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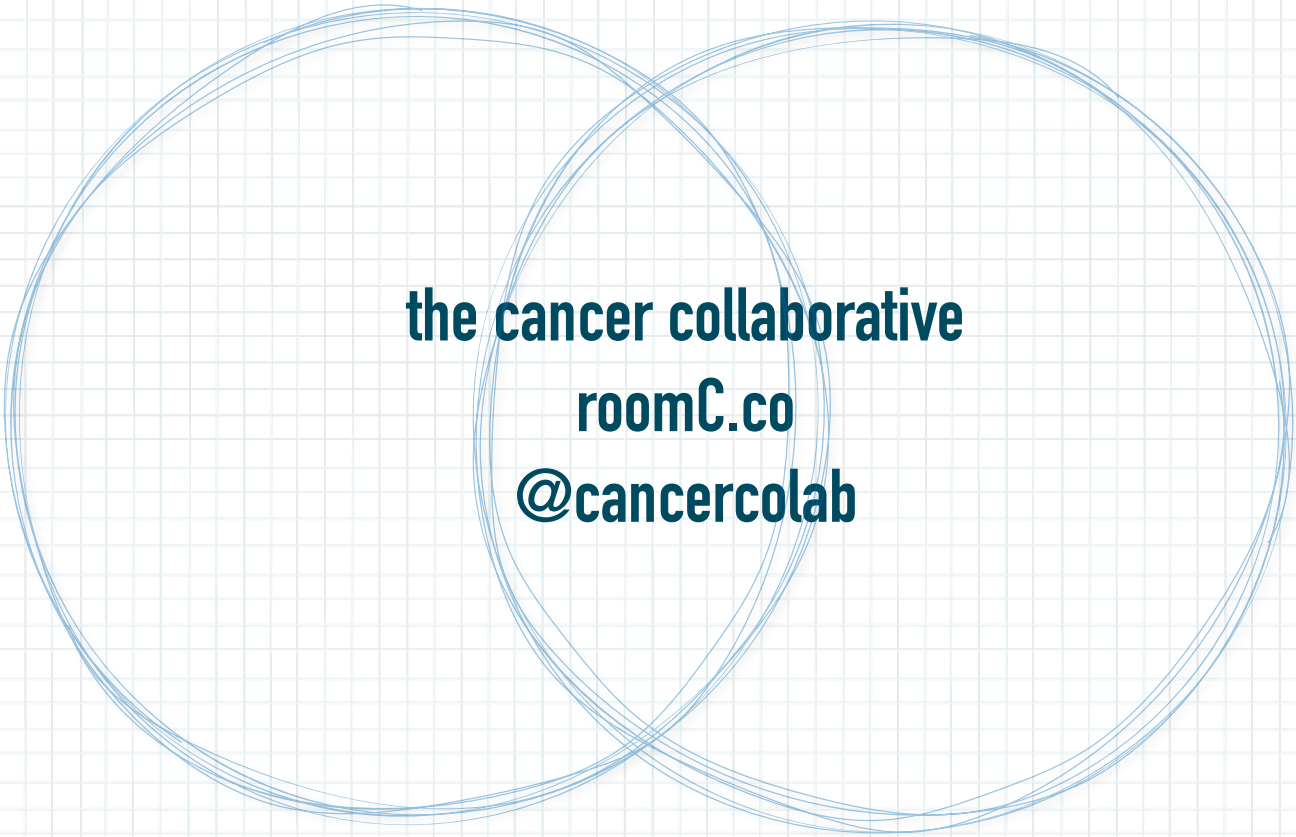

the cancer collaborative
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@cancercolab

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caring for every patient. learning from every patient

the theme of this year's ASCO meeting is intended to drive home the message that every patient deserves equal access to the highest quality care and the opportunity to participate in research, and not just some patients but EVERY patient and to make sure that we, as clinicians, decision makers, payors, advocates and manufacturers use every single opportunity to do better until suffering from cancer is no longer part of our world.

the only way to truly learn from every patient is to engage with patients and each and every encounter with a patient is an opportunity to think about the different interventions, the different services that are necessary and the opportunity to think about how we can do this better for patients, for their families for healthcare systems and ultimately for society.

the ASCO theme should get everyone asking themselves how can we improve patient | scientist | clinician | decision maker collaboration and not only asking how can we learn from every patient, but how do we then translate these learnings so that we can make the greatest impact for patients, from improving quality of life, to survivorship, better drug development, better decision making and finally even a cure?

“

what a powerful vehicle for progress we would have if every person challenged by a cancer diagnosis had access to the care that they need.
think about how powerful it would be if every person’s experience could contribute to making a better future.

monica bertagnolli,
ASCO president
the presidential address, ASCO 2019

saturday june 1.2019

presidential plenary.

guest speaker address. will we be technicians or counsellors?

atul gawande. MD. MPH

clinicians, family members, societies, and professionals struggle with the question - what do we want for patients in this moment, what do we think is great care, what is actually our goal? the answer is unclear.

in 2010 jennifer temel ran a study at mass general hospital with stage IV lung cancer [early palliative care for patients with metastatic non small cell lung cancer]. they randomized all of the stage IV lung cancer patients to two arms. the control group got the usual oncology care. and the intervention group received early palliative care at diagnosis. the group who received the early palliative care were less likely to be receiving chemotherapy by about half at two months before end of life. they were about 90% less likely [to receive chemo] in the final two weeks. they had less suffering. they spent more time at home. they spent less time in the hospital. they had about a 1/3 less chemotherapy costs. and they lived 25% longer.

what do we want for patients in this moment?

what do we think is great care?

what is actually our goal?

the most powerful thing that they did was that they simply asked people what those priorities were.

from this study clinicians saw that they could reduce patient suffering, improve quality of life without harming quantity of life and perhaps even improving it. the job of palliative care clinicians is to bring the best of medicine to serving the quality of life of patients. so this study [temel et al.] wasn't about pain or nausea. and it wasn't about depression. but rather they were asking fairly simple questions. and these questions became very fundamental to how clinicians understand their role. questions like what are your goals for your quality of life, what are your priorities for your quality of life, what matters to you most, and what does it mean in detail in the everyday aspects of your life?

clinicians for the most part understand their goal is giving patients the best options for their best health, independence and survival. to give people the facts of their situation; give them their options, talk about the risks, the benefits; and then give them their choices. what palliative care clinicians are doing, and the geriatricians, and the hospice workers, and also great oncologists is they were learning from people what their goals were. they learned that people have priorities for their life besides just survival. they have priorities for their quality of life. they have goals for how they want to live. and those goals and priorities change over time and are different from person to person.

when we don't ask, and more than 75% of time we don't ask, the care we provide is out of alignment with people's priorities.

what's your understanding of where you are with your illness? how much information would you like about what is ahead for you? what might be ahead for you here. what are your goals if your health situation worsens? what are your biggest fears and worries? what are you willing to go through and what are you not willing to go through for the sake of more time. people end up telling you are their goals and then treatment recommendations come out of it.

dana farber cancer institute recently published a trial where the entire outpatient oncology disease centre was randomized. 91 oncology clinicians participated with a 72% participation rate. and then their patients were tracked [278]. half received an intervention in which three things were done. clinicians in the study received a 2.5 hour communication training with palliative care experts, followed by supportive coaching. the program also has patient and family conversation tools to prepare patients for conversations and support ongoing discussions with their family at home.

the result was that, first of all, the timing of these conversations moved earlier to about five months before those who came to the end of their life died. furthermore, the quality was better, with 90% discussing their values and goals. they were far more likely to have had a discussion of prognosis and illness understanding. they were double the likelihood of documenting their preferences for life sustaining treatment. and in addition to demonstrating that there was no harm to survival, we showed that we cut their likelihood of severe or moderate anxiety by half and of depression by half. they had more conversations, better conversations, and better results.

bottom line. our job is to design with them a life worth living and then use our medical capability to enable that. and this is not just about those who might be approaching end of life, this is about the way we are and work as clinicians. its about setting goals, making a plan and ensuring that its executed and all the whole optimizing for the patients well being for their satisfaction and for their affordability.

sessions.

tweets, chats, and posts: using social media to transcend boundaries and create opportunities for patients

miriam knoll. MD

patients are eager for participatory discussions and those who participate in those discussions demonstrate high rates of knowledge improvement, including information on surgery, reconstruction, radiation, chemotherapy, and clinical trials. this demonstrates that the flow of information on social media and the relationships that form between healthcare stakeholders is multi-directional between patients, patient advocates, and physicians. and this can also be an active and formalized process.

physicians and researchers are looking to where the patients are and what's online and on social media. social media is particularly valuable for recruiting patients for clinical trials. patients are influencing cancer care in unprecedented ways. patients and patient advocates who are behind the growing legislation for dense breast notifications.

organizations are looking to bridge the gap between patients and researchers and they're asking patients directly to share their data, to share their medical history, and partner with researchers directly. so whether it's policy, advocacy, research dollars, clinical trials, social media is ushering in a new paradigm for cancer research and advocacy. and its potential is limitless.

> **"interact with patients and patient advocates on social media. listen to what they're saying. they're the true health care stakeholders and they have the investment in changing cancer care.**

the metastatic breast cancer project. engaging patients, advancing research.

what if we could generate a public database of clinical genomic molecular and patient reported data, to enable researchers to find patterns in this data and help accelerate discoveries in the development of new treatment strategies?

studies have shown that at least 70% to 90% of americans use the internet to seek health information. technology, social media, and cultural changes now provide a new opportunity to engage cancer patients and directly partner with them in this research. social media comes in a variety of forms and for patients, there are a variety of goals in accessing social media.

platforms for patient engagement

WhatFriendsDo
engagement with family and friends. a central mechanism for updates that allows patients to upload updates after a scan report, instead of having to call 30 individual people and tell them how that scan went.

smart patients and patients like me
for patient to patient engagement. the purpose really is to learn from each other, share stories, and provide peer to peer support.

metastatic breast cancer project [MBC]
with investigators and education about the disease they may have. the goal of MBC was really to create an opportunity to pair clinical, genomic, and molecular research initiatives independent of the location where that patient may receive their care.

patient support
there are online chat groups on facebook and twitter from the american cancer society, cancer.net, livestrong, the NCCN, komen, as well as hundreds others. they can be a very general cancer support group versus incredibly specific based on the tumour type, whether they have early disease or metastatic disease and even more specific to molecular alterations such as EGFR resisters and the ROS1 cancer.

count me in [a part of the metastatic breast cancer MBC project]

count me in

a nonprofit organization that brings together patients and researchers as partners to accelerate discoveries in cancer research.

the goal was to enable cancer patients from anywhere to share their information and samples with researchers everywhere. patients go online and provide information about themselves and their cancer and give permission for researchers to collect medical samples and medical records. they also partner with the researchers, receiving updates about the status of the project and any discoveries.

over 5,000 women and men with metastatic breast cancer from all 50 states now have joined the MBC project in the past 3½ years. with over 1,700 institutions representative. the project is unique in that the researchers can contact participants and collect additional data based on what they learn. this iterative process is the ultimate expression of the patient partnership.

it also offers a distinctive repository of data for metastatic breast cancer patients, it includes whole exome data, RNA-sequenced data, cell DNA; and it is linked to detailed demographic, diagnostic, pathologic, radiologic, treatment, duration on therapy, what people go on to after therapy, in addition to patient reported data. it all goes into an open clinical genomic database [cBioPortal, national cancer institute genomic data commons] and the data is updated and refreshed every 6 months and is available to anyone online.

with the data, researchers are learning about the genomic landscape of metastatic breast cancer and tumour heterogeneity; clinical behaviour, including response and resistance, side effects, and toxicities; and response by tumour alterations and patient subsets [exceptional responders, young people, men, and those with rare subtypes]. how therapies are sequenced, novel targets, not only for resistance mechanisms, but also to inform new drug discovery.
meaningful questions that otherwise, can't be asked from typical databases.

patients have a desire to participate in research and advance the field

how is this different

- it's patient centred, including patients treated in the community. it's not about one clinical trial or one institution thus enabling more diversity in research.

- there's a potential to enrol large numbers, ask questions that cannot otherwise have been answered in typical data sets. to merge clinical, genomic, and patient reported data that is all linked together. and most importantly, the data is shared publicly as it's generated.

70% of Americans indicate that they'd like to participate in clinical trials, but they don't know how, because they're not aware of them, because they don't know how to be referred to a clinical trial, because they physically can't get to a clinical trial

- it's also a patient research partnership. angiosarcoma, prostate cancer, and gastroesophageal cancer are already up and running. and over the next few years, their goal is to launch projects in every major cancer type as well as paediatric and rare cancers.

lessons learned.
clinical information and genomic molecular data needs to be linked. meaningful questions can be asked when we have data that's annotated by treatment and outcome. we can better identify mechanisms of resistance and novel therapeutic targets.
data and information should not be siloed. pooled resources can answer many more questions than no one group or no one trial ever can.

walk this way. wearable devices and remote monitoring for patients with cancer.

muhammad shaalan beg. MD. MS

incorporation of mobile, and sensor, and wearable technology has a lot of potential in oncology. it will allow us to do monitoring away from the clinic during some very critical periods of care.

it enables the collection of objective data, a step up from self-reporting, and often times in real-time which provides a different window and a different picture into what the patients are experiencing.

overcomes a lot of the common barriers. It's very difficult to remember the pain you felt last week,

what is the value proposition for wearable devices and remote monitoring in oncology? can best practices be identified for storing and interpreting data produced by these devices and how can they be integrated into electronic health records [EHR] to evaluate the current landscape and determine the costs involved with implementing remote monitoring?

researchers conducting a feasibility trial with wearable physical activity monitors for cancer patients to see if patients would use it. oncology specific performance status measurements provide a sense of what life is like at home for the patient. there is a clear differentiation of patients who are an ECOG 0 and those that are ECOG 4. but what about the patients who fall in between those ranges, there isn't a really good way to measure.

24 patients were enrolled to see if they would use it for at least half the time that they had the devices. and most patients were able to do that. clinicians assigned ECOG performance status and compared it with the steps measured and found that there was a big difference in the folks who were ECOG 0/1 versus 2.

the wearable device measures were correlated with quality of life questionnaires, with symptom tools for depression and fatigue. and interestingly, it wasn't the maximum number of steps that somebody achieved that correlated with these outcomes, it was the minimum number of steps that patients were achieving that correlated with their quality of life, their depression and fatigue scores.

'providing a different story on what their disease trajectory has been like and on how they're tolerating their cancer treatments.'

drs. vijayvergia and farma from fox chase cancer centre, took this a step further to see if wearable devices can predict toxicity in patients receiving cancer treatments. colorectal cancer patients who were either receiving surgery or chemotherapy and compared normal standard measurement tools with wearable device tools and found that the measures from the wearable devices were much more predictive of grade 3 and above toxicities than the standard clinical parameters.

this demonstrated that these devices may have an ability to tell who is going to do well, so we can try to match the right patient with the right treatment.

the next question is to see if it's any better than the standard clinical measures and the hope is that the study will provide the ability to assess physical activity with time and also compare the differences in physical activity between treatments.

wearable technology can improve the ability to longitudinally measure physical activity. we know that wearable derived data can correlate with clinician assessed physical status. and both researchers and clinicians should work to systematically incorporate relevant wearable technologies. but there are many questions that remain before this can become standard practice

the value proposition of wearable technologies and remote monitoring in oncology care

wearable technologies obviously are apparent in terms of what they mean. when we think about remote monitoring, it can also include wearables. it can include mobile applications and mobile technology. it also can include tele-health and tele-medicine.

patients have, for a very long time, experienced most of their cancer care at home. they see their physicians periodically and encounters are perhaps not as long as patients would like. there's an opportunity to bridge that gap and to provide a connection. patients and caregivers have a heavy burden and responsibility to monitor and evaluate a number of different and complicated symptoms, and then also to make some complicated decisions on whether to contact their nurse or their physician or go to the ER. so there's another opportunity there to bridge that gap and to provide some assistance and support.

with regard to clinical trials, if there was an ability to reach patients through remote and wearable technology for trials, they may not have to travel in as often. it may make

participation more appealing for them. and then finally, with the survivor population, there are opportunities for monitoring. for learning more about their experiences, and possibly for engaging them in interventions after they've completed their treatment.

there's a tremendous capacity for data storage. so this makes it potentially scalable & cost effective. those are still some questions to work out, this may improve our health related outcomes.

because information is being relayed more quickly and at a more granular level, interventions can happen more quickly. the ability to track our health over a period of time gives us a picture into the symptom profile of what patients might be seeing or might be experiencing, and gives us new insights into the disease and again how we can provide support.

there are currently over 70 studies in cancer that are using wearables to either promote or measure physical activity. there may be a way to increase recruitment and possibly retention through the use of wearables. and it may provide better data or more specific data on health outcomes that might help to interpret some of the treatment data. they also might aid in terms of determining exclusion | inclusion criteria, particularly when looking at things like functional status. but there's been, to date, more limited adoption of some of the wearables and the sensors.

the first step is to really identify the problem, identify what is the data need that these devices | technology can potentially help address. and then consider the feasibility, the validity, and the clinical utility. does it inform outcomes and research being done and will it eventually be adopted by patients and providers into the workflow. this could present a culture change much like electronic health records presented a culture change.

feasibility
- patient acceptance, satisfaction, adherence
- functional [battery lie, connectivity]
- multiple vs single function, cost

validity
- accuracy
- predictive capability

clinical utility
- timing and quantity of data
- meaningfully informs clinical care or research
- adoption by patients and providers into work flow

there's increasing interest in using these, promising feasibility and early efficacy data. the challenges are going to be accuracy and validity. the analytics of it are still being figured out and may continue to be fleshed out as the data comes in.

multifunctional platforms will enable us to more efficiently capture more data.

global access to essential [cancer] medicines.

nicola magrini. MD WHO

what is an essential medicines list [EML]? medicine that responds to the priority health care needs. although it has no explicit definition, it introduced the idea that some medicines are more important than others. the world health organization [WHO] published the first model list of essential medicines [EML] in 1977 and many considered it a revolution in public health

prioritising cancer medicines for benefit.

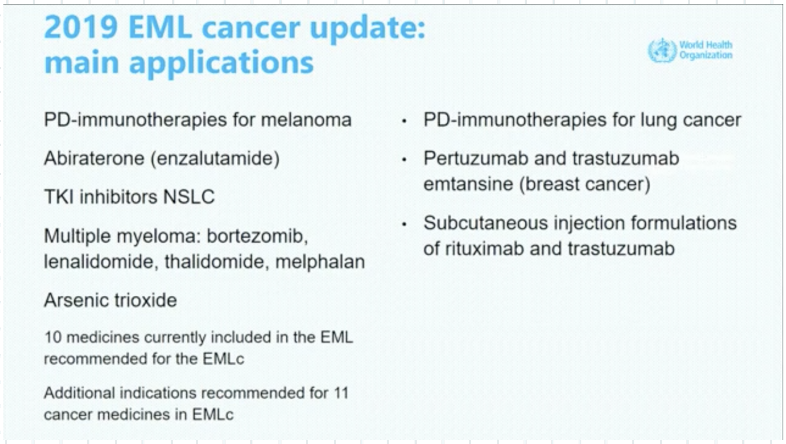
cancer is different, much more complex, much more demanding than many other diseases that can have an approach of test and treat. and this is not possible for cancer.

EML has listed the vast majority of all antibiotics, drugs for neglected diseases, drug for mental health, or drugs for pain, including morphine, chronic disease and cancer. the EML lists new hepC combinations, dolutegravir and prep for HIV, all new TB drugs, most contraceptives, surfactant and all highly effective treatments. EML does not list drugs for memory loss and dementia, hepatoprotectants and immunostimulants, medicines for dubious conditions [disease mongering | medicalization of life conditions]

'a revolution in public health.' médecins sans frontières

why cancer is different?

in 2015 the EML was updated to include cancer therapies through an approach prioritising for benefit. by prioritising for the most curable cancers [leukaemia, lymphomas, early breast, early colon, and a few other highly curable tumours]. with medium priority for manageable cancers and low priority for less curable cancers. an algorithm based on best available evidence was developed for 22 adult cancers and 12 paediatric cancers.



[the 2019 list was under embargo at the time of the presentation but is now available here]

the cancer medicines working group [CMWG] recommended WHO endorse the need to have overall survival as the main eligibility criterion of a medicine proposed for EML listing. further the CMWG recommended endorsement of an interval for overall survival of at least 4-6 months for first line treatments as a general guiding principle.

the essential medicines list seeks to include only therapies that prolong life meaningfully for the patients that receive them

among the considerations that supported the 4-6 months overall survival interval were

- a strong clinical and ethical conviction that for OS less than three [3] months, the benefits seem weak, marginal or not relevant [depending on cancer type].
- a three [3] month survival threshold has been endorsed by both ASCO and ESMO scales, with different implications in their respective scales.
- clinical trials estimates tend to overestimate the benefits due to patient selection, risk of bias and spurious findings. patients included in clinical trials often differ from those seen in real life settings: benefits in patients seen in everyday practice might be less convincing as compared to those selected in trials. trials often have important methodological limitations, leading to biased estimates of intervention effectiveness. single studies are often exposed to type I error. finally interventions studied in trials might not be directly transferable in LMICs as capacity centres to deliver essential medicines and manage related toxicity might be diminished.
- the list is an important tool not just advocacy but for setting a common standard. and also not taking into account the cost implication when listing, but discussing on affordability and sustainability, once these drugs are listed. the list can be useful to identify the 10%-20% of new drugs approved that show a large magnitude of benefit.

we also note that the prices are disproportionately high in comparison to the benefit of several drugs approved and that we have to define new mechanisms to improve access to these essential medicines once they are listed.

but the issue is not just having enough money at the country level, it's much more complex than that.

a study of the novartis access program showed that providing drugs at low cost [1USD$ per month] still does not improve access although it can improve availability. another study found that of the different cancer drugs [51] approved in the last 15 years, 37 showed differing magnitudes of benefit within the same price range.

so why cancer is much more complex? because it needs a fully functioning system. it needs the majority of the capacity and competencies available, often in a complex infrastructure.

selection of the essential medicines and discussions such as this one do provide the basis for benefit packages showing the idea that there should be one standard. and this standard should be led by the most impactful and useful medicines, not just access to all.

cancer and universal healthcare [UHC]
health system capacity and financing - a coordinated set of interventions is needed

- set priorities based on the EML
- define target populations
- define health system requirements
- define quality target of screening programs and other health system capacities

'a health system that is ready for cancer is a fully functioning and resilient healthcare system.'

possible actions for sustainable cancer management in UHC era include prioritising cancer in the next two decades for benefit packages and social protection [universal healthcare], use of current convergence on magnitude of benefit. on sustainability and high prices- the use of the new EML for new and ad hoc global agreement to improve access. and finally a coordination of all stakeholders in a health system perspective.

'for cancer we don't need a new ad hoc funding mechanism but rather a collective investment on health as a development issue'

mCODE [minimal common oncology data elements] in cancer practice.

travis john osterman. DO, MS

nearly 40% of americans at some in their lifetime will be diagnosed with cancer, yet only 3% of those will go to participate in clinical trials, which continues to be the gold standard by which decisions are made in oncology practice. 15 million cancer patients have records that reside within electronic health records, but because they don't participate in clinical trials, it is more difficult to learn from each and everyone of those patients.

one of the biggest challenges is that approximately 1500 different electronic health records [EHR] platforms exist and their data models are not compatible, meaning data from one system can't easily be combined and compared with data from another system, making it very challenging to be powered to make inferences from all patients. despite increasing EHR adoption rates over the last decade in both inpatient and outpatient settings, which have been driven mainly by policy, like HITECH act and meaningful use, a corollary increase in the ability to learn from those patients is not being seen even though their data is now stored electronically in each of the records systems.

EHR data set has a very large volume of information and its a very deep and rich data set. on the downside they are partially structured, at best. meaning some of the data is very straightforward to extract in most medical record systems, visit dates, vital signs, common laboratories and diagnoses can easily be extracted. however these data sets are unlikely to provide any meaningful answers in oncology today. data sets like cancer staging, treatment regimens and molecular data are paramount to learn from each and every patient.

mCODE wants to create a data standard that is more focused on the ability to actually answer meaningful oncology questions. that means leveraging current data standards and building on those to fill in the gaps of areas that we are currently missing.

to develop and maintain standard computable data formats-known as minimal common oncology data elements or mCODE-to achieve data interoperability and enable progress in clinical care quality initiatives, clinical research, and health care policy development. by leveraging the EHR data model for each of those vendor specific data models, mCODE layers on this, a set of mCODE domains [patient, disease, lab/vitals, genomics treatment, outcomes]. within each set of domains are sets of clinical data elements. these specific data elements are then accessed via standard data access standards [SMART on FHIR]. applications can also be developed to combine data across healthcare systems and

SMART. substitutable medical applications, reusable technologies

FHIR. fast healthcare interoperability resource

also applications that can them be moved from one electronic health record to another and still be viable. use for this type of system include being able to compare patient treatment and toxicities, identification of patients for clinical trials, quality measures in reporting and population health management.

the guiding principles of the mCODE project - highly collaborative, iterative use case development, maintenance is reductionist and parsimonious, developed and maintained by its users, non commercial data standard.

as the data standard is updated, new use cases and new oncology questions that need to be answered will be identified. and consideration around what new minimal clinical data elements need to be included in the standard. the goal of learning from every patient is represented here.

the first clinical pilot is underway at intermountain healthcare, leveraging a newly developed application called compass, with the goal of demonstrating the use of mCODE data models to allow providers and patients to make informed, shared, data driven decisions and provide data back to generate new knowledge- in line with the principles of the project. compass is a SMART on FHIR application, and it uses the patient's mCODE data elements as derived from the medical record and then is able to transmit those data elements to CancerLinQ to identify a similar set of patients that are already populated within the CancerLinQ database so that learnings from the experiences of those patients in the clinic room with that provider are captured.

the EHR is accessed through application programming interfaces, or APIs, both that are proprietary to the EHR and that are based on the FHIR data standard. those are mapped to the mCODE proxy and then matched up with the data elements of the EHR.

once that data is extracted it can be extracted to CancerLinQ and again return results that can be learned from. such as outcomes and toxicities of other patients and providers experiences. this is the goal of answering clinically meaningful questions, especially in matching patients that don't have good evidence based clinical trial information on treatment and toxicities.

future directions include continuing to identify meaningful questions that need to be answered to update the set of use cases which informs what clinical data elements are included in the standards. part of this is convening a cancer data summit [being planned] it is also critical to continue to engage vendors, especially EHR vendors in hopes of promoting adoption of this standard and in engaging cancer practices in cancer centres to help advocate for and promote adoption of this data standard to get to the next phase of truly being able to learn from every patient.

first results from TITAN. a phase III double-blind, randomized study of apalutamide [APA] versus placebo in patients with metastatic castration sensitive prostate cancer [mCSPC] receiving androgen deprivation therapy [ADT]. [abstract 5006]

kim n. chi. MD. FRCPC

background. TITAN was designed to determine whether apalutamide, a selective next-generation androgen receptor inhibitor, plus ADT improves radiographic progression-free survival [rPFS] and overall survival [OS] compared with placebo plus ADT in patients with mCSPC.

methods. in this randomized, double-blind phase III study, patients with mCSPC regardless of extent of disease were randomized [1:1] to apalutamide or placebo, added to ADT, in 28-day cycles. patients with prior treatment for localized disease or prior docetaxel for mCSPC were allowed. all patients received continuous ADT.
dual primary end points were rPFS and OS. secondary end points were time to a. initiation of cytotoxic chemotherapy b. pain progression c. chronic opioid use, D. skeletal-related event. this first planned OS interim analysis took place after ~50% of expected events.

results. 525 patients were randomized to apalutamide and 527 to placebo. median age was 68yrs; 8% had prior treatment for localized disease; 11% had prior docetaxel. 63% and 37% had high- or low-volume disease, respectively. at median 22.6 mo follow-up, 66% apalutamide and 46% placebo patients remained on treatment. apalutamide significantly improved rPFS, *with a 52% reduction in risk of death or radiographic progression*; benefit was observed across all subgroups analyzed. median rPFS was not reached in the apalutamide group and 22.1 months in the placebo group. apalutamide also significantly improved OS with a 33% reduction in risk of death. median OS was not reached in the apalutamide or placebo group. time to initiation of cytotoxic chemotherapy was significantly improved with apalutamide.

based on these results, the independent data monitoring committee recommended unblinding to allow crossover of placebo patients to receive apalutamide.

rates of grade 3 | 4 adverse events [AEs] - [42% APA, 41% PBO] were similar, and discontinuations due to AEs [8% APA, 5% PBO] were low.

conclusions. in the TITAN study patients with mCSPC, including patients with high- and low-volume disease and prior docetaxel, addition of apalutamide to ADT significantly improved rPFS and OS, and the safety profile was tolerable. these results support the addition of apalutamide to ADT for treatment of patients with mCSPC.

clinical trial information: NCT02489318

TOPARP-B. a phase II randomized trial of the poly[ADP]-ribose polymerase [PARP] inhibitor olaparib for metastatic castration resistant prostate cancers [mCRPC] with DNA damage repair [DDR] alterations. [abstract 5005]

joaquin mateo. MD. PhD

background. the antitumour activity of olaparib against molecularly unselected mCRPC was previously reported [TOPARP-A; mateo et al NEJM 2015]. TOPARP-B, a phase II trial for patients with mCRPC preselected for putatively pathogenic DDR alterations is now being reported.

methods. patients with mCRPC progressing after ≥ 1 taxane chemotherapy underwent targeted sequencing of tumour biopsies and were deemed eligible when alterations [germline or somatic; mono- or bi-allelic] in any DDR gene were detected. patients were randomized 1:1 under a "pick-the-winner" design 400mg or 300mg of olaparib BID.
primary endpoint response rate [RR] was defined as radiological response [RECIST 1.1] and/or PSA50% fall and/or CTC count conversion, confirmed after 4-weeks. analyses of RR per gene alteration subgroup was pre-planned. secondary endpoints included progression-free survival [PFS], tolerability.

results. overall, 98 patients [median age 67.6yrs] were randomized, with 92 patients treated and evaluable for the primary endpoint [70 RECIST-evaluable; 89 PSA50%-evaluable; 55 CTC-evaluable]. all had progressed on ADT; 99% were post-docetaxel, 90% post-abiraterone/enzalutamide, 38% post-cabazitaxel. the overall RR was 54% meeting threshold for primary endpoint in the 400mg cohort and 37% in the 300mg cohort. with a median follow-up of 17.6 months, the overall median PFS [mPFS] was 5.4 mo.

subgroup analyses per altered gene identified indicated response rates for: BRCA1/2 of 80% mPFS 8.1mo; PALB2 57% mPFS 5.3mo; ATM 37% mPFS 6.1mo; CDK12 25% mPFS 2.9mo; others [ATRX, CHEK1, CHEK2, FANCA, FANCF, FANCG, FANCI, FANCM, RAD50, WRN] 20% mPFS 2.8mo. the highest PSA50% response rates were observed in the BRCA1/2 [73%] and PALB2 [67%] subgroups.

conclusions. olaparib has antitumour activity against heavily pre-treated mCRPC with DDR gene defects, with BRCA1/2 aberrant tumours being most sensitive but with confirmed responses in patients with other DDR alterations.

clinical trial information: NCT01682772

impact of darolutamide [DARO] on pain and quality of life [QoL] in patients with non metastatic castrate resistant prostate cancer [nmCRPC]. [abstract 5000]

karim fizazi. MD. PhD.

background. DARO is a structurally distinct androgen receptor antagonist for which in vitro and phase 1/2 studies suggest low risk of adverse events [AEs] and drug–drug interaction. in the ARAMIS study of DARO in nmCRPC, metastasis-free survival [MFS] was significantly prolonged vs placebo [40.4 vs 18.4 mo] and interim overall survival [OS] favoured DARO ,

methods. 1509 patients were randomized 2:1 to DARO [n = 955] or PBO [n = 554] while continuing androgen deprivation therapy [ADT]. primary endpoint was metastasis free survival [MFS]. secondary endpoints included OS and time to pain progression. QoL was assessed by european organisation for research and treatment of cancer [EORTC] QoL prostate cancer module [EORTC-QLQ-PR25] at baseline [BL] and every 16 weeks until end of treatment. analysis of time to deterioration in EORTC-QLQ-PR25 subscales, defined as first occurrence of a minimally important difference.

results. DARO significantly delayed pain progression vs PBO [40.3 vs 25.4 mo]; this was maintained beyond end of study treatment. time to deterioration of EORTC-QLQ-PR25 outcomes showed statistically and clinically significant delays with DARO vs PBO for urinary symptoms [25.8 vs 14.8 mo]. time to deterioration of hormonal treatment-related symptoms was comparable with DARO vs PBO [18.9 vs 18.4 mo]. DARO was well tolerated. exposure-adjusted incidences [patients per 100 years' exposure] of AEs of interest were similar/lower with DARO vs PBO [fatigue | asthenic conditions [11.3 vs 11.1], hypertension [4.7 vs 5.1], hot flush [3.7 vs 4.1], fracture [3.0 vs 3.5], falls [2.7 vs 4.1], cognitive disorder [0.3 vs 0.2], and seizure [0.2 vs 0.2]].

conclusions. for nmCRPC patients, DARO prolongs MFS, is well tolerated, maintains QoL, and delays worsening of pain and disease-related symptoms compared with PBO.

clinical trial information: NCT02200614

end of phase I results of ZUMA-3, a phase 1/2 study of KTE-X19, anti-CD19 chimeric antigen receptor [CAR] T cell therapy, in adult patients with relapsed/refractory [R/R] acute lymphoblastic leukemia [ALL]. [abstract 7006]

bijal d. shah. MD

background. KTE-X19 is an autologous anti-CD19 CAR T cell therapy under investigation for adult R/R ALL. in an interim analysis of phase I of ZUMA-3, manageable safety and encouraging efficacy of KTE-X19; 72% of patients achieved a complete remission [CR] or CR with incomplete bone marrow [BM] recovery was reported.

methods. adults with R/R B cell ALL, > 5% BM blasts, and ECOG 0-1 received 2, 1, or 0.5 × 106 KTE-X19 cells/kg after conditioning chemotherapy. revised adverse event management [rAE mgmt] was implemented for additional patients in a 1 × 106 dose cohort. corticosteroids were given earlier at onset of grade ≥ 2 neurologic events [NEs] and tocilizumab was used only for active toxicity.
primary endpoint was the dose-limiting toxicity [DLT] rate. key additional endpoints were KTE-X19 levels, incidence of AEs, minimal residual disease [MRD], and CR/CRi [incomplete hematologic recovery] rate.

results. as of 9.27.18, 45 patients had received KTE-X19 [median follow-up [f/u], 16 mo]. the median age was 46yrs [range, 18–77]; 30 patients [66%] had ≥ 3 prior therapies and the median pre-conditioning BM blasts was 70% [range, 0–97]. six [6], 23, and 16 patients received 2, 1, and 0.5 × 106 cells/kg, respectively. there were no dose limiting toxicities [DLTs] in the DLT-evaluable patients. the most common Grade ≥ 3 AEs were hypotension [38%], pyrexia [38%] and thrombocytopenia [31%]. there were two [2] previously reported KTE-X19–related grade 5 AEs of cerebral infarction and multi-organ failure, both in the context of cytokine release syndrome [CRS]. grade ≥ 3 CRS and NEs occurred in 13 [29%] and 17 [38%] patients, respectively. of 41 patients with ≥ 2 mo of f/u, 68% had CR/CRi, and 73% had undetectable MRD. of 19 patients with ≥ 2 mo of f/u treated with 1 × 106 cells/kg, 16 (84%) had a CR/CRi and the median event-free survival was 15mo. in 9 patients treated with 1 × 106 cells/kg and rAE mgmt, 2 [22%] had grade 3 CRS and 1 [11%] had grade 3 NE with no grade 4/5 events.

conclusions. KTE-X19 dosing and safety management have been successfully refined by testing three [3] cell doses and evaluating a new AE management guideline with altered corticosteroids/tocilizumab use for NE/CRS. pivotal phase II is ongoing at the 1 × 106dose with rAE mgmt.

clinical trial information: NCT02614066

ENGOT-OV43/KEYLYNK-001. a phase III, randomized, double-blind, active- and placebo-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA-nonmutated advanced epithelial ovarian cancer [EOC]. [abstract TPS5603]

ignace vergote. MD. PhD

background. there is a significant unmet need to develop new regimens for BRCA1/2-nonmutated advanced ovarian cancer [OC]. The PARP inhibitor olaparib is approved for women with platinum-sensitive, recurrent OC regardless of BRCA1/2status and, more recently, for newly diagnosed women with BRCA-mutated OC. in the TOPACIO/KEYNOTE-162 study, the combination of the PD-1–blocking antibody pembrolizumab [pembro] and niraparib demonstrated efficacy in platinum-resistant relapsed OC irrespective of BRCA1/2 status.

methods. patients with stage III or IV BRCA-non-mutated EOC, primary peritoneal cancer, or fallopian tube cancer will be stratified by surgery status [no residual tumour after primary debulking surgery [PDS], residual tumour after PDS, or planned interval debulking], bevacizumab use, and PD-L1 status. after one lead-in cycle of chemotherapy [CT], patients will be randomized 1:1:1 to receive: CT + pembro followed by olaparib maintenance; CT + pembro followed by placebo; or CT + placebo followed by placebo. the CT regimen will be administered for five [5] cycles, and pembro [200 mg Q3W] will be administered for 35 infusions. olaparib [300 mg BID] maintenance therapy will start after the end of CT as concomitant treatment with pembro until discontinuation or for 2 years if the patient has a complete response. bevacizumab use is permitted at investigator's discretion and determined pre-randomization.

primary endpoints are investigator-assessed progression-free survival [PFS] per RECIST 1.1 criteria and overall survival. key secondary endpoints are PFS per RECIST 1.1 assessed by blinded independent central review, PFS after next-line treatment, and safety.

enrolment is currently ongoing.

clinical trial information: NCT03740165

phase Ib study of MIW815 (ADU-S100) in combination with spartalizumab [PDR001] in patients with advanced | metastatic solid tumours or lymphomas. [abstract 2507]

funda meric-bernstam

background. MIW815 [ADU-S100] is a novel synthetic cyclic dinucleotide that activates the STimulator of INterferon Genes [STING] pathway impacting tumour cells, tumour microenvironment, vasculature, tumour-associated fibroblasts, and priming antigen presenting cells [APC] and CD8+ t cells. spartalizumab is a humanized IgG4 mAb that blocks the binding of PD-1 to PD-L1/2. preclinical data support synergistic antitumour effects when MIW815 [ADU-S100] is combined with checkpoint inhibitors.

methods. in this phase Ib dose escalation study, patients with advanced | metastatic solid tumours or lymphoma received MIW815 [ADU-S100] [intratumoural injections [50–800 µg] either weekly [3 weeks on | 1 week off] or Q4W] and spartalizumab [400 mg IV Q4W]. injected and non-injected tumour biopsies were obtained at baseline and on treatment.
primary objectives are to determine safety and identify a dose | schedule for future studies. preliminary activity, pharmacokinetics [PK], and pharmacodynamics [PD] are also being explored.

results. as of jan 11. 2019, 66 patients [median age: 61yrs] with various solid tumours or lymphomas have been treated. treatment was discontinued in 49 patients [74%] due to disease progression [n = 28], pt/physician decision [n = 18], AE [n = 2], or death [n = 1]. no DLTs were reported during the first cycle at any dose level. most common [≥5 patients] treatment-related AEs [TRAEs] were injection site pain [12%], pyrexia [11%], and diarrhea [9%]. grade 3 | 4 TRAEs [in ≥2 patients] were increased aspartate aminotransferase [AST] and alanine aminotransferase [ALT] [3% each]. serious TRAEs were pyrexia [3%], increased amylase, increased lipase, diarrhea, fatigue, hyperthyroidism, partial seizures, dyspnea, and pneumonitis [all 2%]. partial responses in patients with PD-1–naive TNBC and PD-1–relapsed | refractory melanoma have been observed. MIW815 [ADU-S100] plasma exposure generally increased in a dose-dependent manner with a rapid terminal half-life. response data, PK and PD analyses will be presented.

conclusions. MIW815 (ADU-S100) + spartalizumab has demonstrated antitumour activity in PD-1 naïve triple negative breast cancer [TNBC] and PD-1–relapsed | refractory melanoma. the combination is well tolerated, with no DLTs reported to date.
the MTD has not been reached and dose escalation is ongoing.

clinical trial information: NCT03172936

a randomized double-blind placebo-controlled phase II trial comparing gemcitabine monotherapy to gemcitabine in combination with adavosertib in women with recurrent, platinum resistant epithelial ovarian cancer. a trial of the princess margaret, california, chicago and mayo phase II consortia. [abstract 5518]

stephanie l'heureux. MD. PhD.

background. platinum resistant ovarian cancer [OC] remains a therapeutic challenge. high grade serous OC [HGSOC] harbours TP53 mutations leading to increased dependency on S- and G2-phase checkpoints. wee1 inhibition with adavosertib [AZD1775] induces G2 checkpoint escape. gemcitabine is an antimetabolite therapy and blocks the progression of cells through the G1 | S phase. hypothesized that combining gemcitabine + adavosertib would be synergistic and overcome resistance.

methods. a multicentre double-blind 2:1 randomized phase II trial was conducted to assess the progression free survival [PFS] in women with recurrent platinum-resistant | refractory HGSOC receiving gemcitabine + adavosertib or gemcitabine+placebo [PBO]. eligibility required measurable disease and feasibility of paired tumour biopsies; no limitation in prior lines of therapy. non HGSOC histologic subtypes were enrolled in a separate non-randomized exploratory cohort. adavosertib | placebo was given orally [175mg QD on D1-2, D8-9 and D15-16] with gemcitabine [1000mg/m² IV D1, D8 and D15] in a 28-day cycle until progression or unacceptable AE. tumour staging was scheduled every eight [8] weeks. TP53 mutations were analyzed on archival tissue with sanger sequencing, TAm-Seq and immunohistochemistry [IHC]. TP53 mutation will be also assessed in circulating tumour DNA [ctDNA]. whole exome and RNA sequencing were performed on paired tumour tissues.

results. 124 patients with median of [3] prior lines of therapy [range 1-10] from 12 centres across canada and US were enrolled between sept14 to may18, with 99 patients randomized [65 in arm G+A and 34 in G+P]. five [5] patients were ineligible; 64 patients died. median follow-up was 14.3 months. main related AE was hematologic toxicity [Anemia G≥3: 31% in G+A vs 18% in G+P; thrombocytopenia G≥3: 31% vs 6%; Neutropenia G≥3: 62% vs 30%].
PFS was significantly improved from 3.0 to 4.6 months. significant improvement in overall survival [OS] from 7.2 to 11.5 months. partial response by RECIST 1.1 was observed in 13 [21%] and 1 [3%] patients for arms G+A and G+P, respectively. from the 25 patients in the exploratory cohort, 3 [12%] partial responses were observed.

conclusion. addition of adavosertib to gemcitabine in women with platinum resistant | refractory OC improved response rate, PFS and OS with manageable toxicity.

clinical trial information: NCT02151292

genome-wide cell-free DNA [cfDNA] methylation signatures and effect on tissue of origin [TOO] performance. [abstract 3049]

minetta c. liu. MD

background. for multi-cancer detection using cfDNA, TOO determination is critical to enable safe and efficient diagnostic follow-up. previous array based studies captured < 2% of genomic CpGs. genome wide fragment level methylation patterns across 811 cancer cell methylomes representing 21 tumour types [97% of SEER cancer incidence], and define effects of this methylation database on TOO prediction within a machine learning framework was reported.

methods. genomic DNA from 655 formalin-fixed paraffin-embedded [FFPE] tumour tissues and 156 isolated cells from tumours was subjected to a prototype 30x whole genome bisulfite sequencing [WGBS] assay, as previously reported in the circulating cell free genome atlas [CCGA] study. two independent TOO models, one with and one without the methylation database, were fitted on training samples; each was used to predict on the test set. a WGBS classifier was used to detect cancer at 98% specificity; reported TOO results reflect percent agreement between predicted and true TOO among those detected cancers [166 cases: 81 stage I-III, 69 stage IV, 16 non-informative].

results. genome wide methylation data generated from this database allowed analysis and coverage of ~30 million CpGs across the genome [~60-fold greater than array-based approaches]. incorrect TOO assignments decreased by 35% [20% to 13%] after incorporating methylation database information into TOO classification. improvement was observed across all cancer types and was consistent in early-stage cancers [stage I-III]. respective performances in breast cancer [n = 23] were 87% vs 96%; in lung cancer [n = 32] were 85% vs 88%; in hepatobiliary [n = 10] were 70% vs 90%; and in pancreatic cancer [n = 17], were 94% vs 100%. results using an optimized approach informed by these results in a large cohort of CCGA participants will be reported.

conclusions. initial results from the ongoing second sub-study of CCGA showed targeted methylation simultaneously detected multiple cancer types, at early stages, at a specificity (99%) appropriate for population screening. Detection of multiple cancers was achieved with a single, fixed, low false positive rate. This approach also accurately localized the TOO, which could streamline subsequent diagnostic work-up. incorporating data from a large methylation database improved TOO performance in multiple cancer types. this supports feasibility of this methylation-based approach as an early cancer detection test across cancer types.

clinical trial information: NCT02889978

to view the poster

what this actually means- a single blood test is able to detect multiple cancer types at early stages with a low false positive rate. the test also identified where the cancer originated in the body in 90% of cases. the test was granted breakthrough device designation by the FDA in may2019, which uses a proprietary database and machine-learning algorithms.

an initial analysis of 2,301 patients that showed an overall detection rate of 55% for more than 20 cancer types across all stages. the detection rate for 12 of the most lethal cancer types was 76%. broken down by cancer type for stages I through III, detection rates were 59% for lung cancer, 74% for colorectal cancer, 64% for hormone receptor negative breast cancer, 70% for lymphoma, 78% for pancreatic, 86% for head and neck, 71% for multiple myeloma, 67% for ovarian, 76% for esophageal, 68% for liver, 79% for anorectal and 78% for gastric.

detection at early stages in the 12 deadliest cancer types was 34% at stage I, 77% at stage II and 84% at stage III.

what does this mean for cancer- if the deadliest cancers can be caught at earlier stages this means that patients are more likely to survive, they are less likely to undergo expensive and long treatment regimens, they are more likely to return to normal, including work and life and they are less likely to require increased healthcare costs from depression, side effects, metastatic disease, etc.

the circulating cell free genome atlas [CCGA] study. follow-up [F | U] on non cancer participants with cancer like cell-free DNA signals. [abstract 5574]

background. a noninvasive cell-free DNA [cfDNA] based cancer detection assay offers the hope of a blood test that might reduce morbidity and mortality of cancers, particularly those without recommended screening tests [eg. some gynecologic cancers]. CCGA is a prospective, multi-center, longitudinal, case-control study evaluating models for discriminating cancer versus non-cancer. control participants who demonstrated a cancer-signal in CCGA are reported in this follow up.

methods. clinically evaluable samples [N = 2508] from patients enrolled without a cancer diagnosis [dx; NC] and treatment naive patients with newly diagnosed cancer [C] were divided into training [n = 1564; 580 NC, 984 C] and test [n = 944; 368 NC, 576 C] sets. classification performance [cancer | non-cancer] was assessed via three [3] prototype assays: whole genome bisulfite [WGBS], whole-genome [WGS], and targeted [507 gene] sequencing. notable outlier NC patients were identified with cancer like scores in either ≥2 assay classification results or by the presence of known cancer drivers with ≥1 assay classification result suggesting cancer. all patients are currently in F/U in accordance with study protocol [to date: 80% with > 10 mo and 15% with > 22 mo F/U].

results. among training and test sets, 8 [< 1%] NC patients were identified with a cancer like signal. to date, two [2] have been diagnosed with a gynecologic malignancy: one [1] stage IIIc clear cell endometrial carcinoma and one [1] stage IIIc ovarian cancer, three [3] and two [2] months post enrolment [PE], respectively. among cancer patients in the study, sensitivity [at 98% specificity; WGBS] in these cancer types was: uterine | endometrial: 11% [n = 27 train] and 22% [n = 9 test]; ovarian: 82% [n = 17] and 71% [n = 7]. in addition, a third non cancer patient was diagnosed with a stage IV lung cancer 15mo PE.

conclusions. this cfDNA based assay detected a cancer like signal that anticipated a clinical presentation of cancer in undiagnosed patients as early as 15mo prior to the actual diagnosis. high specificity [> 99%] requires accounting for undiagnosed cancers in study design and analysis. together, these data suggest that this prototype assay may have high performance detecting a variety of gynecological and other cancers.

clinical trial information: NCT02889978

sessions.

translating IDEA to practice and beyond. managing stage II and III colon cancer.

jeffrey a. meyerhardt. MD. MPH. FASCO

adjuvant fluoropyrimidine based chemotherapy has been the standard of care for resected stage III colon cancer since the 1990s; the evolution from 12 to 6 months of fluoropyrimidine therapy and the addition of oxaliplatin to fluoropyrimidine therapy have led to the current accepted standard of care recommending adjuvant therapy to all patients with stage III disease. because there were no other drugs at the time, an evolution in how to give FU occurred. eventually came the introduction of chemotherapies and a host of studies that lead to the conclusion that adding oxaliplatin to fluoropyrimidine had a benefit for patients, particularly with stage III disease. however, controversies remain.

the MOSAIC trial had patients who received either fluoropyrimidine alone using an infusional regimen, to adding oxaliplatin with the primary endpoint being three year disease free survival both for stage II and stage III patients. five year disease free survival was statistically significant, and a clear benefit in disease free survival and overall survival particulary for stage III patients was seen. the addition of oxaliplatin created several additional side effects, particularly the neurotoxicity side effects.

and so this led to questions regarding the benefit of adjuvant chemotherapy in stage II disease, and in whom; the optimal duration of adjuvant chemotherapy; how should patients with early stage colon cancer be followed after surgery and adjuvant treatment?

this led to an international effort and collaboration looking at these basic questions including the international duration evaluation of adjuvant therapy [IDEA] collaboration, which is the largest, prospective study in colon cancer with 12,834 patients.

this review discusses current and future risk stratification strategies in stage II disease: the optimal duration of adjuvant oxaliplatin-containing chemotherapy in stage II and III disease according to the IDEA study, and the recent evidence and updated recommendations for surveillance of early stage colon cancer after resection.

- in the absence of convincing direct evidence, the identification of high risk stage II subgroups permits a justification for adjuvant chemotherapy in node-negative disease. current stratification relies largely on clinicopathologic criteria, but the role of biomarkers and ctDNA is the subject of active investigation.

- the concept of thinking of patients in terms of their risk, and this is a clinical risk, looking at both their T stage and their N stage of disease- the IDEA subgroup analysis by T and N stages in stage III disease demonstrated noninferiority for three [3] months versus six [6] months of adjuvant oxaliplatin containing therapy in low risk [T1–3, N1] colon cancer but not in high risk [T4 and/or N2] disease.

- three [3] recent pragmatic randomized trials and a large retrospective study suggest that the frequency of carcinoembryonic antigen testing and CT imaging recommended by the ASCO national comprehensive cancer network surveillance guidelines may be too intensive. future recommendations could include tailored surveillance strategies based on individualized assessment of recurrence risk.

an estimated 145,600 new cases of colorectal cancer will be diagnosed in 2019. resection remains the only curative modality. for patients with resected node positive or stage III colon cancer, the benefits of adjuvant chemotherapy are well established, using a combination of a fluoropyrimidine and oxaliplatin [or, more commonly, infusional fluorouracil, leucovorin, oxaliplatin [FOLFOX] or capecitabine + oxaliplatin [CAPOX], which was established as the standard of care in 2004.

the ASCO recommendations that same year for adjuvant chemotherapy for stage II colon cancer concluded that there was no direct evidence to support the routine use of adjuvant chemotherapy for patients with stage II colon cancer, but indirect evidence of benefit could be considered for patients with high-risk stage II disease. since, multiple subsequent trials have failed to improve upon the adjuvant benefit observed with FOLFOX or CAPOX. there have been notable advances to inform the optimal strategy for treatment of patients with resected stage II and III colon cancer.

the IDEA collaboration, the largest prospective effort in colon cancer, conducted and demonstrated the feasibility of publicly funded international research. although the hope and assumption were that there would be a simple answer regarding noninferiority, the IDEA results taught us that one size may not fit all in terms of decision making for adjuvant therapy in colon cancer. in addition, this work taught the importance of international collaboration to ask and answer questions that require larger sample sizes than would be feasible in a single network or country. in the future, more results will emerge from IDEA as the data mature and biospecimen analyses are conducted from several of the trials, which will ultimately result in modelling by phenotype and molecular markers to individualize the duration of adjuvant therapy for each patient with colon cancer.

decision-making for stage II colon cancer: to treat or not to treat?

sharlene gill. MD. MPH. MBA

what is the current landscape for the management of early stage colon cancer and the risk stratification in stage II disease, the management of stage II and stage III disease in the era of IDEA, evidence and lack thereof to support chemotherapy. clinicians are still debating the role of chemotherapy in stage II disease because the uncertainty, both around the magnitude of benefit and which patients are most likely to benefit.

a pooled analysis that included 3,300-plus patients of which 44% were node-negative, individual patient data analysis was drawn from seven randomized trials. and overall, in the stage II and III patients, a 30% proportional reduction in risk of recurrence, and a 26% proportional reduction in risk of death was observed. and this benefit was maintained across all exam subgroups [gender, T staged tumour location, and nodal status]. there was evidence of a differential treatment benefit for adjuvant 5-FU-based chemotherapy. it was suspected that the influence of a higher preponderance of deficient mismatch repair disease in stage II colon cancer may have somewhat driven this reduced benefit.

five years later in one of the earlier adjuvant meta-analyses almost 21,000 patients, of which 34% were node-negative, were included in this analysis across 18 adjuvant 5-FU-based trials. in this meta-analysis, there was this statistically-significant benefit observed with adjuvant 5-FU chemotherapy. in absolute terms it was a 5% improvement, an eight-year overall survival.

in this landscape, the trial that is most commonly cited is the UK QUASAR trial. QUASAR had a very pragmatic trial eligibility criteria, and patients following resection of a colorectal cancer who were deemed to have an uncertain indication for chemotherapy were randomized in a 1:1 fashion to either observation alone or a 5-FU-based chemotherapy. QUASAR demonstrated a statistically significant survival benefit in this study that translated into a five year survival difference of 3.6%. [this was not a purely stage II colon cancer study, although 90% of the patients were stage II and 70% were primary colon].

based on this data there may be a modest, disease free survival and potentially an overall survival benefit with 5-FU in stage II disease, but the magnitude of benefit is likely 3-5%. what about the addition of oxaliplatin to 5-FU, which is the current standard in stage III disease?

MOSAIC trial included stage II patients, 40% of the patients had stage II disease. stage stratified outcomes observed, the disease free survival benefit seen [five year analysis for stage III patients] was an absolute improvement of 7.5%, which was statistically significant. for patients with stage II disease, the absolute benefit was quite modest and it was not statistically significant although this was a smaller cohort. in the subsequent six year overall survival analysis from MOSAIC, the overall survival benefit in stage III disease was about 4%. and virtually no difference with the addition of oxaliplatin to 5-FU was observed in the overall survival for patients with stage II disease.

MOSAIC did include an exploratory analysis zeroing in on patients with stage II disease who had at least one high-risk feature, and these features were defined as one of either T4 tumour perforation, bowel obstruction, poor differentiation, vascular invasion, or inadequate nodal sampling. and almost 600 patients in this subgroup analysis. look at the three-year disease-free survival in this group, that 7% approximates the magnitude of benefit that was seen in stage III disease. In the longer-term disease-free survival and overall survival data in this high-risk stage II population, the five-year DFS was maintained at about 7% to 8%, but the benefit in overall survival at six years was still very modest at 1.7% and not statistically significant.

ASCO's last updated guidelines in 2004 in stage II disease setting did not recommend the routine use of adjuvant chemotherapy for stage II disease. the ESMO guidelines from 2012 also did not recommend adjuvant therapy in stage II disease- both have it listed as consideration for patients with high risk disease.

and so the question is how is high risk stage II colon cancer risk defined. in considering the AJCC subgroup criteria for staging - patients with T4 disease [especially T4b disease] outcomes are inferior, especially in comparison to outcomes seen in patients with stage III disease. and so recognizing T4 is a very impactful clinical pathologic prognostic influencer.

there is a fair degree of uniformity between what ASCO, ESMO and NCCN have identified as high risk, these typically include poor differentiation, with the exception of those patients who have deficient mismatch repair disease; presence of obstruction; inadequate nodal sampling; lymphovascular invasion; perineural invasion, and positive margins. all of ehich could potentially influence a decision to consider adjuvant chemotherapy. and often patients with MSI-H | dMMR there is a presence of a BRAF mutation. deficient mismatch repair is estimated to be seen in approximately 15- 20% of

stage II colon cancer, and a preponderance of it in patients with primary tumours present on the right side.

several studies have demonstrated the favourable prognostic impact of deficient mismatch repair, patients with deficient mismatch repair have considerably more favourable outcomes in terms of recurrence free survival and overall survival that translates into an almost 60- 70% proportional reduction in the risk of one of these outcomes. while patients with proficient mismatch repair stage II disease have an associated improvement in recurrence, that improvement was not seen in patients with deficient mismatch repair disease, suggesting that 5-FU mono-therapy is a consideration of adjuvant chemotherapy in dMMR stage II cancer is unlikely to be of benefit.

patients with resected stage II colon cancer, the two most important prognostic influences are going to be T stage and mismatch repair status. for patients who are T3 and deficient mismatch repair, observation alone is a reasonable consideration, and those patients should not be offered adjuvant chemotherapy. for patients with T4 disease or proficient mismatch repair and the presence of a high-risk factor, chemotherapy could be a consideration, but many patients fall into low risk and so questions around how to better stratify these patients emerge.

there is interest in the use of genomic classifiers and this could be helpful to guide adjuvant therapy for these patients. but it's unclear what the predictive value of these are in terms of guiding adjuvant therapy benefit. as a consequence, there is no current guideline recommendation for routine use in order to guide adjuvant therapy in stage II disease. looking forward, an area of great interest is the use of circulating tumour DNA to evaluate for minimal residual disease in patients and inform adjuvant therapy decision making.

the potential prognostic impact of ctDNA was demonstrated in a prospective correlate of biomarker study where 230 patients with stage II colon cancer were prospectively followed with ctDNA blood collection drawn post operatively, and then every three months for two years. patients with stage II disease who did not receive chemotherapy, positive ctDNA was observed in about 8% of patients. patients who had positive post operative ctDNA had a significantly inferior recurrence free survival. patients with no chemotherapy in this cohort, the impact ctDNA was much more significant - 90% three year relapse free survival in patients with ctDNA negative disease, but almost all patients with ctDNA positive findings recurred.

the question then is that can ctDNA guide adjuvant therapy in resected stage II colon cancer? and secondarily, can adjuvant chemotherapy convert to ctDNA-positive to ctDNA-negative? [COBRA trial]

finally, the routine use of adjuvant chemotherapy in stage II colon cancer is not recommended. a rational decision-making approach based on an individualized assessment of the patient's estimated prognosis as determined by evaluation of mismatch repair status and recognized clinical pathologic high-risk features is needed. bear in mind associated treatment risks and toxicities, as well as patient factors, particularly patient preference in terms of what magnitude of benefit is clinically meaningful for the patient, and what risk would they be willing to accept for that. for patients with pT3N0 disease and no high risk features, currently observation is an accepted standard, and, even much more so in patients who have deficient mismatch repair. the utility of liquid biopsies to guide adjuvant therapy will be addressed in the COBRA study, and will hopefully further inform the landscape in stage II colon cancer.

sunday june 2.2019
abstracts

affordable care act [ACA] medicaid expansion impact on racial disparities in time to cancer treatment. [abstract LBA1]

blythe j.s. adamson | flatiron health

background. racial disparities in cancer outcomes remain a societal challenge. the ACA sought to improve equity in healthcare access and outcomes by permitting states to expand medicaid and provide subsidies for purchase of private insurance. the impact of medicaid expansions on racial disparities in time to treatment among patients with advanced cancer was assessed.

methods. selected patients aged 18-64yrs with advanced or metastatic cancer [NSCLC, breast, urothelial, gastric, colorectal, renal cell, prostate, and melanoma] diagnosed between january 1.2011 and december 31.2018 from the nationwide flatiron health electronic health record derived database.

medicaid expansion-related changes in the rate of "timely treatment," an outcome defined as first-line treatment start within 30 days of advanced or metastatic diagnosis was estimated. regression model covariates included race [white, african american, asian, and other], age, sex, practice type, cancer type, stage, and unemployment rate, using time and state fixed-effects.

results. the study included 34,067 patients [median age 57 years; 12% african american]. racial disparities were observed pre-expansion: african american patients were 4.9% less likely to receive timely treatment [see table]. regardless of race, medicaid expansion trended toward an increase in timely treatment overall. expansion was associated with a differential benefit for african american vs white patients [6.9% and 1.8 %].

prior racial disparities were no longer observed after medicaid expansion.

conclusions. implementation of medicaid expansions as part of the ACA differentially improved african american cancer patients receipt of timely treatment, reducing racial disparities in access to care.

APACT. phase III, multicenter, international, open label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine vs gemcitabine for surgically resected pancreatic adenocarcinoma. [abstract 4000]

margaret a. tempero. MD, FASCO

background. in metastatic pancreatic cancer [PC], nab-paclitaxel + gemcitabine demonstrated significantly longer overall survival [OS] vs gemcitabine. APACT assessed efficacy and safety of nab-paclitaxel + gemcitabine vs gemcitabine in surgically resected pancreatic cancer [PC].

methods. treatment naive patients with histologically confirmed PC were eligible. treatment was initiated ≤ 12 weeks post surgery. patients received nab-paclitaxel [125 mg/m2] + gemcitabine [1000 mg/m2] or gemcitabine [1000 mg/m2] on days 1, 8, 15 of six 28-day cycles.
primary endpoint was disease free survival [DFS]. secondary endpoints were overall survival [OS] and safety.

results. 866 patients were randomized. median age was 64yrs [range, 34 - 86]. 69% of patients completed six [6] treatment cycles [nab-P/G, 66%; G, 71%]. median follow up for OS was 38.5 mo. median independant reviewer [IR]-assessed DFS [439 events] was 19.4 mo [nab-P/G] vs 18.8 mo [G]. investigator-assessed DFS (571 events) was 16.6 mo [nab-P/G] vs 13.7 mo [G]. interim OS (427 events) was 40.5 mo [nab-P/G] vs 36.2 mo [G].

grade ≥ 3 treatment emergent adverse events [TEAEs] were reported in 86% vs 68% of patients with nab-P/G vs G. the most common grade ≥ 3 hematologic & nonhematologic TEAEs with nab-P/G vs G were neutropenia (49% vs 43%) & fatigue [10% vs 3%]. TEAEs led to death in two [2] patients in each arm.

conclusions. IR DFS with nab-paclitaxel + gemcitabine was not significantly longer vs gemcitabine; median DFS with gemcitabine was longer than historical data. DFS by investigator [sensitivity analysis] and interim OS were improved with nab-P/G vs G. adjuvant nab-P/G may be an option for patients who are ineligible for FOLFIRINOX. additional OS follow-up may better support nab-P/G as an option in the adjuvant setting.

clinical trial information: NCT01964430

ANNOUNCE. a randomized, placebo controlled, double-blind, phase III trial of doxorubicin + olaratumab versus dox + placebo [PBO] in patients with advanced soft tissue sarcomas [STS]. [abstract LBA3]

william d. tap. MD

background. doxorubicin [dox] is standard therapy in soft tissue sarcoma [STS]. in a phase II trial, olaratumab [a human IgG1 antibody targeting PDGFRα] + dox improved overall survival [OS] and progression free survival [PFS] vs dox. ANNOUNCE aimed to confirm the OS benefit in advanced STS.

methods. adult patients with unresectable locally advanced or metastatic STS [anthracycline-naïve] were eligible. patients were randomized 1:1 to olaratumab or PBO on days 1 and 8 of each 21-day cycle combined with dox on day 1 for up to eight [8] cycles. after eigth [8] cycles, patients with disease control continued olaratumab or PBO until progression or toxicity.
primary endpoints were OS in the intent-to-treat [ITT] population and | or leiomyosarcoma [LMS] subset of the ITT population; the study was designed to be positive if either primary endpoint was met. secondary endpoints included PFS, response | disease control rates, safety, and pharmacokinetics. dexrazoxane use was allowed to mitigate dox-related cardiotoxicity.

results. 509 patients were randomized- 258 in the investigational and 251 in the control arm. baseline patient characteristics were well balanced. dexrazoxane was received by 63.0% vs 65.1% of patients [investigational vs control arm]. in the ITT population, median OS was 20.4 vs 19.8 months and was 21.6 vs 21.9m in LMS patients. median PFS was lower in the investigational arm in the ITT population [5.4 vs 6.8 m] and in LMS pts [4.3 vs 6.9m]. median dox exposure was six [6] vs seven [7] cycles. safety was similar between arms. olaratumab serum concentrations reached levels expected from prior trials. additional subgroup | biomarker results will be presented.

conclusions. ANNOUNCE did not confirm that olaratumab + dox, followed by olaratumab monotherapy, improves OS over dox in patients with advanced STS. further analyses are warranted to explore the inconsistent outcomes between the phase III and phase II studies.

clinical trial information: NCT02451943

olaparib as maintenance treatment following first-line platinum based chemotherapy [PBC] in patients with a germline BRCA mutation and metastatic pancreatic cancer [mPC]. phase III POLO trial. [abstract LBA4]

hedy l. kindler. MD. FASCO

background. pancreatic cancer [PC] patients with a germline BRCA1 and | or BRCA2 mutation [gBRCAm] have shown response to the PARP inhibitor [PARPi] olaparib [kaufman 2015]. POLO is the first phase III trial to evaluate efficacy of maintenance treatment with a PARPi in PC.

methods. POLO is an international, randomized, double-blind, placebo controlled trial of patients with a gBRCAm and pancreatic adenocarcinoma [PC] who had received ≥16 weeks of first-line platinum based chemotherapy for metastatic disease without progression. patients were randomized 3:2 to maintenance olaparib [O] tablets or placebo [PBO]. treatment began 4–8 weeks after last PBC dose, continuing until investigator-assessed progression or unacceptable toxicity.
the primary endpoint was progression-free survival [PFS] by blinded independent central review [modified RECIST 1.1].

results. 3315 patients were screened, 247 were identified with a gBRCAm, randomized 154 [O 92, PBO 62], and treated 151 [O 90, PBO 61]. patient characteristics [O | PBO] median age 57years [37–84] | 57years [36–75]; male, 58% | 50%. PFS was significantly improved with olaparib vs. placebo [median PFS was 7.4 vs. 3.8 months] and consistent irrespective of response to prior PBC. from 6mo, the percentage of patients progression free in the O arm was more than twice that in the PBO arm .
grade ≥3 adverse events [AE] occurred in 40% of olaparib- and 23% of plaebo-treated patients; 5.5% and 1.7% of patients, respectively, discontinued treatment due to an AE.

conclusions. maintenance olaparib provided a statistically significant and clinically meaningful improvement in PFS in mPC patients with a gBRCAm who had not progressed on PBC. safety was consistent with the known profile for olaparib.

POLO is the first phase III trial to validate a biomarker-driven treatment in PC.

clinical trial information: NCT02184195

pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction [G/GEJ] adenocarcinoma. the phase III KEYNOTE-062 study. [abstract LBA4007]

josep tabernero. MD. PhD.

background. KEYNOTE062 was a randomized, active controlled study of first line pembrolizumab or pembrolizumab + chemotherapy vs chemotherapy in patients with PD-L1 combined positive score ≥1 [CPS ≥1], HER2-negative, advanced GC.

methods. eligible patients were randomized 1:1:1 to pembrolizumab, pembrolizumab + chemotherapy or placebo Q3W + chemotherapy.
primary endpoints were overall survival [OS] in CPS ≥1 and CPS ≥10 for pembrolizumab + chemotherapy vs chemotherapy and pembrolizumab vs chemotherapy and PFS [RECIST v1.1; central review] in CPS ≥1 for pembrolizumab + chemotherapy vs chemotherapy. overall response rate [ORR] [RECIST v1.1; central review] in CPS ≥1 for pembrolizumab + chemotherapy vs chemotherapy was the secondary endpoint. final analysis cutoff date was march 26. 2019.

results. 763 patients [281 with CPS ≥10] were randomized to pembrolizumab + chemotherapy [257], pembrolizumab [256], or chemotherapy [250]. median follow-up was 11.3mo. pembrolizumab was non inferior to chemotherapy for OS in CPS ≥1 per prespecified margins. pembrolizumab vs chemotherapy prolonged OS in CPS ≥10 [median 17.4 vs 10.8 mo] but wasn't tested per analysis plan. pembrolizumab + chemotherapy vs chemotherapy was not superior for OS in CPS ≥1 or CPS ≥10, with a favourable trend for pembrolizumab + chemotherapy. pembrolizumab + chemotherapy did not significantly prolong PFS in CPS ≥1. ORR was higher for pembrolizumab + chemotherapy vs chemotherapy.
grade 3-5 drug-related AE rates were 17% [pembrolizumab], 73% [pembrolizumab + chemotherapy], and 69% [chemotherapy].

conclusions. as first line therapy for advanced GC, pembrolizumab was non inferior to chemotherapy for OS in CPS ≥1 with clinically meaningful improvement for OS in CPS ≥10. pembrolizumab + chemotherapy did not show superior OS and PFS in CPS ≥1 and OS in CPS ≥10. the safety profile was more favourable for pembrolizumab vs chemotherapy.

clinical trial information: NCT02494583

overall survival [OS] results of a phase III randomized trial of standard of care therapy with or without enzalutamide for metastatic hormone sensitive prostate cancer [mHSPC]. ENZAMET [ANZUP 1304], an ANZUP led international cooperative group trial. [abstract LBA2]

christopher sweeney. MBBS

background. patients with high burden of disease have shorter survival. until 2014 testosterone suppression [TS] was the backbone of treatment for mHSPC. OS is improved by the addition of early docetaxel [DOC] or abiraterone to testosterone suppression. ENZAMET assessed the effects of enzalutamide [ENZA], an androgen receptor [AR] inhibitor, versus a nonsteroidal anti androgen [NSAA: bicalutamide, nilutamide, or flutamide] in addition to standard of care [SOC] [TS with or without DOC] in mHSPC.

methods. men with mHSPC were randomly assigned 1:1 to receive TS plus either ENZA or NSAA. the primary endpoint was overall survival. accrual of 1100 men provided 80% power to detect a 25% reduction in the hazard of death with up to four [4] interim analyses [IA], the first planned to occur after 235 deaths.

results. 1125 patients were randomly assigned from march 31. 2014 to mach 24.2017. the treatment groups were well balanced for all important baseline factors. criteria for early reporting were met at the first IA [February 28. 2019] after a median follow up of 33mo. overall survival was prolonged by enzalutamide. at 3 years, 36% NSAA vs 64% enzalutamide were still on their assigned study treatment.

serious adverse events [regardless of attribution] within 30 days of study treatment occurred in 42% enzalutamide vs 34% NSAA, commensurate with the different durations of study treatment.

conclusions. early enzalutamide significantly improved time to progression and OS when added to SOC in mHSPC. enzalutamide added to testerone suppression represents an appropriate option for men with metastatic prostate cancer commencing TS. there is a clear benefit for patients with low and hogh volume metastatic disease [delays progression and improvement in OS. more expected toxicity was seen with enzalutamide alone. more DOC related toxicity was reported with the addition of enzalutamide]. the benefits appeared lower in those planned to receive early DOC.

clinical trial information: NCT02446405

phase I | IIb trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumours including central nervous system [CNS] tumours. [abstract 10009]

giles w. robinson. MD

background. entrectinib is a CNS penetrant oral inhibitor of TrkA |B|C, ROS1 and ALK tyrosine kinases. the efficacy of entrectinib in children with recurrent/refractory solid or CNS tumours was reported.

methods. Patients ≤ 20yrs with recurrent | refractory solid tumours were eligible. after determination of the recommended dose in all comers, disease specific expansion cohorts of CNS and solid tumours harbouring target aberrations in NTRK1/2/3, ROS1 or ALK, and neuroblastoma [NBL], regardless of mutation spectrum, were enrolled. response, assessed by investigator, was classified as complete response [CR], partial response [PR], stable disease [SD] or progressive disease [PD] using RANO for CNS tumours, RECIST for solid tumours, and curie score for NBL.

results. between may 2016 and october 2018, 29 patients aged 4.9m–20yrs [median 7yrs] were enrolled and 28 were evaluated for response. entrectinib was well tolerated. dose limiting toxicities [DLTs] were elevated creatinine, dysgeusia, fatigue and pulmonary edema. the recommended dose was 550 mg/m2 daily. all responses occurred at doses ≥ 400 mg/m2. in CNS tumours [n = 6], all high grade with gene fusions: one [1] achieved a CR [ETV6-NTRK3]; three [3] achieved a PR [TPR-NTRK1, EEF1G-ROS1, EML1-NTRK2]; one [1] achieved an unconfirmed PR [GOPC-ROS1]; and one [1] has yet to be evaluated [KANK1-NTRK2]. in extracranial solid tumours [n = 8], six [6] had a fusion of whom one [1] achieved a CR [DCTN1-ALK] and five [5] achieved a PR [TFG1-ROS1, EML4-NTRK3, ETV6-NTRK3, KIF5B-ALK, ETV6-NTRK3]. in NBL [n = 15]: one [1] achieved a CR [ALK F1174L]. median duration of therapy was 85days [6–592d] for all patients; 56days [6–338d] for non responders; and 281days [56–592d] for responders. median time to response was 57days [30–58d].

conclusions. entrectinib produced striking, rapid and durable responses in all children with refractory CNS and solid tumours harbouring NTRK1/2/3, ROS1 or ALK fusions [11 out of 11] as well as in an ALK-mutated NBL. no responses were seen in tumours lacking aberrations in target kinases. these results support the continued evaluation of entrectinib as a targeted therapeutic in solid tumours with NTRK1/2/3, ROS1 and ALK fusions, especially in high grade CNS neoplasms. entrectinib has very promising anti tumour activity and PFS in patients with gene fusions, especially malignant CNS tumours [as a result the study will remai open to accrual for patients with target gene fusions]. entrectinib was generally well tolerated, the recommended dose of the clinical trial formulation in children is 550mg | m2 daily.

clinical trial information: NCT02650401

clinical benefit of breakthrough cancer drugs approved by the united states food and drug administration

consolacion molto. MD

background. the breakthrough therapy program was established in july 2012 to expedite drug development and approval by the FDA. the characteristics of clinical trials leading to FDA approval as well as the magnitude of clinical benefit and value framework scores of breakthrough designated and non breakthrough-designated cancer drugs was compared.

methods. the drugs@FDA website for cancer drug approvals from july 2012 and december 2017 was searched. for each indication, the value frameworks and used thresholds of high clinical benefit developed by american society of clinical oncology value framework version 2 [ASCO VF v2; scores ≥45], the ASCO cancer research committee [OS gains ≥2.5 months PFS gains ≥3 months], the european society for medical oncology magnitude of clinical benefit scale version 1.1 [ESMO-MCBS v1.1; grade of A or B for trials of curative intent and 4 or 5 for those of non-curative intent], and the national comprehensive cancer network [NCCN] evidence blocks [scores of 4 and 5] was applied. trial characteristics and value framework scores were compared using chi squared or mann whitney U tests.

results. 106 pivotal trials supporting the approval of 52 individual drugs for 96 indications were identified. of these indications, 38 [40%] received breakthrough designation. compared with trials for non breakthrough drugs [n = 62], trials for breakthrough drugs [n = 44] had smaller sample size [median 373 vs 612], were less often randomized [57% vs 86%] and more likely to be open label [84% vs 53%]. trials for breakthrough drugs were more likely to demonstrate high clinical benefit using ASCO VF [68% vs 31%] and NCCN evidence blocks [86% vs 56%]. a similar proportion of trials supporting breakthrough and non breakthrough drugs demonstrated high clinical benefit using the ASCO cancer research committee [82% vs 68%] and ESMO-MCBS [35% vs 33%] frameworks.

conclusions. in patients with advanced solid tumours, cancer drugs approved under breakthrough therapy designation were more likely to demonstrate high clinical benefit as defined by the ASCO VF and NCCN value frameworks. a similar proportion of approved breakthrough and non breakthrough therapy drugs met the high benefit thresholds using the ASCO cancer research committee and ESMO-MCBS frameworks. 40% of cancer drugs receive breakthrough designation. trials supporting breakthrough therapy drug approvals were more likely to be smaller, to explore experimental biological therapies, to be open label and phase I or II, to use single arm design and to be approved on subgroup analysis. cancer drugs approved under breakthrough designation had higher odds for substantial clinical benefit according to the ASCO VF - NHB v2 and NCCN evidence blocks; lower odds for substantial clinical benefit according to ESCAT; similar odds of meeting the thresholds for substantial benefit using ESMO - MCBS v1.1 and ASCO's CRC; higher median monthly price.

advances in our understanding of the molecular and genetic cancer lesions have led to new challenges to the design of clinical trials, with many drugs approved based on surrogate endpoints that not always reflect benefit to patients. the desire to provide earlier access to highly effective drugs should be linked to rigorous confirmatory studies and robust and transparent criteria for breakthrough designations.

IMpower150. analysis of efficacy in patients with liver metastases. [abstract 9012]

mark a. socinski. MD

background. atezolizumab + bevacizumab + chemo [carboplatin + paclitaxel [CP]; ABCP] showed improved PFS and OS vs bev + CP [BCP] in patients with chemo naive NSCLC [IMpower150]. benefit with ABCP vs BCP extended to key subgroups, including patients with baseline [BL] liver mets, which is a poor prognostic factor in metastatic NSCLC. similar outcomes were not seen with atezo + chemo [IMpower150 [atezo + CP; ACP]; IMpower130; IMpower132], suggesting that the addition of bev to atezo + chemo is important for conferring clinical benefit in these patients. characteristics and responses of patients with BL liver mets in IMpower150 are further explored.

methods. 1202 intent to treat [ITT] patients were randomized 1:1:1 to receive ABCP, ACP or BCP. doses were: a. 1200 mg; b. 15 mg/kg; c.AUC 6 mg/mL/min; P, 200 mg/m2.
co primary endpoints were OS and investigator assessed PFS in ITT wild-type patients. exploratory analyses included efficacy and safety in patients with liver mets.

results. the data capture ≥ 20mo follow-up in ITT patients [data cutoff: jan 22.2018]. 162 patients had BL liver mets [ABCP, n = 52; ACP; n = 53; BCP, n = 57], with a median of three [3] metastatic sites and median BL tumour sum of longest diametre [SLD] of 109 mm [range, 10-249]. BL characteristics in these patients were generally balanced across study arms. PFS and OS were improved with ABCP vs BCP. grade 3 | 4 treatment related AEs occurred in 52.1%, 36.5% and 54.5% of pateints with liver mets in the ABCP, ACP and BCP arms, respectively.

conclusions. in patients with NSCLC presence of liver metastases represents a poor prognositic factor with higher rates of PD due to new lesions vs those without liver metastases, which might be suggestive of more aggressive or dispersed disease in these patients. improved clinical outcomes with ABCP vs BCP were observed in patients with and without liver metastases; higher ORR and durable DOR were also seen with ABCP vs BCP in patients with liver metastases; interaction tests suggested a trend towards improved PFS and OS favouring ABCP in patients with liver metastases, lack of statistical significance is likely due to small sample size; patients with liver metastases. ABCP was well tolerated regardless of baseline liver metastases status; the safety profile of ABCP in patients with liver metastases remained consistent with that observed in the ITT population, there were no new safety signals in this patient subgroup; ABCP is an important new treatment option for patients with advanced nonsquamous NSCLC, particularly those with liver metastases. ABCP reduced the risk of death in patients with liver mets by 48% vs BCP and may represent an important new treatment option for this population.

clinical trial information: NCT02366143

a phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed | refractory multiple myeloma [RRMM]. [abstract 8004]

paul g. richardson. MD

background. the primary objective of this phase III trial was to demonstrate progression free survival [PFS] improvement of isatuximab [isa], a novel anti CD38 monoclonal antibody, combined with pomalidomide [P]/dexamethasone [d] versus pomalidomide/dexamethasone [Pd]. CD38 functions as a receptor and an ecotoenzyme, uniformly expressed on multiple myeloma [MM]. isatuximab, a IgG1 monoclonal antibody targeting CD38 transmembrane glycoprotein in MM with multiple modes of action.

methods. patients with RRMM who received ≥2 prior lines, including lenalidomide [len] and a proteasome inhibitor [PI], refractory to last therapy were enrolled. isaPd arm received isa 10 mg/kg IV weekly for first 4 weeks, then every 2 weeks. both arms received approved schedules of pomalidomide and dexamethasone [4mg PO days 1-21; 40mg [20mg if >75 yrs] PO or IV weekly] every 28 days until progression or unacceptable toxicity.

results. 307 patients [154 isaPd, 153 P]) were randomized and analyzed [ITT]. patient characteristics were well balanced across arms. median age: 67yrs(36-86); median prior lines of therapy: 3 (2-11); estimated GFR: <60ml/min in 33.9% patients; 92.5% refractory to len, 75.9% to PI; and 19.5% patients had high-risk cytogenetics. at median follow up of 11.6mo. median PFS was 11.5mo isaPd vs 6.5mo Pd; (95% CI 0.44-0.81). PFS benefit was consistent across all major subgroups. ORR [≥PR] was 60.4% isaPd vs 35.3% Pd. very good partial response [VGPR] rate or better was 31.8% isaPd vs 8.5% Pd, and MRD negativity [NGS, 10-5] was seen in 5.2% IsaPd patients vs 0% Pd. at analysis date, overall survival [OS] was immature [99 events] but a trend to OS improvement in IsaPd [vs Pd] was observed. median treatment duration was 41weeks isaPd vs 24 weeks Pd; median isa infusion [inf.] duration was 3.3h at 1st inf. and 2.8h at subsequent inf. grade ≥3 AEs were observed in 86.8% isaPd vs 70.5% Pd; 7.2% isaPd and 12.8% Pd patients discontinued due to AEs; 7.9% isaPd and 9.4% Pd patients died due to AEs. inf. reactions were reported in 38.2% [2.6% grade 3 | 4] isaPd. grade ≥3 infections were seen in 42.8% isaPd and 30.2% Pd, grade ≥3 neutropenia in 84.9% [febrile 11.8%] isaPd and 70.1% [febrile 2.0%] Pd.

conclusions. isatuximab is an anti CD38 mAb that targets MM differently through a specific epitope. ICARIA MM is the first randomized phase III study to demonstrate a significant prolonged PFS benefit of an antibody in combination with Pd in RRMM; PFS with isaPd is the longest observed in this patient population; isaPd demonstrated consistent improvement in PFS among subgroups including len refractory patients; consistent clinical benefit observed with isaPd across other efficacy parameters; significant improvement in overall response and depth of response; adding isatuximab to pd increases the reversal of renal impairment; trend in overall survival benefit observed in isa pd arm [median not reached]; significant delay in time to next treatment with isa pd. isaPd had a manageable safety profile and maintained patients QoL. isaPd is a new treatment option for RRMM patients. isaPd significantly improved PFS and ORR vs Pd, with a manageable safety profile. isaPd is an important new treatment option for the management of RRMM.

clinical trial information: NCT02990338

eflapegrastim, a novel and potent long acting GCSF for reducing chemotherapy induced neutropenia. integrated results from two phase III trials in breast cancer patients. [abstract 539]

lee s. schwartzberg. MD. FACP

background. chemotherapy induced neutropenia [CIN] and its associated complications remain a clinical challenge despite considerable improvements in cancer treatment. eflapegrastim [E] is a novel long acting granulocyte colony stimulating factor [GCSF] comprised of recombinant human GCSF covalently linked to human IgG4 Fc fragment via a PEG linker [MW, 72 kDa]. eflapegrastim showed increased potency vs pegfilgrastim [P] in preclinical and phase I and II trials. two identically designed phase III pivotal trials were conducted globally with a fixed dose of 13.2 mg eflapegrastim containing 3.6 mg GCSF to evaluate eflapegrastim vs pegfilgrastim [6 mg] in patients receiving chemotherapy for early stage breast cancer.

methods. each open label trial randomized patients 1:1 to a single subcutaneous dose of eflapegrastim 13.2 mg/0.6 mL or pegfilgrastim 6 mg/0.6 mL on day 2 of each of four 21-day cycles following day 1 adjuvant | neoadjuvant docetaxel 75 mg/m2 + cyclophosphamide 600mg/m2 [TC]. the primary endpoint was to demonstrate eflapegrastim non inferiority [NI] to pegfilgrastim as measured by mean duration of severe neutropenia [DSN] in cycle 1.

results. a total 643 intent to treat [ITT] patients [314 E | 329 P] with median age 60yrs [24–88] were enrolled. cycle 1 mean [SD] DSN was 0.24 [0.581] vs 0.36 [0.789] days for eflapegrastim and pegfilgrastim, confirming NI and suggesting statistical superiority. DSN NI was also shown across cycles 2–4. among subgroups, including elderly [≥65 yrs] and overweight [> 75kg] patients, DSN was reduced for E vs P. in cycle 1, eflapegrastim showed an absolute risk reduction for severe neutropenia of 6.5% vs P (27.1% relative risk reduction, $p < .043$). Neutropenic complications (hospitalization and/or anti-infective use) were 2.9% and 4.0% for eflapegrastim and pegfilgrastim [p = ns]. incidence of FN was low for both eflapegrastim and pegfilgrastim, 1.6% vs 1.8% in Cycle 1 and 3.2% vs 3.0% overall. ANC profiles showed sustained increased levels for eflapegrastim vs pegfilgrastim in the recovery phase across all cycles. safety profiles were similar for eflapegrastim and pegfilgrastim, including primarily for expected hematologic AEs and for bone pain and other musculoskeletal pain.

conclusions. phase III trials enrolling over 600 patients met non inferiority if eflpegrastim for the primary endpoint of DSN in cycle 1 at a lower GCSF doses versus pegfilgrastim. secondary endpoints of DSN in cycles 2-4 were also met. the incidence of FN and neutropenic complications were not statistically different between the treatment arms in any of the four [4] cycles in either trial. most common adverse events were hematologic due to chemotherapy with similar rates of > grade 3 events. adverse events of special interest of any grade were similar between treatment groups. the data suggests the potential for increased potency of eflapegrastim to deliver improved clinical benefit a possibility that warrants further studies. these integrated pivotal trial results confirm a similar safety profile and non-inferiority in reducing neutropenic risk for E at a lower GCSF dose vs P. the data also suggests the potential for increased potency of E to deliver improved clinical benefit, a possibility that warrants further clinical trials.

clinical trial information: NCT02643420, NCT02953340

EV 201. results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer previously treated with platinum and immune checkpoint inhibitors. [abstract LBA4505]

daniel peter petrylak. MD

background. locally advanced or metastatic urothelial cancer [la/mUC] remains a lethal disease with limited treatment options for patients who progress on or after platinum and/or checkpoint inhibitor [CPI]. enfortumab vedotin [EV] is an antibody-drug conjugate targeting nectin-4, which is highly expressed in UC. [FDA granted enfortimab vedotin breakthrough designation based on phase I data]. EV 201 is a pivotal, single arm, two cohort study of EV in locally advanced or metastatic urothelial cancer patients with prior checkpoint inhibitor [CPI] and platinum containing chemotherapy [cohort 1] or a CPI and no prior chemotherapy [cohort 2].
preliminary data from cohort 1 was presented at ASCO.

results. between october 2017 and july 2018, EV 201 enrolled 128 patients in cohort 1 [la/mUC patients previously treated with platinum and a CPI], 125 of whom were treated with EV [70% male; median age 69yrs [range 40-84 y]; 34% upper tract; a median of two [2] prior systemic therapies]. as of january 03. 2019, the confirmed ORR was 42%, with 9% CR. the ORR in CPI non responders was 38%, and 36% in patients with liver metastases [LM]. most common treatment related AEs [TRAEs], as determined by investigators, included fatigue [50%], alopecia [48%], and decreased appetite [41%]. TRAEs of interest include any rash [48% all grade, 11% ≥ G3] and any peripheral neuropathy [50% all grade, 3% ≥ G3]. one death was reported as treatment related by the investigator [interstitial lung disease], but was confounded by a suspected pulmonary infection.
TRAEs led to few discontinuations [12%] peripheral sensory neuropathy was the most common [6%].

conclusions. high unmet need for patients with advanced and metastatic urothelial canrcinoma. enfortumab vedotin is the first novel therapuetic to demonstrate substanial clinical activity in patients who progressed after platinum chemotherapy and a PD-1 | L1 inhibitor

- 44% response rate [CR 12%] and 7.6 months median duration of response
- responses observed across all subgroups and irrespective of response to prior PD-1 | L1 inhibitor or presence of liver metastases
- tolerable with a manageable safety profile
- EV 201 results are highly consistent with the phase I EV 201 trial in the same patient population
- this data supports submission to the FDA for accelerated approval
- if approved, enfortumab vedotin may have the potential to become a new standard of care in patients who have progressed after platinum and PD-1 | L1 inhibitors

preliminary results from this EV pivotal study demonstrated a clinically meaningful ORR, consistent with the phase I trial, in la/mUC patients with prior platinum and CPI, including LM pts, where there is a high unmet need. EV was well tolerated with a manageable safety profile in these patients.

clinical trial information: NCT03219333

activity of larotrectinib in TRK fusion cancer patients with brain metastases or primary central nervous system tumours. [abstract 2006]

alexander e. drilon. MD

background. TRK fusions are oncogenic drivers of a variety of cancers, many of which can involve the central nervous system [CNS]. larotrectinib is an FDA approved selective TRK inhibitor for the treatment of TRK fusion cancer [drilon et al, NEJM 2018] in adults and children. while larotrectinib has been shown to cross the blood–brain barrier [ziegler et al, br j cancer 2018], its clinical activity in a series of TRK fusion cancers with primary or metastatic intracranial disease has not been described.

methods. patients with non primary CNS solid tumours with brain metastases, or primary CNS tumours harbouring a TRK fusion treated with larotrectinib in two [2] clinical trials were identified. larotrectinib was administered until disease progression [PD], withdrawal, or unacceptable toxicity. disease status was investigator assessed [RANO and RECIST]. data cut off- july 30.2018.

results. 14 patients were identified- 5 non primary CNS solid tumours [3 lung cancer, 2 thyroid cancer; fusion type: 2 ETV6-NTRK3, 2 SQSTM1-NTRK3, 1 EPS15-NTRK1; age range 25–79yrs] and 9 primary CNS tumours [3 glioma, 2 glioblastoma, 1 astrocytoma, 3 NOS; fusion type: 3 BCR-NTRK2, 2 KANK-NTRK2, 1 each of AFAP1-NTRK1, AGTPBP1-NTRK2, ETV6-NTRK3,SPECC1L-NTRK2;age range 2–79yrs]. in the 5 patients with non primary CNS tumours, the best objective response to therapy was PR in 3 [60%, 1 pending confirmation], stable disease [SD] in 1 [20%], and not evaluable [NE] in 1 [20%]. duration of response ranged from 9 to 13 mo. in the nine [9] patients with primary CNS tumours, disease control was achieved in all evaluable patients [primary PD not observed; 1 patient required dose increase]. the best objective response to therapy was PR in 1 [11%; pending confirmation, −55% tumour shrinkage, ongoing at 3.7 mo], SD in 7 [78%; tumour shrinkage range −1% to −24% for pts with measurable disease, 5 had SD > 4 mo], and NE in 1 [11%]. duration of treatment ranged from 2.8–9.2+ mo.

conclusions. larotrectinib is active in patients with TRK fusion cancers with intracranial disease. confirmed responses and durable disease control were seen in metastatic disease and primary CNS tumours of various histologies. these results further support expanded testing for TRK fusions across all cancers, including primary CNS tumours.

clinical trial information: NCT02637687 and NCT02576431

activity and safety of cabozantinib in patients with gastrointestinal stromal tumour after failure of imatinib and sunitinib. EORTC phase II trial 1317 CaboGIST. [abstract 11006]

patrick schoffski. MD. MPH

background. gastrointestinal stromal tumour [GIST] is the most common mesenchymal malignancy of the gastrointestinal tract. advanced GIST is treated with tyrosine kinase inhibitors [TKIs]. most patients develop resistance over time. reported in 2013 [van looy CTOS] that cabozantinib, a TKI targeting KIT | MET | AXL | VEGFR, showed activity in GIST xenograft models through inhibition of tumour growth, proliferation and angiogenesis, both in imatinib sensitive and resistant tumours [gebreyohannes mol cancer ther 2016;15:2845-28]. Cohen [cancer res 2015;75:2061-70] found that cabozantinib can overcome compensatory MET signaling in GIST in vitro. EORTC 1317 assessed the safety and activity of cabozantinib in patients who had progressed on imatinib and sunitinib.

methods. in this multi centre, open label, single arm phase II study eligible metastatic GIST patients received 60 mg [freebase weight] cabozantinib p.o./d. primary endpoint was progression free survival [PFS] rate at week 12, assessed by local investigator per RECIST 1.1. if at least 21 of 41 eligible and evaluable patients were progression free at week 12, the activity of cabozantinib was sufficient to warrant further exploration [a'hern one stage design].

results. a total of 50 consenting patients were eligible and started treatment between february 2017 and august 2018, with 16 [32%] still continuing cabozantinib at the database cut off in january 2019. the number of three [3] week treatment cycles ranges from 2-28+. among the first 41 eligible and evaluable patients, 24 were progression free at week 12, satisfying the study decision rule. among all 50 patients, 30 were progression free at week 12 [60%, 95% confidence interval (CI) 45-74%]. a total of 7 patients achieved a confirmed partial response [PR] [14%, 95% CI 6-27%] and 33 had stable disease [SD] [66%, 95%CI 51-79%]. progression as best response was seen in 9 patients [18%, 95%CI 9-31%], one was not evaluable. disease control [PR+SD] was achieved in 40 patients [80%, 95%CI 66-90%]. median PFS was 6.0mo [95%CI 3.6-7.7]. the most common cabo-related grade ≥3 adverse events were diarrhea [74%], hand-foot syndrome [58%], fatigue [46%], hypertension [46%], weight loss [38%] and oral mucositis [28%], with 33 [66%] patients requiring dose reductions, 25 [50%] treatment interruptions and no cabo-related deaths.

conclusions. EORTC 1317 met its primary endpoint, with 24/41 patients [58.5%] being progression free at week 12. results of this trial confirm preclinical data and warrant further exploration of cabozantinib in GIST.

clinical trial information: NCT02216578

expanded access for cancer patients. the 5year FDA CBER experience. [abstract e18158]

laronna s. colbert

background. expanded access [EA] refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease rather than to generate scientific data that is generally derived from clinical trials. FDA has long facilitated expanded access to investigational drugs for patients with serious or immediately life threatening diseases and who lack therapeutic alternatives. EA requests include single patient use protocols under existing INDs, single patient investigational new drug applications [INDs or SPIs], and intermediate size or treatment protocols | INDs.

methods. the centre for biologics evaluation and research [CBER] internal databases were searched and all EA requests for cancer patients to receive investigational products regulated by CBER's office of tissues and advanced therapies [OTAT] from 2014-2018 were reviewed. these products included cellular and gene therapies, cancer vaccines and microbe based therapies.

results. from 2014-2018, OTAT received 395 EA requests for solid tumour [ST] or hematologic malignancies [HM]. one hundred ninety seven [197] requests were for individuals who could not be enrolled in an ongoing oncology clinical trial to receive an investigational agent [single patient use protocols]. of 197 requests, 7 [3%] were either withdrawn or canceled by the treating physicians [sponsors]. the remaining 190 [100%] were approved. one hundred seventy three [173] EA requests, 102 for ST and 71 for HM, came from sponsors to make available to patients an investigational agent for which there were no ongoing clinical trials [SPIs]. of 173 requests, 45 [26%] were withdrawn or cancelled by the sponsors. of the remaining 128, 127 [99%] were approved. one request was denied. twenty five of 395 EA requests were for intermediate size or treatment protocols | INDs.

conclusions. from 2014-2018 there has been an increase in oncology EA requests for products regulated by CBER | OTAT, which pose unique challenges for evaluating their risks and benefits. despite the complexities of these novel biological products, nearly all EA requests were approved.

potential EA benefits provide access to patients with serious or life threatening disease who have no other options & are willing to accept greater risk. it can provide patients a measure of autonomy over their own healthcare decision. making treatment IND can help bridge the gap between the latter stages of product development and approval by making a drug widely available during that period. in general, FDA reviews and makes a decision about such applications quickly – hours to days.

sessions.

CAR T. expanding clinical indications

gianpietro dotti. MD. PhD.

beyond checkpoint blockade. looking at an update on engineered t cell therapy and neoantigen application. how is the field moving with t cell engineering CAR, TCR, TILs and neoantigen as a vaccination.

specific t cells are now approved by the FDA for ALL and non hodgkin lymphoma in paediatric patients ALL and adult patients for non hodgkin lymphoma. the goal was to withstand the application of these car t-cell therapies to other diseases, including CD30 for hodgkin lymphoma.

- CD30 is universally expressed in hodgkin lymphoma and anaplastic large cell lymphoma and expressed in a subset of t cell lymphomas
- CD30 has minimal expression in normal tissues reducing potential for on target, off tumour toxicities
- targeting CD30 with brentuximab vedotin is effective in CD30+ lymphomas

24 patients were enrolled [1 enteropathy associated t cell lymphoma, 1 sezary syndrome]. median age 35yrs [range 23-69]. with a median of 7.5 prior lines of therapy [range 3-17]. population of heavily pre-treated patients with several lines of prior treatment, and many received the conventional antibody for CD30 checkpoint inhibition, autologous stem cell transplant and some allogenic stem cell transplant and failed all these lines of therapy.

condition regiment that was optimized for these patients, bendamustine + fludarabine support an ideal cytokine milieu. nice expansion and persistence of these cells with the optimal combination. car t cells are easily detected in the peripheral blood by flow spectrometry. metallurgical toxicity was expected, without any neurotoxicity and the treatment was very well tolerated. four [4] patients developed mild cases of CRS and one responded immediately to anti L6 antibody. nine [9] patients developed a transient skin rash.

CAR.CD30
t-cell expansion in vivo
optimized lymphodepletion.

the response rate here is quite remarkable in this heavily pretreated population, with 78% CR in these patients, with durable responses. now the next challenge for the next 5, 10 years is really to improve this therapy and to transfer this therapy in solid tumours. and the problems in doing this are multiple- firstly, selecting the right antigen. second, the migration of t cells to the solid tumour is completely different in comparison to migration to lymph nodes at bone marrow. and the microenvironment in solid tumours is highly immunosuppressive. and so these issues will need to be addressed in order to make any real progress in solid tumours.

the field for the identification of antigens in solid tumours is very hot and there are many clinical trials now currently ongoing with a significant number of targets that are being explored in phase I and II clinical studies. antigens that are not expressed in normal tissue or with limited expression in normal tissues to avoid any organ toxicity is the goal. targets that are highly expressing tumours and homogeneously expressed in all tumours. ideally, the antigen would be critical for the tumour growth and metastases to prevent antigen escape. and researchers have been highly focused on B7-H3 target in solid tumours.

B7-H3 is a member of the B7 family [CD80, CD86, ICOS ligand and PD-L1]. the ligand for B7-H3 is unknown but assumed to be an inhibitory receptor. it has limited expression in normal tissue and is very highly expressed in many solid tumours including pancreatic, ovarian, colon, prostate and others.

an example antibody 37696 in pancreatic cancer, expression of the antigen is very high and is not only detectable in the tumour cells but also in tumour associated macrophages and fibroblasts. and in the development of the car, control of tumour growth activity is seen by car t cells targeting B7-H3. there is slight expression in normal tissue, especially adrenal glands and salivary glands, however the density of this expression of the antigen on target cells is really critical to dictate the anti tumour activity.

so it seems that there is a therapeutic window based on the expression of the target tumour cells to distinguish between tumour cells and normal tissues, the anti tumour activity of these in immunocompetent mice was analyzed, and no toxicity was seen.

with t-cell migration | infiltration of car t cells in solid tumours - where this is an issue in terms of anti tumour activity. natural killer t cells [NK] , a subset of T cells, which differ to conventional t cells because they have an invariant t cell receptor and do not recognize peptides, but rather glycolipids in CD1 polymorphic receptor. and these are part of the innate t cell immunity. the infiltration of these NK T cells in

neuroblastoma correlate with better survival of paediatric patients. now these cells are engineered to be tumour specific by retaining the native capacity of these cells to recognize CD1 deposit targets, which are usually macrophages associated with the tumour. after infusion, expansion of these cells into the patient are seen. and importantly these cells localize at the tumour site and they also localize in the bone marrow. a frequent location of metastatic neuroblastoma.

and the outcome in the first patients treated at dose level one is remarkable anti tumour activity, with complete elimination of the lesion in the bone [regression of bone metastases in the sternum], who have relapsed many times on conventional treatment.

and finally the tumour micro environment [TME] is immunosuppressive in solid tumours, and these needs to be overcome in order to make car t successful in solid tumours. of course the combination of car t cell therapy with immunotherapies or agents that target tumour associated macrophages in myeloid derived suppressive cells is currently being studied.

researchers are also very engaged in further modifying car t cells to combine them with the capacity to directly overcome immune suppression. reverse engineering of PD-1 in these t cells to receive a positive signal instead of a negative signal from PD-L1. and IL-5 is also another way to this can improve the activity of car t cells in suppressive environments, giving the cells an additional capacity to use a cytokine not usually present in the TME. [clinical study at UNC for paediatric neuroblastoma now open].

in conclusion, CD30 car t cells are safe and effective in patients with CD30 positive autoimmune lymphoma. B7-H3 may represent a largely applicable target for car T cells in solid tumours if it can be proven that on target of tumour toxicity is not detectable in patients. NK T cells represent an alternative platform for car T cells fro car engraftment, and may result in better trafficking to the tumour site. Il-15 expressed by car T cells may improve their persistence in anti tumour activity in several subset solid tumours.

tumour infiltrating lymphocytes for patients with metastatic cancer.

stephanie l. goff. MD

t cells are really the basis of what we feel is immunotherapy for cancer and in a very simple model of a t cell, with negative and positive regulators taking advantage of this powerful cell through non specific stimulation. where the inhibition that our bodies have normally put onto these T cells to prevent them from attacking normal tissues, and also prevents them from attacking cancer. and this also occurs through checkpoint blockade, by anti CTLA 4, anti PD-1 and anti PD-L1. cytokines also can start that positive situation through active immunization. researchers are trying to do this both with the insertion of peptides or with entire antigen presenting the cell itself, dendritic cell system, through cancer vaccines.

the focus has been on the passive transfer of activated cells, taking the t cells out of the body that may or may not be able to recognize a tumour, engineering them in the lab, cultivating them in the lab, growing them to larger numbers and them giving them back to patients, to see if it will make the cancer go away. this is adopted immunotherapy.

this is the basic schema for adoptive transfer cell- the tumour is resected from a patient and goes directly to the lab, where it will be chopped into small fragments which will then be grown into high doses of IL-2. and they grow into what seemingly looks like oligoclonal T cell populations. during this time the patient is prepared for infusion to create a cytokine rich microenvironment. and followed by high dose IL-2. this proved to be efficient in melanoma.

in a young melanoma patient, 12 days after infusion of TILS, subcutaneous disease started to melt away. he was followed for five years at which point he disappeared back into survivorship.

it has also been seen to work in visceral disease- liver deposits present in a melanoma patient had been increasing, and just one month after TIL infusion all the tumours were gone and seven years later remain this way.

lymphyoctes are sometimes felt to not have the capacity to penetrate the blood brain barrier, however it has been seen to work for parenchymal brain disease. in another patient with melanoma who had metastatic deposits in the brain had a complete response just months after treatment. in the current treatment paradigm for melanoma, with patients receiving either a single or in combination checkpoint , it was felt that perhaps TILs were no longer necessary. however, in a patient who

recurred after checkpoint blockade, with metastases to the lungs and bone. his tumour was harvested after sequential checkpoint therapy and remains in complete response five years later.

so looking at melanoma specific survival after adoptive cell transfer of TILs, with 194 patients treated with the TILs regimen. 46 obtained a complete response, with two relapsing and dying of melanoma over 12 years. in addition there are also some long term partial responders, while there may be some radiological appearance of disease, but the lesions are not likely active melanoma. and this signifies that TILs are capable of eliminating the last cancer cell.

so what is the target of the TIL- originally it was believed to be the shared antigens, MART1 and GP100, however that was only about 23% of the TIL cultures that were studied. an additional 16 had reactivity against an autologous antigen that could not be identified and 21% had both the known shared antigens and the unknown autologous reactivities.

so how can the antigen be identified- early on expression cloning was used, but eventually researchers honed down and focused on what might make these tumours look different to the immune system and the whole exome of cancer patients. and when these tumours were looked at, every place where there was a non synonymous mutation could be identified. and so a mini gene was created for each mutation, put into an expression plasmid, the RNA was transcribed and transfected into the patient's own APCs. in essence, a mutation avatar was created for each patient. there is no need then to predict which of the MHC the peptide might bind to and no tumour cell was necessary for this process.

t cells recognizing highly personalized mutations could be identified in responding patients, and this was done in a number of melanoma patients. 78 different neoepitopes were identified in 34 patients. neoantigens were found in 31 of those 34 patients, and all were unique. among the 78 ne-epitomes, none were shared.

in cancers that are not melanoma this looks slightly different- female patient with cholangio was treated with TILs in the way that melanoma patients had been treated but with very minor changes to the tumour. this tumour only had 26 mutations [vs melanoma 1000-1500 mutations]. and so there was no autologous cell line, which are notoriously difficult to grow in the epithelial setting. the patient had a partial response after a second treatment and then recurred and was treated with pembrolizumab with ongoing response.

researchers can look across the spectrum from those cancers that are highly mutated, such as melanoma down to such as cholangiocarcinoma that only have a handful of mutations. so the schema has had to change, tumours are still resected and sent for whole exome sequencing, while TILs are growing. the tandem mini gene is developed and presented back into the tumour mutation avatar that is created with the patients autologous presenting cells. this is how the appropriate t cells are discovered and those are the ones given back to the patient.

this has now been done in 64 patients and 142 neoepitopes were found, about 70% of patients express new antigens and all but two of these neoepitopes were unique. The ones that were shared between two patients were targeting KRAS G12d, a well-known driver mutation, is the only instance in which the mutation, the epitope, and the HLA MHC restriction were exactly the same.

autologous recognition appears to be unique to each individual patient and they are not easy to find. less than 2% of all tested mutations were recognized by T cells in screening assays. so for every one that was found, 49 were tested and weren't.

can these immunogenicity epitopes be accurately predicted? sadly, no.

tumour infiltrating lymphocytes can mediate durable complete responses in patients with metastatic melanoma, objective partial regression in metastatic gastrointestinal cancers, and complete regression of metastatic breast cancer. What are our future directions. these tumour mutation reactive cells are so rare, how can they be found? markers of potential enrichment to find those cells are being sought. isolation of the T cell receptor sequences from those reactive cells to support individualized gene modified T cell therapy is also being investigated.

personalized neoantigen vaccine.

patrick alexander ott. MD. PhD

direct targeting of T cells that are specific for the tumour has the potential to steer the immune response into the tumour and act synergistically with checkpoint inhibition and other immune therapeutics. there is now compelling evidence supporting neoantigens as the targets of effective tumour rejection antigens. neoantigen load has been associated with improved clinical outcome. neoantigen specific t cells are expanded settings of effective anti tumour immunity and there is now direct evidence of cytoxicity of neoantigen-specific t cells. in the context of vaccine design, this has led to a paradigm shift away from native antigens, such as differentiation antigens and cancer | testis antigens towards neoantigens.

each individual patient's tumour, along with normal cells, gets sequenced. mutations are called, and then epitopes are selected based on different methods, usually epitope prediction algorithms, as well as RNA expression and other variables. the format of the vaccine can be a DNA vaccine, RNA vaccine, peptide vaccine, viral-based, or other. and then the vaccine is administered to the patient.

dana farber cancer institute tested a long peptide vaccine in higher risk melanoma patients, with the aim to target up to 20 long peptides. long peptides were formulated into four distinct pools and mixed with a TLR3 agonist poly-ICLC. the vaccines were injected subcutaneously into four non rotating sites on a prime boost schedule. in testing serial PBMCs in ex vivo or interferon gamma ELISPOT assays, de novo, robust interferon gamma responses against multiple pools were found, indicating that multiple vaccine-specific responses were generated in the six patients. across the six patients that 18% of the vaccine epitopes had generated CD4 responses ex vivo. after in vitro stimulation, 60% of the vaccine epitopes induced CD4 responses, and 16% induced CD8.

vaccine-induced t cell responses in the melanoma patients are specific for their mutant versus their wild type peptide, both for C4 and CD8. in three out of six patients, researchers were able to find specificity, or they were able to recognize autologous tumour, those vaccine-specific t cells. and importantly, the functionality of these t cells was also seen demonstrating a transition from naive cells towards a effector memory phenotype.

two patients who had a recurrence while they were vaccinated received pembrolizumab, and both had a complete response after four treatments. interestingly, the repertoire of the T cells in both of these patients were found to persist and broaden over time. de novo responses occurred after PD-1 inhibition that had not been seen after the vaccine.

a study was performed using an identical vaccine approaching glibomastoma multiforme [GBM], where patients received standard of care radiation while the vaccines were being manufactured. access to post vaccination tissue was able to show whether CD4 and CD8 had enhanced frequencies or peripheral responses by the patient and therefore able to ask whether these t cells are in fact specific for the vaccine. found that in the tumour-infiltrating lymphocytes, there were 230 TCR clonotypes and 25 clones. on neoantigen reactive t cells, found 280 clonotypes,as well as 11 clones.

despite sampling less than 300 tumour infiltrating lymphocytes in the post-vaccine tumour, two CD8 TCR clono types and four CD4 TCR clono types that were identical between the tumour infiltrating lymphocytes and the peripheral t cells known to be specific for the vaccine were found.

hypothesizing that these t cell receptors were specific for vaccine they were cloned and exprssed to probe specificity against neoantigens. six shared TCRs were identifies in TILs and peripheral blood was expressed in reporter cell line. TCRs also screens for reactivity against individual immunizing ne-antigens. two clones were found to also be able to discriminate between mutant and wild type.

so the logical next step is to combine this vaccine with PD-1 inhibition. the most mature data are from the NT 001 study performed by neon therapeutics, which used a similar vaccine. in this study, patients with smoking related non-small cell lung cancer, melanoma, and bladder cancer received nivolumab, while the vaccines were manufactured. at Week 12, the vaccines were started. the objectives of the study were safety, clinical efficacy [response rate and durability] and immune response. in depth immune profiling was conducted on this study. leukapheresis blood is obtained, as well as tumour samples prior to nivolumab, prior to the vaccine, and post vaccination. in melanoma patients, which is refractive for all cohorts, a majority of the vaccine epitopes were found to induce t cell responses and were clearly more dominant after the vaccine compared to after nivolumab. the majority of these responses were found to be mutant specific and durable.

determinant spreading is a way to see whether vaccine specific t cells can recognize a tumour, tumour cells that get killed can actually release additional antigens. and these can be recognized by the vaccine induced t cells. 10 patients were tested for neoantigens that were expressed by the tumour but were actually not selected for the vaccine, found that in 9 out of the 10 patients there were responses against these non-vaccine but tumour specific neoantigens.

update on T cell receptor therapy.

cassian yee. MD

there are three different ways, three general modalities for generating T cells for adoptive therapy. infiltrating lymphocytes, T cell receptor and CAR engineered T cells and the last modality is endogenous T cell therapy. Instead of using the tumour, T cells are isolated from the peripheral blood, using enabling technologies because T cells are present in very low frequency.

in contrast to CAR, these T cells target a protein that is processed and present on the surface of MHC. therefore requiring an HLA presentation, but providing a much broader spectrum of potential targets. while there are a significant number of targets available for car T cell based therapy, there are significantly more targets available for TCR based therapies.

points to consider for engineered T cell therapy is the affinity of T cell receptors. is there sufficient, mutating these by phage display and other methods in which that population of affinity maturity T cell receptors for adoptive transfer. Pairing of alpha beta chains may not necessarily be appropriate, and when endogenous alpha beta chains are present some of this can be addressed by gene editing out the alpha chain using transposing based methods like CRISPR or cas 9.

other points to consider are clinical toxicity with engineered cell receptor, some of the associated target toxicities can give rise to uveitis and immunotoxicities that are not seen when patients are treated with a natural occurring MR1 specific t cell. off target target toxicities from HA3, a mutated t cell receptor and may cross and react with other epitomes that are present on vital tissues. CRS can also be seen on the basis of tumour burden. finally, emetogenicity, which the engineered t cells will express may lead to early rejection of T cell or engineered T cells and in some cases the use of high dose lymphodepleton is necessary.

industry is currently leading trials, adaptimmune and GSK study NY ESO1 in positive sarcoma is demonstrating significant responses. 60% response rate in 10 patients who received target cell dose. 50% overall response rate[6/12] in patients receiving any dose of cells and 75% [9/12] of all patients and 90% [9/10] patients who received target dose are alive and on long term follow up. there a number of early phase studies for both in synovial sarcoma and mixed round cell liposarcoma and this has been expanded to other potential targets HA10, HA4, and alpha fetoprotein.

other studies kitepharma MAGE A3/A6, juno/celgene WT1 [mesothelioma. NSCLC] and bellicum PRAME

challenges remain because of limited antigen selection. these are based on known epitopes and largely limited to HLA-A2. there is also consideration of what phenotype of cells should be infused and the risk associated with engineered chimeric antigen receptor and T cell receptor T cell therapy. and manufacturing and regulatory challenges which have been addressed but limit the ability to implement these approaches rapidly.

endogenous T cell therapy are present in very low frequency, as low as one in a million. Using enabling technologies, these cells are isolated and enriched to very large fractions, more than 80%, and in the colonial population to 100%. And expanded to several billion, usually 10 billion /m2 and then subcutaneously infused in patients. Because of the way they are grown they do not require high dose lymphodepletion of high dose IL2. The advantage in endogenous T cell therapy over some of the other approaches are that it selects from a T cell receptor repertoire that's more broadly present and may allow for a self select affinity that doesnt lead to deletion. it is also unbiased in the TIL population and readily accessible from peripheral blood. and because of the way they are given there is also relatively low mobility and essentially outpatient therapy; a certain amount of regulatory simplicity, although these cells can be genetically modified- and rapid deployment from identification or discovery, up until implementation; flexibility which allows to de-risk potential targets. it is however time and labour intensive and technically challenging.

cancer affects one in two patients, and what it does is unbalance the immune systems immunosuppression originally designed to regulate the balance between immunity and autoimmunity [metabolic, checkpoint, hypoxia, Greg, MDSC, TGF-b]. effector cells [TIL, ETC, TCR-T, CAR-T, CD8, CD4, γδ, ND, NK, NKT] can't balance this alone, the tumour needs to be softened with checkpoint inhibitors, agonists, cytokines, chemokine, gene enegeenring and so on.

blockade of immune checkpoint inhibitor CTLA 4 transferred tumour antigen specific T cells enhanced proliferation potential. endogenous tumour antigen specific t cells lower the threshold for activation of the transferred t cells; leads to antigen spreading and multivalent response. eradicate and modulate function of CTLA 4+ tregs. IL20 prime central memory t cells in combination with CTLA 4 therapy led to significant complete responses in patients, some who had failed prior checkpoint therapy, stable disease and also significant partial response.

researchers are faced with two challenges, how do you treat patients who do not have melanoma, how is the process streamlined for non melanoma solid tumour malignancies. using mass spec analysis as well as some sequencing a number of tumours- epitopes were identified. these were then generated into T cells and shown to not only kill the cancer but also HLA A match antigen VGL1 positive tumours. This is expressed in a number of cancer types, pancreatic, bladder, ovarian, glandular carcinoma, TNBC and the A1 which took the VGL1 specific t cells can recognize other tumour types as well. An antigen identified from a single tumour, from a single patient can be used to treat a number of cancers.

what ETC can do here is de risk the identification of these t cell receptors and streamline the process, not only by using clinical grade scale sorting but also table top model of a nanofluid MEMS based device that can be used to store clones and then target a number of different antigens and the roar a number of different tumours in a turnkey fashion. currently work is being done on chip based technology.

then you can treat patients not only with advanced disease but also patients in adjuvant first line therapy, taking this beyond CD and CTLA 4 therapy, treating patients with a combination of PD-1, CD1-37 agonist vaccine therapy, etc.

what researchers are trying to do either via CAR T , TILs or endogenous t cell therapy is provide a transferable cellular biomarker and see the actual effect that these different agonists and the wealth of immune checkpoint inhibitors [ICI] have on the tumour reactive population.

how to implement and disseminate clinical trial and big data results.

david a. chambers. MSc. DPhil NCI

how can research and practice coexist and ideally benefit from one another.

the typical pathway for researchers is to think about the publication, high-impact publications, as the way to try and implement the findings of that research. the original research is completed. submitted. and hopefully it's accepted. and then published. ideally, it gets contained in the various databases from which people draw their systematic reviews, develop guidelines, think about textbooks to train in the field, and then they make their way into practice. however, when trials have negative results, or it's a smaller study, these are harder to publish, and they don't make it into that next line of decision making.

it takes 17 years to turn 14% of original research to the benefit of patient care. and this is a challenge, if we assume that publication is the way to change practice, to change policy, it generally doesn't work. and when it does, it takes a long time and very little of that research that actually translates to benefit patient care.

if we think about any evidence based program for cancer control, it's not just that evidence base that resulted from those trials, but how well its adopted within different systems, within oncology settings. and whether providers are trained, the capacity for providers to be trained to deliver it. even though there are lots of provider trainings that don't necessarily yield changes in practice. and whether those trained providers are in a position to actually deliver it in their practice. and to deliver it to those who would be eligible to those who would benefit.

in the 17year | 14%, the threshold for success is about 50% uptake, clinicians are likely to get an evidence based intervention as they are not, and this isn't optimal.

an evidence based program for cancer control is only as good as how and whether it is adopted, providers are trained to deliver it, trained providers choose to deliver it, and eligible people receive it.

there's a need to harness existing data to understand the impact at each step. NIH is building the knowledge base for how we do a better job of taking evidence based interventions and making sure that they benefit as many people as possible. it's the way of organizing this dissemination implementation research or implementation science agenda across the agency. and not allow the publication to be the one place at which we think practice change is going to occur.

these issues are things that need more work in and things that we envision large sources of data being helpful. thinking about sustainability of our various evidence based practices over time, particularly as health care systems are changing, large data is needed to give a sense of what is affecting sustainability.

thinking about how interventions are adapting or evolving over time, that's an opportunity to look at data of various sorts over a time period. thinking about how interventions are implemented- not just one intervention, but a whole evidence-based system of care around people, or thinking about scaling up practices across health plans, across systems, across networks, and across nations, the data needs to be able to tell us what's working and what isn't. to recognize that there are certain practices that we should probably not be doing, because they're ineffective or potentially harmful, and this data needs to enable us, to support us in thinking about, when do we de-implement? when do we ex-innovate as opposed to innovate?

too often assumptions are made about interventions being well-tailored for the patient population, the provider community, the settings in which they're delivered. and we can't assume that any more if we want to try and optimize care.

data can be used, and particularly large volumes of data, to help understand, how these interventions can be shape these to make them appropriate for use, and for the patient population. try to think more dynamically about evidence base and trying to think about how data can drive that.

if we can create this big data, this sort of cancer data ecosystem around understanding implementation science, that we will do a better job of influencing, of improving, of impacting practice.

the hope is that in the future we are in a position where, as we're thinking about the right fit between our interventions, our patients, our clinicians, our settings, that we can bring as much data in an ongoing way as possible.

areas ripe for exploration

- sustainability of EBPs in a changing context
- adaptability | evolution of EBPs over time
- implementation of a set of ITVs
- impact of dissemination strategies on practice
- scaling up practices across health plans, systems, networks and nations
- de-implementation | exoneration

these are big data areas. how can big data benefit patient care? multiple sources of data aggregated from clinical trials, administrative data, electronic health records.
cross cutting challenges- data quality, representativeness, timeliness

current environment in risk stratification in oncology.

justin e. bekelman. MD

we are at a turning point in cancer care today. research and innovation have led to measurable improvements in cancer care, survival, and quality of life. but the delivery of cancer care can be suboptimal. it's fragmented and costly. suboptimal care accounts for one third of the $3 trillion the US spends on health care every year. but this is not just about costs but about patients.

how can the friction be removed from delivering the highest quality, most efficient cancer care? is predictive analytics the answer- or is it more reality than hype or more hype than reality?

penn medicine's first efforts at predictive analytics in oncology, they took a year to develop the rolls royce predictive analytics algorithm to predict hospitalizations for patients receiving chemotherapy or active treatment for cancer. it had all the bells and whistles and was based on their EHR. and patients hated it. in another initiative where they developed an artificial intelligence augmented chatbot to help patients adhere to their chemo regimens, oral chemo regimens. it's easy to use. there's no app. it benefits patients. it really helps them. patients love it. it's a success story. patients actually love it so much that they anthropomorphized it. when the philadelphia eagles were in the super bowl last year, they were so excited about this chatbot, and they had really linked with it so well that they started texting eagles emojis to it.

will either of these two stories actually be impactful, will they actually lead to better cancer care? much of our attention right now is on predictive analytics in cancer care and thinking about moving forward in this space;

one. is the algorithm serving as a nudge to get physicians or patients to do something? is that something the right thing to do? is it the wrong thing to do? will that something actually work even if the predictive analytics engine is doing its job? and then how would you test that in a small way before you scale it?

two. start small. most feel there is a high bar to getting involved in artificial intelligence or predictive analytics in order to change cancer care. but the reality is that, already, in many of the electronic medical record systems, there are baked in modules or predictive analytic engines that can start experimenting with in order to assess whatever endpoint or whatever event you're trying to get an early-warning sign on. think about working with your IT group or thinking about asking your vendor, what are the available tools you already have?

three. engage with patients, providers, and clinicians. the reason that's so important is because they're going to be able to tell us, how we make it more appealing. how does this get into workflows such that it's useful? how do we actually drive change from different perspectives so that whatever we're designing to predict or our algorithmactually makes it into your care pattern?

how are payers using big data and predictive analytics?

andrew allan. MD FACP

how can payors use available claims and clinical data to partner with oncologists to improve the quality of care by preventing hospitalizations and emergency department use, which will lead to improved patient satisfaction and hopefully generate savings.

OCM episode cost breakdown
50% of the costs are due to drugs. but another 15% to 20% [this number varies from payor to payor] is due to inpatient admissions. physician costs are 11% of the total costs.

the goal is to use the data that in evidence-based medicine to partner with physicians to decrease the spend and improve the quality of care by preventing inpatient admissions and promoting efficient use of the drugs.

typically, the majority of admissions are due to complications of therapy or deterioration of the patient's underlying condition. though there are some admissions for chemotherapy, these are a minority of the total percentage of admissions. the emergency department [ED] is the gateway for hospital admissions with 56% of medicare patients receiving chemotherapy visiting the emergency department each year. and 63% of those visits to the emergency room result in admission.

when patients show up in the emergency room, the majority of emergency department clinicians do not have oncology-specific training. they don't have oncology care pathways and protocols. and often they do not even have access to the oncology medical record. milliman estimated that a chemotherapy related emergency department visit costs about $800USD. but if the patient is admitted, that goes to $22,000USD.

many of the emergency department visits are potentially preventable.

the centre for medicaid and medicare services [CMS] has identified ten [10] conditions for hospitalization which are potentially preventable through appropriately managed outpatient care. anemia, nausea, vomiting due to chemotherapy and chemotherapy induced diarrhea which can lead to dehydration, emesis, fever, neutropenia, which can lead to sepsis and pneumonia, and pain.

the fred hutchinson centre studied emergency department use by patients in western washington from 2011-2016. they found that 27% of 5,800 adults with cancer visited the emergency department at least once. and 53% of those 2,400 visits could have been avoided.

so if these are preventable admissions and preventable trips to the emergency department, if we could identify these patients ahead of time, we could prevent them. this would certainly provide enhanced outpatient care to every patient. but not be cost effective. not every patient needs additional interventions.

interventions to prevent ED trip
change in chemotherapy, phone call or clinic visit 48 to 72 hours after chemotherapy, institution case management. resulting benefits include decreased patient admissions, improved patient satisfaction and value creation.

what kind of data can we use to identify patients who would be at high risk of going to the emergency room?

claims data. claims data is very broad. it looks at patients from multiple practices throughout a region. it gives a very broad view, but not much depth. its unclear by looking at claims data whether that patient is being treated curatively or whether it's metastatic. you might guess by the drugs that you see. but often the patients status cannot be determined. and its not clear in what line of therapy. as well, claims are not timely. and can often the lag as much as 90 days. if the goal is to prevent emergency department visits, seeing a claim 90 days later is probably not going to be incredibly useful.

EMRs. are very deep. they look at each patient within a practice to an incredible depth. but they are not broad. rather than seeing all the patients in a region, we will see the patients from a practice. when data is pulled from an EMR, it needs to interface with the EMR. and in most cases, this that means the information must be entered in defined fields.

clinical pathways. in the clinical pathway, key clinical information is entered and captured in a coded way. the clinical scenario needs to be defined, so the patient status is clear identified. for a lung cancer patient, for eg. we will know if its stage I, II, or III, or if it's metastatic, if it's ALK positive, which line of therapy is being given. and it's very timely. that data is provided before the patient is treated. pathway data could be very useful for trying to estimate the risk of a patient going to the emergency room.

two models were piloted and compared.

one. the 'expert experience model' was a model where a group of medical oncologists and oncology nurses were set aside and asked- if you were going to design a model based on this set of data that we're collecting from clinical pathways, how would you try to predict who was going to go to the emergency room? the same information was given to the data analytics group and asked them to develop a model. experts came up with a model that was based upon certain cancer types that they thought were at higher risk. examples would be head and neck cancer, esophageal cancer. certain key risk factors - the risk of chemotherapy regimen with febrile neutropenia or nausea and vomiting, the line of therapy, the extent of disease progression, and social risk factors. experts felt that living alone would be a higher risk factor and actually, living alone turned out to be a lower risk factor for going to the emergency room and that is most likely due to the spouse or partner who's getting the patient to go to the emergency room. but this that was a very interesting finding.

two. 'data driven methodology' where data consists of risk factors | clinical info from carepro and outcomes [ER and hospital] from claims from a larger payor including medicare advantage patients- 41, 232 unique patients used to train and test the model. 70% of the total data was used to construct the model, with the model learning patterns from this data. 30% of the total data was used to test the model, and the model never saw the data during construction with outcomes blinded. the model's prediction was compared against what truly happened to assess performance. inputs selected by clinicians included demographics therapy information [eg. neyropenia risk associated with regimen] information about the journey [eg. line of therapy] patient health status [eg. ECOG] significant changes in status and history of hosipitilzation and ED visit.

model one. expert driven model predicting ED use.
certain cancer types, key risk factors, eg. neutropenia, disease progression and social risk factors eg. living alone

model two. data driven model.
why build it? captures complexity of processes, interactions captured more easily, ability to weigh factors, not just yes | no logic, is it superior to a model developed from expert clinical experience.

a data driven model technique includes logistic regression, well established statistical method and random forests, which are newer machine learning techniques and rooted in decision trees. both models came up with very similar results and the logistic regression analysis was implemented.

but would the model work with a commercial population - and so it was tested with a large medical centre in the midwest to examine the likelihood of ED visits in the next month. 2.5 million claims with only 1% having visited the ER, accounting for 22,873 unique patient IDs. 238 receiving chemotherapy. 750 authorizations for therapy, 408 which included chemotherapy. the model categorized patients into three [3] risk based on prior authorization data

results.

low risk [N=193] only 2% of patients went to ED
medium risk [N=27] 18% of patients went to the ED
high risk [N=5] 40% of patients went to the ED

by only intervening on the medium and high risk, 15% of the patients identified who accounted for 60% of all ED visit

conclusions. coded key clinical data from clinical pathways utilized for prior authorization can be utilized for the timely identification of patients at high risk for ED | inpatient use

such a data driven model is superior at identifying high risk patients to a model based upon the experience of clinical experts

applications. the model is now being deployed in OCM practices using clinical pathway data to identify patients at high risk for ED | inpatient utilization. additional resources are being devoted to the identified patients in an attempt to decrease ER | inpatient use

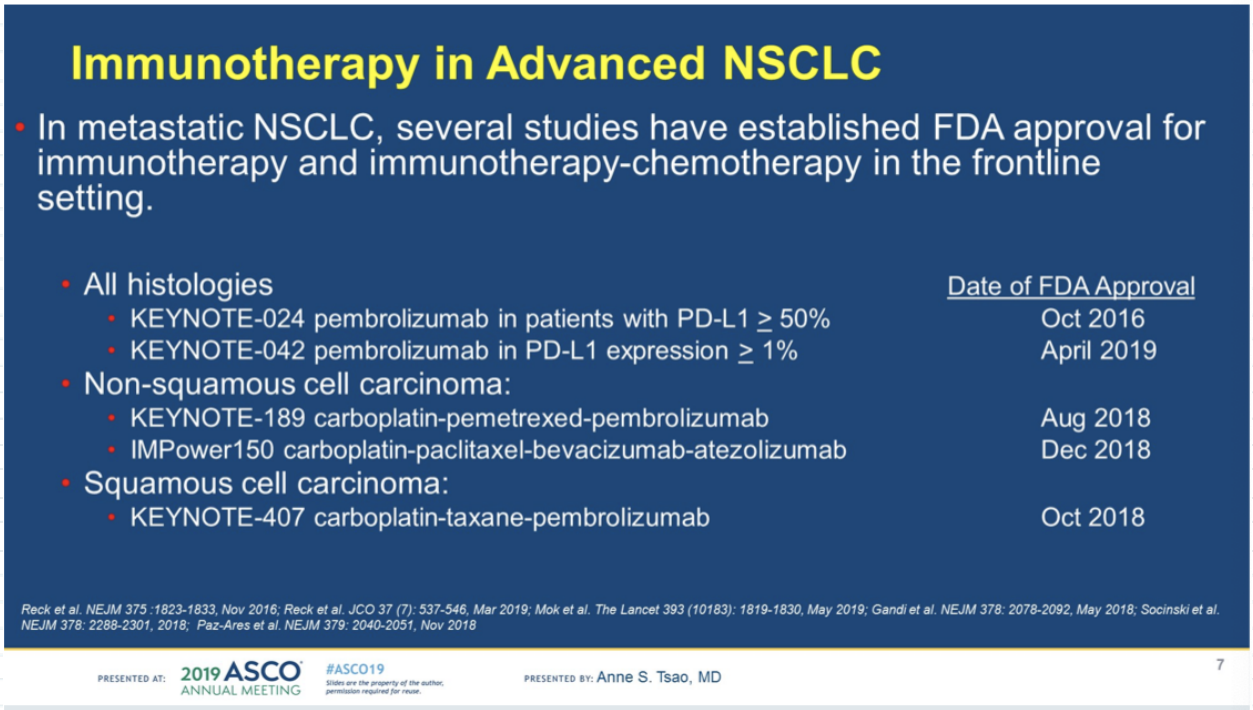
changing the concurrent chemotherapy radiation paradigm. can we replace chemotherapy with immunotherapy?

anne s. tsao.

there are some local regionally advanced non-small cell lung cancer patients that can be cured with multimodality therapy. but stage III is extremely heterogeneic, and individualized therapy is necessary to optimize our rates of cure. the PACIFIC trial was quite a remarkable change and was the first time any agent systemically in the last decade moved the needle in terms of cure rates or survival for patients. currently with the three-year update, 50% of the patients who received durvalumab are alive at 36 months. and this is impressive, considering what we were looking at before.

there is a need to advocate that all patients should have the opportunity for immunotherapy. PD-L1 is not the best biomarker, but it's all that is available at the moment.

in metastatic NSCLC several studies have established FDA approval for immunotherapy and immunotherapy chemotherapy in the frontline setting.



immunotherapy has better tolerability than chemo.
immunotherapy with XRT is safe. its also known that IO has better tolerability than chemo. immunotherapy with radiation is known to be safe and tolerable with potential radiosensitization effects. also known that radiation can upregulate PD-L1 in TILs. and can also release tumour antigens, and thereby, the hypothesis is that radiation could potentially induce better anti tumour effect with immunotherapy.

there is speculation that in early stage disease, IO's may work better [forde et al 43% major pathologic response [MPR] in early stage NSCLC, regardless of PD-L1 with neoadjuvant nivolumab[.

ongoing trials.
SBRT studies. no data on efficacy yet. preliminarily safety appears to be well tolerated. the issue with all of the current trials is that checkpoint inhibitors are being given at different doses, as well as different timing, and different duration of length. and so it may be challenging to tease out and determine whether or not we are truly benefiting these patients.

on the other hand, there is an enormous amount of data that might be helpful in understanding duration of therapy after radiation and whether or not this is a feasible strategy moving forward. none of these trials have a biomarker requirement for eligibility.

stage II | III ongoing consolidation maintenance trials. these trials will probably adjust the current standard of care. eg. PACIFIC 6 will be looking at durvalumab that the 1,500 milligram IV q4 week dosing, and this is for two years.

pembrolizumab study in italy is being given for 35 doses, and will be randomized to observation.

the big 10 cancer research consortium will be giving cohort a. nivolumab for six [6] doses, and in cohort b. nivolumab and ipilimumab. all of these will be conducted in patients who have completed concurrent chemoradiation with no biomarker eligibility requirement.

stage III concurrent chemo radiation immunotherapy trials. there's a large number of IO plus concurrent chemoradiation combination studies. duration of length of adjuvant therapy usually is a year, but in some cases, it is extended beyond that.

no biomarker eligibility requirement for any of these trials.

highlight one trial that does stand out, because all of the other studies are using checkpoint inhibitors, while the EMD serono study is actually using M7824 which is a bifunctional fusion protein. a fully-human IgG1 monoclonal antibody [mAb] to PD-L1 and TGF beta neutralizing trap component that targets the extracellular domain of TGF beta receptor 2. the thought is that this will have an additive anti tumour effect. this trial is currently enrolling all stage III unresectable lung cancer patients. they will have a safety run in 42 patients and then expand to 308 additional patients. they'll have a 1:1 randomization after the safety run in, to the M7824 plus concurrent chemoradiation versus chemoradiation alone. in the consolidation phase of the first cohort [a], they will give M7824 as consolidation.

phase I rutgers study and the deterred trial demonstrated that adding immunotherapy to concurrent chemoradiation followed by immunotherapy or chemo consolidation plus the immunotherapy is feasible. there is some toxicity, about 18% grade 3 or more immune related adverse events [irAEs], and then about 16% grade 2 pneumonitis. anticipate seeing pneumonitis within the radiation field and possibly a little bit around it, so this is to be expected. it does becomes very problematic when it becomes a diffuse pneumonitis however. initial PFS was quite modest, and OS is really too early to assess. 40% of our patients are still being followed on the trial. however, there is a need to consider other strategies to optimize cure for patients.

ECOG-ACRIN phase III trial that is being built off of the work from these other studies. this is still a trial in progress, so it is not definitive yet. But it will enrol unresectable, stage IIIa to c NSCLC. 660 patients to a platinum doublet of the investigator's choice, with and without durvalumab, followed by consolidation durvalumab.

so what is the rationale for these ongoing trials to replace chemotherapy with immunotherapy. concurrent chemoradiation is superior to sequential or radiation alone. no consolidation chemo, nor any consolidation maintenance targeted therapy trials in an unelected population, have ever been shown to have a survival benefit. the only agent, or class of agent, that's ever shown to improve survival in patients has been immunotherapy in this setting.

concurrent chemo regimens generally don't give you the same dosing a systemic dose, and their main benefit with radiation may potentially just be radiosensitization. so there is a hypothesis that this might be something we can replace. studies that demonstrate that immunotherapy can be a radiosensitizer continue to provide positive reinforcement that this might be a viable strategy moving forward. and this is

already being done in front lineNSCLC. patients who have PD-L1 IHC greater than 50%, we are using immunotherapy, and with the recent indication from KEYNOTE-042, it now allows us to do that for patients who have less than 50% PD-L1.

NRG study in high PD-L1 [PD-L1 greater than 50%] using durvalumab,
using a SPRINT trial design, which is a novel design. in this trial they are looking at PD-L1 IHC status. patients with a PD-L1 greater than or equal to 50%, will receive pembrolizumab with radiation, and those with less than 50% receive concurrent chemoradiation.

M.D. Anderson study which is about to open is going to really take a leap of faith. giving ipilimumab | nivolumab alone with radiation in an unselected lung cancer population. this is building off of the premise that there isn't enough understand of biomarkers just yet. and there are patients that will potentially have significant benefit from the immunotherapies. 20 patients with no biomarker selection. this data, of course, will be collected, both from tissue plasma, stool, and microbiome. patients will receive ipilimumab for four [4] doses. each cycle will be given over six [6] weeks, and nivolumab will be given every three [3] weeks for eight [8] cycles during the same time. patients will also be given standard radiation. they will then receive nivolumab at 480 IV every air [4] weeks for eight [8] cycles of therapy. plasma and stool will be collected during several time points.

primary endpoint will be safety, tolerability, as well as feasibility, and secondary endpoints will be clinical outcomes and efficacy.

NRG-LU004 is the phase I trial of accelerated or conventionally fractionated radiotherapy combined with durvalumab in PD-L1 high patients. there is a growing body of literature that suggests that hypofractionated radiation may be synergistic with immunotherapy and may have enhanced anti tumour effect. this study will be testing that hypothesis. patients who have local-regionally advanced disease will be analyzed for PD-L1 at each of their individual centres [greater than or equal to 50% PD-L1]. 24 patients enrolled to this initial trial. three [3] will go into initial safety cohort one, and this is the hypofractionated accelerated radiation arm with durvalumab with durvalumab being given for 13 doses.

once these patients have accrued, they will then move on to cohort two. this cohort has the same amount of durvalumab but will be using standard radiation. if both of these cohorts appear to be safe, then they will go on to be randomized 1:1 to cohort three and four. cohort three will be the hypofractionated arm, and cohort four will be the standard radiation arm. durvalumab will be given for 13 doses in both of these

arms. the plan is to conduct the safety trial and then move onto a randomized phase II study comparing this to the PACIFIC regimen.

future directions in this field- a lot will depend on the efficacy from immunotherapy with SBRT trials, trials with concurrent chemoradiation, and then ultimately, from studies where chemotherapy is being replaced with immunotherapy. several outstanding questions that need to be further delineated, such as sequencing.

duration, how long duration of therapy for immunotherapy in the tail end, hypofractionated versus conventional radiation? what is the role of trimodality therapy with immunotherapy? is there a role of neoadjuvant immunotherapy versus adjuvant immunotherapy? And most especially, the need for predictive biomarkers.

stage III disease is extremely heterogeneic, and so to optimize chances for cure with limitations of toxicity, there will be a need to personalize therapy. these are just potential future strategies, but there may come a time where, if a patient has an unresectablelarge T stage or N3 or bulky or multi-station N2 lymph nodes, they may need to have neoadjuvant chemoimmunotherapy and then potentially concurrent immunoradiation and then one year of immunotherapy. patients who have small T stage, PD-L1 high, and small multi-station N2 disease might be able to get by with concurrent immunoradiation followed by a year of immunotherapy.

those who have a small T stage with PD-L1 low and small multi-station N2 disease, will probably need concurrent chemoradiation followed by a year of immunotherapy, potentially. and large T stage or single-station N2, then maybe neoadjuvant chemoimmunotherapy with surgery, with or without radiation, followed by a year of immunotherapy may be beneficial for them. small T stage with single-station N2, then perhaps neoadjuvant immunotherapy followed by surgery and a year of immunotherapy may be sufficient. these are hypothetical situations, but it's the job of clinicians and researchers to get to this point, where we can increase our rates of cure across all stages of disease.

FDA unveils project facilitate to ease expanded access to experimental cancer treatments.

announced at the 2019 ASCO annual meeting, the FDA is rolling out a pilot program that will provide more information and assistance for acquiring expanded access [EA] to investigational therapies for both oncologists and patients. the program is being called project facilitate and will be run by the FDA oncology centre of excellence, and EA Navigator, which is operated by the reagan-udall foundation for the FDA.

expanded access or "compassionate use" programs make investigational drugs, biologics, and medical devices available to patients who have exhausted other options for treatment and do not qualify for clinical trials that would provide these agents. the joint program would streamline the process of gaining access to investigational agents while helping the FDA obtain information to improve the EA process and better understand investigational agents.

the pilot program is exclusively for improving EA for oncologics. EA has been around, informally, as early as 1960, and was instrumental in efforts to broadly expand access for experimental treatments during the HIV | AIDs epidemic.

the reagan-udall foundation will provide a searchable database that physicians and patients can use to establish whether any clinical trials are available for treatment with the investigational agents. the database will also provide information about EA programs, thereby offering physicians and patients a streamlined information search.

for the first time, those who need quick access to drug availability & expanded access options will find it in 1 place without having to visit site by site or sift through thousands of studies that don't [serve] their needs.

after visiting the foundation's website, physicians would then turn to project facilitate, which is tasked with ushering physicians through the process of reaching out to drug companies for EA. FDA officials said this process would be more coordinated than in the past, as their current focus is broadening access and then following up with physicians about outcomes.

information about outcomes gathered during the process may be shared with trial sponsors. reasons why drug sponsors turn down EA requests will also likely be better understood.

patient outcomes such as benefits from the proposed therapy and adverse events associated with that therapy.

EA can only happen if a drug company agrees to make a drug available outside of a clinical trial. requests are sometimes turned down because only limited supplies of investigational drugs are available, and the FDA cannot require a company to make its drugs available through EA.

a review of EA requests over a 10-year period demonstrated that only 2 drug development programs were ever placed on clinical hold due to AEs in patients receiving EA, and these were temporary.

under the 21st century cures act, companies are required to make information about their EA programs public. the reagan-udall foundation component of this EA pilot is partly an attempt to broadly disseminate that information. a necessary tool and urgent for patients and physicians.

phase III MONALEESA-7 trial of premenopausal patients with HR+| HER2– advanced breast cancer [ABC] treated with endocrine therapy ± ribociclib. overall survival [OS] results. [abstract LBA1008]

sara a. hurvitz. MD

background. the phase III MONALEESA-7 study is the first dedicated trial of endocrine therapy [ET] ± a cyclin dependent kinase 4 | 6 [CDK4 | 6] inhibitor in premenopausal patients with hormone receptor positive [HR+] | HER2– ABC.

methods. premenopausal patients [672] with HR+ | HER2– ABC were treated with ribociclib [RIB] or placebo [PBO] + goserelin and either a non steroidal aromatase inhibitor [NSAI; letrozole or anastrozole] or tamoxifen. this is the 2nd of 3 protocol-specified OS analyses [scheduled to occur after ≈ 189 deaths [75% of the planned total events]]. OS was evaluated by kaplan meier methods.

results. the data cutoff for this prespecified interim analysis was november 30. 2018, and the median follow up was 34.6mo. at cutoff, 173 patients were continuing study treatment [RIB, n=116; PBO, n=57], and OS was evaluated after 192 deaths [RIB, n=83; PBO, n=109]. RIB + ET demonstrated a significantly longer OS than PBO + ET [median, not reached vs 40.9mo]. the result crossed the prespecified stopping boundary for superior efficacy. estimated OS rates with ribociclib + endocrine therapy vs placebo + endocrine therapy at 42mo were 70.2% vs 46.0%, respectively. in patients who received an NSAI [n=495], RIB + ET demonstrated a consistent OS improvement vs PBO + ET. post treatment therapy use was balanced between treatment arms [RIB, 68.9%; PBO, 73.2%].

conclusions. MONALESSA-7 is the only study to date to evaluate CDK 4 | 6 inhibitors exclusively in premenopausal women. ribociclib + endocrine therapy demonstrated a clinically and statistically significant longer OS than ET alone in premenopausal patients with HR+| HER2– ABC. approximate 29% relative reduction in risk of death. approximate 30% relative reduction in risk of death in the NSAI cohort. treatment ongoing in 35% of patients in the RIB arm. the benefit of ribociclib extends beyond initial treatment based on time to subsequent chemotherapy and PFS 2. this is the first time that a CDK4 | 6 inhibitor or any targeted agent + ET has demonstrated significantly longer OS vs ET alone as initial endocrine based therapy in patients with HR + | HER2- ABC.

clinical trial information: NCT02278120

SOPHIA primary analysis. a phase III study of margetuximab + chemotherapy versus trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer [MBC] after prior anti HER2 therapies. [abstract 1000]

background. pretreated HER2+ MBC lacks a defined standard of care, although trastuzumab is commonly used. margetuximab has similar HER2 binding and anti proliferative effects as trastuzumab. by contrast, margetuximab's Fc region is engineered to increase affinity for both alleles of the activating Fc receptor [FcR], CD16A, and decrease affinity for the inhibitory FcR, CD32B. the low affinity CD16A 158F allele [~85% of population] has been associated with diminished clinical response to trastuzumab. In a phase I trial, margetuximab demonstrated acceptable safety, anti tumour activity, and evidence of HER2 specific antibody and t cell responses.

methods. SOPHIA is a randomized, open-label phase III trial, enrolled patients with HER2+ MBC after pertuzumab and 1–3 lines of prior treatment for MBC. patients were randomized 1:1 to margetuximab [15 mg/kg IV q3w +] or trastuzumab [6 [8 for loading dose] mg/kg IV q3w +]), stratified by met sites [≤2, > 2], lines of treatment for met disease [≤2, > 2, and chemotherapy choice [standard dose capecitabine, eribulin, gemcitabine, or vinorelbine].
primary endpoints are central blinded PFS and OS, assessed sequentially using the stratified log rank test. objective response rate [ORR] was a secondary endpoint. 257 PFS events were required to provide 90% power to show PFS superiority at 2 sided $\alpha = 0.05$.

results. intent to treat [ITT] analysis [536 pts: M 266; T 270] occurred after 265 PFS events. margetuximab prolonged PFS over trastuzumab [median 5.8 vs 4.9 mo.] treatment effects were more pronounced in patients with CD16A genotypes containing a 158F allele [median PFS 6.9 vs 5.1 mo.). in 524 patients with baseline measurable disease [M 262; T 262], ORR was higher with margetuximab [22%] vs trastuzumab [16%]. safety profiles were comparable in 529 patients who received study therapy. grade ≥3 AEs and serious AEs occurred in 138 [52%] and 39 [15%] vs 128 [48%] and 46 [17%] patients on margetuximab vs trastuzumab, respectively. PFS data cutoff: 10.10.18.

conclusions. margetuximab is a novel Fc engineered GER2 targeted antibody that stimulates mechansims of both innate and adaptive immunity. in patients with HER2+ MBC progressing after trastuzumab, pertuzumab, chemotherapy and T-DMI; in combination with chemotherapy in pretreated HER2+ MBC, margetuximab improves PFS over trastuzumab with comparable safety. this is the first prospective analysis of CD16A genotype as a predictor of efficacy from anti HER 2 therapy. CD16A genotyping suggests a differential benefit in patients with a 158F allele. OS data are maturing second interim OS analysis expected late 2019.

clinical trial information: NCT02492711

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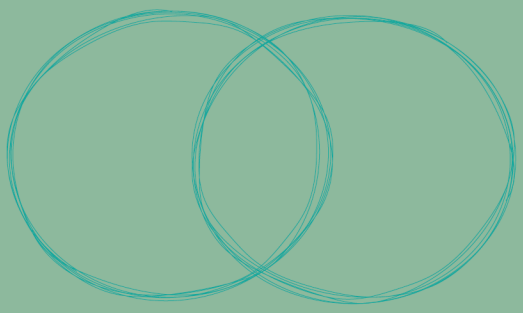

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