And I think there is, after your presentation going to have lots of time for questions. So it is my pleasure to introduce our next speaker. Doctor is Sophie. She's assistant professor in hematology and lymphoma specialist and transplant apparel excellence. An I think after amazing teamwork in a lot. A lot of work in around 2018 errors and team launched the car T cell program and will be hearing about the present and the future.

Thank you very much for the opportunity to present our work over the last one year.

So these are my disclosures. I won't be discussing any off label use of products.

So, just to start the talk. I like to give you a short background on the landscape of car T cell therapy. Then I will discuss some of the commercially available car T cell products. We have what the similarities and differences are between them and then I will introduce to you. Our program here at Yale. I'll provide an overview of the components that are needed for effective management of patients receiving immune effector cell therapy. The regulatory oversight. That’s necessary. And then I will present the outcome data on patients with treated here with commercial products.

I would also like to introduce you the newly created una factor cell therapy. Dart I will present the portfolio of clinical trials that we have and then finally I’d like to end by discussing some future developments in the car T Field, which I find very exciting.

So this is the total number of registered car T cell trials world wild and as you can see, there’s been an explosion in the field of cortisol therapy, especially in the last 4 to 5 years with currently almost 250 Carty clinical trials. Most of them being done in the United States and China but also Europe and since about 2016 industry has really taken over the conduct of this.
Of these clinical trials and these have to do with all the manufacturing costs. The development of new technologies and large scale production that’s necessary.

NOTE Confidence: 0.898651003837585

So how did this cord designs evolve overtime we started with first generation cars with an antigen recognition domain and one singling domain consisting of city 3 say to these cells had killing ability, but then they not multiply and persist very long and then we developed 2nd and 3rd generation cars that In addition to city 3. Zeta contained signal 2, either for 1BB or CD28 Co stimulatory domain, which gave them the ability to multiply secrets Idi kinds.

NOTE Confidence: 0.902677297592163

And persist the second generation cars are currently in late phase clinical trials and what’s actually on the market.

NOTE Confidence: 0.911300241947174

Since my clinical interest is in lymphoma, I will just illustrate with some of the trials and results that we have achieved in lymphoma treatment. So these are the 3 major anti city, 19 cortisol products for lymphoid malignancies.

NOTE Confidence: 0.878327548503876

Executed jeans, I’ll iluso evaluated in early phase. Zuma one clinical trial. This agenda clue sold in Juliet and Lisa Catagen. My loose all entrance end. The first two products are currently on the market. As of 2017 and the last is not yet FDA approved.

NOTE Confidence: 0.905467212200165

They have several differences that have outlined on the left so the construct is different. Some of them use CD 28 as the Co stimulatory domain and some for one BB.

NOTE Confidence: 0.882700264538888

The type of viral vector is different retroviral versus lentiviral. The last product on the right actually delivers the cells in a one to one city, 4 to CD8 ratio.

NOTE Confidence: 0.874444484710693

The dose of the T cell given T cells given was different between trials executed inside. Alusil trials did not allow any bridging therapy for the patients, whereas the other two trials. Most of the patients had received some sort of bridging therapy. The Limbo depletion that they received before car T cells was mostly consisting or fludarabine cytoxan, but the doses used were different.
Assume I won’t try allowed impatient only administration of these cells and that’s how it was approved whereas the other two trials allowed both inpatient and outpatient administration.

So just since I mentioned the city, 4 to CD8. Carty ratio and why that might be important. It is important to have less very variability in the final product specifications and the pure the T cells that are delivered the better the expansion. However, this process is actually very costly. You have to develop 2 cultures in parallel using several sita kinds. And when this product actually comes on the market. There may be a higher than expected rate.

So how does this affect outcomes these are patients with very aggressive relapsed refractory diffuse large B cell lymphoma, they had failed multiple lines of treatment, more than half of these patients had already progressed after an autologous transplant, and their two year overall survival was expected to be less than 10%.

So if we look if we take into account just the most aggressive Histology is you can see that the best overall response rate. There is between 40 and 80% with the best complete response rate of 40 to 62% and a six month. Complete response rate in these patients anywhere between 30 and 46% again. This was unthought of before the era of cortisol therapy and important to outline.

Is that data from both suma one and Juliet shows that patients who achieve remission at the three month mark and especially the patients who maintain their emission status at 6 months may be cured.

What about the toxicities the main types of toxicities we see in these patients are cytokine release syndrome and neurotoxicity and as you can see really great 3 or 4 cytokine release syndrome was seen in 11 percent 23 and 1% of patients with these products and grape 3 in about neurotoxicity, which is actually more common in lymphoma patients was anywhere between 12 to 32%.
Beside a kind release syndrome is typically treated with tocilizumab plus steroids whereas neurotoxicity typically treated with steroids.

NOTE Confidence: 0.923437714576721

Importantly, these trials use different toxicity grading scales and there are a lot of caveats in cross trial comparisons because different eligibility. Criteria were used, and even the dose levels of the T cells as I mentioned in the previous slides was different.

NOTE Confidence: 0.817493140697479

Cetis Agenda Clusa Lenexa Captain Sila Lucille, both targeting city 19 are approved and on the market since 2017.

NOTE Confidence: 0.900019586086273

T’s agenda clueso also treats B cell, acute lymphoblastic leukemia, is the only product currently approved for that indication up until the age of 25 and X accounted inside alusil. In addition to diffuse large B cell lymphoma. Untransformed follicular lymphoma is also approved for primary mediastinal B cell lymphoma.

NOTE Confidence: 0.904578924179077

This year, we expect approval of the 3rd product like socketed in Maluso in lymphoma and also very exciting and anti. BCM McCarty in multiple myeloma. I decapped agenda clue so the FDA issued a statement. In January of 2019 that by twenty twenty they expect to receive over 200. I Indies per year and by twenty twenty five they will be approving 10 to 20 cell and gene therapy products per year and they based that estimate on the current.

NOTE Confidence: 0.91961460800171

Pipeline and this success rates that are being seen.

NOTE Confidence: 0.90348207950592

So how do we select between these products? Well, there are product specific characteristics and also patient and center considerations. So Manufacturing is different. The Co stimulatory domain is different. The cell doses different. The veins vein type is different anywhere from 17 days to over a month. The type and dose of Limbo depletion used is different. The incidence and severity of toxicities an inpatient versus outpatient administration.

NOTE Confidence: 0.91345340013504

As far as patient and center considerations. We need to take into account how sick the patient is and how quickly does he or she need the product? What their age fitness and comorbidities are and what
the actual centers is access to does the center of access to all the commercially available products or not? What is the center’s clinical trial availability?

NOTE Confidence: 0.933290481567383

00:09:33.340 --> 00:09:41.380 Is there an ability for outpatient administration and what is the cost and reimbursement going to look like for the different products?

NOTE Confidence: 0.906796932220459

00:09:43.690 --> 00:09:49.810 So how did we build our team here at Yale? Well, we started very small?

NOTE Confidence: 0.652409553527832

00:09:51.400 --> 00:09:52.870.

NOTE Confidence: 0.917370438575745

00:09:53.870 --> 00:10:08.330 Lisa Barber wrote, I was a program manager and oncology nursing education practice and Kimberly Severino, who’s now smile performance. Manager were actually our first administrative champions, who laid the foundation for the program.

NOTE Confidence: 0.925609707832336

00:10:08.970 --> 00:10:31.500 We realized that we had to develop organ organizational structure. We need to train and educate staff. We had to look at our operational capabilities in the inpatient outpatient, setting in the MCU and ECC. We had to develop a specific budget for car T cell therapy and we also had to comply with the regulatory oversight.

NOTE Confidence: 0.925095617771149

00:10:34.080 --> 00:11:05.690 So we developed this steering committee to oversee the safety and progress of the Carty trials and to address any major operational and financial issues as well as to make key decisions and provide oversight 23 subcommittees. That was the Protocol Review Subcommittee. The inpatient outpatient care subcommittee and the cell collection and processing subcommittee. We needed to prioritize commercial products prioritized clinical trials, we needed to assess or?

NOTE Confidence: 0.892411172389984

00:11:05.690 --> 00:11:19.860 Resources and develop workflows for smooth transitioning of patients from the impatient to the outpatient setting and also workflows between a pheresis cell processing and nursing.

NOTE Confidence: 0.92551052570343

00:11:20.560 --> 00:11:46.340 This led to the eventual creation of the city safe committee, which took on some of the roles of the Protocol Review Committee. An it is now in place to ensure that we have adequate resources to run the
clinical trials and to also choose between commercially available products and to actually track the approved projects and resources that have been utilized.

NOTE Confidence: 0.902270078659058

We had to bring together a large steam team and these are some of the key stakeholders at Yale. We hired a new pro Carty Program Manager Katrina Baisakh and Accardi program. Edgector kindly cook with actually taken on the work initiated by Lisa and Kim and have played a major role in moving the program forward. We had, we identified empties that require training.

NOTE Confidence: 0.891438543796539

Not just from the transplant in Hematology Department, but also McHugh EG neurology neuron cology hospitalist team and the He Monk Fellows, who identified nursing personnel that needed to be trained on MP7 and NP Lebanon. Smilow McHugh emergency room. The Carty coordinators and navigators. The A Pheresis cell processing team pharmacy financial team social work, the epic team who put in place, the order set flags and banners. The data managers who would collect and report to the Center for international blood and marrow transplant inequality.

NOTE Confidence: 0.842621743679047

Improvement team.

NOTE Confidence: 0.885176241397858

So this is the IC program organizational chart. An I’d like to outline that in parallel to the adult program. We also launched the pediatric cortisol program led by Doctor Nikita Shah, who is director of the transplant pediatric transplant program. We have a clinical program, consisting of the empty physicians on the left. We have 7 dedicated APR NS and PS. We hired an outpatient transferred and Carty.

NOTE Confidence: 0.895574748516083

A PRN and we had, we have nursing representation from inpatient and outpatient units.

NOTE Confidence: 0.942186951637268

We have representation from the cell therapy and processing lab.

NOTE Confidence: 0.863213956356049

With medical director, Diane Kraus facility director Doctor Lexie Burson if another stem cell specialist. Donna summers and we have medical director of a pheresis doctor, Jeannie Hendrickson and facility director Doctor Edward slider.
So we realized that in addition to our institutional Carty training, we had to provide all the key Yale stakeholders Rams training. This stands for risk evaluation mitigation strategies. The FDA requires that drugs are biologics that have anticipated greater risks that the personnel be actually trained for Rams.

So all in all, we trained 453 team members and that included him transplant physicians. McHugh neuron call a GE D hospitalist team nursing stem cell transplant coordinators. The SWAT team members. The stem cell lab members 42 pharmacists and we're currently expanding this to NP12 with education of 22 more ahrens.

So fact is the foundation for accreditation of cellular therapy. It provides regulatory oversight. It’s a network of experts and peers who developed evidence based guidelines and standards that apply to cellular therapy processing manufacturing administration and clinical use.

Um accreditation is voluntary, but it does demonstrate the patients physicians manufacturers regulatory agencies and insurance companies that the program is committed to a certain level of quality and it is a requirement for center of excellence designation by insurance companies over 90% of transplant eligible programs hold fact accreditation.

There are some common fact standards that we abide by and then there are facts standards for immune effector cell therapy alone for that apply to programs only performing immune effector cell therapy. And when their effect. JC standards that apply to programs who administer both stem cell therapy an immune effector cell therapy under the same umbrella.

Out of 161 fact accredited transplant programs in the United States only 74. Holt fact immune effector cell therapy. Accreditation 73 of them under the transplant standards and one program accredited as a standalone immune effector cell therapy program under the icy standards.

So this is just an overview of transplant, and cell therapy program history at Yale. We were doing autologous transplants for lymphoma starting in 1994, then allogeneic transplant in 97, the unrelated donor
program started in 2000 haploid tentacle transplants for lymphomas. Starting in 2016 and now we’re offering car T cell therapy to lymphoma patients in 2019.

NOTE Confidence: 0.922937870025635

00:16:57.060 --> 00:17:28.640 The joint from the time that the Joint Steering Committee, was convened in January of 2018. We achieved certification to administer executed Gene Sidhu. So we formalize the city safe committee. We collected the first commercial patient in December of 2018. We hired our program manager and achieved a certification 40. Such an occlusal in January of 2019 and at that time, we treated our first commercial patient by July of 2019.

NOTE Confidence: 0.873568296432495

00:17:28.640 --> 00:17:30.550 We achieved fact accreditation.

NOTE Confidence: 0.889126896858215

00:17:32.260 --> 00:18:02.350 So this is 2019 at a glance. We’ve treated 27 patients 12 have been treated for lymphoma with commercial executed in silo. Lusso forward treated with TT’s agenda occlusal. One lymphoma patient was treated on a Phase 1 clinical protocol with an antibody couple T cell. Receptor cells with Rituxan. We treated 10 patients with multiple myeloma. Minor Phase 1 clinical trial with Anti BCM, a Messenger RNA car T cells.

NOTE Confidence: 0.873637974262238

00:18:02.460 --> 00:18:06.500 And we had two successful audits with kite and Novartis.

NOTE Confidence: 0.910051703453064

00:18:09.680 --> 00:18:27.620 These are the outcomes of our patients treated with commercial products again to remind you this patients had relapsed refractory disease and median survival expected less than 6 months, 12 were treated with AXA Cup to Gene and 4:00 with this agenda clueso.

NOTE Confidence: 0.934377253055573

00:18:28.120 --> 00:18:48.880 And you can see that the complete remission rate is about 50%. Here, we have 8 out of 16 patients in complete remission with a median follow-up of 6, 1/2 months. So the majority of those patients based on currently available data from Zuma, one and Juliet trials are expected to maintain their remission.

NOTE Confidence: 0.926274716854095

00:18:51.350 --> 00:19:00.670 They were heavily pre treated as you can see here there city, 3 absolute lymphocyte count is less than 10 times that of normal patients.

NOTE Confidence: 0.887739360332489
These are some of our metrics and toxicities post Carty infusion are medium length of stay was about 20 days. The median CRS the cytokine release syndrome onset was three days with duration of 5 days.

The median on set of neurotoxicity was 4 days with the majority of cases resolving within a few days. But one patient had to neurotoxicity that lasted for just over a month and the number of outpatient visits up. Today, 100 since discharged averaged 14.

We did not see any great 3 or 4 cytokine release syndrome, thankfully, we did see great or one and 2 and is expected and described in the literature. We saw about 26% Grade 3 and 4 neurotoxicity. There was 18% or so lizum abuse and 30. One percent steroid use.

I'll go into this quick case presentation. This is a 61 year old patient with double hit lymphoma with rearrangements of Semcken BCL 26. These double hit lymphoma’s are the poorest risk group of all LG cell lymphomas. The patient had significant hypercalcemia elevated LDH was treated with standard upfront or chop chemotherapy, but did not achieve remission was treated with Rice salvage chemotherapy followed by high dose beam chemotherapy and stem cell.

The patient maintain remission for a year and then re card was refractory to salvage chemotherapy was refractory to splenic radiation developed a large necrotic splenic mass with official extract into the stomach extension into the chest with a malignant pleural effusion lower mediastinal adenopathy with Asafa Geo compression and retroperitoneal disease.

We admitted the patient in May for AXA Cottage Inside Iluso. She received him for depletion with food. Arabin cytoxan developed great. One cytokine release and great for neurotoxicity developed stress cardiomyopathy required mechanical ventilation had prolonged cytopenias, despite into biotics develop strep Mitis Bacteremia and required prolonged TPN.

As you can see, there was complete resolution of her mediastinal retroperitoneal disease and splenic disease.
The fistula between the stomach and spleen is illustrated on the left and that has closed on the right with only a small remaining focus of uptake that has remained stable to slightly improved on cereal image Ng.

So this was really a success story for a patient who was as sick as she was.

So what does the future hold for these CAR T cell therapies? There are multiple trials that are looking at humanizing the SCF to prevent immune rejection relapses. There are dual targeting cars targeting two more than one antigen. For example, CD 19 and 22 or city, 19 and 20 to prevent antigen escape relapses their armored cars with enhanced function such as those secreting cytokinins.

In there are currently over 20 companies that are exploring gene editing such as placement of the antigen specific car under the transcriptional control of Track Locus. There are cars with modulated items and there are these super cars. Smart universal programmable cars where you have a universal receptor expressed on the T cell, but then you have a tumor targeting SEAV adapter molecule that you can change and target multiple antigens. The activity of these super cars can be finally regulated via multiple mechanisms.

To limit over activation and very exciting.

Is now the development of off the shelf aloe cartis? Where you can disrupt TCR expression to reduce rigidity or you can disrupt the beta 2, Microglobulin Locus to eliminate MHC one expression.

Given the explosion of technologies and the companies doing clinical trials. We decided it was time for us to create the immune effector cell therapy. Dart we hired a clinical child program. Manager Alexandra Dormal, who has done an incredible job at keeping our program together and building it along with us. We have members of the BMT and disease. Specific teams in the dart members of cell processing advanced cell therapy lab CRS cell project manager.
We have clinical research nurse and a clinical research coordinator, who we hired to expand the program. Data manager Chris Fernandez would stun an outstanding job because reporting these toxicities in real time in the Phase 1 trials is very important. These patients actually change their clinical status by the hour.

And this is our portfolio as you can see, there are many pending trials that are about to open in 2019, including some of the technologies I mentioned so we will have a by specific city, 19 city, 20 car. We will have a randomized trial, comparing car T cell to autologous stem cell transplant in lymphoma. We will have trials with off the shelf allogeneic or teeth cells in both T cell lymphoma.

And in renal cell carcinoma. I also wanted to outline a Yale IIT with tells led by doctor Michael Hurwitz. This is a Phase 2 study that will open this year, looking at autologous engineered autologous cells expressing by specific city, 20 and city 19 in refractory lymphomas an as you can see bottom right corner. This is in tandem. This technologies in tandem rear encoding. Two cars on the same chimeric protein using a single vector there also cars.

And then as I mentioned we will have these crisper trials that are.

This is a representation of the ones that Multiplex editing to produce this aloe car T cells. So TCR expression in the centre is disrupted using CRISPR CAS, 9 targeting the track locus to prevent GVHD. The Anti City 70 car construct is that inserted into the track locus by homology directed repair using a Navy template and then to enhance persistent. They may see one expression is illuminated by disrupting the beta 2 market globulin gene.
And finally we have collaboration with Doctor City Chan from a Department of genetics here looking and his technology with a dual car knock in an immune checkpoint gene knockout. The so called kick OSHA. Chico cells and we hope to develop our own IIT here in B cell malignancy’s targeting anti city, 19 in city, 20 and disrupting within 1.

What else is new in the Carl T world there’s a lot more going on. We are identifying new targets so CS one and GRC 5D and multiple myeloma are one in CLL CD-70 in renal cell cancer carcinoma in non Hodgkin Lymphoma Cloud in 18.2 in gastric and pancreatic adenocarcinoma. There’s going to be a revolution in the conditioning that we use pre Carty going a chemo radiation free route.

And antibody based.

There are NK car T cells that may play a good role in solid tumors and there are also nonviral gene delivery methods with many companies currently looking at this technology.

So I just wanted to give a big. Thank you to our patients and their families for having the courage to undergo this type of therapy with these expected side effects an for trusting us with their lives. I’d like to thank the administration led by Doctor Charlie Fuc and all of the support they gave to the building of the program.

I’d like to thank all the physicians involved doctor, Stewart Seropian. The director of the bone marrow transplant program doctor Steve Gore, who is leading the the city safe committee. A doctor Nikita Shah from Pediatrics. Doctor Diane Kraus and the advanced cell therapy lab doctor. Burson EV and the cell therapy processing team doctor Jeannie Hendrickson and they pheresis team doctor bearing from neuron cology doctor her lotion epilepsy team, Peter Marshall and John Signer from McHugh.

Bonnie Ruth Burke from ECC the emergency Department team and again just to go back to our program managers. I cannot think Lisa Barber Open. Kim severino enough for laying the foundations for the program and now Katrina and Alexandra moving both the Carty commercial
program and the clinical trial program forwards Catherine Product, whose are coordinator, Melanie champion who’s our quality manager.

00:29:16.990 --> 00:29:20.720 An epic legal team and also our marketing team.

00:29:22.180 --> 00:29:24.830 And with that I’m happy to take questions.

00:29:31.380 --> 00:29:33.200 We have time for questions.

00:29:37.110 --> 00:30:25.850 There Is everybody’s stunned I think the one thing that one question. I have anything in the pipeline for leukemia. Myeloid is very absent in your list of cartys so actually.

00:30:25.850 --> 00:30:49.240 To either that or observation and you know the as you well know it is difficult, with to target AML with car T cell therapy. But I think we have more trials in the pipeline that are coming through tomorrow for AML with crisper technologies.

00:30:51.980 --> 00:30:49.240 It’s not we’re planning to have a trial in leukemia, I may have overlooked that there but we have an AML trial coming up where we have tumor associated anted where the T cells are stimulated with ABC’s that are that are prepped with this pet mixes with these different tumor. Associated antigens so that trial will take place in post looking at relapse patients and we’ll randomize patients who are negative for minimal residual disease.

00:31:22.460 --> 00:31:54.450 There are somewhere at the time from 375 to 475 thousand dollars and that we're getting paid for that separately, but actual reimbursement for taking care of the patients and covering their McHugh stay should they need it is very low. I mean that’s projected to improve to some
extent, but I don’t think we will necessarily get paid 100% for doing this so I think we need to do things.

NOTE Confidence: 0.90811550617218

00:31:54.450 --> 00:32:14.900 Internally, such as as we have started to do now, that we have treated the first thirty patients were trying to move the conditioning to the outpatient setting we’re trying to manage them in the postcard T period. More outpatient in our day hospital and then you know the hope is that in the future.

NOTE Confidence: 0.928348302841187

00:32:15.590 --> 00:32:38.800 These technologies will become cheaper so they will not be as centralized some at least 1 institution has done this point of care using the Milton E prodigy device and the cost of doing that is only a few $1000. So I think that this is going to change once more products are approved and there’s competition.

NOTE Confidence: 0.906322062015533

00:32:39.550 --> 00:33:10.500 And you know for IIT’s that aspect of it is extremely difficult cause. Even the institutions who started this work like U Penn and the Fred Hutch ultimately needed to collaborate with Pharma Becaus. It’s so difficult to run. These these trials in large scale so it’s very difficult. But we are trying to obtain some find it funding to at least start our first I it internally and we’re always looking for.

NOTE Confidence: 0.945646941661835

00:33:10.500 --> 00:33:22.490 Collaborators and that’s why this was a good opportunity to present here to see if there are internal people who might have an interest in developing or internal Phase 1 portfolio.

NOTE Confidence: 0.877315402030945

00:33:23.290 --> 00:33:50.500 Yes, thank you. You mentioned 30 patients and 64 on the slide. An my question is what are you projecting for say the next 5 years? Yeah, so already we exceeded our expectations for the first year I think I’m we’re currently projecting.

NOTE Confidence: 0.920406937599182

00:33:51.080 --> 00:34:21.090 About 40 patients this year, just based on how many patients with treated so far, but I think as you saw we have a long list of pending trials and I think that number is going to be much higher. One thing to know is that these therapies have extended now beyond lymphoma and we are treating such a large multiple myeloma population here that once we start those click in also when they get the therapies get approved for adult piece LLL.
Which will happen in the near future? I think that it’s not unreasonable to think that the number is going might approach 100.

GOOD, that’s very impressive virus, I must say I said the really neat program. How far along are you in the pancreas studying what targets are you using in pancreas cancer sofa surfer pancreas. We haven’t started the study here yet, so we hope to start. It also in 2020. The target for that is a PS CA. There are Phase 1 trials that have been run.

Elsewhere, with pancreatic cancer mesothelioma ovarian cancer that I’ve seen and also prostate cancer again. They all have treated very few patients so far. It’s very challenging to apply. These technologies to solid tumors. We have to deal with a micro environment and we haven’t really found a good way to get to that and maybe the NK cells or even off the shelf and case cells we will have.

Might be able to.

To help us target that solid tumor population, but so far. We only have the breast cancer trial. That’s open here. We don’t have the pancreatic yet.

I just wanted to augment the answer to Roy about the finances. We had our first look at the first year of experience and honestly, most places that have launched car have taken a economic bloodbath. Cosmo Hospital is a little bit prepared for through really very aggressive work on our contract ING people and it’s really a lot of case by case management and we’ve had a fair number of Medicare and Medicaid patients that were treated.

At least in terms of direct costs were doing extraordinarily well and I think everybody couldn’t be happier. That’s not to say it’s not a challenge, particularly how to pay for the IIT’s but the insurance. I think the coverage is going to become more uniform and clear which hopefully will include the opportunity to treat with phase ones as if they were commercial drugs. Although we still need to obviously have the venture capital to build the I ate product but I really just.
I have to augment what euroset about the great teamwork and very careful planning that Rogerio and Kathy Lions really started. It’s been a really hugely successful rollout and I think it knock on wood really couldn’t have been any better, so then thanks to Eris for heading it up.

OK, well, let’s think both of our speakers doctor Lim.