TRENDS-in-MEDICINE

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by Lynne Peterson

SUMMARY

Among the data presented at ASCO were:

- OlympiAD trial of **AstraZeneca's Lynparza** showed this PARP inhibitor effective in breast cancer.
- Boosters for checkpoint inhibitors continue to be investigated but nothing stands out yet.
- STAMPEDE and LATITUDE trials showed adding **Johnson & Johnson's Zytiga** to ADT improved survival for prostate cancer patients.
- **Loxo Oncology's larotrectinib** showed amazing activity in TRK+ cancers.
- APHINITY showed adding **Roche's Perjeta** to Herceptin in breast cancer improved invasive disease-free survival but only a little.
- **Sirtex Medical's Sir-Spheres** failed to show a significant benefit in colorectal cancer that has metastasized to the liver.

Trends-in-Medicine
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As usual, there were numerous impactful clinical trials presented at ASCO. Some years, there is a focus on a particular cancer, but this year, the results came from many different solid cancers – particularly breast cancer, colorectal cancer, non-small cell lung cancer (NSCLC), and prostate cancer – but also acute lymphoblastic leukemia (ALL).

ASTRAZENECA's Lynparza (olaparib) – breast cancer

The results of the 302-patient Phase III OlympiAD trial, presented at ASCO and simultaneously published in the ***New England Journal of Medicine***, showed that this PARP inhibitor, which has FDA approval in ovarian cancer, also is active in BRCA+ breast cancer. Progression-free survival (PFS), the primary endpoint, was significantly better with olaparib vs. chemotherapy (7.0 months vs. 4.2 months, p= 0.0009, HR 0.58). And the benefit was achieved with fewer side effects (Grade ≥3 adverse events were 36.6% vs. 50.5%).

The principal investigator, Mark Robson, MD, clinic director of the Clinical Genetics Service at Memorial Sloan Kettering Cancer Center, said, "It is our opinion that olaparib could be an effective treatment option for women with BRCA mutations and metastatic HER2-negative breast cancer, including, importantly, women with BRCA mutations in triple-negative disease." ASCO president Daniel Hayes, MD, a breast cancer specialist from the University of Michigan Comprehensive Cancer Center, called the results "a major step forward in translational medicine."

However, Dr. Hayes cautioned that this is applicable only to a subset of breast cancer patients – BRCA+ patients – and there are no long-term safety data and no difference in overall survival.

Checkpoint Inhibitors – how to boost PD-1/L1 inhibitors

A *large* number of agents are being explored as add-on therapies to a PD-1/L1 inhibitor to increase efficacy and responders, but the data are still early. And PD-1/L1s are being explored as boosters for gene therapy. Among the combinations highlighted at ASCO were:

- **Bristol-Myers Squibb's BMS-986156**, a glucocorticoid-induced tumor necrosis factor receptor-related gene (GITR) agonist, added to BMS' Opdivo (nivolumab), a PD-1 inhibitor, in patients with advanced solid tumors. The data showed linear pharmacokinetics (PK), with dose-related increase in exposure and a low incidence of immunogenicity, good tolerability, and biologic activity. There were clinical responses observed.

- **NewLink Genetics and Roche's navoximod (GDC-0919, IDO-IN-7)**, an IDO1 inhibitor added to Roche's Tecentriq (atezolizumab), a PD-L1 inhibitor, in locally-advanced/ metastatic solid tumors. A Phase Ib study in 50 patients, presented at ASCO, showed only a 10% response rate, and days after ASCO, Roche gave the drug back to NewLink.
- **Novartis' CAR T therapy + Merck's Keytruda (pembrolizumab) in ALL.** Giving a PD-1 inhibitor to patients who relapsed after CAR T therapy appears to improve the persistence of CAR T cells and to promote endogenous T cell anti-tumor activity.

JOHNSON & JOHNSON's Zytiga (abiraterone) – prostate cancer

Two studies in prostate cancer, published in the ***New England Journal of Medicine*** and presented at ASCO – STAMPEDE and LATITUDE – are likely to increase the use of abiraterone and move its use earlier, and this has negative implications for Medivation and Astellas' Xtandi (enzalutamide). The key findings were:

STAMPEDE – patients not previously treated with androgen deprivation therapy (ADT)

Adding abiraterone/prednisone to ADT significantly improved both overall survival (primary endpoint) and failure-free survival (FFS), an intermediate primary outcome, vs. ADT alone. The Kaplan-Meier curves were impressive.

Overall survival was 83% vs. 76% ($p<0.001$, HR 0.63). FFS was 75% vs. 45% ($p<0.001$, HR 0.29), or 43.9 months vs. 30 months – a 13.9 month difference. Remember, the first finding, reported at ASCO 2015, was that adding docetaxel to ADT improved FFS in newly, diagnosed, hormone-naïve prostate cancer patients by 10 months, so abiraterone did better than docetaxel, is less toxic, and is easier to administer.

PFS was 80% with abiraterone/ADT vs. 62% for ADT alone ($p<0.001$, HR 0.40). And the benefit to abiraterone held for nearly every subgroup examined.

One surprise: the incidence of hypertension and hypokalemia (known side effects of abiraterone) was higher in these patients than has been observed in metastatic castration-resistant prostate cancer (mCRPC). The numbers are not particularly concerning but unexpected and counter-intuitive.

STAMPEDE was a multi-stage, multigroup study. This analysis included 1,917 men. Half (52%) of the men were metastatic, 20% had node-positive/intermediate non-metastatic disease, and 28% had node-negative, non-metastatic disease. This is the second outcome to be reported from this uniquely-designed trial.

LATITUDE – patients with metastatic, castration-sensitive prostate cancer

Adding abiraterone/prednisone to ADT significantly improved both co-primary endpoints – overall survival and radiographic PFS vs. ADT alone. Again, the Kaplan-Meier curves were impressive.

Overall survival was not reached with abiraterone/ADT vs. 34.7 months for ADT alone ($p<0.001$, HR 0.62).

Radiographic PFS was 33.0 months with abiraterone/ADT vs. 14.8 months with placebo ($p<0.001$, HR 0.47). Again, the benefit to abiraterone held for nearly every subgroup examined. And there were numerous other significant benefits of abiraterone/ADT over ADT alone, including: time to pain progression, time to next subsequent therapy, initiation of chemotherapy, PSA progression, and next symptomatic skeletal event.

LATITUDE was a double-blind, 1,199-patient Phase III trial. This was a preplanned interim analysis at 30.4 months. The interim results were so positive that the independent data safety monitoring committee unanimously recommended the trial be halted and the ADT patients be allowed access to abiraterone.

The same adverse event profile emerged, with a higher rate of hypertension and hypokalemia than expected.

What do these trials mean for treatment of prostate cancer? Scott Tagawa, MD, director of genitourinary cancer at Weill Cornell Medicine, predicted the studies would change practice for patients who fall into the studied categories – which is not all patients, "I think the majority of patients will now get ADT + abiraterone/prednisone as the standard of care – provided there is insurance coverage."

He explained that a long time ago in the U.S. nearly every man who walked in the door had metastatic disease, but with PSA testing that dropped to ~5%, then it went up to ~10% in some settings when PSA testing was cut back, but it may drop again with PSA testing coming back.

Where will docetaxel fit now? Dr. Tagawa said the hazard ratios for abiraterone in the two trials are very similar, and the bias will probably be to use abiraterone instead of docetaxel because it is less toxic.

Asked if cost would limit abiraterone use vs. docetaxel, Dr. Tagawa pointed out that abiraterone can be more expensive because it is taken longer. He said docetaxel is generally given for 4.5 months and abiraterone continuously. But he added that docetaxel toxicity can change the cost comparison.

What do the trials mean for use of Medivation and Astellas' Xtandi (enzalutamide)? Dr. Tagawa said that the earlier use of abiraterone could encourage oncologists to use docetaxel in men who progress to mCRPC instead of enzalutamide, and men who do get enzalutamide for mCRPC may not take it as long (<1.5 years) because it will be after abiraterone, where it doesn't work as well.

The bottom line: Dr. Tagawa said, "Earlier abiraterone clearly works just like earlier docetaxel works."

LOXO ONCOLOGY's larotrectinib (LOXO-101) – solid tumors

This oral pan-TRK inhibitor showed amazing activity in patients who are TRK+ regardless of tumor type. Loxo estimated that annually ~1,500-5,000 patients in the U.S. are diagnosed with a TRK fusion cancer.

In fact, larotrectinib showed activity in 17 different cancers. In the 46 evaluable patients from Phase I and II trials, the overall response rate (the primary endpoint) was 76%, with 12% complete responses. The 6-month duration of response rate was 91%. The effect of the drug appears durable, with 93% of responders and 75% of all patients remaining on treatment or undergoing surgery with curative intent. And this was achieved with "minimal" side effects.

These data suggest larotrectinib could be approved by the FDA based on the data presented at ASCO because the benefit was so dramatic and another trial may not be feasible since experts said it would be impossible to deny the drug to anyone who is TRK+.

The one catch: all cancer patients will need to be routinely screened for TRK status.

ROCHE/GENENTECH's Perjeta (pertuzumab) – breast cancer

The 4,805-patient Phase III APHINITY trial met its primary endpoint, showing a statistically significant (but very small) benefit in invasive disease-free survival (IDFS) over 3 years to adding Perjeta to Herceptin (trastuzumab) vs. Herceptin alone in women with untreated, early-stage HER2+ breast cancer (89.2% vs. 91.8%, p=0.045, HR 0.81). And breast cancer doctors said there is enough benefit that they will offer it to patients – as they are already doing. APHINITY may not expand use of Perjeta, but it won't reduce it either.

The benefit was greatest in node-positive/HR-negative patients, but breast cancer doctors said they will offer it to other patients as well, provided insurance covers the combination. An investigator Gunter von Minckwitz, MD, PhD, president of the German Breast Group in Neu-Isenburg, Germany, said, "From a statistical point of view, we don't see a difference in efficacy in the node-positive vs. node-negative patients or with regard to hormone-receptor status. But with the data we have right now, these results support the use more in the higher-risk patients: node positive and receptor negative."

SIRTEX MEDICAL's SIR-Spheres – colorectal cancer

Summary

- The company insisted that the negative data in metastatic CRC is not negatively impacting the use of SIR-Spheres in primary HCC, and physicians agreed.
- The only possible bright spot in CRC was a hint that SIR-Spheres is effective in right-sided CRC, but that will require another trial.
- The company and investigators were still optimistic about the ongoing SORAMIC trial in HCC.
- While there weren't any positive data to use in marketing against competitors, this is the only SIRT company to have any data, and doctors did give the company points for doing studies.

This Y-90 brachytherapy-type microsphere implant treatment has PMA approval from the FDA to treat inoperable hepatocellular carcinoma (HCC) or as salvage therapy in HCC patients who progress on Bayer's Nexavar (sorafenib). Millions of tiny SIR-Spheres are injected into the blood supply of a liver tumor. The company is hoping to expand approval for use (1) ahead of continuous, oral, systemic therapy with sorafenib in HCC and (2) in liver metastases from other primary cancers, particularly colorectal cancer (CRC). Those indications seem unlikely, given the trial data, particularly the FIREFOX data.

The company has now had five negative trials as well as a negative pooled analysis.

- **SARAH** – A French study, presented at the European Association for the Study of the Liver (EASL) meeting in Amsterdam in April 2017. In this open-label, investigator-initiated, 459-patient, 25-center Phase III trial in locally advanced or recurrent inoperable HCC, SIR-Spheres missed the primary endpoint, failing to improve overall survival (OS) vs. sorafenib 800 mg/day either by intent-to-treat or per protocol analysis.

  David Turner, head of global marketing for Sirtex, said, "SARAH actually helps us because now we have a clearer

picture of the treatment comparison. Hepatologists have embraced it." Ken Thurston, vice president, strategic development and global clinical affairs at Sirtex, added, "The advisory board said it should not have an impact."

- **SIRveNIB** – An investigator-initiated, open-label, 360-patient Phase III trial comparing SIRT (selective internal radiation therapy) with SIR-Spheres to sorafenib in advanced liver cancer patients in 11 Asia/Pacific countries. The trial missed the primary endpoint, failing to show adding SIRT to FOLFOX/bevacizumab provided any benefit – and SIRT added toxicity.
- **FOXFIRE-Global** – A 209-patient comparison of mFOLFOX6 ± SIRT in mCRC.
- **SIRFLOX** – A 530-patient Phase III trial of mFOLFOX6 (± bevacizumab) ± SIRT in mCRC.
- **FIREFOX** – A 364-patient, open-label Phase III trial of mOxMdG (a chemotherapy regimen equivalent to mFOLFOX6) ± SIRT in mCRC.
- **FOXFIRE survival analysis** – A 1,103-patient pooled analysis of survival in three failed trials of chemotherapy ± SIRT in liver metastases from CRC – SIRFLOX, FOXFIRE-Global, and FOXFIRE (U.K.). This analysis failed to show a benefit to first-line SIRT over chemotherapy. In fact, SIRT looked numerically worse than chemotherapy, and it was more toxic. The results will be published soon in ***Lancet Oncology***. This actually could be construed as a disaster for Sirtex.

SIRveNIB

The company hosted a media briefing at ASCO for a small group of reporters to talk about SIRT and SIRveNIB ahead of the FOXFIRE results. The briefing was clearly an attempt to keep the coverage from being entirely negative by making three points:

1. In CRC an exploratory analysis found that there may, just may, be a benefit in right-sided CRC – which occurs in ~25%-33% of mCRC – but not left-sided CRC. The data are thin, but there is a hint.
2. In HCC, SIR-Spheres works as well in Asian patients as in Caucasian patients.
3. SIR-Spheres is more tolerable for patients than sorafenib. And a patient advocate was there to emphasize the greater tolerability of SIR-Spheres.

SIRveNIB Trial Results			
Measurement	**Sorafenib**	**SIRT**	**p-value**
Primary endpoint: Overall survival (by intent-to-treat)	10.02 months	8.84 months	Nss, p=0.360 HR 1.12
Overall survival (treated patients)	10.41 months	11.27 months	Nss, p=0.273 HR 0.86
Tumor response rate (CR+PR by ITT)	1.7%	16.6%	p<0.001
Disease control rate	41.8%	42.7%	Nss

Pierce Chow, MD, PhD, a surgeon from the National Cancer Centre Singapore, reviewed the results of the SIRveNIB trial. He noted that, though SIRT was not better than sorafenib, it also wasn't worse. However, the trial was not designed to show non-inferiority because, as a company official explained, that would have required a much larger number of patients.

Dr. Chow said SIRveNIB is important because "the scientific world needs to know which should be first-line [sorafenib or SIRT] and which should be backup therapy." Even though the trial missed the primary endpoint, Dr. Chow said, "The tumor response rate and disease control rate…in the SIRT arm is clearly ***superior***…because the tumors shrank…with a very wide difference by both ITT and by per treatment analyses."

He also emphasized that SIRT patients had significantly fewer adverse events in the study vs. sorafenib, fewer treatment-emergent adverse events, fewer Grade ≥3 adverse events, and fewer serious adverse events, "So, one therapy is much less toxic…And I think for clinicians and patients this is very important information. Before this trial we couldn't say which treatment was more or less toxic…Based on this, physicians should be able to determine the patient's condition, and patients should be able to make a choice."

The patient advocate, Andrea Wilson, president/founder of Blue Faery, said, "I had a doctor say to my face [that SARAH was] a negative study because the primary endpoint was not met…but that really depends on how you look at it. From a patient standpoint, [SIRveNIB] is a positive study. It comes down to quality of life, and this study clearly shows that quality of life is improved with SIRT. And patients who call me and are on sorafenib almost always take themselves off sorafenib or have the dose lowered so much that we don't know if the drug is effective."

The key adverse events with sorafenib were described as diarrhea, hypertension, and fatigue. In contrast, the adverse events with SIRT were bleeding and liver cirrhosis. Dr. Chow said, "I think all these are reasons our data support SIRT as a less toxic therapy."

Asked about the tumor response rate, Dr. Chow said, "In an institution [like mine] with an active surgical practice, patients with a significant tumor response means…we have been able to take many of these patients to the operating room because the tumor was downstaged."

Dr. Chow said 23% of the patients in this trial were downstaged, but many of the sites did not have the surgical ability to do a resection, so they can't estimate how many patients across the whole trial were downstaged enough to successfully undergo resection. However, he said a manuscript is in process of a pooled analysis of patients who had surgeons who were able to resect them.

Asked why non-curative surgery improves quality of life, Dr. Chow said, "Because the nature of the cancer has changed when it is downstaged."

Asked about survival after resection, Dr. Chow said, "In patients downstaged and resected, it is the same as patients who originally had a small tumor that could be resected."

Asked why the tumor response rate in the sorafenib arm of SIRveNIB was lower than in SARAH, Dr. Chow said, "Our 2% rate is consistent with the original sorafenib approval studies… Our response rate is no different from what is published in the literature."

Asked if another trial is planned with quality of life as the primary endpoint, Dr. Chow said No, explaining, "Whether sorafenib remains the appropriate control is a question. We know other drugs are now being compared against sorafenib… including checkpoint inhibitors…and we believe that checkpoint inhibitors may eventually be the therapy of choice."

Asked how the patients in SIRveNIB differ from the patients in SARAH, Dr. Chow said, "The SARAH patients were French, and the French do have more alcohol use and hepatitis C virus [HCV]. In Asia/Pacific [SIRveNIB] the patients tend to get live cancer from hepatitis B virus [HBV]. What we found is the two studies essentially go in the same direction. This tells us SIRT is effective across a whole range of patients…So, it is not only useful in one subset. In terms of outcomes, the two trials were similar."

Asked how SIR-Spheres differs from BTG's TheraSphere, which has a humanitarian device exemption (HDE) from the FDA, Dr. Chow said, "They are similar but different. The scientific data support the use of Y-90 only in one of the two therapies. It is possible TheraSphere is also effective, but we don't have the data." TheraSphere is not approved in Asia. Sirtex's Thurston said, "There haven't been any trails of TheraSphere, so we don't know the toxicity profile. And TheraSphere has a higher radiation dose and more liver dysfunction."

Asked how he presents SIRT to patients, Dr. Chow said, "From this [SIRveNIB] and SARAH, I will tell patients there are two possible options…One has less toxicity and possibly the tumor may be downsized…We discuss it with a multidisciplinary bloc…and we recommend SIRT as first line for patients. Some patients may not be able to receive SIRT, and then we have sorafenib as backup."

Asked by the patient advocate if SIRT is recommended for Stage 4 patients where the tumor has metastasized outside the liver, Dr. Chow said, "We have a Phase II study addressing this. We found that while the toxicity was higher than SIRT alone, the combination [is more effective]." He said they found they need to wait 14 days after SIRT before starting sorafenib because of toxicity, that 10 days was too soon.

However, a company official said that in the ongoing Phase III SORAMIC trial in HCC testing the combination of sorafenib + SIRT vs. sorafenib alone, sorafenib is started 3 days after SIRT." This study has completed enrollment, and results are expected in 2018. Asked if SIRveNIB provides any reassurance that SORAMIC will be positive, a company official said No, but Dr. Chow said Yes.

Sirtex's Thurston said, "The principal investigator published an analysis of the first 40 patients and saw similar toxicity with sorafenib vs. SIRT/sorafenib. It is only a 3-day gap between the sorafenib and SIRT, but it is a different dosimetry of the spheres, a lower dose."

Asked if SIRT might show a benefit if the SIRveNIB patients were followed longer, Dr. Chow said, "We might, but that is not what the study was designed to do."

Asked about the right-side finding in FOXFIRE, Thurston said, "Basically, in right-sided disease, there is generally lower survival, but in the right side you saw no difference – SIRT was comparable. There is a lot of information in the CRC community that suggest that right-sided primary location has a worse prognosis…and what we are trying to determine is why that is the case. Is it two different diseases? Does it have to do with genetics? However, there is also evidence that even if you factor in genetics, there is a different signal in the right vs. the left."

FOXFIRE pooled analysis

In the FOXFIRE survival analysis, 8.5% of patients in the SIRT arm did not get SIRT, because of clinical deterioration, inappropriate anatomy, or withdrawal of consent. The only other demographic difference was that fewer SIRT patients got bevacizumab as part of their chemotherapy (35.6% vs. 46.6%).

The principal investigator, Ricky Sharma, MD, chief of radiation oncology at University College London, said, "The only

subgroup with a benefit was patients with a primary tumor on the right side…This finding is being validated with other data sets and will be presented at subsequent congresses."

SIRT also appears to reduce radiological progression in the liver – but at the expense of non-liver progression, suggesting local treatment of liver mets is not sufficient to control the disease, that systemic therapy is also needed. Health-related quality of life was not significantly different with SIRT over 24 months, so the quality of life benefit in SIRveNIB was not confirmed in this analysis.

Asked if SIRT could increase extrahepatic metastases, Dr. Sharma said, "There is nothing to suggest there is increased progression extrahepatically. What we have seen is disease control in the liver, but unfortunately the disease tends to progress outside the liver…There is no reason to think there is hyperprogression."

Andrea Cercek, MD, a GI oncologist from Memorial Sloan Kettering Cancer Center, discussed the results, declaring it "a negative trial." She also noted that there was no benefit in resection, PFS, or overall survival, and few patients in the SIRT arm received second-line or third-line chemotherapy – and fewer SIRT patients got a biologic (bevacizumab). And for no benefit, there was increased toxicity with SIRT. She commented, "We often believe that treating the liver mets will improve survival, but in this case it did not."

As for the possible benefit in right-sided tumors, she noted that this was not pre-planned and was a retrospective subset analysis, concluding, "While the data are intriguing…and hypothesis generating, they do not support use in routine practice…This could be investigated further, but that should be done in a clinical trial…There is no role for SIRT in the first-line setting [in metastatic CRC]."

FOXFIRE Survival Analysis			
Measurement	**Chemo n=549**	**Chemo + SIRT n=554**	**p-value**
Primary endpoint: Overall survival	23.3 months	22.6 months	Nss, p=0.609, HR 1.04
PFS	10.3 months	11.0 months	Nss, p=0.108, HR 0.90
Liver-specific PFS (radiological progression in the liver)	---	---	p<0.001, HR 0.51
First extrahepatic progression or death without radiological progression	---	---	p<0.0011, HR 1.76
Resection rate	---	---	Nss, p=0.669, OR 1.07
Results by study			
	FOXFIRE	**SIRFLOX**	**FOXFIRE-Global**
Survival	HR 1.04	HR 1.06	HR 0.95
PFS	HR 0.87	HR 0.97	HR 0.79
Resection rate	OR 1.19 Nss, p=0.509	OR 1.11 Nss, p=0.676	OR 0.80, Nss, p=0.550
Adverse events ≥3			
Any Grade ≥3	66.5%	74.0%	---
Neutropenia	24.2%	36.7%	---
Febrile neutropenia	2.8%	6.5%	---
Thrombocytopenia	1.2%	7.7%	---
Leukopenia	2.3%	5.9%	---
Fatigue	4.9%	8.5%	---
Abdominal pain	2.3%	6.1%	---
Peripheral neuropathy	5.8%	3.6%	---

What does all this mean for SIRT use?

These data are unlikely to expand use, but none of these failed trials disputed the efficacy of the therapy in the *approved* indication, so use is not expected to decrease. Company officials said they have not seen any impact on their core business from the negative results – at least not yet. And oncologists questioned at ASCO about the outlook for SIR-Spheres agreed that the therapy has a role in the currently approved salvage situation, and they don't expect that to increase or decrease over the next year.

Physician comments about SIRT and SIR-Spheres included:

- *Ohio:* "I use spheres for HCC…I may consider it for mCRC patients with metastases to the liver, but I usually give chemotherapy instead. A systemic treatment is better, but if the patient can't tolerate chemotherapy, then spheres are an option."
- *New York:*
  - ✓ "I had two CRC patients in SIRFLOX, one on chemotherapy and one on SIRT. Both are still alive.
  - ✓ "We were nervous about resection after SIRT, and do only limited local resections.
  - ✓ "I use SIR-Spheres outside of trials now for patients with liver involvement that are inoperable…SIRT is not used rarely, and it isn't last line. The question comes up second-line or third-line in CRC.
  - ✓ "I have access to both SIR-Spheres and TheraSphere, but there is no easy scientific choice; it's what gets through insurance…I have a slight preference for TheraSphere because of the small beads.
  - ✓ "If FOXFIRE is negative, I will stay as selective in choosing patients as I am now…For patients with liver-only mets, I give chemotherapy first. If I can't get the patient to resection, then I consider Y-90 with or without chemotherapy to get the patient resectable – or sometimes to buy the patient chemo-free time."

- *Germany:*
  - ✓ "We do SIRT occasionally in mCRC patients. There is limited evidence for first-line use…We give chemotherapy for three months, and if the disease stays confided to the liver, we then give SIRT…The SIRT patient is someone who is not amenable to microwave or surgery because of the number of liver lesions.
  - ✓ "I just use SIR-Spheres, not TheraSphere…My experience with SIRT has been mostly good. Of course, some patients progress rapidly outside the liver, but maybe three months of chemotherapy is not enough for them.
  - ✓ "I do feel we are extending PFS and overall survival…but I don't have data on that yet…If FOXFIRE is negative, the company will need to prove a benefit in a subset of patients, but I would still use SIRT in salvage patients.
  - ✓ "Outside of a clinical trial, insurance covers SIRT about half the time."
- *Texas:*
  - ✓ "I think using SIRT for HCC is different than for liver mets…SIRT has a much more defined role in the patient who only has liver mets. If a patient is doing well with systemic therapy, and the only area of progression is the liver is where SIRT has a role.
  - ✓ "Systemic treatment is not practitioner-dependent, but SIRT is. A skilled physician who does hundreds of SIRTs will be different from a doctor who does 1-2 a year, so it is hard to generalize the SIRT data.
  - ✓ "I don't think there will be a change in who the appropriate patient for SIRT is after ASCO.
  - ✓ "The data raise an important question on when to do this, but it doesn't mean we should never do this…Will these data increase the number of patients getting SIRT? Certainly not."

OTHER STUDIES OF INTEREST

Biliary cancer:
ROCHE's Xeloda (capecitabine) and generics

The 3-year, 447-patient, U.K. Phase III BILCAP trial, presented by John Primrose, MD, a surgeon from the University of Southampton, found a 14.7 month improvement in overall survival when biliary cancer patients were given capecitabine instead of just being observed.

The difference was not statistically significant (p=0.097), but after a sensitivity analysis adjustment, the findings were highly significant (p=0.007), and toxicity was "modest."

Dr. Primrose said, "Capecitabine should now become the standard of care for patients following curative resection of biliary cancer." ASCO president Dr. Hayes called this a "very important finding," but he wondered if the results will apply equally to Asian patients.

Another investigator, John Bridgewater, MBBS, PhD, from University College London Hospitals, said, "I don't think there is any doubt there is a genuine effect there…And the effect size is large…So, we really have no doubt there is a genuine effect. This is an uncommon cancer, and no one will ever re-run this study…This will be the standard of care."

Could another chemotherapy be used instead? Dr. Bridgewater said only capecitabine was available when this study was started, but the ongoing Phase III ACTICCA-1 trial in adjuvant cholangiocarcinoma (biliary cancer) compared gemcitabine + cisplatin (which is an established treatment in advanced biliary cancer) to observation, and that trial is now being changed to compare gemcitabine/cisplatin to capecitabine.

Colorectal cancer (CRC):
Diet and exercise

A 9-year prospective, observational study of 992 patients from the ALLIANCE (CALGB-89803) trial, presented by Erin Van Blarigan, ScD, from the University of California, San Francisco, found that patients who followed the American Cancer Society guidelines for nutrition and physical activity after a diagnosis of early-stage CRC had a longer disease-free survival and a 42% lower risk of death vs. patients who did not follow the guidelines. ASCO's Dr. Hayes commented, "This tells us…people living a healthy lifestyle live longer…This is not to suggest you don't need to take chemotherapy your oncologist recommends."

A prospective, observational study presented by Temidayo Fadelu, MD, from Dana-Farber Cancer Institute, also used patients in the ALLIANCE trial, following 826 patients for 7 years. The researchers found a 42% improvement in disease-free survival and a 57% improvement in overall survival among CRC patients who consume tree nuts vs. CRC patients who did not eat tree nuts. The benefit did not extend to peanuts or peanut better. Dr. Fadelu said the mechanism of action is unknown, but it is "likely related to the effect of nuts on insulin resistance."

Non-small cell lung cancer (NSCLC):
ASTRAZENECA's Iressa (gefitinib)

Yi-Long Wu, MD, from Guangdong General Hospital in China, presented the results of a Phase II trial (CTONG-1104) comparing Iressa to chemotherapy (vinorelbine/cisplatin) as adjuvant treatment in Stage II/IIIa NSCLC patients who are EGFR+. The question was whether 2 years of an EGFR-TKI (Iressa) could replace 12 weeks of chemotherapy (the current standard of care) for post-surgery lung cancer patients with an EGFR mutation, and the answer was Yes. Survival was 10 months longer with Iressa. Both therapies have toxicity, but the toxicity profiles are different.

The results might also extend to Roche's Tarceva (erlotinib), though that wasn't studied in the trial.

ASCO president-elect Bruce Johnson, MD, from Dana-Farber Cancer Institute, commented, "We are encouraged by the initial [Kaplan-Meier curves for disease-free survival], but the curves begin to come together beyond three years…I haven't changed my approach [to treating EGFR+ NSCLC] yet, but I will follow this closely to see what happens with overall survival."

Richard Schilsky, MD, chief medical officer of ASCO, added, "What I suspect will happen is many doctors will begin testing lung cancer tumors right after surgery to see if they have an EGFR mutation. That is not currently standard of care. Typically, testing is not done until the cancer recurs or becomes metastatic, so that way patients and doctors will know if a TKI is an option. If it isn't, many factors will come into play…One is waiting for overall survival data, but it is also important to keep in mind that…it is a big commitment on the part of patients to adhere to 2 years of continuous treatment [with Iressa]…And it should not be lost on us that the cost of gefitinib is far, far greater than 12 weeks of chemotherapy…Once the survival data are known, doctors and patients will have to have a thoughtful discussion on the magnitude of overall survival, what the burden is on the patient of 12 weeks of chemotherapy vs. two years of chemotherapy in terms of toxicity – and cost…A lot of the ultimate decision-making will be highly dependent on whether there is an overall survival benefit."

Cancer screening

An American Cancer Society study found that more early-stage cancers were detected in 2014, after the implementation of the Affordable Care Act (ACA), vs. the previous year, without the expanded insurance coverage provided by the ACA.

There were slightly more Stage I (vs. Stage II) breast, cervical, CRC, and lung cancers detected under ACA, but significantly fewer prostate cancers.

The increase in early-stage detection of CRC and cervical cancer only occurred in the states that adopted Medicaid expansion under ACA, not states without Medicaid expansion. Early-stage diagnosis of prostate cancer worsened in both states with and without Medicaid expansion.

ASCO's Dr. Johnson said, "We think this is an important study …Obviously, the changes are not enormous, not dramatic, but because the uptake of screening is relatively slow, this [showed] that by doing additional screening you can potentially find more Stage I patients, and the earlier the stage, the more likely to find a cure…The ACA mostly covered screening, and whatever reform healthcare takes over the next several years, we advocate for early access to screening."

Head and neck cancer:
HPV vaccine reduces oral HPV infections

Head and neck cancer is the fastest growing cancer among young, white U.S. men, with >90% of cases caused by HPV16, but vaccine uptake has been slow and low. Maura Gillison, MD, PhD, from MD Anderson Cancer Center, reported on an analysis of 2,627 people (age 18-33) in the NHANES study, and found only 18.3% (29.2% of women, 6.9% of men) had gotten at least one dose of an HPV vaccine.