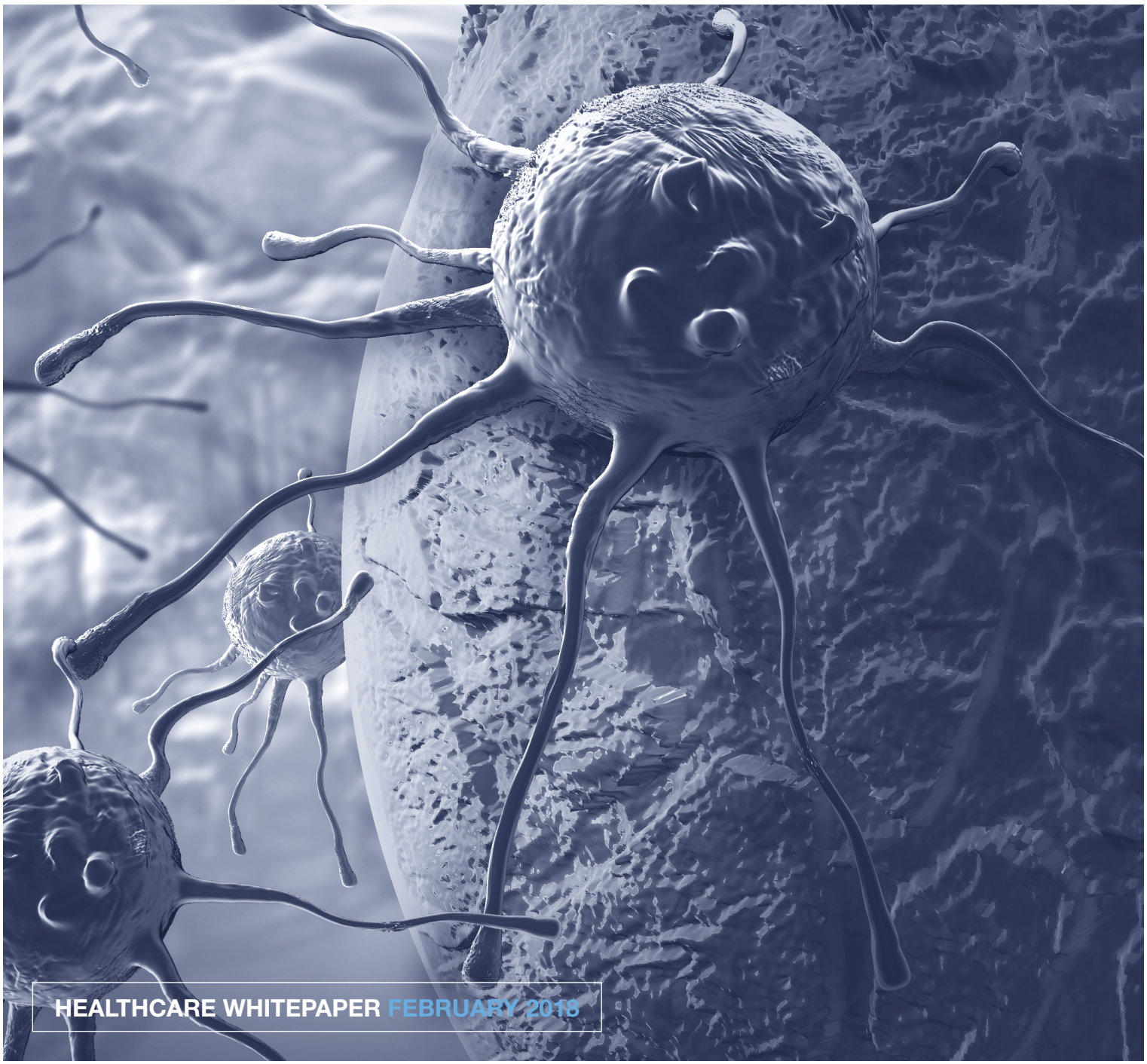
BRYAN, GARNIER & CO

Advancing Therapies

2017'S MOST IMPORTANT ONCOLOGY AND HAEMATOLOGY TREATMENTS REVIEWED



HEALTHCARE WHITEPAPER FEBRUARY 2018

Contents

As always, 2017 was rich in major advances in the field of haemato-oncology. This white paper provides a summary of the key take-aways of the year, including ESMO and ASH meetings, where central questions were raised in oncology and haematology respectively.

This report will therefore take lung cancer and B-cell lymphoma as illustrations of key advances of 2017 and while they are not exhaustive at all of what happened last year, are representative of segments which are being transformed by some game-changing technologies like immuno-oncology drugs and CAR-T therapies.

ERIC LE BERRIGAUD
Managing Partner
Equity Research Analyst
Pharmaceuticals

MARION LEVI
Equity Research Analyst
Biotechnology

Part 1: IO to be the backbone in the treatment of NSCLC… until when?

Lung cancer is the leading cause of cancer mortality with about 1.8 million newly-diagnosed cases per year and a growing incidence worldwide despite the first signs of a decline in the Western part of the world (mainly as a consequence of a declining exposure to asbestos).

Now, behind lung cancer is a wide variety of different diseases and we will here only address the non-small cell (NSC) form of lung cancers, which are said to represent about 85% of the total. Within NSC lung cancers, three main types are then often described (adenocarcinoma, squamous cell carcinoma and large-cell carcinoma) but this is not how we will approach the stratification here. Most, if not all, of the theraputic options we are talking about, either in the targeted category or in the IO field, are usually referring to stage IV NSCLC, i.e. the most advanced form which corresponds to the metastatic forms of the disease.

FIG. 1: CURRENT SOC GIVES LOW mOS FOR NON-METASTATIC CANCER TYPE

- 1980: radiotherapy alone: median OS 10 m
- 1990: chemotherapy added: median OS 14 m

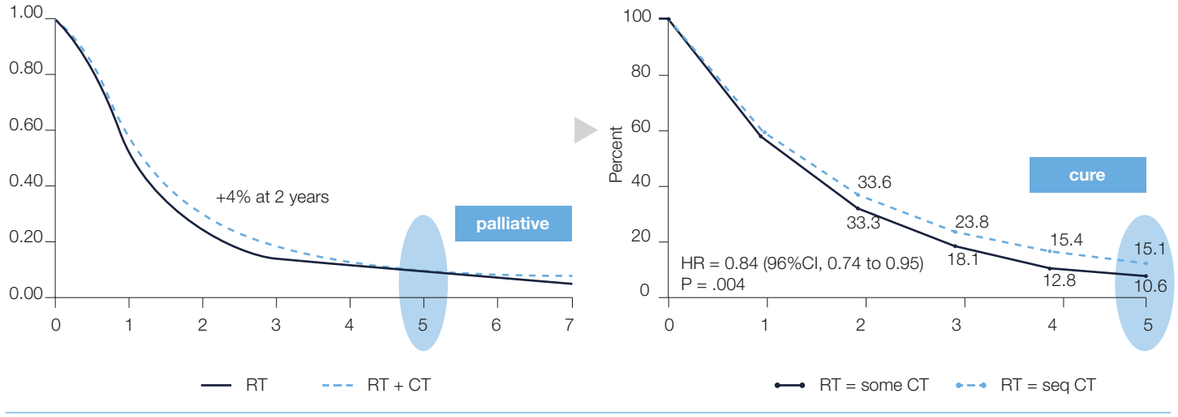
Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

PACIFIC – SETTING
> unresectable stage III NSCLC

- 2000: concurrent chemoradiotherapy: median OS 18 m

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell lung cancer

SURVIVAL



Source: Presentation at ESMO 2017

Data on last line/advanced disease

This year at ESMO, several data were presented that we believe will be practice-changing in their respective segments of NSCLC. In this white paper, we choose to focus on three main trials assessing promising drug-candidates in the advanced lines of NSCLC: PACIFIC, FLAURA and IMPower150. One is a new therapeutic option when there was none in stage III unresectable NSCLC after CT and RT (PACIFIC) with durvalumab monotherapy (AstraZeneca); the second is a marked improvement vs current SoC

FIG. 2: A VERY HOMOGENEOUS ANALYSIS OF mPFS BY SUBGROUPS

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All Patients	476	237	0.55 (0.45-0.68)
Sex			
Male	334	166	0.56 (0.44-0.71)
Female	142	71	0.54 (0.37-0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32-0.57)
≥65 yr	215	107	0.74 (0.54-1.01)
Smoking status			
Smoker	433	216	0.59 (0.47-0.73)
Nonsmoker	43	21	0.29 (0.15-0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40-0.71)
IIIB	212	107	0.59 (0.44-0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50-0.92)
Nonsquamous	252	135	0.45 (0.33-0.59)
Best response			
Complete response	9	7	–
Partial Response	232	111	0.55 (0.41-0.75)
Stable disease	222	114	0.55 (0.41-0.74)
PD-L1 status			
≤25%	115	44	0.41 (0.26-0.65)
<25%	187	105	0.59 (0.43-0.82)
Unknown	174	88	0.59 (0.42-0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35-1.64)
Negative	315	165	0.47 (0.36-0.60)
Unknown	132	58	0.79 (0.52-1.20)

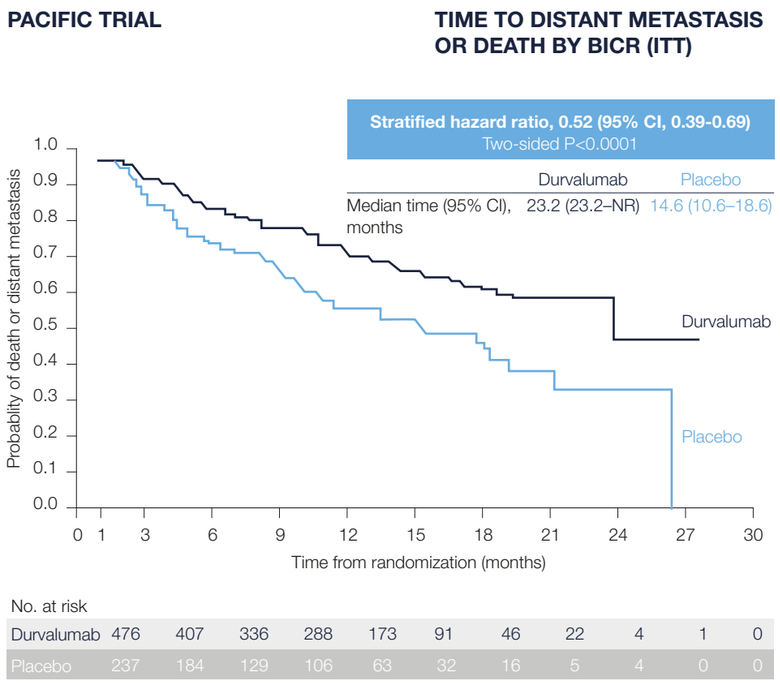
Source: The New England Journal of Medicine (NEJM)

in EGFR mutation-positive NSCLC with more potent TKI osimertinib (FLAURA, an AstraZeneca-sponsored study); and the third, is a combination of Tecentriq (Roche) with CT and with or without Avastin in stage IV non-squamous NSCLC patients without ALK and EGFR mutations and who had not been treated with chemotherapy (IMPower150).

PACIFIC UNVEILS UNEXPECTEDLY HIGH mPFS

PACIFIC was designed to recruit all-comers patients, provided they had stage III locally-advanced, non resectable NSCLC that has not progressed after concurrent chemoradiotherapy (cCRT) of two or more cycles. After randomization, 476 were allocated to the durvalumab arm (given at the 10 mg/kg dose every two weeks for up to 12 months) and 237 to the placebo arm.

FIG. 3: TIME TO DISTANT METS INCREASED VERY SIGNIFICANTLY



Source: Presentation at ESMO 2017, AstraZeneca

As shown in Fig.1, the current SoC in unresectable stage III NSCLC, i.e. cCRT, established almost two decades ago, is not offering more than 18 months of median overall survival (mOS) and has not since then been seriously investigated with new agents, until PACIFIC. Considering how much IO had already impacted the treatment paradigm in stage IV NSCLC, there were high hopes that durvalumab might be equally beneficial in stage III NSCLC (the trial was known to be positive).

The study remained blinded to OS until the pre-planned number of deaths was reached to get the final analysis. The study has been designed in such a way that it has a greater than 85% power to detect an HR of 0.73 with 491 deaths. Median PFS was the primary endpoint of the PACIFIC trial and this was met in a highly significant manner since median PFS was brought from 5.6 months with the placebo up to 16.8 months in the durvalumab arm, representing a HR of 0.52 or a 48% risk reduction of disease progression or death. We do not report here the PFS curves but it was also pleasant to note that the curves separated very early (during the second month) and stayed well separated over the observation period. What we report in Fig.2 is how homogeneously mPFS was improved across most, if not all, pre-specified subgroups, irrespective of age, smoking status, response rate to cCRT, histology and even more interestingly PD-L1 status. No testing for PD-L1 levels of expression should be needed before initiating treatment with durvalumab if it is approved. If any, the only subgroup where the benefit looks less well established is in EGFR-mutation positive patients but this pool of patients was very small (43 in total).

The second very interesting piece of information we obtained to measure the magnitude of the benefit of durvalumab in this setting was the report assessing the impact of treatment vs observation on the time to distant metastasis or death, which is a slightly different measure of risk reduction of disease progression. This does not only reflect the recurrence of the disease but also its spread to a distant organ, actually representing progression from stage III to stage IV. And the result is equally positive, as illustrated in Fig.3, since the risk of developing distant mets or death is reduced by 48% too, with a very similar curve pattern to mPFS.

Moreover, although OS data are still immature, discussant Prof. Johan Vansteenkiste (University Hospital Leuven, Belgium) said that if distant mets are not OS, they are a good indicator in stage III NSCLC and confirm the thesis that radiotherapy and CPI immunotherapy “can be excellent partners” since RT promotes release of danger chemokines and release of neo-antigens and upregulates PD-1/PD-L1.

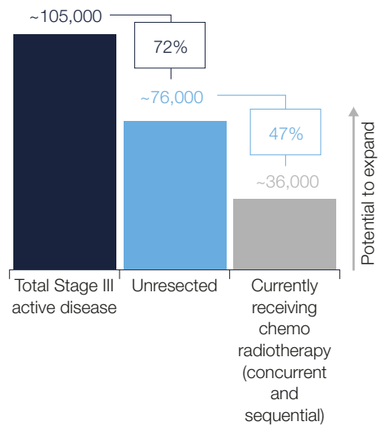
Last but not least, for a loco-regional form of NSCLC where observation was recommended post cCRT, safety is key to change practice. If, as stated above, cCRT is the preferred option in stage III unresectable NSCLC, it is however associated with a high rate of reversible oesophagitis and, more concerning, grade 3 or higher radiation pneumonitis (60-66 Gy in 30-33 daily fractions is recommended for cCRT whereas the max overall treatment time should not exceed 7 weeks). So, in PACIFIC, the rate of pulmonary side-effects when adding durvalumab in the maintenance phase were particularly observed.

Even though side-effects were more frequent in the active arm, few were of grade 3 or 4. Total grade 3-4 side-effects were seen in 29.9% of patients in the durvalumab arm vs 26.1% in the placebo arm, including 3.4% vs 2.6% of pneumonitis and radiation pneumonitis. So, from a safety perspective too, durvalumab as a 12-month maintenance therapy looks like a very valuable, clinically-positive new therapeutic option for stage III unresectable NSCLC. So much so that discussant Prof. Vansteenkiste referred to it as a “tsunami” and concluded about PACIFIC by saying that it was “the first strong interim-PFS positive phase III trial on systemic therapy for stage III NSCLC over decades”.

It is estimated that about 20%-30% of lung cancers are diagnosed when they are in stage III. This translates into an epidemiology of about 100,000-105,000 new patients per year for the G7 market.

Five-year survival rates for these patients remain low. Based on relatively old databases, the American Cancer Society suggests 14% for stage IIIA and 5% for stage IIIB. However, more recent but less documented sources suggest 23% and 10% respectively. In any case, there is a clear unmet medical need left for this disease, hence the excitement around PACIFIC. Dr David Planchard (Institut Gustave Roussy, Villejuif, France), who was invited by AstraZeneca to discuss the results, estimated that about only 15% of

FIG. 4: ESTIMATE SHOWING MARKET POTENTIAL



Source: AstraZeneca, presentation made at the ESMO congress in September 2017

patients with stage III NSCLC have long-term remission.

Now, considering the design of the PACIFIC trial and, in particular, the eligible population, AstraZeneca estimates that about 35-40% of the total market could be addressed by durvalumab as a maintenance therapy if only unresectable patients having received and being stable after CRT are considered (see Fig.22).

The addressable market would therefore be about 36,000 patients per year in the G7 world only. There are obviously other markets outside the G7 which will contribute to Imfinzi's sales.

FLAURA: SHOULD THE WINNER TAKE IT ALL?

This study aims to assess Tagrisso's efficacy in patients suffering from advanced NSCLC and known to be carrying an EGFR mutation.
This specificity gives to the patients a particular profile sensitive to certain therapeutic strategies. EGFR-mutation positive NSCLC is known to represent about 10-15% of all lung cancers. These patients with NSCLC correspond to those whose tumors have EGFR exon 19 deletion or exon 21 substitution mutations, easily detected by companion diagnostic tests like Cobas EGFR Mutation Test or Therascreen EGFR Test.

It is usually considered that Tagrisso is the first member of the third generation of tyrosine-kinase inhibitors (TKi) which have been specifically designed for use in patients with EGFR+ NSCLC since they produced the higher response rates, longer PFS and improved QoL compared to standard platinum-based doublet CT. First generation TKis is composed of gefitinib (Iressa) and erlotinib (Tarceva). Second generation TKis is made up of afatinib (Boehringer Ingelheim) and dacomitinib (Pfizer) and present the advantage of blocking a wider range of signalling pathways, resulting in an increased efficacy, although all differences were not statistically and clinically meaningful while dose reductions are commonly performed to avoid severe toxicities.

Now the majority of patients treated with any of the EGFR+ TKis of first or second generation will progress after 9-12 months of treatment since various mechanisms of resistance will develop. However, the most common of these mechanisms (50-60%) is the acquisition of a single recurrent missense mutation within exon 20 called T790M mutation. This mutation leads to the substitution of threonine by methionine at position 790, resulting in increased affinity for ATP, causing resistance to competitive inhibition by EGFR TKis.

In order to specifically address this issue, AstraZeneca has designed a third generation EGFR TKi called osimertinib which not only irreversibly binds to the kinase domain of the receptors but has activity against T790M mutations.

As a consequence, Tagrisso was approved in late 2015 in the US and early 2016 in Europe as a once-daily oral 80-mg tablet for the treatment of EGFR+ T790+ NSCLC detected by appropriate tests when the previous first generation TKis have failed. This was based on the results of the open-label phase III trial AURA3 which demonstrated a clear improvement in the median PFS with the risk of disease progression reduced by 70% (HR=0.30), including in those with CNS metastases.

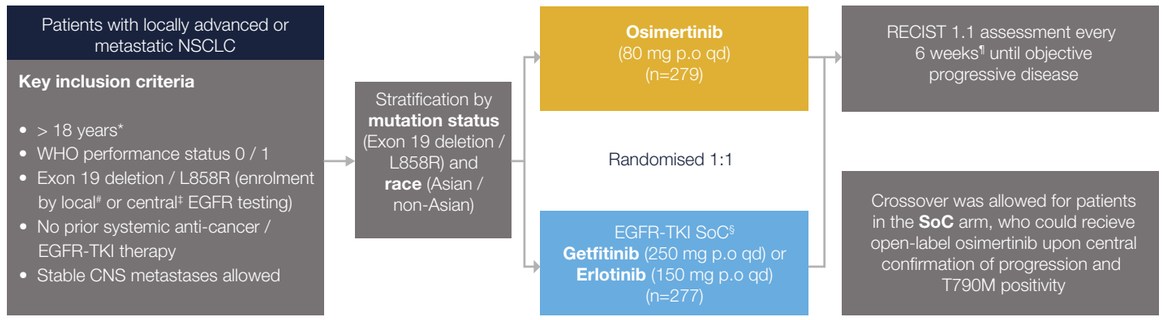
In FLAURA, what AstraZeneca wanted to test was the hypothesis that osimertinib had the characteristics to improve outcomes in EGFR-mutation positive NSCLC naïve patients compared to first-generation TKis (Iressa and Tarceva were both tested as comparators), i.e. to represent a new standard-of-care in this setting. Answering 'yes to the question would allow Tagrisso not only to move from 2L/3L to 1L but, equally importantly, to remove the selection of patients based on T790 mutation testing.

The efficacy results were simply outstanding when considering that the comparative arm was composed of other EGFR TKis. Not only was the primary endpoint of median PFS reached with high statistical

FIG. 5: DESIGN OF FLAURA PHASE III TRIAL

FLAURA TRIAL

FLAURA DOUBLE-BLIND STUDY DESIGN



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) a two-sided alpha-level of 5%

Source: AstraZeneca, presentation made at the ESMO congress in September 2017

significance but this was true across all the subgroups as illustrated in Fig.6. Median PFS was increased from 10.2 months to 18.9 months (HR=0.46) and the results were very homogeneous across the various subgroups, irrespective of the type of EGFR mutation, of the history of smoking and maybe more importantly of the presence or not of CNS mets, which was not the case with older EGFR TKis, whereas it is associated with a poorer prognosis for the patient.

Improved blood-brain penetration of osimertinib compared to first generation compounds is obviously a major argument for use of Tagrisso in early lines of treatment. Obviously, the only missing element at the present time is OS and data in both AURA3 and FLAURA now have to mature. That said, with the very rapid separation of the curves and the benefit on brain mets, the likelihood of an OS benefit is high. The interim analysis already showed HR of 0.63 with a p-value of 0.0068 whereas at the 25% maturity point a p-value below 0.0015 would have been needed to reach statistical significance, but the signal is already very strong. The only limit to a proper reading of the survival benefit with osimertinib is the possibility offered in FLAURA to cross-over patients in the SoC arm upon confirmation of progression and T790M positivity. The percentage of patients who are likely to receive osimertinib in 2L is therefore quite high and will increase with time, representing a risk of a confounding data reading. However, we believe that a DCO at 50% maturity is very likely to show a significant OS benefit in favour of osimertinib without too much influence from cross-over at this stage yet.

At this point we would like to address the question of the right sequence, with some being tempted to keep osimertinib for 2L because, if used in 1L, it would leave physicians with no valuable option thereafter.

As mentioned by Prof. Jean-Charles Soria (IGR, Villejuif), the issue is that "only" 50-70% of EGFR+ patients are moving from 1L to 2L at some point and to get Tagrisso in 2L one has to have the T790M mutation and "only" about 60% do so. Altogether this represents a loss of chance which is unacceptable to take.

Moving to safety, the results can be considered as equally good and this is where osimertinib differentiates the most from second-generation EGFR TKis afatinib and dacomitinib against which it has not been compared. Although they can be considered as challengers to erlotinib and gefitinib, they have demonstrated superiority in ORR and PFS against them and can therefore be considered as more potent. But patients were not allowed to receive one of the two more recently-marketed drugs, which could have left open the question as to whether osimertinib would have been as effective against them.

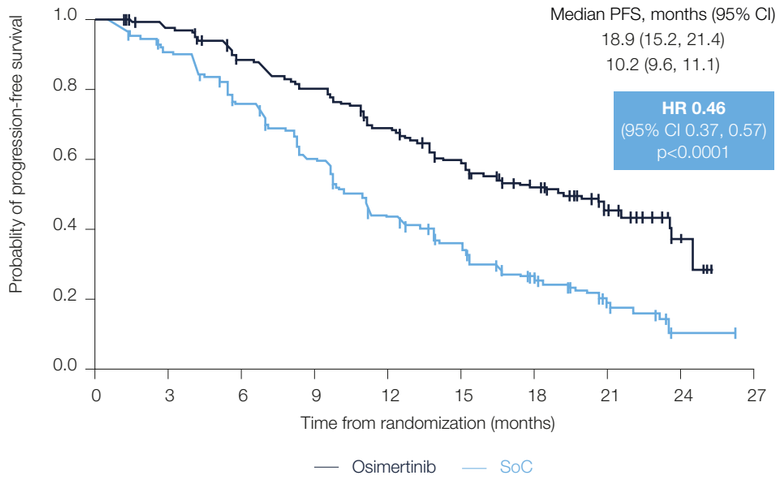
However, if PFS data suggest superiority anyway, Fig.8 shows clearly where osimertinib is undoubtedly better: on safety. In FLAURA, patients receiving osimertinib where only 18% likely to develop drug-related adverse events

FIG. 6A: REPRESENTATION OF PFS DATA IN FLAURA

FLAURA TRIAL

PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 EVENTS IN 556 PATIENTS AT DCO: 62% MATURITY; OSIMERTINIB: 136 EVENTS (49%), SoC: 206 EVENTS (74%)



No. at risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
SoC	277	239	197	152	107	78	37	10	2	0

Source: AstraZeneca, presentation made at the ESMO congress in September 2017

of grade 3 or more, i.e. 10% less than with SoC. Both the principal investigator and the discussant of FLAURA made the definitive statement that "safety with osimertinib is much better" than with second-gen EGFR TKis.

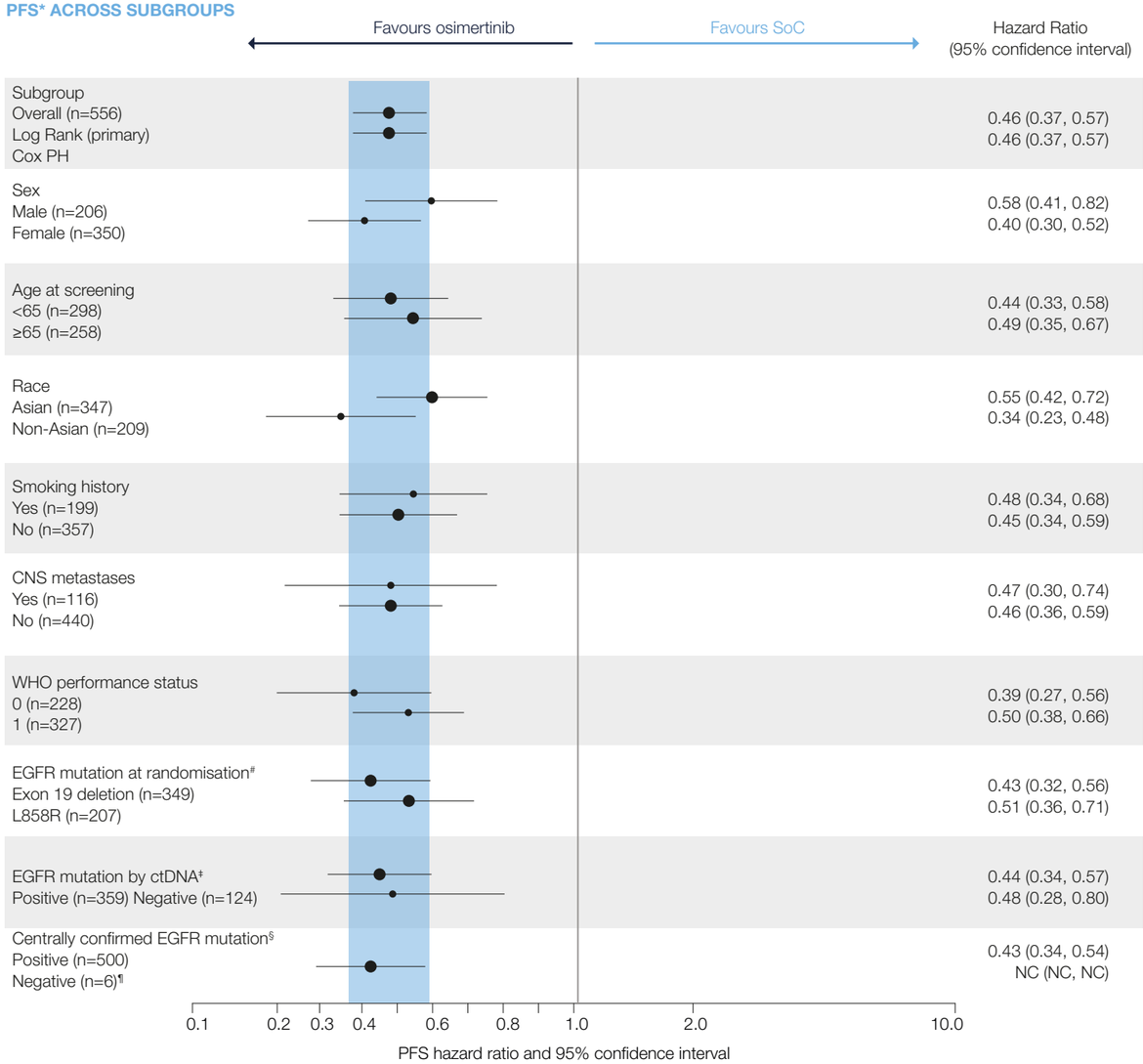
According to Prof Mok, FLAURA is "a winner", but the question of "can it take all the market?" remains open. In our view, FLAURA benefits from two main advantages,

i.e. (i) osimertinib has a meaningful impact on CNS metastases and works equally well irrespective of the presence or not of brain mets; (ii) the results compared well with second-generation TKis too, notably on the toxicity side.

FIG. 6B: REPRESENTATION OF PFS DATA IN FLAURA

PACIFIC TRIAL

PFS* ACROSS SUBGROUPS



Source: AstraZeneca, presentation made at the ESMO congress in September 2017

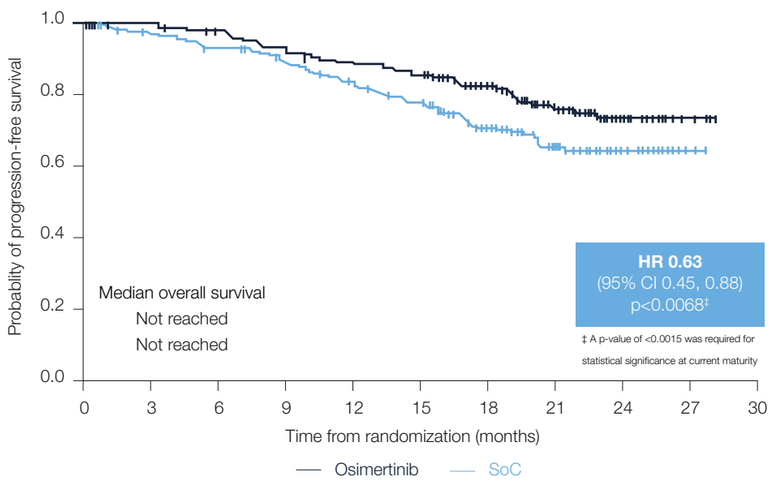
Therefore, the only real remaining question is that of the optimal sequence of treatment because using Tagrisso in 2L when the patient develops T790M mutations has very meaningfully increased OS to about 27 months. As a consequence, in order to fully back the use of osimertinib in 1L, the drug would have to show "significantly higher than 30 months" median survival. The data will be updated once AURA3 delivers its full and final set of data (PFS HR was 0.30). Now as said before, we see the possibility of keeping Tagrisso for 2L as a loss of chance for the patients since there is no means to detect who will develop the T790M mutation beforehand and that only a subset of patients will be able to benefit from it in 2L (some will die before they have a chance to receive 2L and some will develop metastases). We see FLAURA as a very well-designed, highly significant and conclusive phase III head-to-head trial and, once the results are reflected in the label, we expect a massive adoption of Tagrisso in 1L EGFR mutation-positive NSCLC.

FIG. 7: ENCOURAGING (ALTHOUGH IMMATURE) OS DATA

FLAURA TRIAL

OVERALL SURIVIAL INTERIM ANALYSIS

141 DEATHS IN 556 PATIENTS AT DCO: 25% MATURITY; OSIMERTINIB: 58 DEATHS (21%), SoC: 83 DEATHS (30%)



No. at risk											
Osimertinib	279	276	269	253	243	232	154	87	29	4	4
SoC	277	263	252	237	218	200	126	64	24	1	0

Source: AstraZeneca, presentation made at the ESMO congress in September 2017

IMPOWER150: THE MUTATIONAL LOAD IS KEY

During the breakfast meeting that we organized with a KOL in Paris, he mainly confirmed our thoughts about PACIFIC and FLAURA, and most of the time was spent putting IMpower150 data in perspective in stage IV NSCLC. First of all, pembrolizumab looks like a no-brainer in PD-L1 high expressers and the drug will be difficult to challenge. Thereafter and in short, Roche may benefit from a first-mover advantage in PD-L1 low-to-no expressers with its quadruple therapy but the speaker doubted it would become a durable standard option. In 1L, physicians would like to remove CT and reduce toxicity as much as possible and this is not what cohort B in IMpower150 is about. Many studies with a read-out in 2018 should help think about a hierarchy.

If we now look at the epidemiology of the disease, we see that EGFR mutation-positive NSCLC is very heterogeneously distributed over the globe with a relatively low prevalence in the western world where they usually represent about 10% of all NSCLC whereas it is about 40% in Asia.

About 60% of lung cancers are diagnosed when already at stage IV. The first decision is then to identify a possible molecular alteration, which happens in about 15-20% of all cases, the first of which being EGFR mutation (10-12%), while others are much less frequent (ALK, B-Raf, ROS-1…) with very limited overlap. When there is such a mutation, then targeted therapy is what gives the best responses and here the speaker advocated very clearly in favour of Tagrisso and Alecensa respectively for EGFR+ and ALK+ NSCLC. In their respective settings, they are very comparable drugs and are very likely to become SoC since duration of response is much longer, efficacy to prevent metastases much higher and toxicity lower. It has to be stressed that next-generation ALK inhibitors are already in phase III whereas no fourth-generation EGFR TKi has been identified.

When there is no alteration, which is the central case, there are two cases: epidermoid carcinoma (or squamous-cell) and adenocarcinoma or non-squamous cell carcinoma with an incidence of 30% and 70% respectively. In first-line of treatment, before IO started delivering some results in recent years, SoC was CT. Over time, CT used changed and Alimta/platinum tended to become standard both because it was less toxic than CarboTax but also because number of CT cycles was reduced from 6 to 4. In non-sq-NSCLC, Avastin was eventually an add-on to CarboTax but its penetration is variable and much lower in Europe vs the US (no more than 30% in France for instance).

Then came a wave of phase I/II trial results with CHECKMATE-026 and KEYNOTE-024 in particular with a clear advantage going to pembrolizumab suggesting that all drugs in the class are not equal. Even when restating results with similar PD-L1 cut-off, nivolumab does not seem as potent as pembrolizumab. Now, PD-L1 status is tested at the same time as EGFR and ALK and if and when it is at about or above 50%, then pembrolizumab monotherapy is the new standard.

FIG. 8: COMPARATIVE TKI-RELATED TOXICITY AMONG RECENT TK INHIBITORS

	Drug	Sample size	RR	PFS	OS	
FLAURA	Osimertinib	279	80%		NR	HR 0.63 (0.45-0.88) p=0.0068
	Gefitinib or erlotinib	277	76%	10.2m	NR	
LUX Lung 7	Afatinib	160	70%		27.9m	HR 0.85 (0.66-1.09) p=0.1950
	Gefitinib	159	56%	10.9m	24.5m	
ARCHER 1050	Dacomitinib	227	75%		NA	NA
	Gefitinib	225	71.2%	9.2m	NA	

Ramalingham et al ESMO 2017; Park et al Lancet Oncology 2016; Mok et al ASCO 2017

Source: Presentation at ESMO 2017 (discussant Pr Tony Mok, Hong-Kong)

Even if other PD-1 or PD-L1 agents show benefit in monotherapy in 1L NSCLC, the speaker considers it difficult to challenge the now-acquired strong position of pembrolizumab, which recently delivered an impressive median OS of 30 months (vs 14.2 months, HR=0.63), similar to what is achieved with EGFR or ALK inhibitors.

The question which comes next is whether a combination can do better than monotherapy but even more importantly, what kind of equivalent improvement can be made for those who are not PD-L1 high expressers (i.e. about 70% of tested patients at this stage). First interesting data from this perspective came from KEYNOTE-021 cohort G phase II trial which, despite a relatively small number of patients, delivered very solid results both in PFS and in OS. Use in combination with Alimta/platinum is also perceived positive. Although the results were validated by the FDA, the BLA was withdrawn

in Europe where phase III data are required to get an approval.
Our speaker said that should KEYNOTE 189 more or less reproduce phase II data, the vast majority of physicians would opt for it unless IO/IO combinations show outstanding OS data.

So what about IMpower150? Feedback was mixed to say the least. On the one hand, it is the first well-designed sizeable phase III study to show a clear benefit in 1L sq-NSCLC with a lot of granularity into subgroup analysis.

IMpower150 is a multicentric, open-label, randomized, and controlled Phase III study evaluating the efficacy and safety of TECENTRIQ in combination with chemotherapy (carboplatin and paclitaxel) with or without Avastin in people with stage IV non-squamous NSCLC who had not been treated with chemotherapy for their advanced disease. It enrolled 1,202 people of which those with ALK* and EGFR mutations were excluded from the primary ITT analysis. People were randomized (1:1:1) to receive:

- TECENTRIQ plus carboplatin and paclitaxel (Arm A), or
- TECENTRIQ and Avastin plus carboplatin and paclitaxel (Arm B), or
- Avastin plus carboplatin and paclitaxel (Arm C, control arm).

So, the first step was to compare arm B with arm C and what is seen as positive is the number of patients neither progressing nor dead at 12 months (37% vs 18%) because what is carried after is duration of response. More mature OS data are awaited since preliminary data (HR=0.775, 19.2 vs 14.4 months) very not impressive. Equally, the expert was not impressed by the Teff-high stratification since Teff-high and PD-L1 high expressers did show almost similar benefit (while it takes more time and is more expensive).

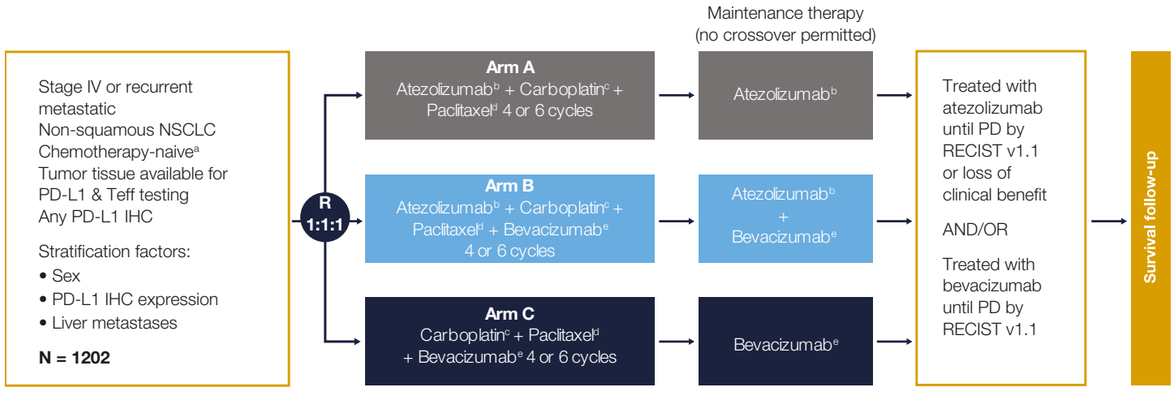
Last but not least in relation to IMpower150, the single slide show which compared arm A with arm C was very disappointing: no difference in ORR and HR of 0.88 and 0.94 for OS and PFS respectively. This could mean that it is either a quadruple combination or nothing to show a benefit in first-line. Whether data are strong enough to support a return to/ an adoption of a CarboTax/ Avastin companion regime is uncertain.
It could be the case only during a transient period until something more convincing in terms of balance between survival and toxicity emerges. It has to be noted that the discontinuation rate due to side effects in arm B was 33%.

In summary, for PD-L1 low expressers, SoC is CT today and is likely to become CT/Avastin/ atezo tomorrow but for a relatively short period of time. That said, Roche is developing several other combinations in non-sq-NSCLC including with carbo/Abraxane (IMpower130) and Alimta/platinum (IMpower132) which makes this quadruple therapy only one option among many others and potentially the first to reach the market.

Our understanding from the meeting however is that the monotherapy arm will be used to assess the value of the PD1/PD-L1 component considering that accumulated clinical evidence

FIG. 9: DESIGN OF IMPOWER150

IMpower150 study design



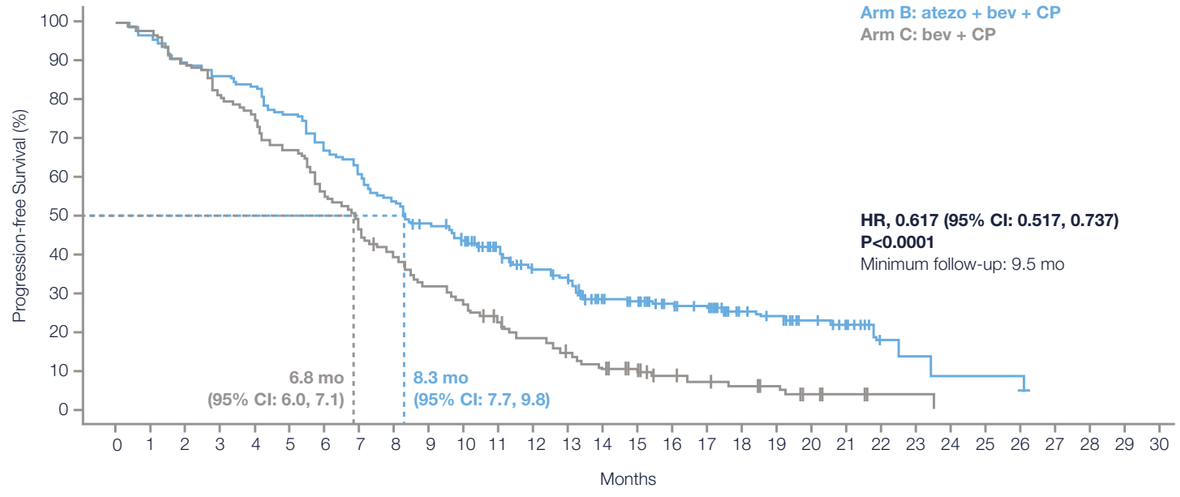
The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a]Patients with a sensitising EGFRmutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved target therapies. [b]Atezolizumab: 1200mg IV q3w. [c]Carboplatin: AUC 6 IV q3w. [d]Paclitaxel: 200mg/m² IV q3w. [e]Bevacizumab: 15mg/kg IV q3w.
Reck M, et al. IMpower150 PFS analysis.

Source: IO-ESMO 2017

FIG. 10A: FIRST KEY CLINICAL DATA FROM IMPOWER150

INV-assessed PFS in ITT-WT (Arm B vs Arm C)



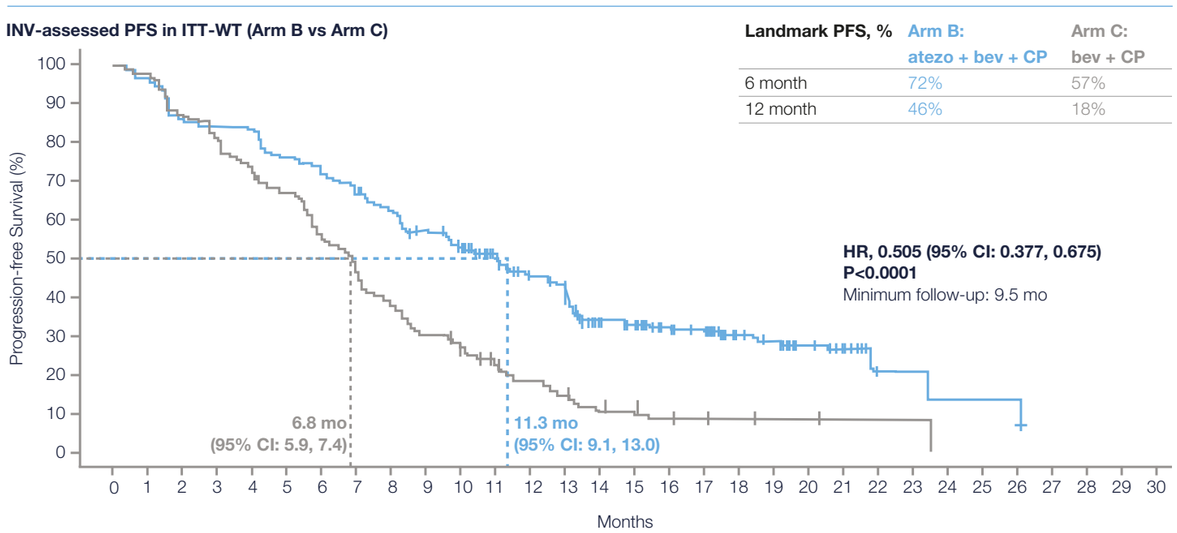
No. at risk

Atezo + Bev + CP	356	332	311	298	290	265	232	210	186	151	124	111	87	77	58	55	42	39	27	24	16	12	4	3	2	2	2
Bev + CP	336	321	292	261	243	215	179	147	125	91	69	55	39	32	21	18	12	9	7	6	3	2	1	1			

Source: IO-ESMO 2017

Acceleration of segmentation: the urgent need for biomarkers

FIG. 10A: FIRST KEY CLINICAL DATA FROM IMPOWER150



Landmark PFS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
6 month	72%	57%
12 month	46%	18%

Source: IO-ESMO 2017

already suggest that all agents are not equal. From that perspective, pembrolizumab has set the bar very high for competition.

Before we move to earlier stages of the disease, the discussion was confirmatory of our impression at ESMO that bTMB (tumor mutational burden in blood) was becoming another predictive biomarker like PD-L1 status. Our speaker confirmed this and the fact that some companies were strong promoters of its use, which should be of particular interest in SCLC and in former smokers.

Ending with the earlier stages of the disease i.e. stage III with the PACIFIC trial but also adjuvant settings, the limit is the possibility to detect cases early enough. Today "we are not good" but there is no easy way to do a proper job of detection, said the physician. So, about 40% of diagnosed lung cancers are localised of which about half in a stage III (20-25%) and so eligible to PACIFIC.

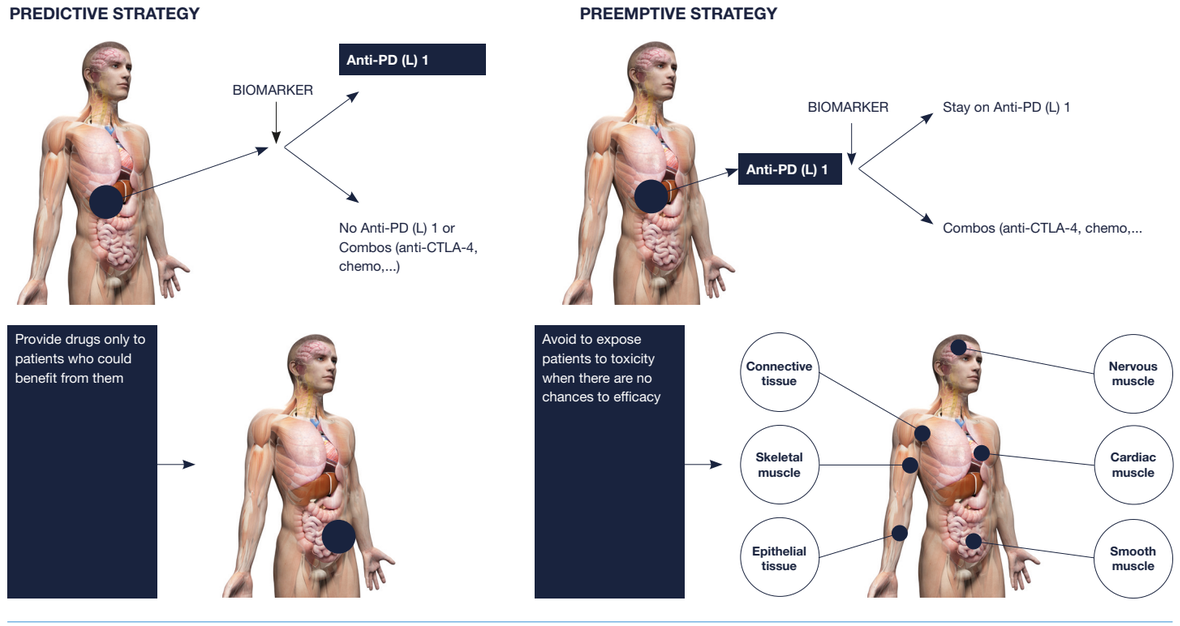
All companies have also started neo-adjuvant and adjuvant trials with their respective PD1 and PD-L1 agents. A success would be transformative for lung cancer treatment practice and would certainly ask new questions for SoC in stage III and IV. That said, it is very hypothetical to see a benefit since the tumor is no longer present in adjuvant and so only peritumoral tissue will be treated: is this enough to show a benefit?

From one congress to the next, we see step changes in the way IO is endorsed, since clinical evidence accumulates to support the fact that IO is life-changing for physicians and patients. From ESMO 2016 in Copenhagen to ESMO 2017 in Madrid, doors opened wider in favour of a large adoption of these treatments in a growing number of solid tumors.

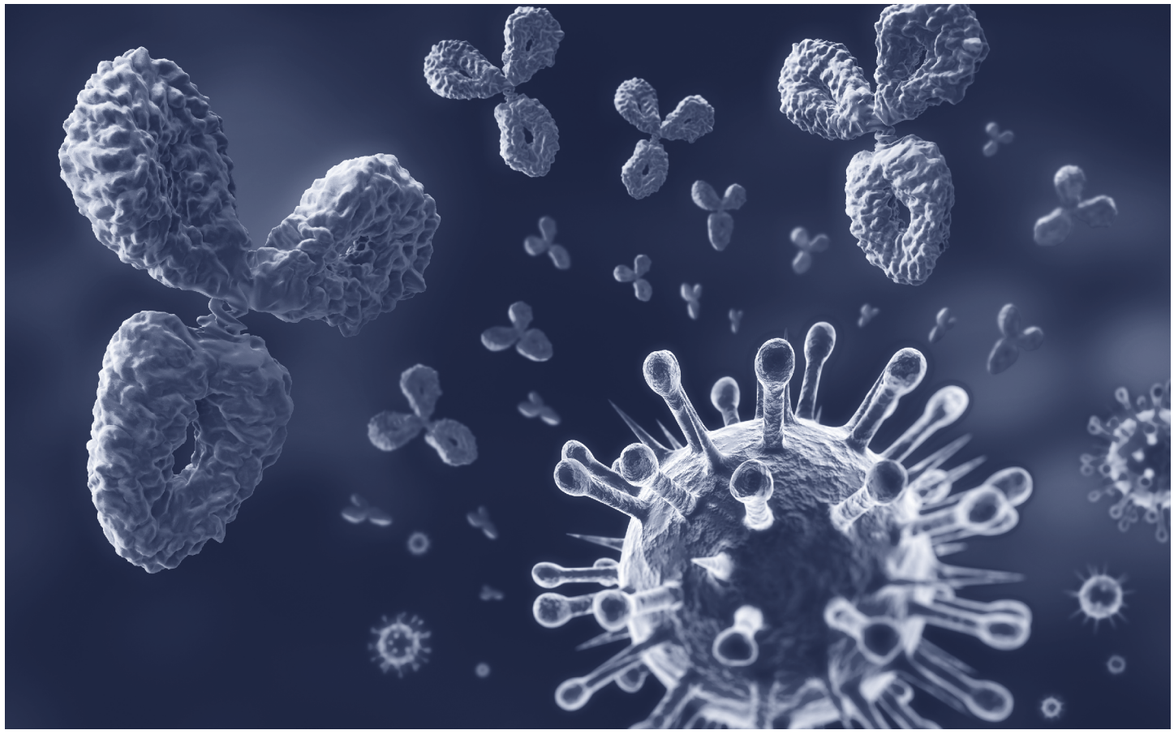
When the medical community was still trying to assess how much IO would transform their daily practice last year, we had the feeling this year that the key question had changed from "should I give IO to my patients?" to "which patients should I give IO to?". And, every year, a new group of physicians is adding to the existing list to form a bigger community of convinced people. It started by specialists in dermato-oncology, since melanoma was the first cancer-type to be revolutionized by IO drugs and then expanded to pneumo-oncologists and urologists because of first data showing benefit in 2L/3L and then in 1L PD-L1+ NSCLC and in advanced bladder cancer respectively, brought clear evidence of efficacy. Nephrologists added to the list with a first success in 2L mRCC and this year 1L showed benefit too, etc.

So with a growing audience backing the use of IO drugs in common practice now, a better understanding about who to give these drugs to has become a central and urgent matter for the sake of maximum efficacy, to avoid undeserved side-effects to those who are unlikely to benefit and, lastly, to implement the most responsible cost allocation in increasingly tough times.

FIG. 11: WHEN ARE BIOMARKERS MORE LIKELY TO HELP?



Source: Presentation at ESMO 2017 – Dr A. Marabelle, IGR

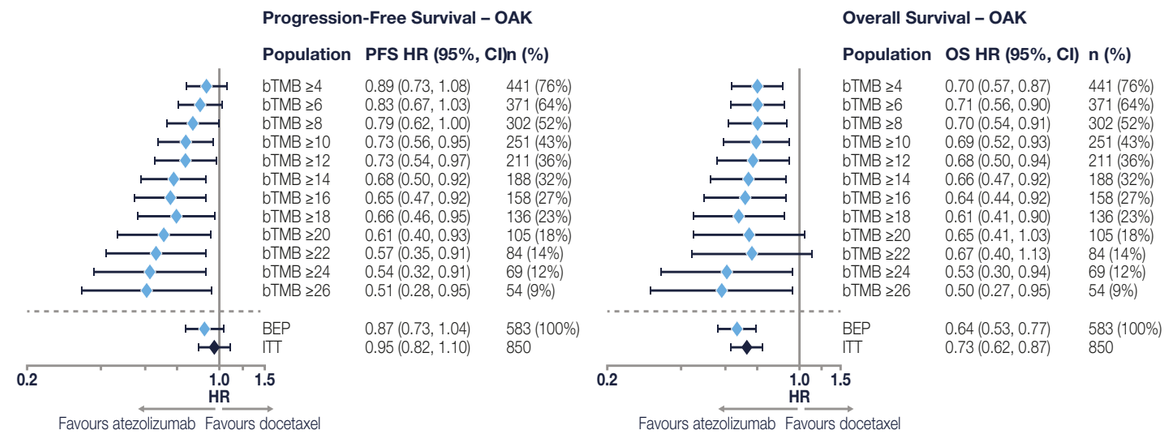


The need for biomarkers to optimize the use of IO drugs becomes a central matter and it obviously raised more questions than it answers because not only is it too early to draw definitive conclusions but it is also fair to say that the first lessons do not all converge. One interesting presentation was made by Dr Aurelien Marabelle from IGR (Villejuif, France) who suggested to prioritize a “predictive strategy” over a “pre-emptive strategy”, i.e. use biomarker(s) to optimize IO treatment rather than use it to assess if IO makes sense (see Fig.12). This is first because there is no universal biomarker to detect who is going to respond (if response means anything here) and also because it takes time to influence the immune system so that the outcome with the biomarker test can differ with timing and conditions.

One of the hypotheses tested during some of the presentations was the influence of two quite popular tests, namely bTMB (stands for “tumor mutational burden in blood”) and PD-L1 status, including the potential for a correlation between the two.

Foundation Medicines made much noise about its new assay to measure bTMB which is presented as a “non-invasive predictor of response to immunotherapy”, based on a retrospective data analysis from Roche’s POPLAR and OAK clinical studies. As illustrated in Fig.11, there is a very clear correlation between bTMB levels and survival benefit with atezolizumab in NSCLC while it has to be remembered that

FIG. 12: bTMB LOOKS LIKE A GOOD PREDICTOR OF RESPONSE/SURVIVAL



Enrichment of PFS benefit was observed in the bTMB ≥16 subgroup, while OS was consistent between the bTMB ≥16 subgroup and the BEP.

Population	ORR %	Median OS, months (95%)	Median PFS, months (95%)	PD-L1 tumor expression	ORR %	Median OS, months (95%)	Median PFS, months (95%)
All treated N = 270	20.0	8.57 (6.05-11.270	2.00 (1.87-2.63)	<1%, n = 146	15.8	5.95 (4.37-8.06)	1.87 (1.77-2.04)
				≥1%, n = 124	25.0	11.63 (9.10-NR)	3.53 (1.94-3.71)
TMB evaluable n = 139	20.1	7.23 (5.72-11.63)	2.00 (1.87-2.63)	<1%, n = 69	17.4	5.68 (4.40-NR)	1.87 (1.71-3.02)
				≥1%, n = 70	22.9	10.28 (6.05-NR)	2.30 (1.87-3.71)
TMB high n = 47	31.9	11.63 (5.82-NR)	3.02 (1.87-NR)	<1%, n = 23	30.4	NR (4.70-NR)	3.02 (1.81-NR)
				≥1%, n = 24	33.3	10.60 (5.82-NR)	3.52 (1.87-NR)
TMB medium n = 46	17.4	9.66 (4.76-NR)	1.87 (1.68-3.65)	<1%, n = 21	23.8	4.53 (2.23-NR)	1.77 (1.54-5.78)
				≥1%, n = 25	12.0	11.30 (5.85-NR)	1.94 (1.68-3.71)
TMB low n = 46	10.9	5.72 (4.21-11.30)	1.91 (1.84-3.15)	<1%, n = 25	0	4.96 (2.92-NR)	1.77 (1.68-2.10)
				≥1%, n = 21	23.8	8.57 (4.21-NR)	3.12 (1.87-7.23)

*ORR based on blinded independant review commitee assessment
CI = confidence interval, NR = not reached

Source: Presentation at ESMO 2017 – OAK trial on the left, CHECKMATE-275 on the right

PFS endpoint was not reached when the overall population is considered.

In the biomarker-evaluable population, the overlap between high bTMB and high PD-L1 expression levels was non-significant (unlike bTMB with smoking status). Those who qualified for at least one of the two criteria, i.e. bTMB>16 and TC3 or IC3 all did much better on PFS than the average of the OAK population with HR=0.62 or HR=0.64. But, even more clearly, the best response was obtained when both criteria were met, i.e. when patients both had bTMB high and were PD-L1 high expressers because then HR was 0.38 as showed in Fig.3. This is indeed a very informative and practice-relevant point for atezolizumab in NSCLC which, however, deserves further investigation to assess whether it can become a more systematic approach to stratify patients. Another way to look at the results is to consider that maybe only patients with bTMB<16 AND PD-L1 low expressers should not receive PD-1/PD-L1 agent in the front-line. We note in Fig.2 that similar results were obtained with nivolumab in CHECKMATE-275 based on ORR. This dual approach is unlikely to be used in haematological cancers where TMB are usually very low.

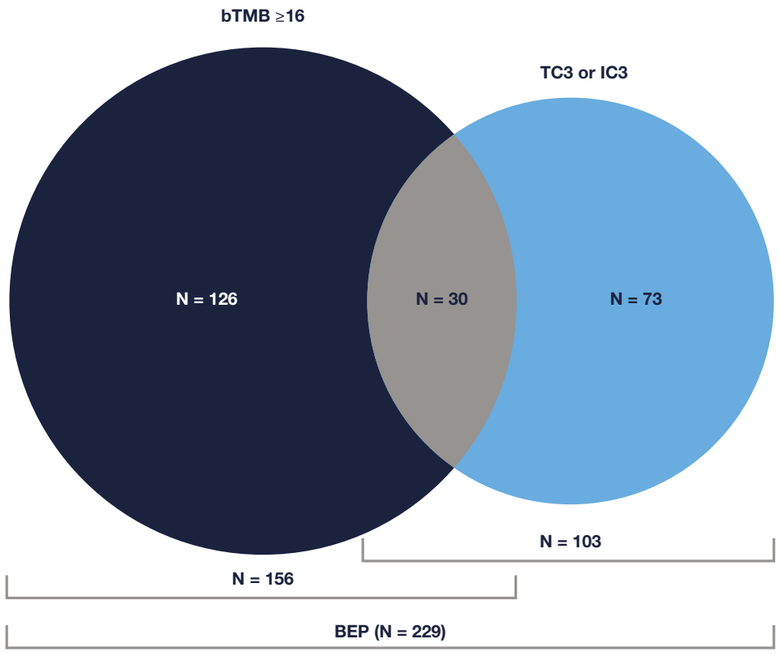
It is probably fair to say that, currently, the PD-L1 expression level is the easiest and most convenient biomarker in different settings to decide whether to start treatment with PD-1/PD-L1 targeting agents. That said, even what could be considered relatively consensual is not, for various reasons. An obvious one is the cut-off to make the best measure of PD-L1 expression (1%, 5%, 25%, 50%) since comparing KEYNOTE-024 and CHECKMATE-026 results, for instance, could make people think that a 5% expression level is not discriminating enough whereas 50% is. However, using a cut-off of 50% for PD-L1 expression would not have made CHECKMATE-026 positive, whereas TMB was a much better biomarker of efficacy. Moreover, the higher the level of PD-L1 expression and the smaller the population who can benefit from the treatment. Fig.14 below shows that the results have been highly heterogenous and leave room for controversy.

Nevertheless, that is the bet that Roche seems to take with its trial assessing the combination of multiple biomarkers as predictors of the response to atezolizumab. This is very probably the consequence of the internal work done with Roche Diagnostics and with Foundation Medicine and we are curious to see if and how it can help Roche fill the gap with the competition since it is fully aligned with what physicians are asking for and looking for. Provided the clinical results are positive of course, atezolizumab might benefit here from a significant differentiating factor vs other PD1/PD-L1 agents. At this time, based on data cutoff, the combination of three biomarkers targeting tumor cells as well as cells in the tumor environment, give evidences that the effectiveness of atezolizumab should be improved by a better understanding of the interaction between the tumor and its microenvironment, and an optimized biomarkers combination reflecting this interaction.

Last but not least, after making the right assessment for the relevant biomarker, then one has to contemplate which endpoint to take. Since ORR and PFS are usually the first endpoints to be studied as early as in phase II trials but also in phase III trials of course, these are the preferred ones also when it comes to discrimination of the results by subgroups and to identify so-called "best responders", but some speakers including Dr Marabelle suggested looking at the biology of patients with complete responses since it does not always correlate. It is fair to say, for instance, and this will be developed in one of the following parts of this report, that in CHECKMATE-214 the combination nivo/ipi showed superior efficacy results in PD-L1 positive patients and this could make PD-L1 status a good biomarker for a decision to treat. But, when complete responders are considered, with a cut-off of 1% for PD-L1 expression, 7% of complete responses were seen in low-PD-L1 expressers: treating only on the basis of PD-L1 expression status would be a major loss of chance for these patients. Unless there is a better sequence to consider.

FIG. 13: CROSSING DATA WITH BTMB AND PD-L1 EXPRESSION IN OAK

LIMITED OVERLAP BETWEEN bTMB ≥16 AND PD-L1 EXPRESSION[a] (OAK BEP)



Non-significant overlap between the bTMB ≥16 and TC3 or IC3 subgroups (Fisher exact test, P = 0.62)
19.2% of tumors with bTMB ≥16 were also TC3 or IC3
29.1% of tumors with TC3 or IC3 also had bTMB ≥16

	PFS HR (95% CI)	OS HR (95% CI)
bTMB ≥16	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB ≥16 and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

Source: Presentation at ESMO 2017 (TC3 = Tumor Cells at least 50% PD-L1 positive cells; IC3 = Immune Cells at least 10% PD-L1positive cells

FIG. 14: NO CONSENSUS TOWARDS PD-L1 EXPRESSION AS PREDICTIVE FACTOR ACROSS TRIALS

MAJOR RANDOMIZED PHASE II/III TRIALS OF PD-1/PD-L1 INHIBITION VS. CHEMOTHEROPY; IMPACT OF PD-L1 EXPRESSION

Trial	Drug	Type	Line	Antibody	Cut-off	OS HR	Impact of PD-L1 level
CheckMate 017	Nivo	Sq	2	28-8; Dako	no	**0.59**	no
CheckMate 057	Nivo	Non-Sq	2	28-8; Dako	no	**0.73**	yes
CheckMate 026	Nivo	All	1	28-8; Dako	5%	**1.02**	no
KEYNOTE-010	Pembro 2mg Pembro 10mg	All All	2	22C3; Dako	1%	**0.71**** **0.61****	yes
KEYNOTE-024		All	1	22C3; Dako	50%	**0.60**	NA
POPLAR	Atezo	All	2-3	SP142; Ventana*	no	**0.73**	relative
OAK	Atezo	All	2-3	SP142; Ventana*	no	**0.73**	relative

**Measured on tumor cells and TILs; **HR 0.54 and 0.50, respectively for cutoff 50%*

Source: Presentation at ESMO 2017

Refining the treatment sequence for a better patient care

The segmentation treatment approach, through the identification and use of biomarkers, should have several virtues. The first is obviously to better target patients and identify those who should actually benefit from treatment.

This being said, other benefits for the patient should emerge from this approach, particularly that of better guiding him in his care path in terms of choice of therapeutic strategy. In fact, the use of predictive biomarkers should make it possible to better predict the sequence of care that could benefit each patient according to his genetic profile but also his mutational load.

Once we have a valuable biomarker, provided there is one, the following question that comes is the right sequence of treatments to implement across the various lines to get the best possible outcomes for each individual based on aetiology, stage or co-morbidities.

In addition, better targeting and referral of patients to a suitable therapy will allow de facto to reinforce the rationale of a therapy and thus allow a rise of treatment lines.

The introduction of IO drugs to treat some cancers like melanoma, non-small-cell lung cancer or metastatic renal-cell carcinoma, has been transformative for medical practice. But since, in most cases, these drugs have started being investigated in very advanced stages before moving to earlier lines of treatment, often succeeding in all settings, the question that comes is “what is the best sequence to use them?”.

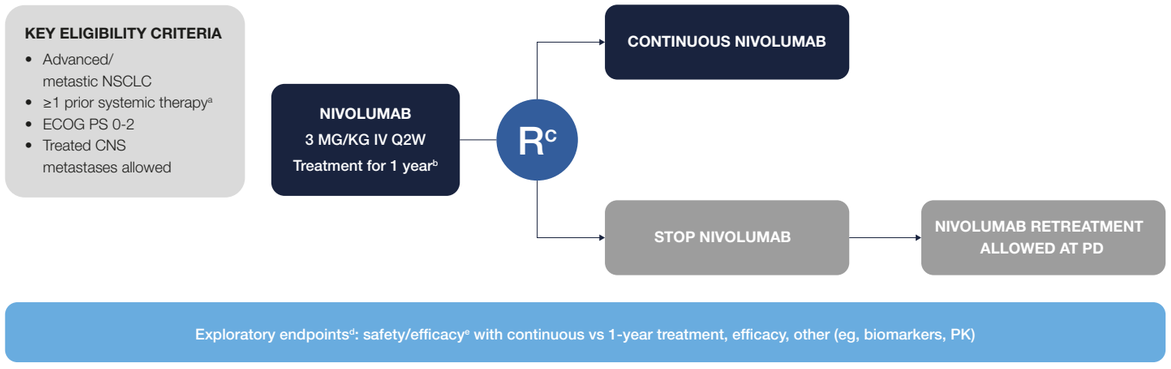
Actually, what we realised during some of the sessions we attended was that cross-over in trials has virtue. When it is permitted, cross-over is often approached as a limitation to capture fully the benefit of an investigated drug or regimen because as soon as cross-over starts, the trial loses a significant part of its statistical power to assess secondary endpoints, for instance, and/or longer-term OS benefit. However, our understanding is that cross-over can also be very informative because it allows patients who are not receiving the investigational drug/regimen (and therefore often receiving current SoC) to be switched to the active arm, for instance after progression, which can offer a comparison between 1L use and 2L use or between 2L and 3L use, usually based on OS data. This is the type of question asked when assessing which of immunotherapy or VEGF-targeting approach should be used first in mRCC (until a combination of the two delivers results). And there are pros and cons about using CT or targeted therapies first.

The question of the right sequence relates also to the fact that the benefit seen with some of the IO drugs is sometimes short. Therefore, it has to be understood how to maximise their efficacy both in intensity and in duration. That is why we see new original designs of clinical studies being built to assess various hypotheses. We show below one example of these in Fig.6 with the design of CHECKMATE-153 which tested a continuous nivolumab-based regimen after already one year of treatment compared to a therapeutic window followed by nivolumab only if the patient progresses.

Since the results were clearly in favour of the continuous maintenance regimen, this supports the idea that maybe with IO drugs, like with other treatments, the rationale is strong to treat for longer than a year and why not until progression.

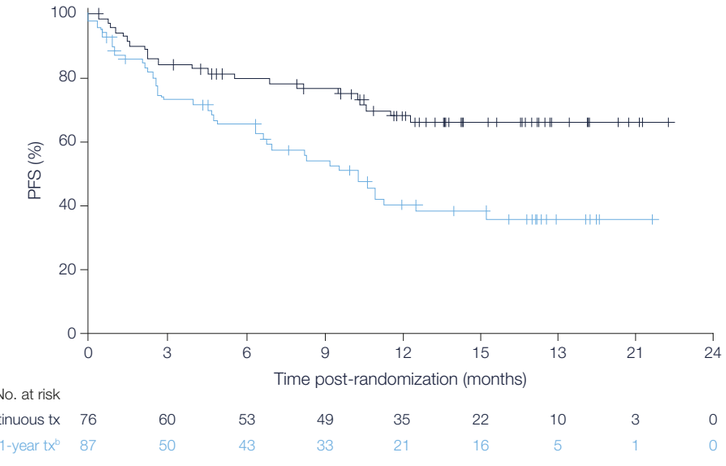
FIG. 15: LONGER DURATIONS OF TREATMENT DESERVED WITH IO DRUGS?

CHECKMATE 153: CONTINUOUS VS 1-YEAR NIVOLUMAB STUDY DESIGN



- At database lock (may 15, 2017), minimum/median follow-up time randomization was 10.0/14.9 months

CHECKMATE 153: CONTINUOUS VS 1-YEAR NIVOLUMAB PFS FROM RANDOMIZATION[a]



	Median, months (95% CI)	PFS rate, % 6-month	1-year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)

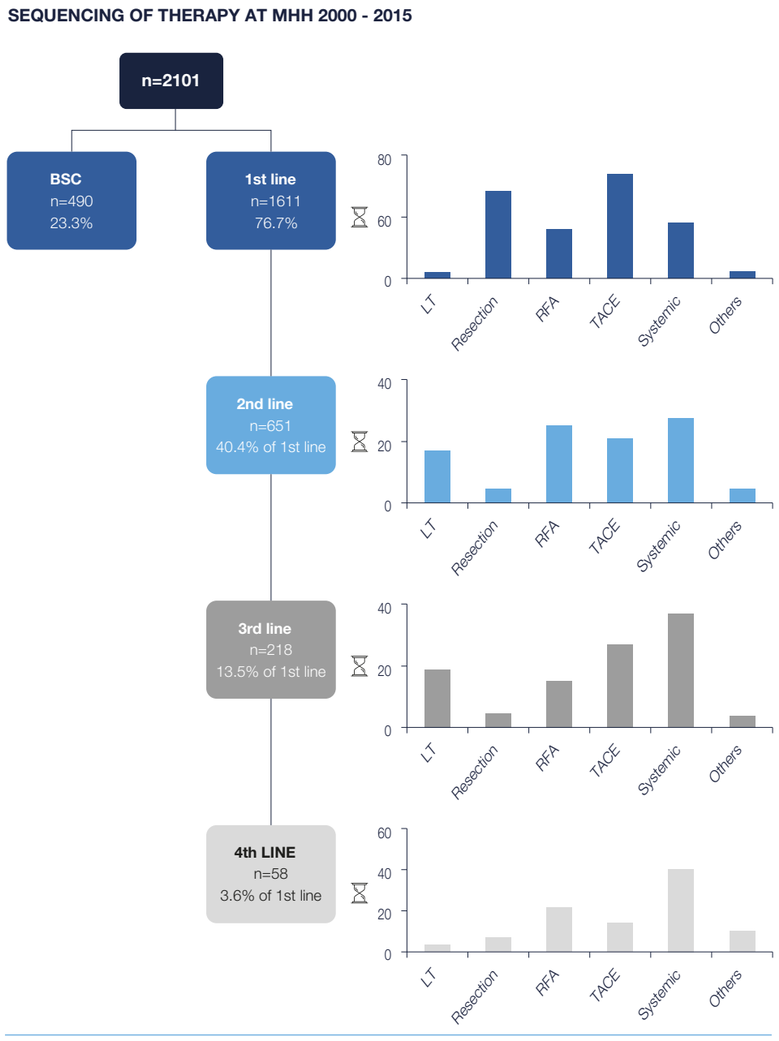
Source: Presentation at ESMO 2017

This question was also raised when PACIFIC data were presented because durvalumab was tested against observation in the maintenance setting, after concomitant RT-CT, for one year. But since data pointed to a 16.8-month median PFS with the active arm (vs only 5.6 months with placebo), the question about further expanding the benefit if the drug is administered longer than 12 months and maybe at least until progression was found to be legitimate. It is going to be interesting to see if the label mimics the PACIFIC design and so recommends a 12-month treatment duration (if so, then most physicians would stick to it and comply with it). In any case, some physicians are likely to go beyond this and real-life data should tell in the future whether it is worth doing otherwise.

As we expect to see more and more positive efficacy data with cocktails/ combinations of innovative drugs, the question of sequencing will also be increasing accurate, because overall survival across the whole spectrum of successive lines of treatment will be the only criterion to care about at the end of the day.

Of course, the best possible option will have to be given as early as possible to benefit the largest available population to minimise the loss of chance: we commented last year about data presented at ESMO 2016 about the percentage of patients having the

FIG. 16: MEANINGFUL LOSS OF PATIENTS WHEN MOVING ACROSS THE TREATMENT LINES - HCC



Source: Presentation at ESMO 2017

chance to benefit a second-line of treatment after progressing in mRCC, i.e. only 43% and we report this year similar numbers in HCC where only about 40% of 1L patients actually receive 2L.

If the main reason to look for the right sequence is efficacy – for instance is CT-then-IO better than IO-then-CT or CT/IO combined? – it also relates to the acceptable toxicity (including when non-systemic alternatives are available) and to some extent when two options are close to the associated cost of each one.

This is why the early signals of response are useful to allow for quick changes to protocols of treatment, why also biomarkers and the sequence of treatment are of course closely linked.

The role of radiotherapy (RT) and even more significantly of chemotherapy (CT) towards new IO-based regimes is probably one of the key questions asked by physicians. In one of the symposiums at ESMO dedicated to the CT-IO rationale, it was hypothesised that CT in an induction phase before IO would make sense, as well maybe as an induction before a re-challenge after first failure with an IO drug. How many sequences it is worth giving and how long is of course unknown yet.

We also heard support from several participants in the congress for IDO

FIG. 17: KOL'S FEEDBACK ABOUT USING PD1S IN SEQUENCE

DO NOT USE PD-1 AND PD-L1 INHIBITORS IN SEQUENCE

Journal for Immuno Therapy of Cancer

CASE REPORT OPEN ACCESS

Response to single agent PD-1 inhibitor after progression on previous PD-1/PD-L1 inhibitors: a case series

Source: Presentation at ESMO 2017

inhibitors, maybe for the first time so loudly this year, probably as a reflection of good first late-stage data disclosed with Incyte's drug in combination with pembrolizumab in melanoma and in lung. Obviously, it raised questions about the efficacy of IDO inhibitors in tumor-types with lower TMB but at least in melanoma it also suggested a possible role in combination with PD1/PD-L1 agents in PD-L1 positive patients when PD1/ PD-L1+ CTLA4 would be preferred for PD-L1 negatives.

In conclusion, we would say that we are far from having answers to most of the questions asked about sequence of treatment but the obvious increase in the number of questions is testimony, in our view, to the increased intention to use these drugs with a concomitant need to know how to do it best.

Before we move to the next topic, we would like to draw attention to another statement made during one of the presentations at ESMO and represented in Fig.17. Again, this is one view whose intention is not to represent either a guideline or a consensus but a single opinion. But it is a rather clear statement: "do not use PD-1 and PD-L1 inhibitors in sequence", meaning that re-induction so far has not showed very promising results. And this is an important question since many PD-1 and PD-L1 agents are in development in very close – if not similar – settings and are accumulating evidence of efficacy across different lines of treatment. So, the question of using them in 1L, in 2L and/or in later lines is an obvious one because they are likely to be approved in all. In melanoma, in RCC and in lung, it is already an option to use one of the agents in several consecutive lines. It looks as if it is not the best option, but it requires further investigation.

Part 2: Haematological malignancies, CAR-T are no longer science-fiction

What are CAR-T? A technology backed by billion-dollar deals

The strategy behind CAR-T is to use the immune system to fight cancer with T-cells. T-cells are dedicated cells responsible for recognizing and destroying foreign agents such as viruses, bacteria… but also cancer cells. Cancer cells can acquire antigenicity (and hence immunogenicity through the expression of antigens that can be recognised as "non-self"). The problem is that in cancer patients, these T-cells are compromised, either fail to target or recognize cancerous cells, or are too few in number to lead a strong attack. Hence cancer may grow and spread (metastasis).

Adoptive Cell Therapy has the potential to treat cancer by overcoming a patient's limited immuno-surveillance by increasing the effectiveness of the immune response and the number of a patient's cancer-specific T-cells.

CAR—Chimeric Antigen Receptors—are genetically engineered protein constructs that can be incorporated into a patient's own T cells to help them to recognize and fight cancer cells. This protein construct combines DNA from several genes to create a new T-cell receptor that binds to antigens found on tumor cells and activates the T-cell in response to that binding.
T-cells which are engineered to express CAR specifically recognize their target antigen in a simplified manner, resulting in a more efficient elimination of cancer cells.

"CAR" redirects the specificity of "T-cells" to better destroy cancer cells. Infusing large quantities of modified T-cells is aimed at:

- Making T-cells recognize and target cancer cells specifically through the presence of a given antigen
- Making T-cells stronger so they can thrive in a very hostile tumor environment
- Restoring a number of good quality T-cells.

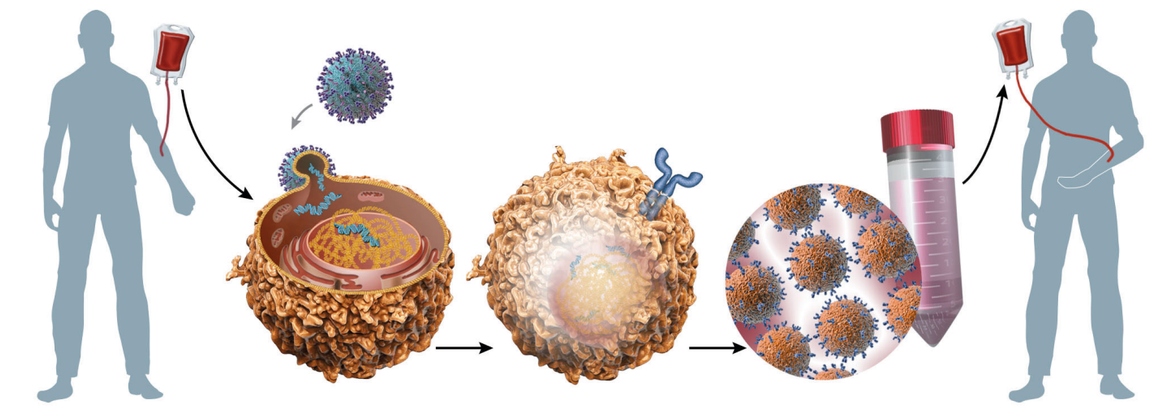
CAR-T Cell Therapy changes a cancer patient's own weak T cells into more potent cancer cell killers.

The concept of CAR-T Cell Therapy became more sophisticated around the end of the 80s when Dr Steven Rosenberg experimented with the direct introduction of Tumor Infiltrating Lymphocytes (TIL) isolated directly from a patient's tumor expanded ex vivo in the laboratory, and infused back to the patient in an attempt to overwhelm the tumor.

TIL are polyclonal, meaning that they can target several tumor-antigens presented.

While cumbersome, this approach allowed a more specific targeting of patient-unique tumor-associated antigens (TAA). Tumor-infiltrating

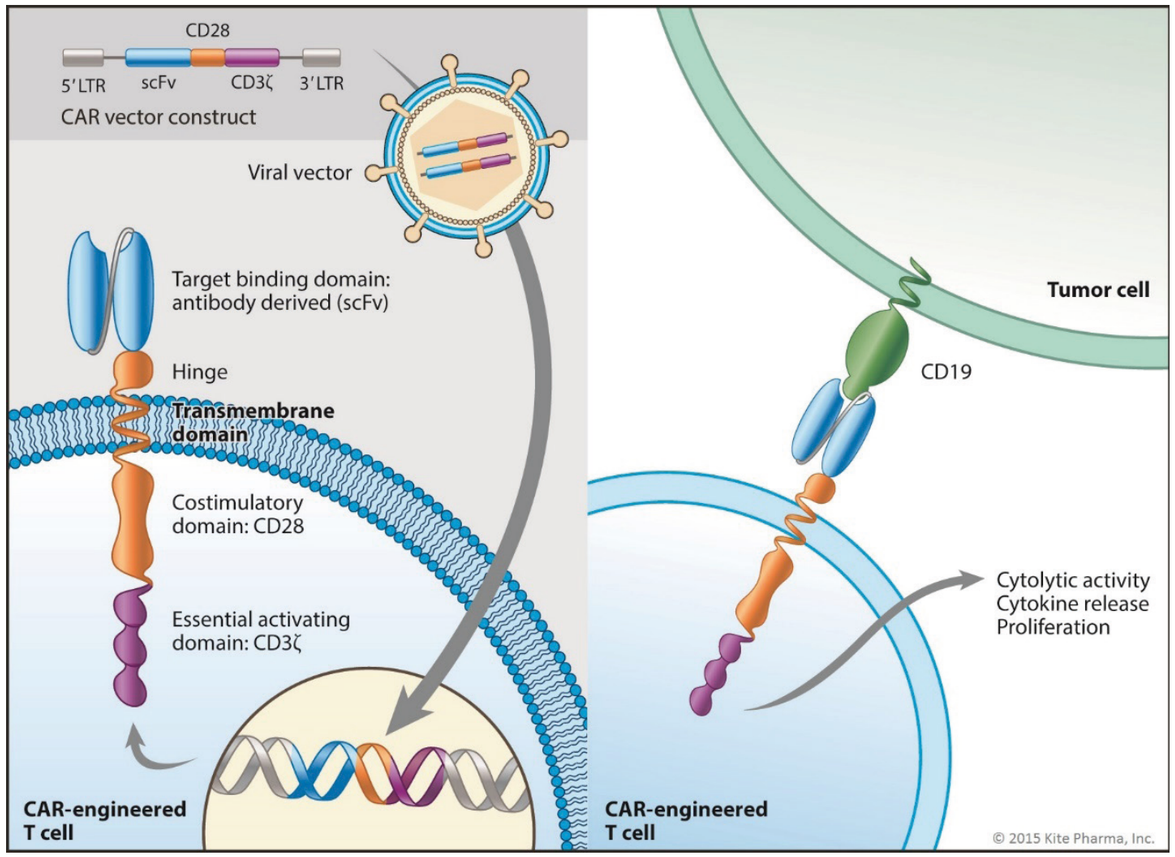
FIG 18: THE CAR-T CELL THERAPY: AN ADOPTIVE CELL THERAPY



1. T cells are collected from the patient. A machine reomoves the desired cells from the blood, the returns the rest back to the patient
2. A modified virus (blue) is used to transfer DNA to the patient's T cells so they will produce CAR proteins.
3. CARs have two ends: a binding site (blue) specific to the tumor cells, and a signaling engine that activates the T cell to kill the tumor it binds to.
4. Once designed millions of engineered CAR T cells are grown in the laboratory.
5. The expanded population of CAR T cells is infused into the patient through a standard blood transfusion

Source: Hartmann, Schubler-Lenz, Bondana, & Buchholz, 2017 | HaemaLogiX, 2017

FIG 19: CAR CONSTRUCT



Source: Kite Pharma, Inc, 2014

A technology that triggers an increasing interest

Lymphocytes (TIL) represent the simplest approach to adoptive cell therapy as these TIL are not modified. The reasons why the TIL approach is not more commonly adopted in the industry, is that it is randomly efficacious. Indeed, within the cellular TIL mixture, some non-tumor targeting cells, or some cells that cannot directly kill, are present, diluting the anti-tumoral effect of some specific T-cells. On re-infusion, and without the modifications offered in CAR T cells, the TILs also become subject again to the immune suppressive and escape mechanisms of the tumors.

So, rather than trying to find the T-cell in one billion that binds the desired antigen, Dr Zelig raised the T-cell therapy to the next level, by artificially manipulating T-cells to redirect them to the desired cancer cell target (introduction of a single chain antibody variable fragments (scFv) into alpha and beta chains of their T-cell receptor (TCR)). Few years later (1983), these constructs were simplified (into single-chain antibody fragments that were linked to the zeta chains of a TCR) the first reported generation of functional CAR-T.

Despite having been in the clinic for many years, no trials applying CAR-T before 2000 have produced exciting data. Up until 2009, specialized biotech and biopharma overlooked the field while the academic institutions continued to conduct the scientific work.

Engineered T-cells with a Chimeric Antigen Receptor (CAR) require the use of a delivery vehicle (or viral vector) containing the CAR gene to integrate (or transduce) that gene into the DNA (T-cell's genome). The CAR gene encodes the single chain CAR protein that will play the role of cancer-specific receptor at the cell surface. CAR constructs are composed of the three following elements:

- **Target Binding Domain:** At the end of the CAR is an extracellular target-binding domain of an antibody that is specific to the target antigen of interest (e.g. CD19), present on the cancer cell surface. This domain extends out of the engineered T-cell into the extracellular space, where it can recognize target antigens on tumor cells surface. The target-binding domain consists of a single-chain variable fragment (scFv) of an antibody, which is comprised of variable domains of heavy and light chains joined by a short linker. This makes a CAR single chain protein at the T-cell surface

- **Transmembrane Domain and Hinge:** This middle portion of the CAR links the scFv target-binding domain to the activating elements inside the cell. The CAR is anchored to the cell membrane through this transmembrane domain. This portion provides structural flexibility to facilitate optimal binding of the CAR's scFv target binding domain with the target antigen on the cancer cell's surface

- **Activating Domains:** located within the T-cell's intracellular space, two regions of the CAR are responsible for activating the T-cell upon binding to the target cell. The CD3 zeta element delivers an essential primary signal within the T-cell, and a second element (CD28 or 4.1BB or OX40) delivers an additional, co-stimulatory signal. Together, these signals trigger T-cell activation, which result in proliferation of the CAR-T cells and direct killing of the cancer cells.

In addition to direct killing, CAR-T cells can induce indirect tumor killing by triggering "antigen spreading". Indirect killing results from 1/ the activation of our innate immune cells (tumoricidal neutrophils, macrophages, dendritic cells, natural killer cells) by cytokines released after CAR engagement, that in turn 2/ activate our adaptive immune cells (i.e. CD8+ and CD4+ T-cells).

There has been significant deal activity in the CAR-T space, although given the commercial potential one could reasonably think it has been relatively sparse. While the scientific rationale is validated, several factors have dampened bio-pharmaceutical companies to massively invest in entering the CAR-T segment until recently. 1/ it took time before the technology underwent a massive de-risking with the first FDA approval in 2017, 2/ supply chain and manufacturing not optimized yet and 3/ the therapy entry price could be seen prohibitive by some.

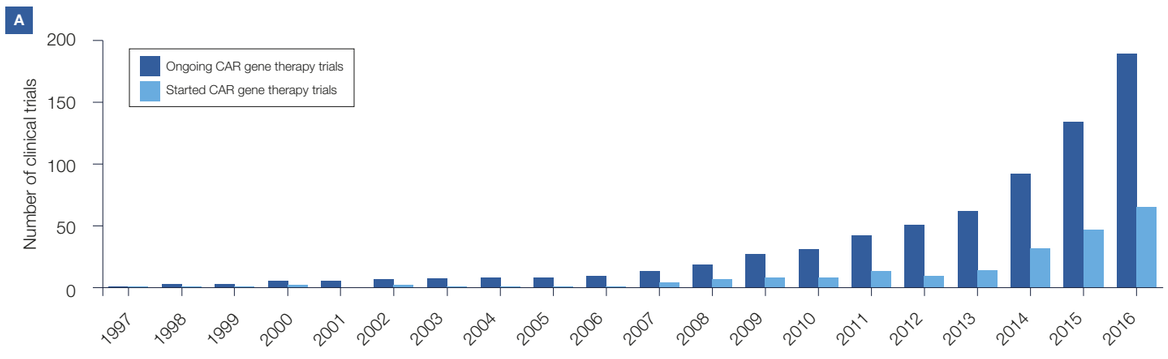
However, deals have been done. The first big pharma to enter the CAR-T space was Novartis in 2012, through its alliance with the University of Pennsylvania.

On August 2017, Gilead, which had not jumped into the "Immuno-Oncology" space, nor developed any cellular or gene therapies, announced the acquisition of Kite Pharma for USD11.9bn. Does that mean that other big pharma that missed the "Immune checkpoint inhibitor" wave, will pay whatever it takes to avoid missing another opportunity to secure long-term growth such as emerging breakthrough therapies like CAR-T cells?

Two days after the Kite Pharma buyout by Gilead, the FDA brought the first gene therapy to the US market. By approving Novartis' CAR-T cell therapy (known as CTL019 or tisagenlecleucel). The therapy is commercialized under the brand name Kymriah, for the treatment of B-cell acute lymphoblastic leukaemia (ALL).

Now that the technology is seen as more de-risked, the obvious question is what further deals might get done. We believe that 1/small early-stage discovery tie-ups are likely to continue since biopharma and biotech need to acquire novel technologies or novel targets; 2/ it is by no means ruled out that a big pharma or a large biotech could make the kind of endorsement Celgene made in 2015; 3/a consolidation could take place among current CAR-T players: as for example a CAR-T player could acquire another one to own a particular technology or a promising target that could leverage its pipeline and surpass its competitors. Hence, we do not rule out that the following company's might attract the interest of players not already in the CAR T space.

FIG 20: CAR-T: A "HOT" TOPIC



Source: Hartmann, Schubler-Lenz, Bondana, & Buchholz, 2017

- **Bellicum** could be the next target for its CAR-T suicide switch that is less dangerous than Juno's one.

- **BlueBird Bio** could also be a target since its CAR-T aims at treating patients with multiple myeloma (MM) while most of the main CAR-T players, are primarily addressing leukemia and lymphoma. Moreover, bb2121 delivered positive interim clinical data last year in 2016, which placed the bar high for future entrants addressing MM.

- **Celyad** has a differentiated approach with its autologous NKG2D CART, addressing both liquid (AML), and solid cancers and is developing both autologous and allogeneic CAR-T cell therapies. Despite its earlier development stage, it has a robust allogeneic patent estate validated by two structuring deals and the could be leveraged with further licensing agreements with CAR-T players.

Note that beyond the above-mentioned deals, and apart from payments made by corporates to get their hands on academic work in CART, there have also been several smaller but important technology deals. One hurdle that might have discouraged big pharma from entering the CAR-T space is the high projected list price of CAR-T, owing to subsequent COGS (complexity of the manufacturing process, supply chain management), rather than because of the health-economic grounds, typical of other premium-priced drugs.

Also, another argument that may have negatively weighed in the balance of entering the CAR-T space or not, is that CAR-T is not the only approach that aims at redirecting T-cells to tumor tissues, as bi-specific T-cell engaging antibodies represent another competing drug modality. Importantly, antibodies are much easier to produce, their COGS are significantly lower, hence their reduced list price compared to cellular therapeutics.

Novartis chose the "pay for performance" scheme meaning anticipated reimbursements are included in the final list price. Novartis will receive payment for 8 out of 10 patients treated (83% CR) meaning it has to budget into the price the fact that 2/10 patients will receive treatment for free. Patients/payers will only pay if there is a response to Kymriah by the end of the first month post infusion. Novartis' Kymriah's price is set at USD475,000 per dose per patient.

FIG 21: MAJOR DEALS WITH CAR-T BIOTECH

Car-T/TCR Biotech	Partner/Acquirer	Total amount
cellectis EDITING LIFE	SERVIER Pfizer	2014-2015 USD 3.6bn
JUNO THERAPEUTICS	Celgene	2015 USD 1bn
bluebirdbio	Celgene	2015 USD 250m
Kite Pharma	MERCK	2015 USD 115m
ZIOPHARM Oncology	AMGEN®	2015 USD 60m
Celyad we care · we cure	NOVARTIS	2017: USD 96m
Kite Pharma	GILEAD	2017: USD 11.9bn (aquisition)
JUNO THERAPEUTICS	Celgene	2017: USD9bn (aquisition)

Source: Bryan, Garnier & Co, 2018

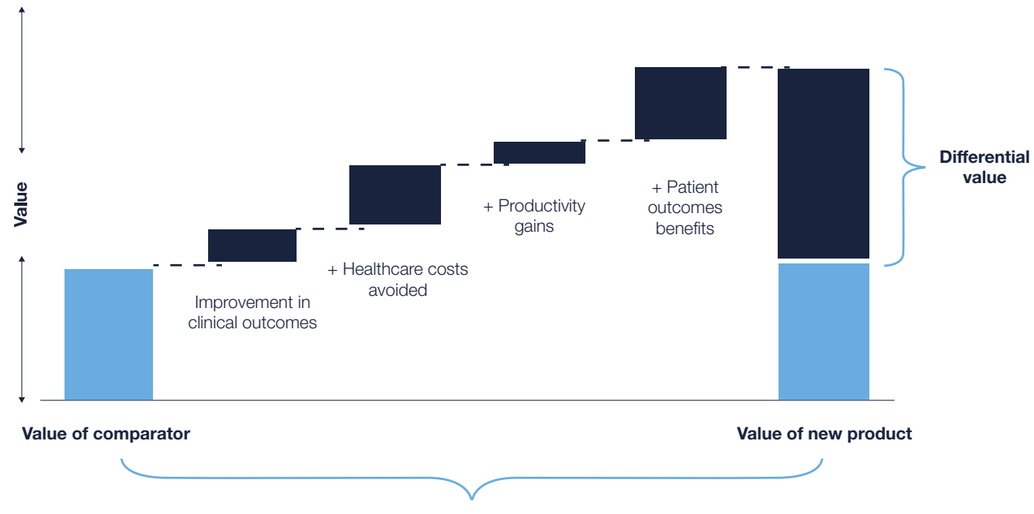
Kite Pharma's Axi-cel (Yescarta) pricing for autologous CAR-T in DLBCL is USD373,000 per patient.

Key questions include: How is outcome-based pricing modelled? Will the pricing scheme reimburse R&D spent for CART development?

There are many factors to take into account to set a list price such as patient population (young, elderly), number of injections, positioning (front-line or last line treatment), additional costs (e.g. lymphodepletion, ICU, treatment-related adverse events) and competition (first to market advantage) to name a few. We believe that the establishment of appropriate payment models will be as relevant to success as the medication itself. Express Script said that one-time treatment like Kymriah will require new payment model. Gene therapy will require novel payment schemes to adapt to care systems. "The healthcare system is not set-up for the arrival of such expensive therapies" (Express Scripts (ES), 2017).

There are increasing worries from payers and patients about the affordability of such breakthrough therapies to treat cancer as the system is already burdened by rising global healthcare costs. Despite drug approval, these CAR-T therapies might not be made available in all EU countries, in particular in the UK, where NIHCE is known to be quite demanding in terms of therapeutic value based on QALY. Given the growing weight of healthcare in developed countries, robust methods to ensure that money is spent wisely are required.

FIG 22: WHERE DOES THE VALUE COME FROM?



Role of health economics and pricing department: develop evidence to support and quantify these value arguments using established scientific rigor

Source: Stephane Regnier, 2016

Latest data at ASH likely to strengthen momentum

Strong results in NHL/DLBCL Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for approximately 40% of all NHL cases globally. There are roughly 72,000 new cases of NHL in the US per year with an estimated 27,650 newly diagnosed DLBCL patients in the US in 2016. Patients with R/R DLBCL have often worse prognosis than other forms of NHL, with a life expectancy of 3 to 4 months.

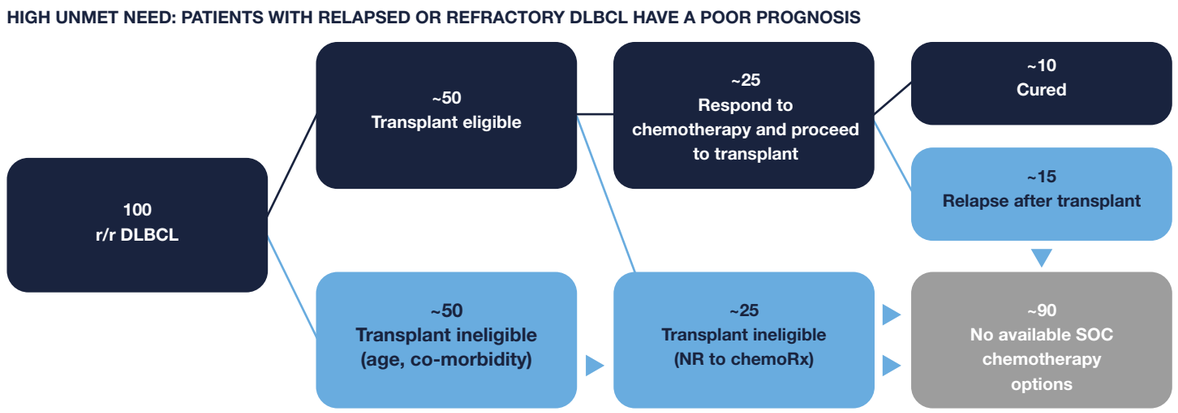
KITE PHARMA presented an updated analysis of the ZUMA-1 trial. More than one year after a single infusion of Yescarta (15.4 months), 42% of patients continued to respond to therapy, including 40% in CR and 2% in PR. The median duration of response (mDOR) was 11.1 months. However, in patients who have achieved a CR, the mDOR was not reached. Median overall survival had not been reached with an overall survival (OS) rate at 18 months of 52%.

Across the combined 108 patients included in the trial, the most common Grade 3/4 adverse events included: CRS (13%), neurologic toxicities (28%), neutropenia (79%), anaemia (45%) and thrombocytopenia (40%). There were 10 out of 108 patients who experienced a serious adverse event six month after the primary analysis including infections in eight patients. No new CRS or neurologic events were observed in this updated analysis. Early in the study four patients died within two months of treatment: two were attributable to the CAR-T treatment itself and the remaining two deaths were due to disease progression. No additional death was reported.

NOVARTIS presented positive results of the JULIET trial with the best ORR reached 53% with 40% of patients being in Complete Response (CR) and 14% of patients achieving a Partial Response (PR) among 81 infused patients with at least three months follow-up or who discontinued earlier for any reason. At three months post-infusion, the ORR rate was 38% with 32% of CR, which remained consistent at six months. Indeed, among patients evaluable at six months (n=46) the ORR was of 37%, with a CR rate of 30% and a PR rate of 7%.

- The 6-month probability of being relapse-free was 73.5%.
- The 6-month probability of overall survival was 64.5%.

FIG 23: HIGH UNMET MEDICAL NEED FOR R/R DLBCL PATIENTS



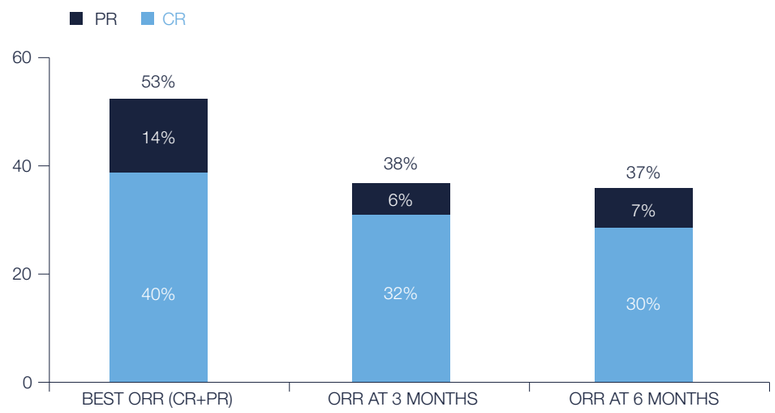
Source: Novartis Investor Call, December 11, 2017

This is the first global study of CAR-T therapy only in patients with DLBCL. Moreover, this update is important because Gilead's Yescarta is already approved in DLBCL, with a 36% complete response rate among 101 patients at six months. Based on these data, Novartis submitted an application to the FDA in October 2017 for CTL019 in adult patients with R/R DLBCL, with a decision from the FDA expected in H1 2018.

Companies like JUNO THERAPEUTICS are not far behind in terms of developing their CAR-T and it seems that JCAR017 could offer a differentiated therapeutic benefit compared to the Novartis' and Kite's CD19 CAR-T therapies. JCAR017 CAR T cell product candidate administered in a defined composition at a precise dose of CD8 and CD4 CAR T cells. The rationale behind the use of a CD4+:CD8+ ratio is to optimize the efficacy, reduce toxicities and lower CAR-T cell doses, hence enhancing the product's quality attributes. In a presentation (Abstract #4471), Juno demonstrated that JCAR017 had a slow expansion profile with peak expansion at approximately 15 days with low rates of CRS and NT and an emerging dose-relationship. JUNO's failed JCAR015 enabled the company to better develop JCAR017 which features a low rate of adverse events.

Results from the Phase I TRANSCEND NHL 001 trial (NCT02631044) evaluating JCAR017 (liso-cel: lisocabtagene maraleucel) in R/R NHL patients confirmed good profile of the drug with a 68% and 50% of CR at 3 and 6-months.

FIG. 24: RESPONSE RATES IN JULIET FROM MONTH THREE TO MONTH SIX



Source: ASH 2017, Abstract #577

Important to note is that the attractive tolerability profile of JCAR017 might allow the therapy to be administered in an outpatient setting, which would be more convenient for patients. We believe JCAR017 could potentially be best-in-class as a result of the therapy's defined cell composition. A BLA filing is expected to be completed in H2 2018 with an approval as early as year-end 2018 or early 2019.

Here are our few highlights from this cross-trial comparison:

- **Clinical phase:** the number of patients is smaller in Juno's trial, so response rates might be slightly lower if there are more patients across clinical sites from different geographic areas
- **Eligible patients:** Kite's trial recruited patients with different NHL subtypes, outside DLBCL. Novartis' trial recruited only R/R DLBCL patients
- **CD19 CAR-T product:** All CARs are not the same. In addition, Juno has a different approach compared to its peers, as it is the only one to have developed a defined product candidate. A defined composition means the "right" cells at the "right" dose
- **Efficacy updates:** Kite/Gilead reported strong durability at 15 months, largely consistent with

prior disclosed data and suggest continued durability of response after 1 year. Longer duration data is even more impressive with context i.e. historic outcomes for patients treated with existing treatments are poor (ORR of 26%, CR of 7% and mOS of 6 months) vs strong durability of CR rates with Yescarta. Also, Kite/Gilead have the quickest turnaround time (17 days) in the industry (from leukapheresis to delivery of CAR-T therapy) and this matters a lot when patients have an aggressive cancer that progresses rapidly. Novartis reported similar efficacy results at 6 months with a CR rate of 30% (vs 36% with Yescarta). Since Kite/Gilead have set the bar high with their long-term data, Novartis' Kymriah will need to deliver as robust long-term data as Yescarta. Novartis' turnaround manufacturing time is 22 days with Kymriah. Note that in the JULIET trial, 9 out of 147 patients could not be infused because of manufacturing failure (vs <1% in ZUMA-1), and 43 patients discontinued before infusion owing to rapid progression of the cancer. However, note that Novartis brought some improvements to its manufacturing process resulting to a manufacturing success of 97% for the last 30 patients. We believe that these manufacturing factors (turnaround time, manufacturing failure rate) are of significant importance in initial adoption of CAR-T therapies in very sick patients. Juno's data at the second dose-level in the "core" group showed higher CR rates at 3-month (74%) and 6-month (50%). Overall, Juno's data appear competitive

- When comparing CRS rates, one should keep in mind that grading scales are different between companies. Despite variability in the grading criteria, JCAR017 seems to benefit from a safer toxicity profile owing to its underlying defined composition nature. There were 60% of patients without any CRS or without any NT

- There is uncertainty around CAR-T cell therapies' reimbursement owing to their highly expensive list price, therefore, the longer the duration of response over time along with the absence of necessity to use additional therapies after a CAR-T cells infusion, will be key argument to defend CAR-T therapies' value

- Tolerability matters a lot.

Questions around outpatient setting are likely to be of increasingly interest for three main reasons: 1/ Reducing risks associated with the inpatient setting: indeed, severely immunocompromised patients are likely to experience infections at hospitals (nosocomial infections); 2/ From a healthcare economy perspective, the outpatient setting would reduce the number of hospitals days; 3/ Improve patients' convenience. The outpatient setting could represent a factor of differentiation between these CD19 CAR-T therapies. The safer the therapy, the more likely the outpatient approach could be considered.

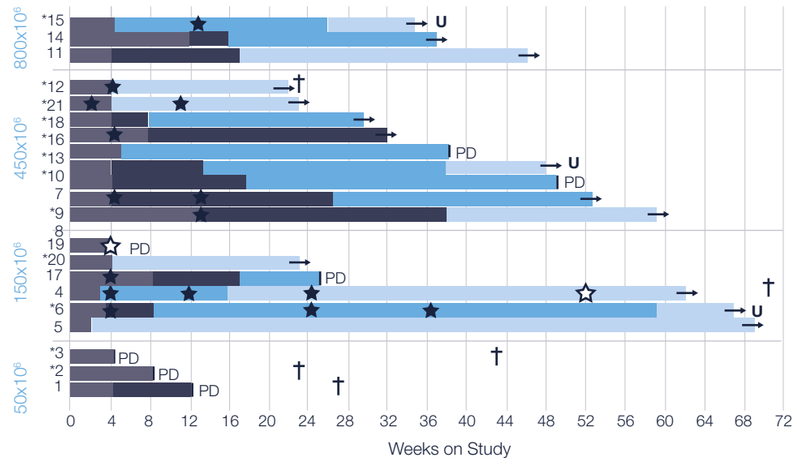
CAR-T therapies going into earlier lines. As one can imagine, when the toxicity profile looks attractive, it allows the therapy to be considered at earlier lines of treatment to treat broader patient populations. In particular, with its attractive safety profile, JCAR017 will be investigated as a second line treatment in CLL (Phase II to be initiated in 2018).

IMPRESSIVE DATA IN MULTIPLE MYELOMA

BLUEBIRD demonstrated that a one-time infusion of bb2121 elicited an 89% ORR rate (n=21) and increased to 94% ORR rate (n=18) at the highest dose. Notably, no patients treated with these higher doses had disease progression. Among the 18 patients who received higher CAR-T cells doses, 10 of them achieved a CR (some very good partial responses turned to be complete responses). The median duration of response is not yet reached nor was the median PFS.

FIG 25: BCMA-SPECIFIC CAR-T THERAPY REPRESENTS A PROMISING SAFE THERAPEUTIC APPROACH FOR R/R MULTIPLE MYELOMA PATIENTS

HIGH FREQUENCY OF DEEP AND DURABLE TUMOR RESPONSE IN ACTIVE DOSE COHORTS



Median follow up of 40 weeks in active dose ccohorts; PFS not yet reached

17/18 (94%) ORR at active doses

56% Complete Response Rate and 89% VGPR or better

9/10 evaluable patients MRD negative

Durable ongoing responses over 1 year

Responses continue to improve as late as month 15 (VGPR to CR)

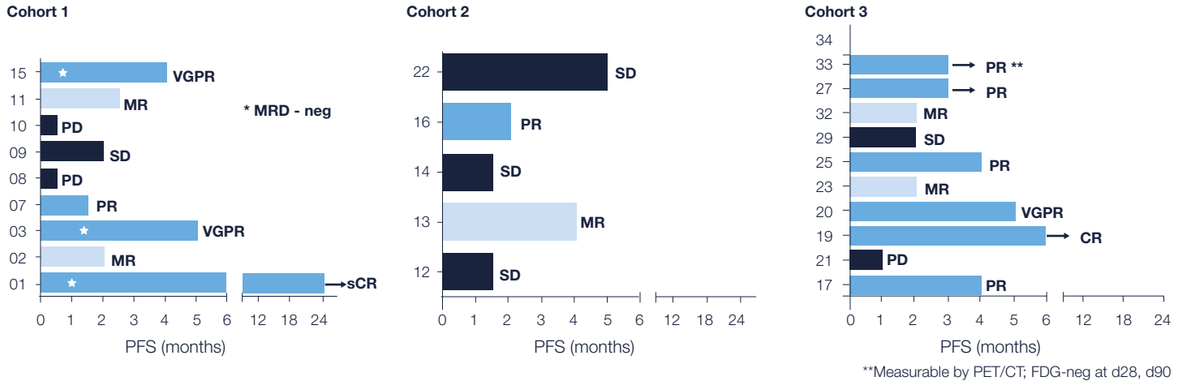
CR/sCR · VGPR · PR · Stable Disease · PD · MRD- · † Diseased · U Unconfirmed response · MRD+

* High Tumor Burden (>50% Bone Marrow Involvement)

Patient 12 died of cardiopulmonary arrest
Patient 4 died of MDS following discontinuation
NASDAQ: Blue

Source: Bluebird Bio, December 2017

FIG 26: CAR-T BCMA DATA: CLINICAL ACTIVITY



**Measurable by PET/CT; FDG-neg at d28, d90

Source: Bluebird Bio, December 2017

The clinical activity of BCMA-CART seems encouraging but might need to be optimized from both a dosing and scheduling perspective. This BCMA-CART is developed in collaboration with the University of Pennsylvania. Scientists at UPenn conducted this phase I trial and have presented their results at the ASH 2017. Based on these data, Novartis plans to initiate a phase II study in 2018 to investigate an improved version of the BCMA-CART product.

JUNO THERAPEUTICS is also developing CAR-T therapies to treat R/R MM patients and showed in a presentation (Abstract #1813) that its fully human BCMA-specific CAR T cell product candidate exhibits little or no off-target activity, killed myeloma cells over a range of antigen densities regardless of the presence of soluble BCMA. Juno plans to initiate a phase I/II clinical trial with JCARH125 in early 2018.

KEY HIGHLIGHTS

- Differences across studies may be related to 1/patient populations, 2/clinical trial designs (lymphodepletion regimen, doses, splitting of doses etc), and 3/ number of prior lines of therapy. While patients recruited in the Bluebird's study had a median seven prior lines, patients in the Nanjing Legend's study had a median of 4 prior lines
- The higher efficacy seen with Bluebirds' and Nanjing Legend's studies vs Novartis' might be due to the positive effect of the lymphodepletion regimen prior to CAR-T cells infusion. Furthermore, in Bluebird's and Nanjing Legend's trials, there was a specific inclusion criterion i.e. > 50% BCMA expression on tumor cells, which was not required in Novartis' study. This could also explain why bb2121 and LCAR-B38M led to higher ORR rates compared to Novartis' BCMA-CART
- Finally, we would say that if Nanjing Legend wants to be considered as a serious competitor to Bluebird and Novartis, the Chinese biotech may need to run additional clinical trials in the US and/or EU to set its credibility worldwide
- Although it is not the prime purpose of our report here, once we will question the market potential of all BCMA CAR-T therapies, the anti-BCMA approach with antibody drug conjugate (ADC) led by GSK will also have to be considered since data presented at ASH this year were also very solid. For instance, with five prior lines of treatment, GSK's ADC achieved 60% ORR and 7.9-month PFS.

In summary, data presented at ASH 2017 speak clearly and here are the conclusions that can be drawn with certainty: 1/CD19-CAR-T cells are new, offering a disruptive therapy alternative to existing treatments, 2/ the costs to generate and administer CAR-T cells are beyond that of standard cytotoxic chemotherapy, 3/CD19-CAR-T cells represent a substantial clinical improvement based upon i) their capacity to kill chemo-resistant cancer cells and ii) their capacity to induce durable clinical benefits which last months beyond the date of administration of the engineered T-cells.

CAR-T cell therapies are increasingly safe owing to three main factors: 1/improved clinical protocols (e.g. with safety algorithms), 2/longer physicians' experience around CAR-T cells related toxicities (e.g. earlier use of tocilizumab, biomarkers to identify high-risk patients who may experience high grade CRS), 3/ next-generation CAR constructs (e.g. including both ON/OFF switches such as the ones from Bellicum).

Safer CAR-T therapies means going into earlier lines. "We believe as you can manage the safety more effectively CAR-T therapy can be moved into earlier lines of therapy to give patients definitive outcomes and we also believe the safety profile will get more manageable as we get into these earlier lines" said David Lebwohl (Novartis) at the Investor Conference Call after the ASH 2017 meeting.

We see an increasing competition in liquid tumors from antibodies with:

1. **Amgen's Blincyto**, a bispecific Ab that can be used to bridge the gap between T-cells and cancer cells (blinatumomab: CD19xCD3) approved in ALL
2. **Merck's Keytruda** (pembrolizumab: anti-PD1) recently approved in classical Hodgkin's lymphoma
3. **Roche's Polatuzumab** (anti-CD79b ADC) is in a phase II study to treat R/R FL or DLBCL (NHL)
4. **Affimed's AFM13** (TAndAb recognizing CD30: a tetravalent, bispecific natural killer cell engagers) is in phase Ib combined to pembrolizumab to treat R/R patients with Hodgkin lymphoma and eventually, 5/GSK's GSK2857916 (anti-BCMA ADC) is going in phase II trial to treat Multiple Myeloma.

Generally, antibodies lead to a good initial response rate but the durability of responses might not be as durable as with CAR-T cell therapies. Indeed, CAR-T cell therapies just proved at ASH 2017 that they could be a curative treatment in some patients, as seen with long-term complete response after 6 months and 1 year post single infusion. Patients in complete response at 6 months tend to remain so later on. And this success has not been observed with antibodies so far.

Checkpoint inhibitors have revolutionized treatment of solid tumors and are also now beginning to make inroads into blood cancers. What we understood from the ASH 2017 meeting is that almost all CAR-T players are now considering combining their lead CAR-T product with an anti-PD1/L1. This is the case with Novartis' Kymriah combined to Merck's pembrolizumab (to be initiated in 2018), Kite's KTE-C19 combined to Roche's atezolizumab (ongoing phase I ZUMA-6 trial, NCT02926833), or even Juno's JCAR017 combined to AZN's durvalumab (ongoing phase I/II PLATFORM trial, NCT03310619). One question now is: Is it worth combining CAR-T with additional therapies? Only more mature clinical outcomes will tell, but there is undeniable scientific rationale supporting such combinations.

Despite encouraging data, several issues still need to be addressed

CONTROL CAR SELECTIVITY

There are several strategies for enhancing CAR selectivity:

- **Selecting safer antigen:** CAR can only attack cells expressing the target antigen; hence, the most direct and effective means to surmount off-tumor toxicities while not compromising efficacy is by targeting truly tumor-specific antigens expressed only on the tumor cells. However, the vast majority of CAR targets have been tumor-associated antigens (TAA) that are overexpressed on tumor cells but also shared by some normal cells. Thus far, the only truly tumor-specific antigen for CAR is EGFRvIII, which is strictly confined to human cancer (glioblastoma)

- **Combinatorial antigen targeting:** one strategy to enhance the specificity of CAR is combinatorial antigen targeting rather than single antigen targeting, enabling CAR-T cells to discriminate between target and off-target cells. For instance, if the dual antigens are simultaneously expressed on healthy cells rather than on tumor cells, the combination of inhibitory receptors (known as iCAR) specific for the antigen present on normal but not on tumor cells will protect the normal cells from CAR-T cell-mediated attack because of negative signalling conferred by iCAR

- **Tuning sensitivity of scFv:** it has been demonstrated recently that by tuning the affinity of a CAR (mediated by the antibody-derived scFv recognition of the target), CAR-T cells could discriminate between tumor cells and normal cells that express lower or normal levels of the same antigen while retaining potent efficacy in vivo. Tuning sensitivity of CAR by scFv affinity provides an alternative approach to empower wider use of those targets overexpressed on tumor cells. However, the optimal affinity for an scFv in the CAR will depend on a number of different factors such as the location of the target epitope, antigen density, length of spacer etc.

- **Masked CAR:** protease-activated antibody (pro-antibody) is an antibody characterized by antigen-binding sites that are masked until the antibody is activated by proteases commonly found in the tumor microenvironment (TME). So, an EGFR-targeting pro-antibody CAR would be relatively inert in healthy tissue but activated by the TME.

CONTROL CAR ACTIVITY

In this scenario, a chimeric receptor uses the extracellular domain of a receptor to a ligand that is commonly found in the TME. This is coupled to the intracellular signalling domain of a receptor that has relevant biology to the cell. One good example is the PD-1 receptor extracellular domain chimerized to CD28 intracellular domain (PD1CD28). With this CAR (PD1CD28), binding to PD-L1 present on tumor cells results in stimulation of CAR-T cells rather than the inhibition seen in normal T-cell activity.

Limiting CAR expression: at present, the most common gene transfer strategies are viral techniques using either retrovirus or lentivirus which result in permanent transgene encoding CAR expression.

However, these are disadvantageous when severe toxicity related to CAR-T cells occurs. Thus, one non-viral approach, the electroporation of CAR with mRNA molecules, is regarded as potentially safer than the viral methods because the CAR expression is transient. However, due to this transient CAR expression, multiple infusions are necessary for mRNA CAR-T cell therapy. Curiously, and somewhat perversely, this approach might be more attractive for both the pharma players and healthcare payers, assuming that the price of the product reflected the repeat cycles used for the treatment.

Switchable CART: switchable CAR is a novel design, i.e. dimerizing small molecules and tumor-targeting antibody, opening up opportunities to remotely control or terminate CAR-T cell activity. As for example, in order to broaden the therapeutic window for CAR-T, conditionally activated CAR would require “AND/OR” Boolean gates i.e. antigen A OR antigen B, antigen A AND antigen B, antigen B AND NOT antigen A (activation requires antigen B, but presence of antigen A, signifying healthy cells, would prevent CAR-T activation).

PRICE AND IMPACT OF MANUFACTURING

Streamlining the process to augment performance while reducing costs. The ideal manufacturing should not only increase safety, efficacy and reproducibility, but also decrease the effective T-cell dose and hence the scale of production. Thanks to our different interactions with CAR-T biotech, we understand that what costs the most is the viral vectors and the media for cell culture, hence the need to reduce scale. Importantly, small changes in the manufacturing process can significantly alter the potency and safety profile of expanded T cell populations. For instance, if Novartis brings some changes in the future to its manufacturing process to optimize it, then the next CAR-T cell therapy will not be equivalent to Kymriah, which is manufactured with the current process.

Investing in closed automated systems integrating cell-selection devices, microchips and bioreactors combined with biosensors for in situ monitoring, in order to mitigate costly cGMP operations and limit error-prone manual procedures. Some research teams demonstrated that CD19-CAR-T cells generated using a closed automated GMP cell processing system were comparable to CD19-CAR-T cells produced by the conventional processes in terms of transduction efficiency, phenotype, function and overall yield (Mock, et al., 2016) (Priesner, et al., 2016).

Manufacturing challenges include:

- Use of the optimal vector is crucial for consistent cell processing
- Investigating the long-term safety of viral vectors requires patient follow-up
- Ensuring quality of production in moving from a single institution to a multi-site, large-scale manufacturing process
- Meeting global regulatory expectations (cGMP).

One key concern is: since in most current haematology settings CAR-T is a procedure that serves as a bridge therapy to allow patients to become eligible for an allo-SCT, CAR-T treatment cost is a major consideration and could be hard to support if it is not used as a cure.

One should not only focus on CAR-T efficacy and market opportunity, but also pay particular attention to commercialization plans as it could be a bigger factor for uptake. How the drug is commercialized is almost as important as its therapeutic benefit and should not be overlooked. How comfortable will doctors be using different clinical protocols for apheresis from each CAR-T player? How comfortable will people involved in the process be to administer the product? How to best coordinate all people involved at each step will need to be watched carefully.

MOVING FROM AUTOLOGOUS TO ALLOGENEIC

The successful CAR-T cell therapies have, to date, used autologous T-cells, which imposes individualized cell manufacturing and makes inter-patient variability unavoidable, even with selection of defined subsets. The rationale behind the autologous approach is to prevent a T-cell attack of the recipient and rejection of the therapeutic T-cells by the recipient. Immunosuppressive drugs may mitigate such complications, but they are not an option because they would impede the anti-tumoral effect of the infused T-cells.

The need to manufacture patient-specific products delays the use of the therapy, which has led to some patients not being able to receive their autologous CAR-T product due to disease progression occurring during manufacturing. It is noteworthy that delay in manufacturing also adds costs and complexity given the need to ship product to and from centralized manufacturing facilities.

The main limitations seen with current autologous CAR-T are:

- **Manufacture failures:** some patients do not have enough healthy T-cells, and drug makers fail to manufacture an autologous CAR-T cell therapy at the recommended dose
- **Timing:** by the time autologous CAR-T product is manufactured and shipped, the patient may die (because of aggressive acute cancer that progresses too rapidly)
- **High costs** due to the necessity of designing a bespoke treatment for each patient and the effort consumed in modifying and growing each patient's T-cells
- At present, **autologous treatments** cannot be mass produced and may involve significant production time.

These constraints push companies to set specific inclusion criteria in their clinical trials such as 1/patients' absolute lymphocyte counts or 2/ patients' T-cells' capacity to expand after activation with anti-CD3/CD28 beads, to ensure the manufacturing of autologous CAR-T is possible.

The allogeneic approach aims at delivering an off-the-shelf product with several benefits:

- **Market access:** enabling products to be shipped and stored globally, thereby reducing development obstacles and providing accessibility to a broader patient population
- **Cost-effectiveness:** impersonalized streamlined manufacturing process has the potential to reduce COGS significantly
- **Novel features:** develop products with additional gene-editing specificities (such as disrupting the CS1 cell surface antigen)
- **Consistency:** qualify and develop standardized products that are designed for optimal dosage while reducing batch-to-batch variability
- **Convenience and timing:** patients and clinicians can move into treatment phase more rapidly with a standard off-the-shelf product.

It is noteworthy that the allogeneic approach spurred interest in the field as almost each CAR-T player inked a collaboration agreement with gene-editing biotech to develop allogeneic products, such as BlueBird Bio who bought PreGenEn in 2014, Novartis/Intellia, JNJ/Poseida, Juno/ Editas, Baxalta/Precision Bioscience, Regeneron/Adicet Bio, Kite/UCLA etc.

WHAT ABOUT SOLID TUMORS? LET'S WAIT AND SEE...

To date, CAR-T cells have demonstrated tremendous success in eradicating hematologic malignancies (e.g. CD19 CAR-T in leukemia). However, this success has yet to be replicated in solid tumors, as clinical results in solid tumors have been much less encouraging.

However, Celyad' approach with its CAR-NKG2D targeting 6-lignad expressed in over 80% of solid tumors seems promissing and has already yielded positive results in colorectal cancer.

BRYAN, GARNIER & CO

White Paper Contributors

OLIVIER GARNIER
Managing Partner, Investment Banking
Healthcare
ogarnier@bryangarnier.com

ERIC LE BERRIGAUD
Managing Partner, Equity Research Analyst
Pharmaceuticals
eleberrigaud@bryangarnier.com

HERVE RONIN
Partner, Investment Banking
Healthcare
hronin@bryangarnier.com

HUGO SOLVET
Equity Research Analyst
Medical Technology & Biotechnology
hsolvet@bryangarnier.com

DR JAMILA EL BOUGRINI
Equity Research Analyst
Biotechnology
jelbougrini@bryangarnier.com

MARION LEVI
Equity Research Analyst
Biotechnology
mlevi@bryangarnier.com

Heathcare Investment Banking Team

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PARTNERS
Olivier Garnier | Healthcare
Hervé Ronin | Healthcare

MANAGING DIRECTORS
Sandrine Cailleteau | Healthcare
Dan Dysli | Healthcare
Pierre Kiecolt-Wahl | Equity Capital Markets
Phil Walker | Healthcare
Dominic Wilson | Healthcare

DIRECTORS & VICE PRESIDENTS
Romain Ellul
Dr Nicholas Hanser
Dr Anne Moore

ANALYSTS & ASSOCIATES
Mickael Dubourd
Rémi Negre
Jean de Pracomtal

Healthcare Equity Research Analyst Team

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MANAGING PARTNER
Eric Le Berrigaud | Healthcare

MANAGING DIRECTORS
Olivier Pauchaut | Head of Research
Dr Gary Waanders | Healthcare

ANALYSTS
Dr Jamila El Bougrini | Biotechnology
Marion Levi | Biotechnology
Hugo Solvet | Medical Technology & Biotechnology

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BRYAN, GARNIER & CO

LONDON
Beaufort House
15 St. Botolph Street
London, EC3A 7BB
UK

T: +44 (0) 207 332 2500
F: +44 (0) 207 332 2559

Authorized and regulated by the Financial Conduct Authority (FCA)

PARIS
26 Avenue des Champs Elysées
75008 Paris
France

T: +33 (0) 1 56 68 75 00
F: +33 (0) 1 56 68 75 01

Regulated by the Financial Conduct Authority (FCA) and the Autorité de Contrôle prudential et de resolution (ACPR)

MUNICH
Widenmayerstrasse 29
80538 Munich
Germany

T: +49 89 242 262 11
F: +49 89 242 262 51

ZURICH
Theaterstrasse 4
8001 Zurich
Switzerland

T: +41 44 991 3300

NEW YORK
750 Lexington Avenue
New York, NY 10022
USA

T: +1 (0) 212 337 7000
F: +1 (0) 212 337 7002

FINRA and SIPC member

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