2022 | Issue 2

Physicians office Resource

Resources for You, Your Patients, & Your Practice



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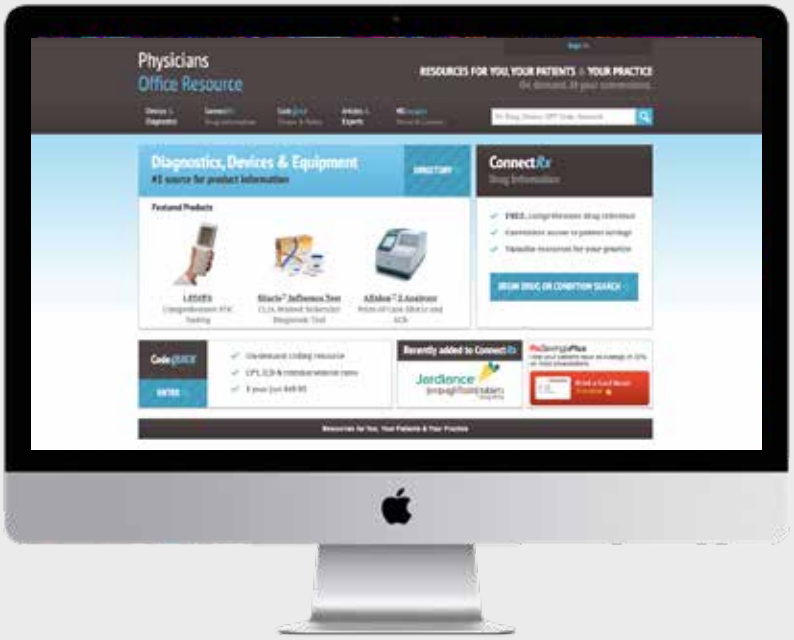
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PUBLISHED BY
Medical Education Resources, LLC

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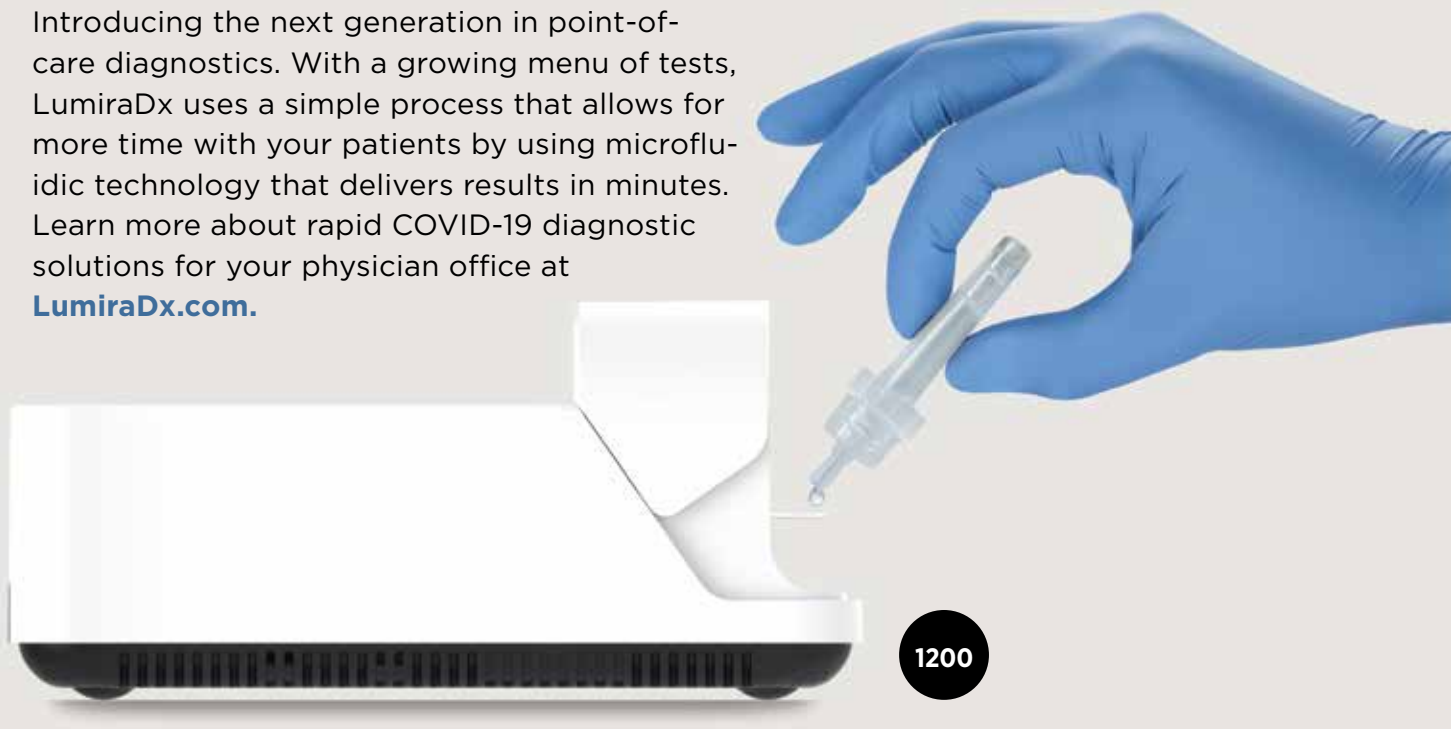
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10

HOW TO HAVE THE LIFESTYLE YOU WANT NO MATTER WHAT YOUR SPECIALTY IS

—

The stratification starts in medical school. Before anyone has matched into their residency — conversations have already started about who is pursuing what specialty.

20

WHICH FLU TEST IS RIGHT FOR YOUR OFFICE?

—

Each year, despite forewarnings, the United States and European countries are sometimes caught off guard with a “Perfect Storm” of challenges for the influenza season.

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POINT OF CARE DIAGNOSTICS: A CLINICIAN’S VIEW

—

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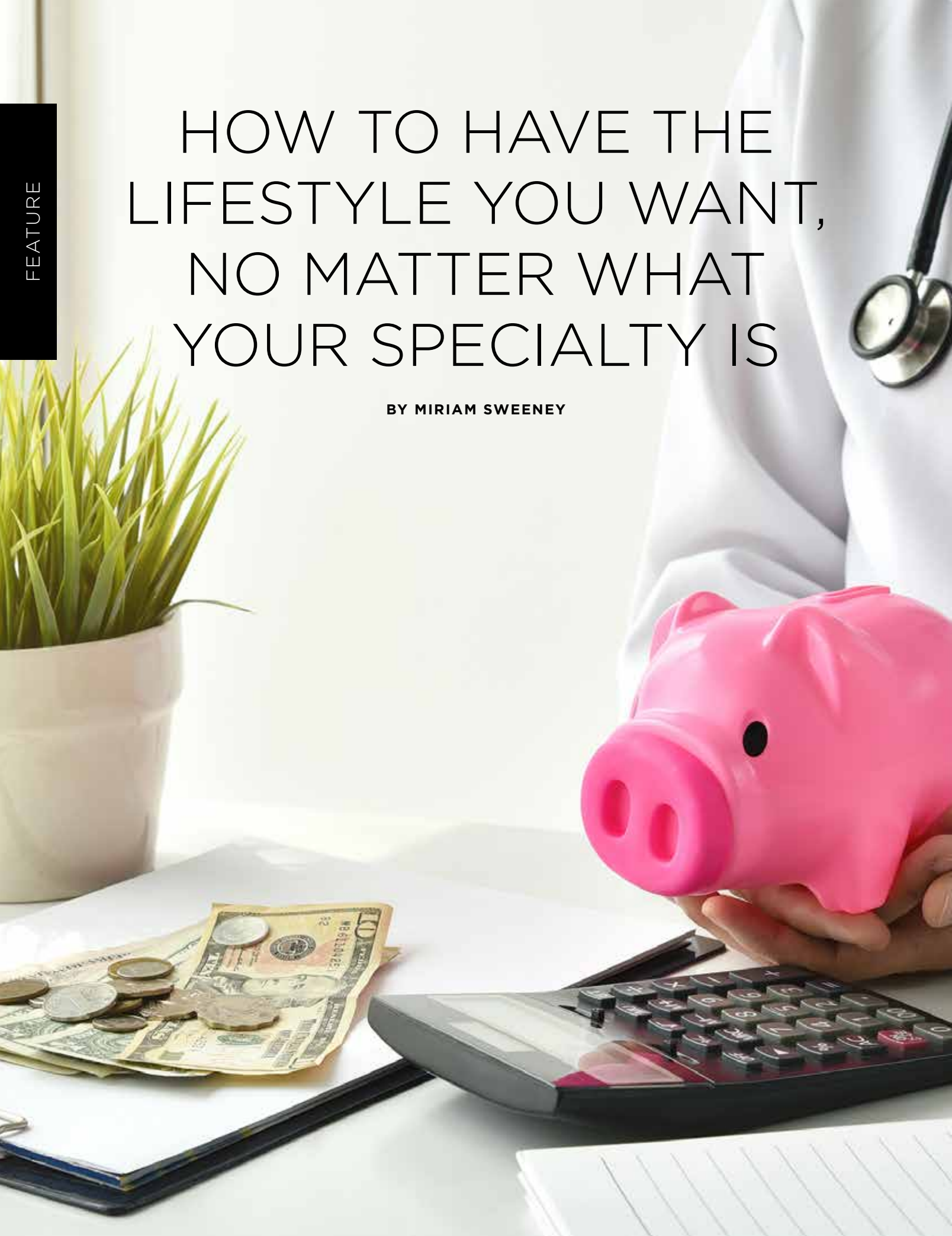
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FEATURE

HOW TO HAVE THE LIFESTYLE YOU WANT, NO MATTER WHAT YOUR SPECIALTY IS

BY MIRIAM SWEENEY



The stratification starts in medical school. Before anyone has matched into their residency — long before attention has shifted from Step One and Two to writing a round of personal statements and preparing for interviews — conversations have already started about who is pursuing what specialty.

And in schools that emphasize class rank, pitting students against each other in preparation for a career where collaboration is key, medical students may already be making assumptions about their peers' future specialties based on their class ranking or rumored scores. "There's no way Sahil will match into ortho with a ranking like that." "Emily may say she wants to be a pediatrician, but with a step score like that and the way she's been buddying up to the attendings, she'd be a shoo-in for derm."

In a field that requires immense financial and time commitment from its newest members, medicine shakes out to have very different compensations on the other side of residency depending on a physician's specialty. There are ways of ensuring stability for everyone, especially the majority of medical students who graduate with medical debt. Having a solid understanding of investing, loan repayment options, and intentional spending can lay the path to success for someone making $150k or $500k. Tools like ScrubMoney — a free mobile app — that help support physician financial education and planning can be key in this process. But just understanding the nuances of why we spend the way we do can also go a long way in making sure we're using what we have to build the life we want.

I'd recommend two basic focuses to achieving the lifestyle you want, no matter your income or specialty.

Focus I: The bold and swaggering decision to define what you want

We all grew up with motivational posters inviting us to go for our dreams, right? Those posters never took the time to help us understand how to know what our dream is, or how to form a dream in the first place.

You can't get to where you're going without knowing where you're going, and too few of us take the time to really pinpoint where we want to be. I'm not talking about knowing our own tastes; it's one thing to see something interesting, be it a style of a home or a fashion choice or a job description, and know if it's for us or not. It's an entirely different arrow in your quiver to visualize that home or outfit or job before any options are presented to you.

I've adapted a few different researchers' and influencers' ideas[1] of what this process can look like and simplified it for this column.

1. Sit with the idea of what a successful life looks like. We don't like talking about it, but physicians know it better than most: our lives are finite, and we don't get endless opportunities for course correction. When you think of a successful, happy life, what does that look like for you?

Focus on what you can control. You have less control, for instance, over whether you live to a ripe old age or are a casualty of irresponsible driving next month. Nevertheless, your life was a life, legitimate in spite of its abbreviated length. What will have made it successful?

2. Now that you've pictured your own brand of success, consider: in order to get to that success, **what are the non-negotiables involved?** What is irreplaceable in your picture of a life that leaves you happy and proud of what you've done and how you've spent your time?

3. Now, it's a simple (or not) matter of defining how to go about shaping your decisions around those non-negotiables. **How will you prioritize what's most important?** If your self-defined success has anything to do with an existing life partner, this process of planning for priorities might be one of deciding how to encourage habits that keep that relationship strong. If success requires something that must be checked off as a binary, it may be worth your time to think through what it's going to take to mark that box.

Many people who get this far stop there. That would still be a productive exercise. But without the next step, it's still not necessarily going to help with making your resources — time and money — work for you.

4. Decide what to cut out. Do you have goals you're actively working towards that aren't reflected in your life success rubric? Are you spending your precious time or your hard-earned money on something that's unattached to your idea of a successful, happy existence? This step requires confidence in yourself. Are you bold enough to cut out something that may matter greatly to other people, but isn't central to your own life success?

A big part of this step is understanding how to use your money in a way that will make you happy. Money can't buy happiness, but according to researchers at the University of British Columbia, Harvard, and the University of Virginia 2 , the way you spend your money can lead to happiness.

Don't take it from me. Listen to the experts, as described in Chapter II of our effort to use money intentionally to get the life we want regardless of specialty or circumstance.

Focus II: "If Money Doesn't Make You Happy Then You Probably Aren't Spending It Right"

When aligning your actions with your definition of personal life success, the decision of how to allocate your resources can make a considerable difference in your progress. The question of how to spend your time belongs in another column. But the question of how to spend your money, happily, has been answered and peer-reviewed for us. Let's break down the researchers' findings.

1. Buy more experiences and fewer material goods. This notion is backed up by many studies, as cited in the paper itself. The gist is that we become accustomed to material possessions, but we never dull a happy memory when recalling it; on the contrary, a happy memory may become even happier when mentally reliving it. A treat yo'self day might be better spent on a visit to a spa or a chocolate tasting night instead of a new bathrobe or quality dark chocolate.

2. Use your money to benefit others rather than yourself. In a study that asked Americans to report about how much they spend on bills and expenses, gifts for themselves, gifts for
others, and donations to charity, there was no significant correlation between spending money on the self (the first two categories) and happiness. There was, however, a strong relationship between people who spent money on others and self-reported happiness, even after controlling for income.

3. Buy many small pleasures rather than fewer large ones. I'll admit, this one caught me off guard. Lots of little things instead of bigger, more significant things? It almost seems to contradict #1 on this list. But the research holds out, and it's worth diving into the article itself to review the citations. The line that resonated most with me: "Eating two 6 ounce cookies on different days may be better than eating a 12 ounce cookie at a single sitting."

4. Eschew extended warranties and other forms of overpriced insurance. This piece of advice feels remarkably specific for a list that otherwise boasts great general applicability. But this principle has less to do with specific retail tactics and more to do with human resilience.

There is insurance that makes a lot of sense, and this article isn't talking about it. This article is talking about the kind of insurance you get when you're over concerned about losing something material, like the integrity of your new TV. Interestingly enough, the research suggests that, while the prospect of inconvenient loss is devastating, the experience of inconvenient loss tends to be one people recover from reliably and quickly.

5. Delay consumption. This principle essentially suggests that, if you plan a getaway to the tropics, plan it for nine months away, not two weeks. You will enjoy the experience more because you spent so much longer anticipating it.

6. Consider how peripheral features of your purchases may affect your day-to-day life. In other words, it's easy to picture a dream of ours and only see the positives. Filtering out the negative effects of a decision may lead to disappointment when the time comes to enjoy a wish come true. Both the past and the wished-for future can be distorted with rose-colored glasses.

7. Beware of comparison shopping. Comparison shopping — looking for things based on how they measure up to each other instead of based on what you want in the first place — is designed to distract us from what we really want and make us make purchase decisions based on the best deal, not whatever is right for us.

This holds true whether in a literal shopping situation or a more metaphorical situation that involves searching and decisions. (Dating and home browsing apps wouldn't have anything to say about this, would they?)

8. Pay close attention to the happiness of others. Not to encourage a herd mentality, but, according to this article, "Research suggests that the best way to predict how much we will enjoy an experience is to see how much someone else enjoyed it." It may be a good exercise to think about someone who you would define as successful or happy in your circle, then have a frank, humble conversation with them about what they think has made them happy and what might help you reach some of your intangible goals. We are all unique, but this research makes it look like we wax and wane in our satisfaction with things and experiences in concert with our peers.

It can be easy to assume that people with x will be guaranteed success in life, but success is a personal, arbitrary measurement.

If we can first a) define success for ourselves, along with a healthy foundational education of the elements that influence our success (like financial, mental, and social wellbeing, for instance), then b) follow best practices when spending our resources (our time and money), we're more likely to reach our goals and be proud of our lives than if our personal rubric for success remains undefined or suffers from moving goalposts.

Find out what resources your institution and community offer to support you in designing an intentional, satisfied life.

About the Author

Miriam Bay Sweeney is a co-founder and Head of Product of ScrubMoney, an app designed to help physicians lay the foundation for financial independence. She's been fascinated by personal finance ever since learning as a young adult that sticking her paychecks and babysitting money she made as a teenager in a savings account was a crummy idea. She researches personal productivity and the foundational aspects — including financial confidence — that enable a person to innovate and thrive creatively. ScrubMoney is her way of giving back to the community of physicians that so many of her friends are part of, because we ought to think about taking care of the people who dedicate their lives to taking care of us.

Sources

1. Thanks to Clayton Christsensen, Ramit Sethi, Eric Barker, Dave Burnet, Bill Evans, James Clear, and likely a handful of others whose writing influences my perspective subconsciously
2. https://scholar.harvard.edu/files/danielgilbert/files/if-money-doesnt-make-you-happy.nov-12-20101.pdf

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Sofia® 2 Fluorescent Immunoassay Analyzer and Rapid Diagnostic Test Kits Sofia 2 takes rapid testing to a new level. Proven lateral-flow technology and advanced fluorescent chemistry are all integrated into this small benchtop analyzer which can be used in any point-of-care setting. Sofia 2 kits are easy to use and adaptable to any healthcare setting. Excellent performance, objectivity, quality control, LIS capabilities, and an expanding test menu make Sofia 2 the perfect solution for the physician's office laboratory.

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TOXICOLOGY

TOXICOLOGY URINE DRUG SCREENING REAGENTS

From Abbott

Prescription drug misuse and illicit drug abuse is a growing public health challenge in this country. Building a test profile that covers highly misused drugs has never been so vital. With over 20 relevant assays to choose from Abbott's suite of Immunalysis reagents allows you to easily screen for relevant substances. Our complete line of assays, calibrators, and controls enables you to implement an efficient drug screening program in office.

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TOXICOLOGY SCREENING SIMPLIFIED ABBOTT'S IMMTOX 270 BENCHTOP ANALYZER NOW WITH 14 ASSAYS CLIA CATEGORIZED AS MODERATE COMPLEXITY

From Abbott

The ImmTox270 benchtop analyzer offers comprehensive toxicology screening solutions for physician offices, treatment centers and independent laboratories.

Broad test menu with over 20 assays to choose from including 14 that are now available as moderately complex.

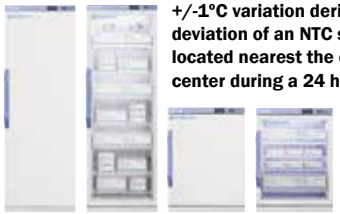
With complete laboratory solutions from consultation to licensure, and compliance the Abbott Clinical Laboratory Solutions team has you covered.

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VACCINE FREEZERS and REFRIGERATORS

- Built-in readout for current & high/low temperature
- Audible & visual high/low temperature alarms
- Optimized efficient performance for stable temperature
- Eco-friendly natural refrigerants for a greener footprint

Solid & Glass Door Refrigerators From 1 to 15 Cu.ft.



+/-1°C variation derived from the maximum deviation of an NTC sensor in a 1 oz. vial located nearest the champer geometric center during a 24 hour test period

1240

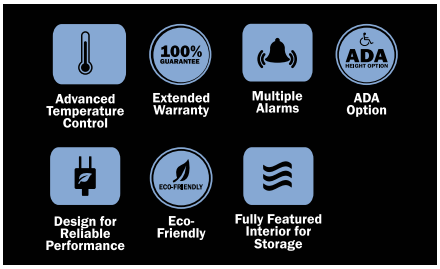
Refrigerators & Freezers From 23 to 49 Cu.ft.



Refrigeration designed and purpose-built for pharmacy, medication, and vaccination applications to support meeting CDC/VFC vaccine storage guidelines

Advanced Temperature Control & Durable Performance

- Intelligent microprocessor digital temperature controller
- Adjustable operating control range from +2 to +8°C
- Digital display of the min/max temperature in Celsius or Fahrenheit
- Password protected control parameters beyond setpoitn
- Optimized forced air cooling for excellent stability & uniformity with rapid recovery
- Open door and high/low temperature alarms
- Factory installed lock conveniently located towards the top of each unit
- Adjustable shelving can be spaced in ½" intervals for flexible storage



Pharma-Vac Refrigerators

Accucold	Capacity	Height	Width	Depth	Door	PRICE
ARS1PV	1 cu.ft.	21.5"	17.5"	19.5"	White	**936.00**
ARG1PV	1 cu.ft.	21.5"	17.5"	20"	Glass	**949.00**
ARS3PV	3 cu.ft.	33.75"	18.5"	19"	White	**1,059.50**
ARG3PV	3 cu.ft.	33.75"	18.5"	19.5"	Glass	**1,072.50**
ARS6PV	6 cu.ft.	32.5"	23.5"	24.5"	White	**1,180.40**
ARG6PV	6 cu.ft.	32.5"	23.5"	25"	Glass	**1,193.40**
ARS8PV	8 cu.ft.	50"	23.38"	24.5"	White	**1,497.60**
ARG8PV	8 cu.ft.	50"	23.38"	25"	Glass	**1,510.60**
ARS12PV	12 cu.ft.	61.75"	23.38"	24.5"	White	**2,002.00**
ARG12PV	12 cu.ft.	61.75"	23.38"	25"	Glass	**2,015.00**
ARS15PV	15 cu.ft.	72"	23.5"	24.5"	White	**2,294.50**
ARG15PV	15 cu.ft.	72"	23.5"	25"	Glass	**2,307.50**

models with data loggers are available

Pharma-Lab Refrigerators

Accucold	Capacity	Height	Width	Depth	Door	PRICE
ARS23ML	23 cu.ft.	83.75	27.5	31	(1) Stainless	**2,762.50**
ARG23ML	23 cu.ft.	83.75	27.5	31	(1) Glass	**3,113.50**
ARS49ML	49 cu.ft.	83.75	55.25	31	(2) Stainless	**4,413.50**
ARG49ML	49 cu.ft.	83.75	55.25	31	(2) Glass	**4,771.00**

Pharma-Lab Freezers

Accucold	Capacity	Height	Width	Depth	Door	PRICE
AFS23ML	23 cu.ft.	83.75	27.5	31	(1) Stainless	**3,178.50**
AFS49ML	49 cu.ft.	83.75	55.25	31	(2) Stainless	**5,063.50**

visit www.medicaldevicedepot.com for all product information and options

Choosing the Right Sized Unit

Below are a few handy steps for determining the ideal Accucold refrigerator size for your clinic:

1 Estimate the maximum number of doses of publicly-provided vaccine and privately purchased vaccine that will be in your refrigerator.

Refrigerator: Add the number of doses on hand (current inventory) from your last order form.

Public Vaccine _____

Private Vaccine + _____

Total doses = _____

Multiply (max inventory) x 1.25

Maximum doses = _____

2 Match your maximum doses with the minimum cubic feet needed to safely store your vaccine

Max. Doses	Minimum Cubic Ft.
2,000+ doses	may need more than one refrigerator
1000-2000	40 cu.ft
900-1000	36 cu.ft
801-900	21-23 cu.ft
701-800	17-19.5 cu.ft
400-700	11-16.7 cu.ft
100-399	4.9-6.1 cu.ft

For product application suggestions or recommendations please feel free to contact our product specialists to discuss your options at:

877-646-3300

Medical Device Depot Inc.

www.medicaldevicedepot.com



Which flu test is right for your office?

Each year, despite forewarnings, the United States and European countries are sometimes caught off guard with a "Perfect Storm" of challenges for the influenza season. Physician offices should be stocking up on flu tests and other supplies in preparation for this year's flu season. What do they need to know before they choose a flu test?

BY SEKISUI DIAGNOSTICS

Planning Ahead

So much of flu season is a guessing game, especially when trying to plan. The World Health Organization (WHO), the Center for Disease Control (CDC), and the Food and Drug Administration (FDA) weigh in with their recommendation to which strains should be included in the upcoming flu vaccine well before the season gets started. Their prediction on what strains should be included will dictate how effective the vaccine will be. How severe the flu season is difficult to predict ahead of time, and the key indicators used by the WHO, CDC, and others can only be obtained after flu season begins!

So, what can clinicians and distributors do to prepare?

First, conducting a business assessment of what the clinicians experienced last year and looking at historical data can help dictate a plan to ensure they procure enough product.

Second, weigh the pros and cons of the tests they are currently using and tests they might be considering. Clinicians should consider the following:

- Performance—Is test sensitivity and specificity the most critical?
- Volume—How many tests does your facility perform during an average flu season?
- Ease of Use – how simple is the test to perform?
- CLIA Complexity – Does the facility require Waived Complexity or Moderate Complexity Tests?
- Results reporting—Is it important for your facility to have an instrument-based result or visual read result, or is either one acceptable?
- Sample type—Does the test need to allow for multiple sample types (nasal, nasopharyngeal, aspirate/wash, and/or viral transport media (VTM))?
- Connectivity—Does the device need to be able to transmit the results electronically?

How severe the flu season is difficult to predict ahead of time, and the key indicators used by the WHO, CDC, and others can only be obtained after flu season begins!

- Cost of the test
- The time to result
- Does the test require confirmation testing for negative results?

What's Out There?

There are several types of flu tests available on the market.

- Rapid molecular tests detect the genetic material of the virus and typically produce results in 30 minutes or less. These are considered to be more accurate than other methods.
- Rapid lateral flow immunochemical tests can be either read visually or by an instrument and are intended to detect the presence (or absence) of a target antigen in 15 minutes or less.

Depending on what characteristics are important to the clinician will help determine what type of test is a good fit for the facility. The manufacturer and distribution representative would be able to help guide the clinician to a product that is just right for them.

It should be noted that no flu test provides 100% accuracy. Results depend on the type of test used, the strain of virus and the integrity of the sample. It is very important when bringing on any test to review any limitations of the test, such as strain detection, any patient age limitations and performance data, along with sample collection and handling best practices and make sure that all staff is trained to provide the best in class testing.

The Importance of Testing

Due to the known performance issues surrounding the rapid tests, some physicians may argue that it's not necessary to administer a flu test in order to diagnose and treat.

Testing does not usually change how a patient will be treated for a flu diagnosis, so why bother? It turns out there are several reasons.

- Empirical treatment has a disadvantage in that many more patients are receiving treatment than actually have the flu giving rise to a possible antiviral shortage and possibly delaying the right treatment for another health issue.
- Testing patients provides valuable information to the clinician that can enable them to rule out other illnesses, helps determine a more direct therapy plan, and reduces the risk of unnecessary antiviral or antibiotics therapy, while increasing the chances that the patient will receive anti-viral therapy early when it is most effective.
- Testing will also help determine whether an outbreak of flu is occurring. Since the implementation of rapid molecular tests and the drive by the FDA reclassification to have better RIDTs into the market clinicians can have the opportunity to utilize a highly accurate test to be more confident in the results to drive direct therapy.

How Sekisui Diagnostics Can Help

Sekisui Diagnostics offers three flu tests, using three different technologies, to help clinicians master the art of influenza testing.

The CLIA-Waived OSOM®Ultra Plus Flu A & B Test is rapid lateral flow qualitative test with performance equivalent to or exceeding reader devices, without the need for an instrument.

The CLIA-Waived AcucyTM Influenza A&B Test, used on the AcucyTM System, provides clinicians flexibility in workflow and accurate, standardized results for improved patient care. It utilizes a traditional rapid lateral flow test paired with a reader.

The 5 "Ps"

In the end, it comes down to the 5 "Ps" – Proper Preparation Prevents Poor Performance! Don't be afraid to keep stock of flu tests all year round. Understand new options—with the fear of changing strains, new technologies are more important than ever. Just remember, you have choices!

Learn more about your options at www.flutesting.com.

Flu Diagnostic Testing Comparison

DIAGNOSTIC CHALLENGES

There are a number of diagnostic options available. However, choices may have to be made in terms of:

ACCURACY
Patient receives correct diagnosis

TIME
Patient receives correct diagnosis in a timely manner

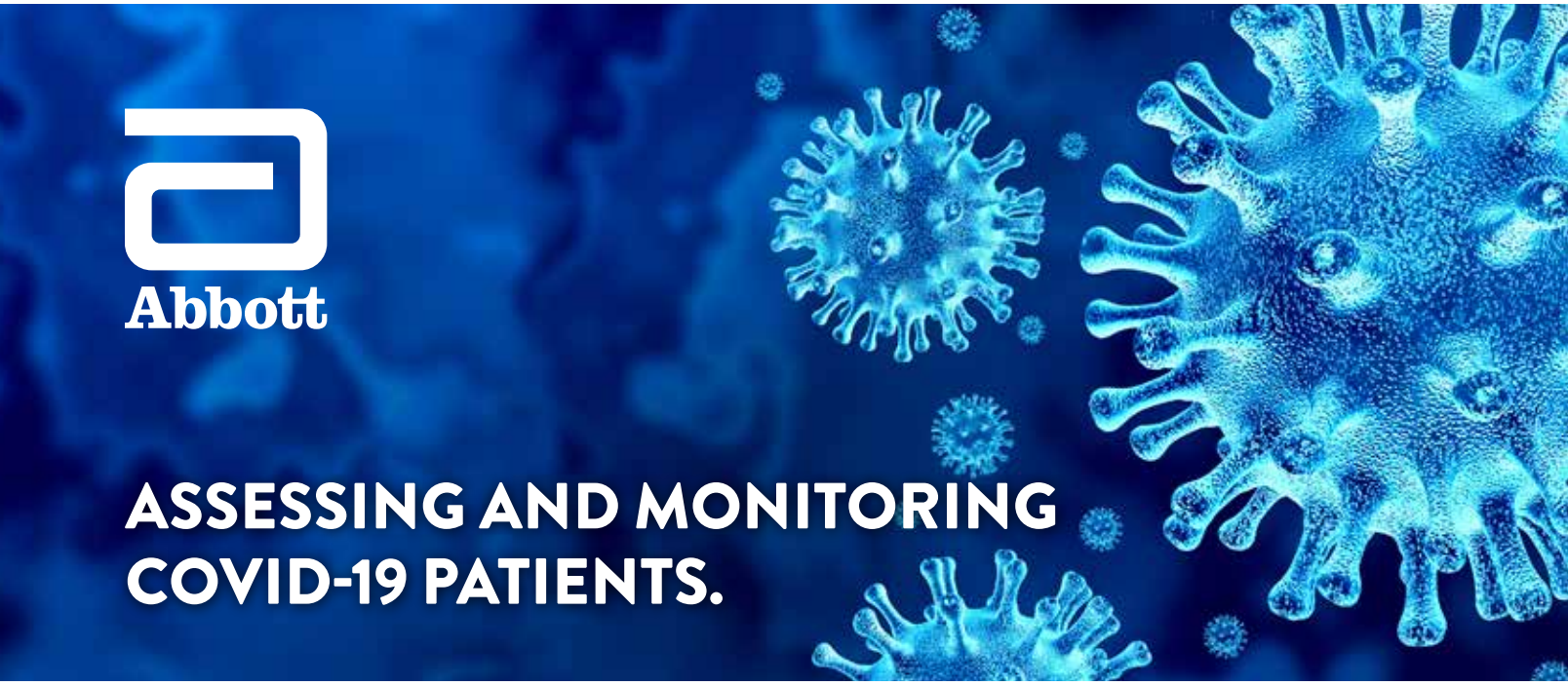
COST
Diagnosis is obtained cost-effectively and affordably

METHOD	FEATURES			
CLIA WAIVED VISUAL MOLECULAR	• Rapid PCR molecular platforms can be smaller and faster, and can be brought closer to the patient, for improved clinical impact • Molecular performance • Next generation molecular assays have focused on ease of use providing the familiar workflow of traditional lateral flow assays • Cost is less than traditional molecular with same reimbursement • Considered a Gold Standard of testing along with viral culture[1]			
TRADITIONAL MOLECULAR	• Highly accurate and definitive results • Labor-intensive workflow • Cost of rapid molecular tests is higher than lateral flow, but that may be offset by reducing unnecessary use of antibiotics • Considered a Gold Standard of testing along with viral culture[1]			
READER IMMUNOCHEMICAL	• Easy to perform • Affordable, making them suitable for use in a variety of settings from laboratories to near-patient • Typically provide results in minutes, allowing clinicians to test and treat quickly • Improves objectivity by removing visual read			
VISUAL IMMUNOCHEMICAL	• Easy to perform • Affordable, making them suitable for use in a variety of settings from laboratories to near-patient • Typically provide results in minutes, allowing clinicians to test and treat quickly • Better accuracy with the FDA Flu Reclassification[2]			

1 https://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm
2 Federal Register / Vol. 82, No. 8 / Thursday, January 12, 2017 / Rules and Regulations

WHAT'S OUT THERE?

There are several types of flu tests available on the market. Rapid molecular tests detect the genetic material of the virus and typically produce results in 30 minutes or less. These are considered to be more accurate than rapid influenza diagnostic tests (RIDTs). RIDTs are lateral flow immunochemical membrane tests that can be either read visually or by an instrument and are intended to detect the presence (or absence) of a target antigen in 15 minutes or less.



Abbott

ASSESSING AND MONITORING COVID-19 PATIENTS.

Urgent care facilities, primary care practices, and other outpatient settings at the front lines of the COVID-19 pandemic need on-site testing solutions to support patient assessment and monitoring. With-patient testing can lead to better healthcare performance by facilitating decisions that can optimize patient outcomes in real time, improving the quality of patient care.

For facilities treating COVID-19 patients, having rapid, accurate diagnostic test results may be useful when assessing or monitoring patients for:

- **C-Reactive Protein (CRP)**
  Levels may be elevated in COVID-19 cases, especially severe cases.[2-15]
- **Liver, Kidney and Cardiac function**
  Elevated levels of the following biomarkers may be indicators of COVID-19 severity:[16-27]
  - Alanine Aminotransferase (ALT)[16,17,20-27]
  - Albumin (ALB)[16,19-22,25-27]
  - Aspartate Aminotransferase (AST)[16,17,19-21,23-26]
  - Creatine Kinase (CK)[16,18,20,22-24]
  - Creatinine (CREAT)[16,22,23,25,27]
  - Total Bilirubin (TBILI)[16,20,25,27]



1241

piccolo xpress chemistry analyzer

For *in vitro* diagnostic use only.

The Piccolo Xpress does not directly diagnose COVID-19.

ON-SITE TESTING MADE EASY: PICCOLO XPRESS.®

The Piccolo Xpress portable diagnostic analyzer offers a full complement of blood chemistry tests, including CLIA-waived tests.

Get accurate results in minutes, at the point-of-care.

SEE A LIST OF KEY PICCOLO XPRESS PANELS ON BACK.



KEY PICCOLO XPRESS PANELS.

CLIA-WAIVED PANELS



Comprehensive Metabolic Panel
Na+, K+, CI-, tCO_2, Ca, BUN, Crea, Glu, ALB, ALP, ALT, AST, TP, tBIL, eGFR*



MetLyte 8
Na+, K+, Cl-, tCO_2, BUN, Crea, Glu, CK, eGFR*



Liver Panel Plus
ALB, ALP, ALT, AMY, AST, GGT, tBIL, TP

*Calculated

MODERATELY COMPLEX PANELS



BioChemistry Panel Plus
ALB, ALP, ALT, AMY, AST, BUN, Ca, Crea, Glu, GGT, TP, UA, CRP, eGFR*



MetLyte Plus CRP
Na+, K+, Cl-, tCO_2, BUN, Crea, Glu, CK, CRP, eGFR*



Hepatic Function Panel
ALB, ALP, ALT, AST, tBIL, dBIL, TP

To learn how the Piccolo Xpress portable diagnostic analyzer can help transform your patient care, contact your Abbott Point of Care Representative or visit www.pointofcare.abbott

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COVID-19 Channel Brochure - US 2994Rev.1 09/20

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lumiraDx™



Point of Care Diagnostics: A Clinician's View 2021

An annual review of U.S. clinicians' expectations and experiences with diagnostics

Quality healthcare begins with a diagnosis, and point of care (POC) testing has the ability to make this diagnosis more accessible, more affordable, and more reliable for patients. However, while the pandemic has brought awareness to POC and its ability to provide rapid results there is still uncertainty in its opportunity to persist in the longer term as well as the role it can fill in the diagnostics space.

This survey was conducted to better understand clinicians' pain points and perceptions of POC and laboratory diagnostics today in their quest to provide the best in patient care. Through these questions we uncovered the importance of speed, performance, simplicity, cost and footprint for clinicians when evaluating a diagnostic solution.

Here's what we found:

SPEED:
Time is valuable for clinicians in the delivery of results to their patients

• 81% of clinicians agreed that the speed at which they receive lab test results is a moderate to high concern.



Over 1/2
of clinicians said their greatest pain point with lab tests is the wait for results, cited at double the rate of importance than other issues, including accuracy, cost and access.

PERFORMANCE:
Clinicians expect POC to meet high standards for accuracy



of clinicians said *"lack of sensitivity"* and *"reliability of results"* are leading sources of reluctance when ordering POC tests.

SIMPLICITY:
The less room for interpretation the better

3-in-5 clinicians rated ease of understanding test results a concern when ordering a lab test.

COST:
Perceived costs are prohibitive when it comes to ordering diagnostics

• When ordering lab tests, 76% of clinicians are concerned about cost to their patients that have high-deductible insurance plans.

4-in-5 clinicians are reluctant to use POC testing due to the cost of the devices and testing materials, with a further **62%** stating they are too *"expensive for my practice."*

FOOTPRINT:
Multiple instruments for multiple tests are a source of frustration

• Two-thirds of clinicians believe that *"too many devices are required to access all potential POC tests needed."*

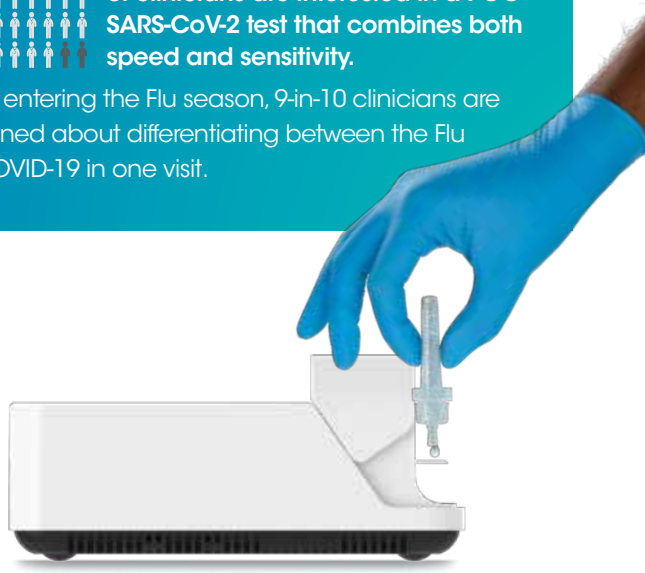
97% of clinicians are interested in using a single POC device that can perform a wide range of tests.

COVID-19 TESTING:
We also wanted to better understand clinician concerns when it came specifically to testing during the COVID-19 period.

• When questioned, the top 3 features required for a POC SARS-CoV-2 test are:
Quick results | Sensitivity | Ease of use

98% of clinicians are interested in a POC SARS-CoV-2 test that combines both speed and sensitivity.

• Upon entering the Flu season, 9-in-10 clinicians are concerned about differentiating between the Flu and COVID-19 in one visit.



About the Survey:
A third-party online poll of n=300 American clinicians was conducted anonymously between September 10 – 16, 2021. The sample included 150 primary care clinicians and 150 urgent care clinicians, as self-identified. The overall margin of error is ± 5.7%.

For more information and to view the full survey detail

Why Compromise?

LumiraDx's next-gen point of care Platform provides speed without compromising sensitivity at the point of care. With a growing menu of tests, LumiraDx's single, easy-to-use, portable instrument and microfluidic technology can aid in diagnosis and allows clinicians to deliver lab comparable results to patients in just minutes.

Learn more about how LumiraDx delivers lab comparable results, at a low cost with rapid results at lumiradx.com

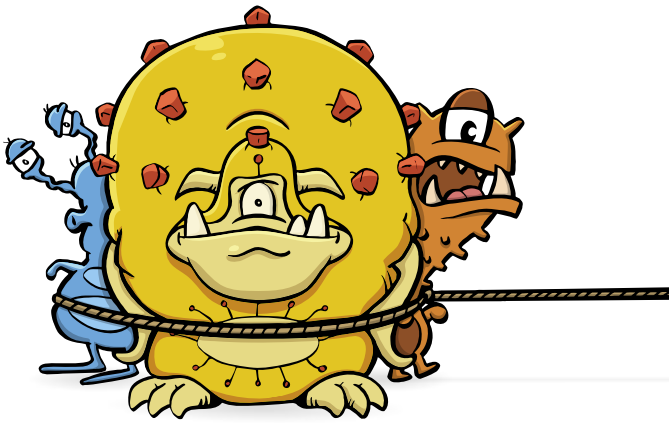
The LumiraDx SARS-CoV-2 Ag Test and the LumiraDx SARS-CoV-2 Ab Test have not been cleared or approved by FDA, but have been authorized for emergency use by FDA under an EUA for use by authorized laboratories. The LumiraDx SARS-CoV-2 Ag Test has been authorized only for the detection of SARS-CoV-2 nucleocapsid protein. The LumiraDx SARS-CoV-2 Ab Test has been authorized only for detecting the presence of total antibodies to SARS-CoV-2. They have not been authorized for use to detect any other viruses or pathogens. The emergency use of these Tests are only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostic Tests for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

S-COM-ART-01874 R1

PIONEERING DIAGNOSTICS

BIOMÉRIEUX

Round up SARS-CoV-2 and 18 other pathogens.



The new BioFire® Respiratory 2.1-EZ (RP2.1-EZ) Panel (EUA)[1] covers SARS-CoV-2 detection and so much more.

Right now, SARS-CoV-2 is everyone's top suspect, but many other respiratory bugs can cause similar, overlapping symptoms. Testing for just SARS-CoV-2 or influenza could mean running the risk of missing the real culprit, leading to missed infections, or even coinfections. Additionally, many rapid diagnostic tests sacrifice accuracy for speed, with sensitivities oftentimes ranging from 50–70%.[2]

Now you can test for 18 common respiratory pathogens in your clinic, including SARS-CoV-2 in patients suspected of a COVID-19 infection with syndromic testing from the BioFire RP2.1-EZ Panel—now available under an FDA Emergency Use Authorization (EUA).[1,3] Syndromic testing means all it takes is one test and about 45 minutes to round up SARS-CoV-2—and all the other usual respiratory suspects. What's your frontline solution for respiratory season and beyond?

To learn more, visit **biofiredx.com**



1242

BioFire RP2.1-EZ Panel (EUA)

Overall 97.1% sensitivity and 99.3% specificity (prospective specimens)[4]

SARS-CoV-2 98.0% sensitivity and 100% specificity (archived specimens)[5]

SARS-CoV-2 100% PPA and 100% NPA (contrived specimens)[6]

BIOFIRE®

1. This test has not been FDA cleared or approved. This test has been authorized by FDA under an EUA for use by authorized laboratories. This test has been authorized only for the detection and differentiation of nucleic acid of SARS-CoV-2 from multiple respiratory viral and bacterial organisms. This test is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of invitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. 2. http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm 3. For use with the CLIA-waived BioFire® FilmArray® 2.0 EZ configuration. 4. Based on the prospective portion of the clinical study for the BioFire® FilmArray® Respiratory 2 (RP2) Panel. 5. Based on the archived specimen study in the BioFire Respiratory 2.1 (RP2.1) Panel EUA submission 6. Based on the contrived specimen study in the BioFire Respiratory 2.1 (RP2.1) Panel EUA submission.

BFR0001-0517-02

TECENTRIQ + AVASTIN® (bevacizumab)
IN 1L UNRESECTABLE OR mHCC

THE STRENGTH OF SUPERIOR SURVIVAL



The first and only cancer immunotherapy combination to demonstrate sustained survival benefit vs sorafenib, **with updated data available**

- Primary analysis: median OS was not reached with TECENTRIQ + Avastin vs 13.2 months with sorafenib (HR=0.58; 95% CI, 0.42, 0.79; *P*=0.0006)[1]

See pivotal data and updated OS results based on follow-up analysis.

NCCN CATEGORY 1, PREFERRED OPTION

Atezolizumab (TECENTRIQ) + bevacizumab (Avastin) is the only preferred first-line systemic therapy option (Category 1) for patients with unresectable or metastatic hepatocellular carcinoma (Child-Pugh Class A) in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[2*†]

*NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way. See the NCCN Guidelines® for detailed recommendations.

†Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

1L=first line; CI=confidence interval; HR=hazard ratio; mHCC=metastatic hepatocellular carcinoma; NCCN=National Comprehensive Cancer Network; OS=overall survival.

TECENTRIQ®
atezolizumab 840 mg / 1200 mg INJECTION FOR IV USE
CONNECT WITH PURPOSE

Indication

TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Important Safety Information

Serious Adverse Reactions

Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. The following immune-mediated adverse reactions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions can occur in any organ system or tissue and at any time after starting a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, they can also manifest after discontinuation of treatment.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TECENTRIQ depending on severity. In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less, then initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on following pages.

Median follow-up of 8.6 months

UNPRECEDENTED OVERALL SURVIVAL IN 1L UNRESECTABLE OR mHCC[1]

TECENTRIQ + Avastin (bevacizumab) (n=336)		Sorafenib (n=165)
MEDIAN OS NOT REACHED (95% CI, NE, NE)	VS	**13.2 MONTHS** (95% CI, 10.4, NE)

HR=0.58 (95% CI, 0.42, 0.79; *P*=0.0006)

- OS was a coprimary endpoint

Coprimary endpoint: significantly improved progression-free survival[1]

- 6.8 months median PFS with TECENTRIQ + Avastin (95% CI, 5.8, 8.3) vs 4.3 months with sorafenib (95% CI, 4.0, 5.6) (HR=0.59; 95% CI, 0.47, 0.76; *P*<0.0001)*

Secondary endpoint: more than double the overall response rate vs sorafenib[1*†]

- 28% ORR with TECENTRIQ + Avastin (n=93/336; 95% CI, 23, 33) vs 12% with sorafenib (n=19/165; 95% CI, 7, 17) (*P*<0.0001)
  - 7% of patients demonstrated a complete response vs 0% with sorafenib, while 21% of patients demonstrated a partial response vs 12% with sorafenib

IMbrave150 was a Phase III, multicenter, international, open-label, randomized trial that compared TECENTRIQ + Avastin to sorafenib in 501 patients with locally advanced unresectable and/or metastatic HCC who had not received prior systemic therapy. Patients were randomized (2:1) to receive either TECENTRIQ 1200 mg IV followed by Avastin 15 mg/kg IV on the same day q3w or 400 mg sorafenib given orally twice daily, until disease progression or unacceptable toxicity. The major efficacy outcome measures were OS and IRF-assessed PFS per RECIST v1.1 in the ITT population. Key secondary endpoints included ORR‡ and DoR.[1,3‡]

ADA=antidrug antibody; DoR=duration of response; HCC mRECIST=hepatocellular carcinoma modified Response Evaluation Criteria In Solid Tumors; IRF=independent review facility; ITT=intent to treat; IV=intravenous; NE=not estimable; ORR=overall response rate; PFS=progression-free survival; q3w=every 3 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

*Assessed by IRF per RECIST v1.1.
†Confirmed responses.
‡Assessed by IRF per RECIST v1.1 and HCC mRECIST.

Additional OS analysis[1]

- Exploratory analyses showed that the subset of patients (20%) who were ADA positive by Week 6 appeared to have reduced efficacy as compared to patients (80%) who tested negative for treatment-emergent ADA by Week 6. ADA-positive patients by Week 6 appeared to have similar OS compared to sorafenib-treated patients. However, the analyses were inconclusive due to the low number of events in ADA subgroups

Important Safety Information (cont'd)

Immune-Mediated Pneumonitis

- TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation
- Immune-mediated pneumonitis occurred in 3% (83/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.8%), and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.5% and withholding of TECENTRIQ in 1.5% of patients. Systemic corticosteroids were required in 55% (46/83) of patients with pneumonitis

Immune-Mediated Colitis

- TECENTRIQ can cause immune-mediated colitis. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies
- Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients. Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 26 patients. Of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis

Immune-Mediated Hepatitis

- TECENTRIQ can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 25% (12/48) of patients with hepatitis. Hepatitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated treatment with TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

- TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated
- Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 1 patient and withholding of TECENTRIQ in 1 patient. Systemic corticosteroids were required in 81% (9/11) of patients with adrenal insufficiency; of these, 3 patients remained on systemic corticosteroids. The single patient in whom TECENTRIQ was withheld for adrenal insufficiency did not reinitiate TECENTRIQ

Hypophysitis

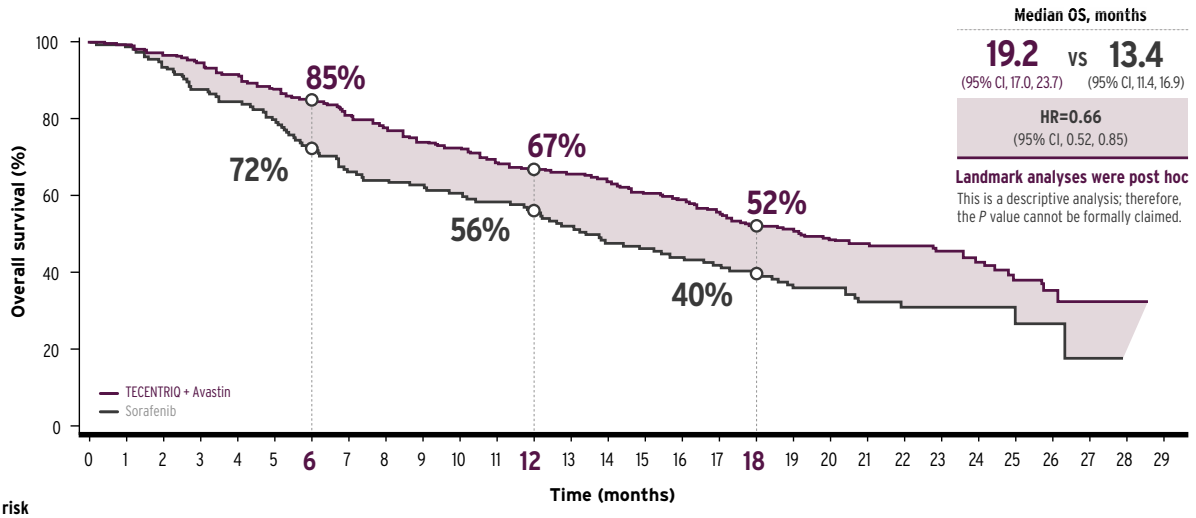
- TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated
- Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (1 patient, <0.1%) adverse reactions.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on following pages.

Median follow-up of 15.6 months

DESCRIPTIVE FOLLOW-UP ANALYSIS: NUMERICAL IMPROVEMENT OF 5.8 MONTHS IN MEDIAN OS

TECENTRIQ + Avastin OS data vs sorafenib[4]



Number at risk																												
TECENTRIQ + Avastin	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Landmark analyses were not powered to demonstrate statistically significant differences and no conclusions can be drawn from these analyses. The OS rates at 6, 12, and 18 months were estimated with the use of Kaplan-Meier methodology for each treatment arm.

Important Safety Information (cont'd)

Immune-Mediated Endocrinopathies (cont'd)

Hypophysitis led to permanent discontinuation of TECENTRIQ in 1 patient and no patients required withholding of TECENTRIQ. Systemic corticosteroids were required in 50% (1/2) of patients with hypophysitis. Hypophysitis did not resolve in these 2 patients

Thyroid Disorders

- TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated
- Thyroiditis occurred in 0.2% (4/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (<0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 1 patient. Hormone replacement therapy was required in 75% (3/4) of patients with thyroiditis. Systemic corticosteroids were required in 25% (1/4) of patients with thyroiditis. Thyroiditis resolved in 50% of patients. The single patient in whom TECENTRIQ was withheld for thyroiditis reinitiated TECENTRIQ; this patient did not have recurrence of thyroiditis
- Hyperthyroidism occurred in 0.8% (21/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.1% of patients. Antithyroid therapy was required in 29% (6/21) of patients with hyperthyroidism. Of these 6 patients, the majority remained on antithyroid treatment. Of the 3 patients in whom TECENTRIQ was withheld for hyperthyroidism, 1 patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism
- Hypothyroidism occurred in 4.9% (128/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (3.4%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.6% of patients. Hormone replacement therapy was required in 81% (104/128) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 17 patients in whom TECENTRIQ was withheld for hypothyroidism, 8 reinitiated TECENTRIQ after symptom improvement

Type 1 Diabetes Mellitus, Which Can Present With Diabetic Ketoacidosis

- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated
- Type 1 diabetes mellitus occurred in 0.3% (7/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (<0.1%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of TECENTRIQ in 1 patient and withholding of TECENTRIQ in 2 patients. Treatment with insulin was required for all patients with confirmed Type 1 diabetes mellitus and insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both reinitiated TECENTRIQ treatment

TECENTRIQ®
atezolizumab
840 mg | 1200 mg
INJECTION FOR IV USE

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Nephritis With Renal Dysfunction

- TECENTRIQ can cause immune-mediated nephritis
- Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ as a single agent, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient. This patient required systemic corticosteroids. In this patient, nephritis did not resolve

Immune-Mediated Dermatologic Adverse Reactions

- TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes
- Immune-mediated dermatologic adverse reactions occurred in 0.6% (15/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 20% (3/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 87% of the 15 patients. Of the 4 patients in whom TECENTRIQ was withheld for immune-mediated dermatologic adverse reactions, none reinitiated TECENTRIQ

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received TECENTRIQ or were reported with the use of other PD-1/PD-L1 blocking antibodies
  - *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis
  - *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
  - *Ocular*: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
  - *Gastrointestinal*: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis
  - *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic
  - *Endocrine*: Hypoparathyroidism
  - *Other (Hematologic/Immune)*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-Related Reactions

- TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses
- Infusion-related reactions occurred in 1.3% of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) reactions
- The frequency and severity of infusion-related reactions were similar across the recommended dose range

Complications of Allogeneic HSCT After PD-1/PD-L1 Inhibitors

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody
- Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause)
- These complications may occur despite intervening therapy between PD-1/PD-L1 blockage and allogeneic HSCT
- Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT

Embryo-Fetal Toxicity

- Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus, resulting in fetal death
- Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose

Use In Specific Populations

Nursing Mothers

- There is no information regarding the presence of TECENTRIQ in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown
- Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

Fertility

- Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment

Most Common Adverse Reactions

The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ in combination with bevacizumab for HCC were hypertension (30%), fatigue/asthenia (26%), and proteinuria (20%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see Brief Summary of TECENTRIQ Prescribing Information on following pages, and full Avastin Prescribing Information for additional Important Safety Information.

References: 1. TECENTRIQ Prescribing Information. Genentech, Inc. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 16, 2021. To view the most recent and complete version of the guideline, go online to www.NCCN.org. **3.** Finn RS, Qin S, Ikeda M, et al; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905. **4.** Data on file. Genentech, Inc.

Learn more at **TECENTRIQ-HCP.com/uHCC**

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TECENTRIQ®
atezolizumab 840 mg / 1200 mg INJECTION FOR IV USE
CONNECT WITH PURPOSE

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TECENTRIQ® [atezolizumab]

Initial U.S. Approval: 2016

This is a brief summary of information about TECENTRIQ. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

- are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, or
- are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Non-Small Cell Lung Cancer

- TECENTRIQ, as a single-agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA *[see Clinical Studies (14.2)]* non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.
- TECENTRIQ, as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations *[see Dosage and Administration (2.1)]*.
- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving TECENTRIQ.

1.3 Small Cell Lung Cancer

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

1.4 Hepatocellular Carcinoma

TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

1.5 Melanoma

TECENTRIQ, in combination with cobimetinib and vemurafenib, is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma *[see Dosage and Administration (2.1)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*. In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

TECENTRIQ as a Single Agent:

Immune-mediated pneumonitis occurred in 3% (83/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.8%), and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.5% and withholding of TECENTRIQ in 1.5% of patients.

Systemic corticosteroids were required in 55% (46/83) of patients with pneumonitis. Pneumonitis resolved in 69% of the 83 patients. Of the 39 patients in whom TECENTRIQ was withheld for pneumonitis, 25 reinitiated TECENTRIQ after symptom improvement; of these, 4% had recurrence of pneumonitis.

In IMpower010 immune-mediated pneumonitis occurred in 3.8% (19/495) of patients receiving TECENTRIQ as a single agent, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 0.8% of patients.

Systemic corticosteroids were required in 63% (12/19) of patients with pneumonitis. Pneumonitis resolved in 84% of the 19 patients.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated pneumonitis occurred in 13% (29/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 3 (1.3%) and Grade 2 (7%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 2.6% and withholding of TECENTRIQ in 7.4% of patients.

Systemic corticosteroids were required in 55% (16/29) of patients with pneumonitis. Pneumonitis resolved in 97% of the 29 patients. Of the 17 patients in whom TECENTRIQ was withheld for pneumonitis, 10 reinitiated TECENTRIQ after symptom improvement; of these, 50% had recurrence of pneumonitis.

Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

TECENTRIQ as a Single Agent:

Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients.

Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 26 patients. Of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis.

Immune-Mediated Hepatitis

TECENTRIQ can cause immune-mediated hepatitis.

Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 25% (12/48) of patients with hepatitis. Hepatitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated treatment with TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated hepatitis occurred in 6.1% (14/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 4 (1.3%), Grade 3 (1.7%) and Grade 2 (1.3%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 1.7% of patients.

Systemic corticosteroids were required in 50% (7/14) of patients with hepatitis. Hepatitis resolved in 93% of the 14 patients. Of the 4 patients in whom TECENTRIQ was withheld for hepatitis, 3 reinitiated TECENTRIQ after symptom improvement; of these, 33% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in one patient.

Systemic corticosteroids were required in 82% (9/11) of patients with adrenal insufficiency; of these, 3 patients remained on systemic corticosteroids. The single patient in whom TECENTRIQ was withheld for adrenal insufficiency did not reinitiate TECENTRIQ.

In IMpower010 immune-mediated adrenal insufficiency occurred in 1.2% (6/495) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 0.6% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 83% (5/6) of patients with adrenal insufficiency; of these, 4 patients remained on systemic corticosteroids.

Hypophysitis

TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (1 patient, <0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of TECENTRIQ in one patient and no patients required withholding of TECENTRIQ.

Systemic corticosteroids were required in 50% (1/2) of patients with hypophysitis. Hypophysitis did not resolve in these 2 patients.

Thyroid disorders

TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Thyroiditis:

Thyroiditis occurred in 0.2% (4/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (<0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in one patient.

Hormone replacement therapy was required in 75% (3/4) of patients with thyroiditis. Systemic corticosteroids were required in 25% (1/4) of patients with thyroiditis. Thyroiditis resolved in 50% of patients. The single patient in whom TECENTRIQ was withheld for thyroiditis reinitiated TECENTRIQ; this patient did not have recurrence of thyroiditis.

In IMpower010, thyroiditis occurred in 1.2% (6/495) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Thyroiditis led to withholding of TECENTRIQ in one patient.

Hormone replacement therapy was required in 67% (4/6) of patients with thyroiditis. Systemic corticosteroids were required in 33% (2/6) of patients with thyroiditis. Thyroiditis resolved in 50% of patients.

Hyperthyroidism:

TECENTRIQ as a Single Agent:

Hyperthyroidism occurred in 0.8% (21/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.1% of patients.

Antithyroid therapy was required in 29% (6/21) of patients with hyperthyroidism. Of these 6 patients, the majority remained on antithyroid treatment. Of the 3 patients in whom TECENTRIQ was withheld for hyperthyroidism, one patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism.

In IMpower010 hyperthyroidism occurred in 6% (32/495) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.4%) adverse reactions. Hyperthyroidism led to permanent discontinuation of TECENTRIQ in 0.8% and withholding of TECENTRIQ in 2.8% of patients.

Antithyroid therapy was required in 38% (12/32) of patients with hyperthyroidism. Of these 12 patients, the majority remained on antithyroid treatment. Of the 14 patients in whom TECENTRIQ was withheld for hyperthyroidism, 9 patients reinitiated TECENTRIQ.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Hyperthyroidism occurred in 19% (43/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 3 (0.9%) and Grade 2 (7.8%) adverse reactions. Hyperthyroidism led to permanent discontinuation of TECENTRIQ in 0.4% and withholding of TECENTRIQ in 10% of patients.

Antithyroid therapy was required in 53% (23/43) of patients with hyperthyroidism. Of these 23 patients, the majority remained on antithyroid treatment. Of the 24 patients in whom TECENTRIQ was withheld for hyperthyroidism, 18 patients reinitiated TECENTRIQ; of these, 28% had recurrence of hyperthyroidism.

Hypothyroidism:

TECENTRIQ as a Single Agent:

Hypothyroidism occurred in 4.9% (128/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (3.4%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.6% of patients.

Hormone replacement therapy was required in 81% (104/128) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 17 patients in whom TECENTRIQ was withheld for hypothyroidism, 8 reinitiated TECENTRIQ after symptom improvement.

In IMpower010 hypothyroidism occurred in 17% (86/495) of patients receiving TECENTRIQ as a single agent. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 1.6% and withholding of TECENTRIQ in 1.6% of patients.

Hormone replacement was required in 57% (49/86) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 8 patients in whom TECENTRIQ was withheld for hypothyroidism, 3 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Platinum-based Chemotherapy:

Hypothyroidism occurred in 11% (277/2421) of patients with NSCLC and SCLC receiving TECENTRIQ in combination with platinum-based chemotherapy, including Grade 4 (<0.1%), Grade 3 (0.3%), and

Grade 2 (5.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 1.6% of patients.

Hormone replacement therapy was required in 71% (198/277) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 39 patients in whom TECENTRIQ was withheld for hypothyroidism, 9 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Hypothyroidism occurred in 26% (60/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 2 (9.1%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 2.6% of patients.

Hormone replacement therapy was required in 52% (31/60) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 6 patients in whom TECENTRIQ was withheld for hypothyroidism, 4 reinitiated TECENTRIQ after symptom improvement. The majority of patients with hypothyroidism required long term thyroid replacement.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Type 1 diabetes mellitus occurred in 0.3% (7/2616) of patients receiving TECENTRIQ, including Grade 3 (0.2%) and Grade 2 (<0.1%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in two patients.

Treatment with insulin was required for all patients with confirmed Type 1 diabetes mellitus and insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

Immune-Mediated Nephritis with Renal Dysfunction

TECENTRIQ can cause immune-mediated nephritis.

TECENTRIQ as a Single Agent:

Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ as a single agent, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient.

This patient required systemic corticosteroids. In this patient, nephritis did not resolve.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated nephritis with renal dysfunction occurred in 1.3% (3/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 2 (1.3%) adverse reactions. Nephritis led to permanent discontinuation of TECENTRIQ in 0.4% and withholding of TECENTRIQ in 0.9% of patients.

Systemic corticosteroids were required in 67% (2/3) of patients with nephritis. Nephritis resolved in all 3 of these patients. Of the 2 patients in whom TECENTRIQ was withheld for nephritis, both reinitiated TECENTRIQ after symptom improvement and neither had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Immune-mediated dermatologic adverse reactions occurred in 0.6% (15/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 20% (3/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 87% of the 15 patients. Of the 4 patients in whom TECENTRIQ was withheld for immune-mediated dermatologic adverse reactions, none re-initiated TECENTRIQ.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% (unless otherwise noted) in patients who received TECENTRIQ or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

5.2 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.3)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers, in combination with other antineoplastic drugs in NSCLC and SCLC, and across the recommended dose range (840 mg Q2W to 1680 mg Q4W).

5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockage and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single arm studies (PCD4989g, IMvigor210, BIRCH, FIR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%). In addition, the data reflect exposure to TECENTRIQ as a single agent as adjuvant therapy in 495 patients with early stage NSCLC enrolled in a randomized study (IMpower010).

In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in 2421 patients with NSCLC (N = 2223) or SCLC (N = 198) enrolled in five randomized, active-controlled trials, including IMpower150, IMpower130 and IMpower133. Among the 2421 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 29% were exposed to TECENTRIQ for longer than 12 months. Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with other antineoplastic drugs, the most common adverse reactions in ≥20% of patients were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%) and decreased appetite (27%).

The data also reflect exposure to TECENTRIQ administered in combination with cobimetinib and vemurafenib in 230 patients enrolled in IMspire150. Among the 230 patients, 62% were exposed to TECENTRIQ for longer than 6 months and 42% were exposed to TECENTRIQ for longer than 12 months.

Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 1), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy *[see Clinical Studies (14.1)]*. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 15 weeks (0 to 87 weeks).

Five patients (4.2%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, cardiac arrest, myocardial infarction, respiratory failure, or respiratory distress. One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression at the time of death.

Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%). Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion-related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism.

Tables 4 and 5 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 1).

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue[1]	52	8
Peripheral edema[2]	17	2
Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[3]	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[4]	15	0.8
Metabolism and Nutrition		
Decreased appetite[5]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8
Rash[6]	17	0.8
Infections		
Urinary tract infection[7]	17	5
Respiratory, Thoracic, and Mediastinal		
Cough[8]	14	0
Dyspnea[9]	12	0

[1] Includes fatigue, asthenia, lethargy, and malaise
[2] Includes edema peripheral, scrotal edema, lymphedema, and edema
[3] Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
[4] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
[5] Includes decreased appetite and early satiety
[6] Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
[7] Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis
[8] Includes cough and productive cough
[9] Includes dyspnea and exertional dyspnea

Table 5: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Laboratory Abnormality	Grades 3–4 (%)
Chemistry	
Hyponatremia	15

Table 5: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1) (continued)

Laboratory Abnormality	Grades 3–4 (%)
Hyperglycemia	10
Increased Alkaline Phosphatase	7
Increased Creatinine	5
Hypophosphatemia	4
Increased ALT	4
Increased AST	4
Hyperkalemia	3
Hypermagnesemia	3
Hyperbilirubinemia	3
Hematology	
Lymphopenia	9
Anemia	7

Graded per NCI CTCAE v4.0.

Non-Small Cell Lung Cancer (NSCLC)

Adjuvant Treatment of Early-stage NSCLC

IMpower010

The safety of TECENTRIQ was evaluated in IMpower010, a multicenter, open-label, randomized trial for the adjuvant treatment of patients with stage IB (tumors ≥ 4 cm) - IIIA NSCLC who had complete tumor resection and received up to 4 cycles of cisplatin-based adjuvant chemotherapy. Patients received TECENTRIQ 1200 mg every 3 weeks (n=495) for 1 year (16 cycles), unless disease progression or unacceptable toxicity occurred, or best supportive care *[see Clinical Studies (14.2)]*. The median number of cycles received was 16 (range: 1, 16).

Fatal adverse reactions occurred in 1.8% of patients receiving TECENTRIQ; these included multiple organ dysfunction syndrome, pneumothorax, interstitial lung disease, arrhythmia, acute cardiac failure, myocarditis, cerebrovascular accident, death of unknown cause, and acute myeloid leukemia (1 patient each).

Serious adverse reactions occurred in 18% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>1%) were pneumonia (1.8%), pneumonitis (1.6%), and pyrexia (1.2%).

TECENTRIQ was discontinued due to adverse reactions in 18% of patients; the most common adverse reactions (≥1%) leading to TECENTRIQ discontinuation were pneumonitis (2.2%), hypothyroidism (1.6%), increased aspartate aminotranferase (1.4%), arthralgia (1.0%), and increased alanine aminotransferase (1.0%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 29% of patients; the most common (>1%) were rash (3.0%), hyperthyroidism (2.8%), hypothyroidism (1.6%), increased AST (1.6%), pyrexia (1.6%), increased ALT (1.4%), upper respiratory tract infection (1.4%), headache (1.2%), peripheral neuropathy (1.2%), and pneumonia (1.2%).

Tables 6 and 7 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower010.

Table 6: Adverse Reactions Occurring in ≥10% of Patients with Early Stage NSCLC Receiving TECENTRIQ in IMpower010

Adverse Reaction*	TECENTRIQ N = 495		Best Supportive Care N = 495	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Skin and Subcutaneous Tissue				
Rash[1]	17	1.2	1.4	0
Pruritus	10	0	0.6	0
Endocrine Disorders				
Hypothyroidism[2]	14	0	0.6	0
Respiratory, Thoracic and Mediastinal				
Cough[3]	16	0	11	0
General				
Pyrexia[4]	14	0.8	2.2	0.2
Fatigue[5]	14	0.6	5	0.2
Nervous System Disorders				
Peripheral neuropathy[6]	12	0.4	7	0.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[7]	14	0.8	9	0.2
Arthralgia[8]	11	0.6	6	0

*Graded per NCI CTCAE v4.0

[1] Includes rash, dermatitis, genital rash, skin exfoliation, rash maculo-papular, rash erythematous, rash papular, lichen planus, eczema asteatotic, dermatitis exfoliative, palmar-plantar erythrodysaesthesia syndrome, dyshidrotic eczema, eczema, drug eruption, rash pruritic, toxic skin eruption, dermatitis acneiform

[2] Includes hypothyroidism, autoimmune hypothyroidism, primary hypothyroidism, blood thyroid stimulating hormone increased

[3] Productive cough, upper airway cough syndrome, cough

[4] Includes pyrexia, body temperature increased, hyperthermia

[5] Includes fatigue, asthenia

[6] Includes paraesthesia, neuropathy peripheral, peripheral sensory neuropathy, hypoaesthesia, polyneuropathy, dysaesthesia, neuralgia, axonal neuropathy

[7] Includes myalgia, bone pain, back pain, spinal pain, musculoskeletal chest pain, pain in extremity, neck pain, non-cardiac chest pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal pain

[8] Includes arthralgia, arthritis

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Early Stage NSCLC Receiving TECENTRIQ in IMpower010

Laboratory Abnormality[1]	TECENTRIQ[2]		Best Supportive Care[2]	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased aspartate aminotransferase	34	2.5	18	0
Increased alanine aminotransferase	30	3.3	19	0.4
Hyperkalemia	24	3.5	15	2.5
Increased blood creatinine	31	0.2	23	0.2

[1] Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).

[2] The denominators used to calculate the rate varied from 78-480 for BSC arm and 483 for atezolizumab are for all tests of interest based on the number of patients with a baseline value and at least one post-treatment value.

Metastatic Chemotherapy-Naïve NSCLC

IMpower110

The safety of TECENTRIQ was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naïve patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations. Patients received TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin with either pemetrexed or gemcitabine (n=263) until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. IMpower110 enrolled patients whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area). The median duration of exposure to TECENTRIQ was 5.3 months (0 to 33 months).

Fatal adverse reactions occurred in 3.8% of patients receiving TECENTRIQ; these included death (reported as unexplained death and death of unknown cause), aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical ileus, sepsis, cerebral infarction, and device occlusion (1 patient each).

Serious adverse reactions occurred in 28% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were pneumonia (2.8%), chronic obstructive pulmonary disease (2.1%) and pneumonitis (2.1%).

TECENTRIQ was discontinued due to adverse reactions in 6% of patients; the most common adverse reactions (≥2 patients) leading to TECENTRIQ discontinuation were peripheral neuropathy and pneumonitis.

Adverse reactions leading to interruption of TECENTRIQ occurred in 26% of patients; the most common (>1%) were ALT increased (2.1%), AST increased (2.1%), pneumonitis (2.1%), pyrexia (1.4%), pneumonia (1.4%) and upper respiratory tract infection (1.4%).

Tables 8 and 9 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower110.

Table 8: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in IMpower110

Adverse Reaction	TECENTRIQ N = 286		Platinum-Based Chemotherapy N = 263	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Gastrointestinal				
Nausea	14	0.3	34	1.9
Constipation	12	1.0	22	0.8
Diarrhea	11	0	12	0.8
General				
Fatigue/asthenia	25	1.4	34	4.2
Pyrexia	14	0	9	0.4
Metabolism and Nutrition				
Decreased appetite	15	0.7	19	0
Respiratory, Thoracic and Mediastinal				
Dyspnea	14	0.7	10	0
Cough	12	0.3	10	0

Graded per NCI CTCAE v4.0

Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower110

Laboratory Abnormality	TECENTRIQ		Platinum-Based Chemotherapy	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	69	1.8	94	20
Lymphopenia	47	9	59	17
Chemistry				
Hypoalbuminemia	48	0.4	39	2
Increased alkaline phosphatase	46	2.5	42	1.2
Hyponatremia	44	9	36	7
Increased ALT	38	3.2	32	0.8
Increased AST	36	3.2	32	0.8
Hyperkalemia	29	3.9	36	2.7
Hypocalcemia	24	1.4	24	2.7
Increased blood creatinine	24	0.7	33	1.5
Hypophosphatemia	23	3.6	21	2

Each test incidence is based on the number of patients who had at least one on-study laboratory measurement available: TECENTRIQ (range: 278-281); platinum-based chemotherapy (range: 256-260). Graded per NCI CTCAE v4.0. Increased blood creatinine only includes patients with test results above the normal range.

IMpower150

The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min intravenously every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

Fatal adverse reactions occurred in 6% of patients receiving TECENTRIQ; these included hemoptysis, febrile neutropenia, pulmonary embolism, pulmonary hemorrhage, death, cardiac arrest, cerebrovascular accident, pneumonia, aspiration pneumonia, chronic obstructive pulmonary disease, intracranial hemorrhage, intestinal angina, intestinal ischemia, intestinal obstruction and aortic dissection.

Serious adverse reactions occurred in 44%. The most frequent serious adverse reactions (>2%) were febrile neutropenia, pneumonia, diarrhea, and hemoptysis.

TECENTRIQ was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonitis (1.8%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hyperthyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

Tables 10 and 11 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin in IMpower150.

Table 10: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Nervous System				
Neuropathy[1]	56	3	47	3
Headache	16	0.8	13	0
General				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
Skin and Subcutaneous Tissue				
Alopecia	48	0	46	0
Rash[2]	23	2	10	0.3
Musculoskeletal and Connective Tissue				
Myalgia/Pain[3]	42	3	34	2
Arthralgia	26	1	22	1
Gastrointestinal				
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

Graded per NCI CTCAE v4.0

[1] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paraesthesia, dysesthesia, polyneuropathy

[2] Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform

[3] Includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, back pain, myalgia, and bone pain

[4] Includes diarrhea, gastroenteritis, colitis, enterocolitis

[5] Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13
Chemistry				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA[1]	44	NA[1]
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA[1]	20	NA[1]
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	NA[1]	19	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with bevacizumab, paclitaxel, and carboplatin range: 337-380); bevacizumab, paclitaxel, and carboplatin (range: 337-382). Graded per NCI CTCAE v4.0

[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

IMpower130

The safety of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130, a multicenter, international, randomized, open-label trial in which 473 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg and carboplatin AUC 6 mg/mL/min intravenously on Day 1 and paclitaxel protein-bound 100 mg/m^2 intravenously on Day 1, 8, and 15 of each 21-day cycle for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*.

Among patients receiving TECENTRIQ, 55% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Fatal adverse reactions occurred in 5.3% of patients receiving TECENTRIQ; these included pneumonia (1.1%), pulmonary embolism (0.8%), myocardial infarction (0.6%), cardiac arrest (0.4%), pneumonitis (0.4%) and sepsis, septic shock, staphylococcal sepsis, aspiration, respiratory distress, cardiorespiratory arrest, ventricular tachycardia, death (not otherwise specified), and hepatic cirrhosis (0.2% each).

Serious adverse reactions occurred in 51% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (≥2%) were pneumonia (6%), diarrhea (3%), lung infection (3%), pulmonary embolism (3%), chronic obstructive pulmonary disease exacerbation (2.5%), dyspnea (2.3%), and febrile neutropenia (1.9%).

TECENTRIQ was discontinued due to adverse reactions in 13% of patients; the most common adverse reactions leading to discontinuation were pneumonia (0.8%), pulmonary embolism (0.8%), fatigue (0.6%), dyspnea (0.6%), pneumonitis (0.6%), neutropenia (0.4%), nausea (0.4%), renal failure (0.4%), cardiac arrest (0.4%), and septic shock (0.4%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 62% of patients; the most common (>1%) were neutropenia, thrombocytopenia, anemia, diarrhea, fatigue/asthenia, pneumonia, dyspnea, pneumonitis, pyrexia, nausea, acute kidney injury, vomiting, pulmonary embolism, arthralgia, infusion-related reaction, abdominal pain, chronic obstructive pulmonary disease exacerbation, dehydration, and hypokalemia.

Tables 12 and 13 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with paclitaxel protein-bound and carboplatin in IMpower130.

Table 12: Adverse Reactions Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower130

Adverse Reaction	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/Asthenia	61	11	60	8
Gastrointestinal				
Nausea	50	3.4	46	2.2
Diarrhea[1]	43	6	32	6
Constipation	36	1.1	31	0
Vomiting	27	2.7	19	2.2
Musculoskeletal and Connective Tissue				
Myalgia/Pain[2]	38	3	22	0.4
Nervous System				
Neuropathy[3]	33	2.5	28	2.2
Respiratory, Thoracic and Mediastinal				
Dyspnea[4]	32	4.9	25	1.3
Cough	27	0.6	17	0
Skin and Subcutaneous Tissue				
Alopecia	32	0	27	0
Rash[5]	20	0.6	11	0.9
Metabolism and Nutrition				
Decreased appetite	30	2.1	26	2.2

Graded per NCI CTCAE v4.0

[1] Includes diarrhea, colitis, and gastroenteritis

[2] Includes back pain, pain in extremity, myalgia, musculoskeletal chest pain, bone pain, neck pain and musculoskeletal discomfort

[3] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

[4] Includes dyspnea, dyspnea exertional and wheezing

[5] Includes rash, rash maculo-papular, eczema, rash pruritic, rash erythematous, dermatitis, dermatitis contact, drug eruption, seborrheic dermatitis and rash macular.

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower130

Laboratory Abnormality	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	92	33	87	25
Neutropenia	75	50	67	39
Thrombocytopenia	73	19	59	13
Lymphopenia	71	23	61	16
Chemistry				
Hyperglycemia	75	8	66	8
Hypomagnesemia	50	3.4	42	3.2
Hyponatremia	37	9	28	7
Hypoalbuminemia	35	1.3	31	0
Increased ALT	31	2.8	24	3.9
Hypocalcemia	31	2.6	27	1.8
Hypophosphatemia	29	6	20	3.2
Increased AST	28	2.2	24	1.8
Increased TSH	26	NA[1]	5	NA[1]
Hypokalemia	26	6	24	4.4
Increased Alkaline Phosphatase	25	2.6	22	1.3
Increased Blood Creatinine	23	2.8	16	0.4
Hyperphosphatemia	21	NA[1]	13	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with paclitaxel protein-bound and carboplatin (range: 423 - 467); paclitaxel protein-bound and carboplatin (range: 218 - 229). Graded per NCI CTCAE v4.0.

[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

Previously Treated Metastatic NSCLC

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.2)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had ECOG performance status of 1.

Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure.

Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (>1%) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain.

Tables 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in OAK.

Table 14: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in OAK

Adverse Reaction	TECENTRIQ N = 609		Docetaxel N = 578	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue/Asthenia[1]	44	4	53	6
Pyrexia	18	<1	13	<1
Respiratory				
Cough[2]	26	<1	21	<1
Dyspnea	22	2.8	21	2.6
Metabolism and Nutrition				
Decreased appetite	23	<1	24	1.6
Musculoskeletal				
Myalgia/Pain[3]	20	1.3	20	<1
Arthralgia	12	0.5	10	0.2
Gastrointestinal				
Nausea	18	<1	23	<1
Constipation	18	<1	14	<1
Diarrhea	16	<1	24	2
Skin				
Rash[4]	12	<1	10	0

Graded per NCI CTCAE v4.0

[1] Includes fatigue and asthenia

[2] Includes cough and exertional cough

[3] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia

[4] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 15: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in OAK

Laboratory Abnormality	TECENTRIQ		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21
Chemistry				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4
Hypomagnesemia	26	1	21	1
Increased Creatinine	23	2	16	1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546–585) and docetaxel (range: 532–560). Graded according to NCI CTCAE version 4.0

Small Cell Lung Cancer (SCLC)

The safety of TECENTRIQ with carboplatin and etoposide was evaluated in IMpower133, a randomized, multicenter, double-blind, placebo-controlled trial in which 198 patients with ES-SCLC received TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.3)]*. Among 198 patients receiving TECENTRIQ, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer.

Fatal adverse reactions occurred in 2% of patients receiving TECENTRIQ. These included pneumonia, respiratory failure, neutropenia, and death (1 patient each).

Serious adverse reactions occurred in 37% of patients receiving TECENTRIQ. Serious adverse reactions in >2% were pneumonia (4.5%), neutropenia (3.5%), febrile neutropenia (2.5%), and thrombocytopenia (2.5%).

TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 59% of patients; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.0%), infusion-related reaction (3.5%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

Table 16: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Adverse Reaction	TECENTRIQ with Carboplatin and Etoposide N = 198		Placebo with Carboplatin and Etoposide N = 196	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/asthenia	39	5	33	3
Gastrointestinal				
Nausea	38	1	33	1
Constipation	26	1	30	1
Vomiting	20	2	17	3
Skin and Subcutaneous Tissue				
Alopecia	37	0	35	0
Metabolism and Nutrition				
Decreased appetite	27	1	18	0

Graded per NCI CTCAE v4.0

Table 17: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Laboratory Abnormality	TECENTRIQ with Carboplatin and Etoposide		Placebo with Carboplatin and Etoposide	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	94	17	93	19
Neutropenia	73	45	76	48
Thrombocytopenia	58	20	53	17
Lymphopenia	46	14	38	11
Chemistry				
Hyperglycemia	67	10	65	8
Increased Alkaline Phosphatase	38	1	35	2
Hyponatremia	34	15	33	11
Hypoalbuminemia	32	1	30	0
Decreased TSH[2]	28	NA[1]	15	NA[1]
Hypomagnesemia	31	5	35	6
Hypocalcemia	26	3	28	5
Increased ALT	26	3	31	1
Increased AST	22	1	21	2
Increased Blood Creatinine	22	4	15	1
Hyperphosphatemia	21	NA[1]	23	NA[1]
Increased TSH[2]	21	NA[1]	7	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 181-193); Placebo (range: 181-196). Graded per NCI CTCAE v4.0

[1] NA = Not applicable. [2] TSH = thyroid-stimulating hormone. NCI CTCAE v4.0 does not include these laboratories.

Hepatocellular Carcinoma (HCC)

The safety of TECENTRIQ in combination with bevacizumab was evaluated in IMbrave150, a multicenter, international, randomized, open-label trial in patients with locally advanced or metastatic or unresectable hepatocellular carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.4)]*. Patients received 1,200 mg of TECENTRIQ intravenously followed by 15 mg/kg bevacizumab (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to TECENTRIQ was 7.4 months (range: 0-16 months) and to bevacizumab was 6.9 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%).

Serious adverse reactions occurred in 38% of patients in the TECENTRIQ and bevacizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to TECENTRIQ discontinuation were hemorrhages (1.2%), including gastrointestinal, subarachnoid, and pulmonary hemorrhages; increased transaminases or bilirubin (1.2%); infusion-related reaction/cytokine release syndrome (0.9%); and autoimmune hepatitis (0.6%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 41% of patients in the TECENTRIQ and bevacizumab arm; the most common (≥ 2%) were liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatase (8%); infections (6%); gastrointestinal hemorrhages (3.6%); thrombocytopenia/decreased platelet count (3.6%); hyperthyroidism (2.7%); and pyrexia (2.1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12% of patients in the TECENTRIQ and bevacizumab arm.

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ and bevacizumab in IMbrave150.

Table 18: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Adverse Reaction	TECENTRIQ in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[2] (%)	Grades 3–4[2] (%)	All Grades[2] (%)	Grades 3–4[2] (%)
Vascular Disorders				
Hypertension	30	15	24	12
General Disorders and Administration Site Conditions				
Fatigue/asthenia[1]	26	2	32	6
Pyrexia	18	0	10	0
Renal and Urinary Disorders				
Proteinuria	20	3	7	0.6
Investigations				
Weight Decreased	11	0	10	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	10	0
Rash	12	0	17	2.6
Gastrointestinal Disorders				
Diarrhea	19	1.8	49	5
Constipation	13	0	14	0
Abdominal Pain	12	0	17	0
Nausea	12	0	16	0
Vomiting	10	0	8	0
Metabolism and Nutrition Disorders				
Decreased Appetite	18	1.2	24	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	12	0	10	0
Epistaxis	10	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion-Related Reaction	11	2.4	0	0

[1] Includes fatigue and asthenia
[2] Graded per NCI CTCAE v4.0

Table 19: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Laboratory Abnormality	TECENTRIQ in combination with Bevacizumab (n=329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				
Increased AST	86	16	90	16
Increased Alkaline Phosphatase	70	4	76	4.6
Increased ALT	62	8	70	4.6
Decreased Albumin	60	1.5	54	0.7
Decreased Sodium	54	13	49	9
Increased Glucose	48	9	43	4.6
Decreased Calcium	30	0.3	35	1.3
Decreased Phosphorus	26	4.7	58	16
Increased Potassium	23	1.9	16	2
Hypomagnesemia	22	0	22	0
Hematology				
Decreased Platelet	68	7	63	4.6
Decreased Lymphocytes	62	13	58	11
Decreased Hemoglobin	58	3.1	62	3.9
Increased Bilirubin	57	8	59	14
Decreased Leukocyte	32	3.4	29	1.3
Decreased Neutrophil	23	2.3	16	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus bevacizumab (222-323) and sorafenib (90-153)
[1] Graded per NCI CTCAE v4.0

Melanoma

The safety of TECENTRIQ, administered with cobimetinib and vemurafenib was evaluated in IMspire150, a double-blind, randomized (1:1), placebo-controlled study conducted in patients with previously untreated BRAF V600 mutation-positive metastatic or unresectable melanoma *[see Clinical Studies (14.5)]*. Patients received TECENTRIQ with cobimetinib and vemurafenib (N=230) or placebo with cobimetinib and vemurafenib (n=281).

Among the 230 patients who received TECENTRIQ administered with cobimetinib and vemurafenib, the median duration of exposure to TECENTRIQ was 9.2 months (range: 0-30 months) to cobimetinib was 10.0 months (range: 1-31 months) and to vemurafenib was 9.8 months (range: 1-31 months).

Fatal adverse reactions occurred in 3% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. Adverse reactions leading to death were hepatic failure, fulminant hepatitis, sepsis, septic shock, pneumonia, and cardiac arrest.

Serious adverse reactions occurred in 45% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) serious adverse reactions were hepatotoxicity (7%), pyrexia (6%), pneumonia (4.3%), malignant neoplasms (2.2%), and acute kidney injury (2.2%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 21% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to TECENTRIQ discontinuation were increased ALT (2.2%) and pneumonitis (2.6%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 68% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to TECENTRIQ interruption were pyrexia (14%), increased ALT (13%), hyperthyroidism (10%), increased AST (10%), increased lipase (9%), increased amylase (7%), pneumonitis (5%), increased CPK (4.3%), diarrhea (3.5%), pneumonia (3.5%), asthenia (3%), rash (3%), influenza (3%), arthralgia (2.6%), fatigue (2.2%), dyspnea (2.2%), cough (2.2%), peripheral edema (2.2%), uveitis (2.2%), bronchitis (2.2%), hypothyroidism (2.2%), and respiratory tract infection (2.2%).

Tables 20 and 21 summarize the incidence of adverse reactions and laboratory abnormalities in Study IMspire150.

Table 20: Adverse Reactions Occurring in ≥10% of Patients on the TECENTRIQ plus Cobimetinib and Vemurafenib Arm or the Placebo plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4 TECENTRIQ in IMspire150)

Adverse Reaction	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Skin and Subcutaneous Tissue Disorders				
Rash[1]	75	27	72	23
Pruritus	26	<1	17	<1
Photosensitivity reaction	21	<1	25	3.2
General Disorders and Administration Site Conditions				
Fatigue[2]	51	3	45	1.8
Pyrexia[3]	49	1.7	35	2.1
Edema[4]	26	<1	21	0
Gastrointestinal Disorders				
Hepatotoxicity[5]	50	21	36	13
Nausea	30	<1	32	2.5
Stomatitis[6]	23	1.3	15	<1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[7]	62	4.3	48	3.2
Endocrine Disorders				
Hypothyroidism[8]	22	0	10	0
Hyperthyroidism	18	<1	8	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction[9]	10	2.6	8	<1
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonitis[10]	12	1.3	6	<1
Vascular Disorders				
Hypertension[11]	17	10	18	7

[1]Includes rash, rash maculo-papular, dermatitis acneiform, rash macular, rash erythematous, eczema, skin exfoliation, rash papular, rash pustular, palmar-plantar erythrodysaesthesia syndrome, dermatitis, dermatitis contact, erythema multiforme, rash pruritic, drug eruption, nodular rash, dermatitis allergic, exfoliative rash, dermatitis exfoliative generalised and rash morbilliform
[2]Includes fatigue, asthenia and malaise
[3]Includes pyrexia and hyperpyrexia
[4]Includes edema peripheral, lymphoedema, oedema, face oedema, eyelid oedema, periorbital oedema, lip oedema and generalised oedema
[5]Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, transaminases increased, hepatitis, hepatic enzyme increased, hepatotoxicity, hypertransaminasaemia, bilirubin conjugated increased, hepatocellular injury, hyperbilirubinaemia, liver function test increased, hepatic failure, hepatitis fulminant and liver function test abnormal
[6]Includes stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, cheilitis and glossitis
[7]Includes arthralgia, myalgia, pain in extremity, back pain, musculoskeletal pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, bone pain, spinal pain, immune-mediated arthritis, joint stiffness and non-cardiac chest pain
[8]Includes hypothyroidism and blood thyroid stimulating hormone increased
[9]Includes infusion related reaction and hypersensitivity
[10]Includes pneumonitis and interstitial lung disease
[11]Includes hypertension, blood pressure increased, hypertensive crisis

Clinically important adverse reactions in < 10% of patients who received TECENTRIQ plus cobimetinib and vemurafenib were:

Cardiac Disorders: Arrhythmias, ejection fraction decreased, electrocardiogram QT prolonged
Eye Disorders: Uveitis
Gastrointestinal disorders: Pancreatitis
Infections and infestations: Pneumonia, urinary tract infection
Metabolism and nutrition disorders: Hyperglycemia
Nervous system Disorders: Dizziness, dysgeusia, syncope
Respiratory, thoracic and mediastinal disorders: Dyspnea, oropharyngeal pain
Skin and Subcutaneous Tissue Disorders: Vitiligo

Table 21: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients Receiving TECENTRIQ Plus Cobimetinib and Vemurafenib Arm or the Placebo Plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4) in IMspire150

Laboratory Abnormality	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Hematology				
Decreased Lymphocytes	80	24	72	17
Decreased Hemoglobin	77	2.6	72	2.2
Decreased Platelet	34	1.3	24	0.4
Decreased Neutrophils	26	2.2	19	1.5
Chemistry				
Increased Creatine Kinase	88	22	81	18
Increased AST	80	13	68	6
Increased ALT	79	18	62	12
Increased Triacylglycerol Lipase	75	46	62	35

Table 21: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients Receiving TECENTRIQ Plus Cobimetinib and Vemurafenib Arm or the Placebo Plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4) in IMspire150 (continued)

Laboratory Abnormality	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Increased Alkaline Phosphatase	73	6	63	2.9
Decreased Phosphorus	67	22	64	14
Increased Amylase	51	13	45	13
Increased Blood Urea Nitrogen	47	NA[1]	37	NA[1]
Decreased Albumin	43	0.9	34	1.5
Increased Bilirubin	42	3.1	33	0.7
Decreased Calcium	41	1.3	28	0
Decreased Sodium	40	5	34	7
Decreased Thyroid-Stimulating Hormone	38	NA[1]	23	NA[1]
Increased Thyroid-Stimulating Hormone[2]	37	NA[1]	33	NA[1]
Decreased Potassium	36	5	22	4.3
Increased Triiodothyronine	33	NA[1]	18	NA[1]
Increased Free Thyroxine	32	NA[1]	21	NA[1]
Decreased Total Triiodothyronine	32	NA[1]	8	NA[1]
Increased Potassium	29	1.3	19	1.4
Decreased Triiodothyronine	27	NA[1]	21	NA[1]
Increased Sodium	20	0	13	0.4

Graded per NCI CTCAE v4.0.

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus cobimetinib and vemurafenib (28-277), placebo plus cobimetinib and vemurafenib arm (25-230).

[1] NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.

[2] Increased Thyroid Stimulating Hormone has a difference <5% (All Grades) between arms and is included for clinical completeness.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to atezolizumab in the studies described above with the incidence of antibodies in other studies or to other products may be misleading.

Among 111 patients in IMvigor210 (Cohort 1), 48% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposures. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 565 patients with NSCLC in OAK, 30% tested positive for treatment-emergent anti-drug antibodies (ADA) at one or more post-dose time points. The median onset time to ADA formation was 3 weeks. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%; 118/560) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 *[see Clinical Studies (14.2)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 487 ADA-evaluable patients with NSCLC who received atezolizumab in IMpower010, 31% (n=152) tested positive for treatment-emergent ADA at one or more post-dose time points. Among 241 patients in the PD-L1 SP263 ≥1% TC Stage II-IIIA population, 28% (n=67) tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative [*see Clinical Pharmacology (12.3)*]. There were insufficient numbers of patients and DFS events in the ADA-positive subgroup (19%; 39/207 by week 7) to determine whether ADA alters the efficacy of atezolizumab. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 364 ADA-evaluable patients with NSCLC who received TECENTRIQ with bevacizumab, paclitaxel and carboplatin in IMpower150, 36% (n=132) tested positive for treatment-emergent ADA at one or more post-dose time points and 83% of these 132 patients tested ADA positive prior to receiving the second dose of atezolizumab. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA negative *[see Clinical Pharmacology (12.3)]*. The presence of ADA did not increase the incidence or severity of adverse reactions *[see Clinical Studies (14.2)]*.

Among 315 ADA-evaluable patients with HCC who received TECENTRIQ and bevacizumab in IMbrave150, 28% (n=88) tested positive for treatment-emergent ADA at one or more post-dose time points and 66% (58/88) of these 88 patients tested ADA-positive prior to receiving the third dose of TECENTRIQ. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative *[see Clinical Pharmacology (12.3)]*. Exploratory analyses showed that the subset of patients who were ADA-positive by week 6 (20%; 58/288) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 6; *[see Clinical Studies (14.4)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 218 ADA-evaluable patients with melanoma who received TECENTRIQ in combination with cobimetinib and vemurafenib in IMspire150, 13% (n=29) tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. There are insufficient numbers of patients with positive ADA to determine whether ADA alters the efficacy or incidence or severity of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death *(see Data)*. Advise females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

The safety and antitumor activity of TECENTRIQ were assessed but not established in a single-arm, multi-center, multi-cohort trial (NCT02541604) in 60 pediatric patients aged 7 months to <17 years with relapsed or progressive solid tumors and lymphomas. No new safety signals were observed in pediatric patients in this study.

In pediatric patients who received TECENTRIQ 15 mg/kg with a maximum dose of 1200 mg every 3 weeks, the steady-state exposure (AUC) of atezolizumab in pediatric patients aged 12 years or older was comparable to that in adult patients who received TECENTRIQ 1200 mg every 3 weeks, while the exposure trended lower in pediatric patients less than 12 years old.

8.5 Geriatric Use

Of 2616 patients with metastatic urothelial carcinoma, metastatic NSCLC, and other tumor types treated with single agent TECENTRIQ in clinical studies, 49% were 65 years and over and 15% were 75 years and over.

Of 2421 patients with NSCLC and SCLC treated with TECENTRIQ in combination with other antineoplastic drugs in clinical studies, 48% were 65 years and over and 10% were 75 years and over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older and younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis *[see Warnings and Precautions (5.1)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for pelvic pain, frequent urination, or unusual swelling. *[see Warnings and Precautions (5.1)]*.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for generalized rash, skin eruption, or painful skin and mucous membrane lesions *[see Warnings and Precautions (5.1)]*.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT after PD-1/PD-L1 inhibitors

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT*[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

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M-US-00002930(v6.0)

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