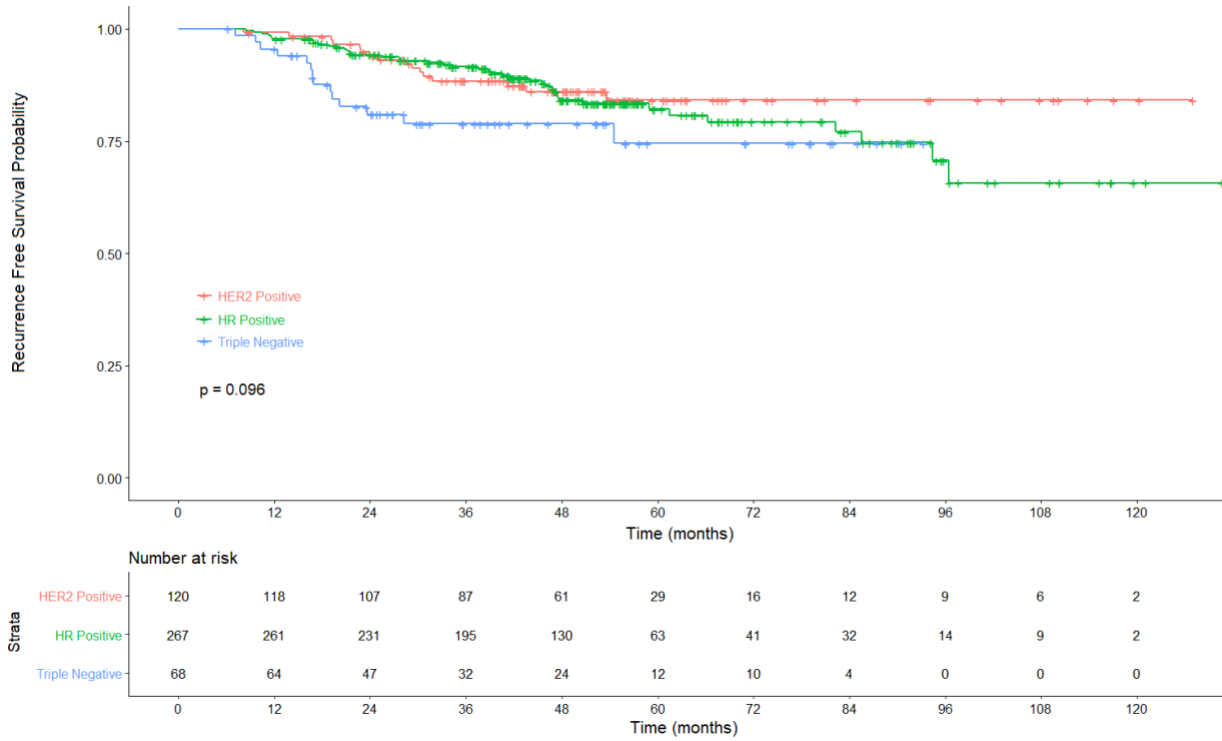
EARLY ONSET PANCREATIC DUCTAL ADENOCARCINOMAS ARE CHARACTERIZED BY A DISTINCT MUTATIONAL LANDSCAPE

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OBJECTIVES
There is a rising incidence of early-onset pancreatic cancer (EOPC; ≤55 years), but reported treatment and survival outcomes in EOPC remain limited. We characterized the genomic and transcriptomic landscapes of EOPC, while also leveraging provincial health data to investigate survival outcomes in advanced EOPC in a separate dataset.

METHODS
We generated a comprehensive and integrative dataset utilizing RNA-seq data and matched clinical metadata for 402 patients with pancreatic ductal adenocarcinoma, encompassing both resectable (ICGC, TCGA) and advanced (Personalized OncoGenomics and COMPASS) disease. Patients were stratified into EOPC (n=96), average-onset pancreatic cancer (AOPC, ≥70 years; n=121) and intermediate (>55 and <70 years; n=185) groups.

Survival analysis in a separate dataset was conducted using 578 patients who received systemic therapy between January 2012-December 2015 in British Columbia, Canada.

RESULTS
CDKN2A SNV/indels were identified in 22% and 26% of intermediate and AOPC patients, and in only 7% of EOPC patients (p<0.01). SNV/indels in epigenetic modifiers KMT2C/D trended towards lower frequency in EOPC (4% and 5%, respectively) compared to intermediate (13% and 13%) and AOPC (13% and 13%), although these observations did not pass multiple test correction (p=0.09, 0.20). Differential expression and gene set enrichment analysis revealed EOPC-specific up-regulation of genes in synaptic signal transduction pathways. In a separate analysis of provincial data, Kaplan-Meier survival analysis revealed similar survival between EOPC vs. AOPC vs. intermediate groups.

CONCLUSIONS
Using an extensive PDAC sequencing dataset, we highlight a novel association between CDKN2A SNV/indel frequency and EOPC. These data indicate potential age-specific differences in the mutational and developmental trajectories of PDAC, and generate novel hypotheses for further study of EOPC.

IMPACT OF VALUE FRAMEWORKS ON THE MAGNITUDE OF CLINICAL BENEFIT: EVALUATING A DECADE OF RANDOMIZED TRIALS FOR SYSTEMIC THERAPY IN SOLID MALIGNANCIES

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OBJECTIVE

In the era of rapid development of new, expensive cancer therapies, value frameworks were developed to quantify clinical benefit. This study assessed how the magnitude of clinical benefit has evolved since the 2015 introduction of the ASCO and ESMO value frameworks.

METHODS

Randomized phase II and III clinical trials assessing new cancer treatments for solid malignancies from January 2010 to July 2019 were evaluated. Study characteristics were recorded, and magnitude of clinical benefit (Δ) was calculated for the endpoints of overall survival (OS), progression-free survival (PFS), response rate (RR), and quality of life (QoL). Multivariable analyses compared ΔOS, ΔPFS, and ΔRR in the 2010-2014 period [pre-value frameworks (PRE)] to the 2015-2019 period [post-value frameworks (POST)].

RESULTS

Of the 290 studies analyzed [60 (21%) PRE and 230 (79%) POST], the most common primary endpoint was PFS (46%), followed by OS (20%), RR (16%), and QoL (8%) with no significant difference PRE and POST. In the POST era, studies evaluating immunotherapy and treatment in the palliative setting significantly increased (Table 1). Studies reporting QoL improvement doubled POST, although this finding was not statistically significant. Median ΔOS was significantly greater POST (N= 140 evaluable studies, 1.3 v -0.2 months, Wilcoxon p=0.005) but there was no significant difference in median ΔPFS or ΔRR. Multivariable analyses revealed significant improvement in ΔOS in the POST era (p=0.018) after adjusting for drug mechanism of action, line of therapy, disease setting, and primary endpoint.

CONCLUSION

After the development of value frameworks, median OS improved very minimally. The introduction of immunotherapy likely contributed to this advance. There was no substantial improvement in other endpoints shown to impact value, such as QoL.

Table 1. Analysis of study characteristics pre- and post-publication of value frameworks.

	Pre-value frameworks: 2010-2014	Post-value frameworks: 2015-2019	P-value (aFisher's exact, bChi squared)
Number of studies*, N=290 (%**)	60 (21%)	230 (79%)	
Primary endpoint			
Overall survival	9 (15%)	50 (22%)	0.07a
Progression-free survival	27 (45%)	107 (47%)	
Response rate	16 (27%)	28 (12%)	
Quality of life	2 (3%)	19 (8%)	
Other	6 (10%)	26 (11%)	
Quality of life			
Not reported	45 (75%)	159 (69%)	0.56a
No improvement	12 (20%)	49 (21%)	
Improved	3 (5%)	22 (10%)	
Experimental drug mechanism of action	21 (35%)	68 (30%)	
Cytotoxic therapy	36 (60%)	113 (49%)	0.0008a
Targeted therapy or antibody	0	39 (17%)	
Immunotherapy	3 (5%)	10 (4%)	
Other			
Line of therapy			
1	27 (45%)	118 (51%)	0.07a
2	32 (53%)	93 (40%)	
>2	1 (2%)	19 (8%)	
Disease setting			
Curative	35 (58%)	88 (38%)	0.005b
Palliative	25 (42%)	142 (62%)	

*If a trial had >1 experiment arm, each experimental arm was counted as a separate study. There were 28 trials with >1 experimental arm.

**Percentages rounded up to the nearest whole number.

NOTES