

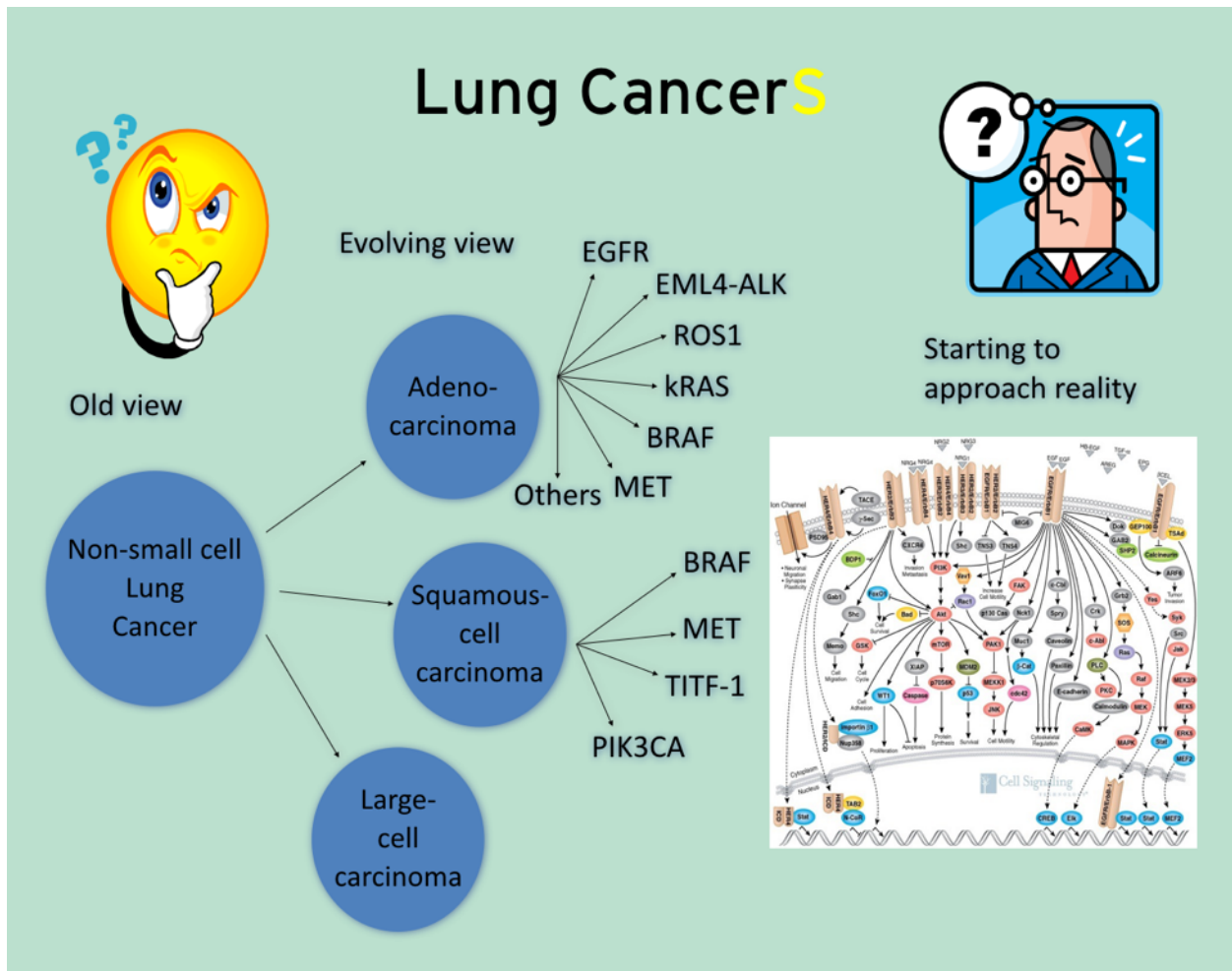


Elderly Patients: Selecting Appropriate Systemic Treatment Agents

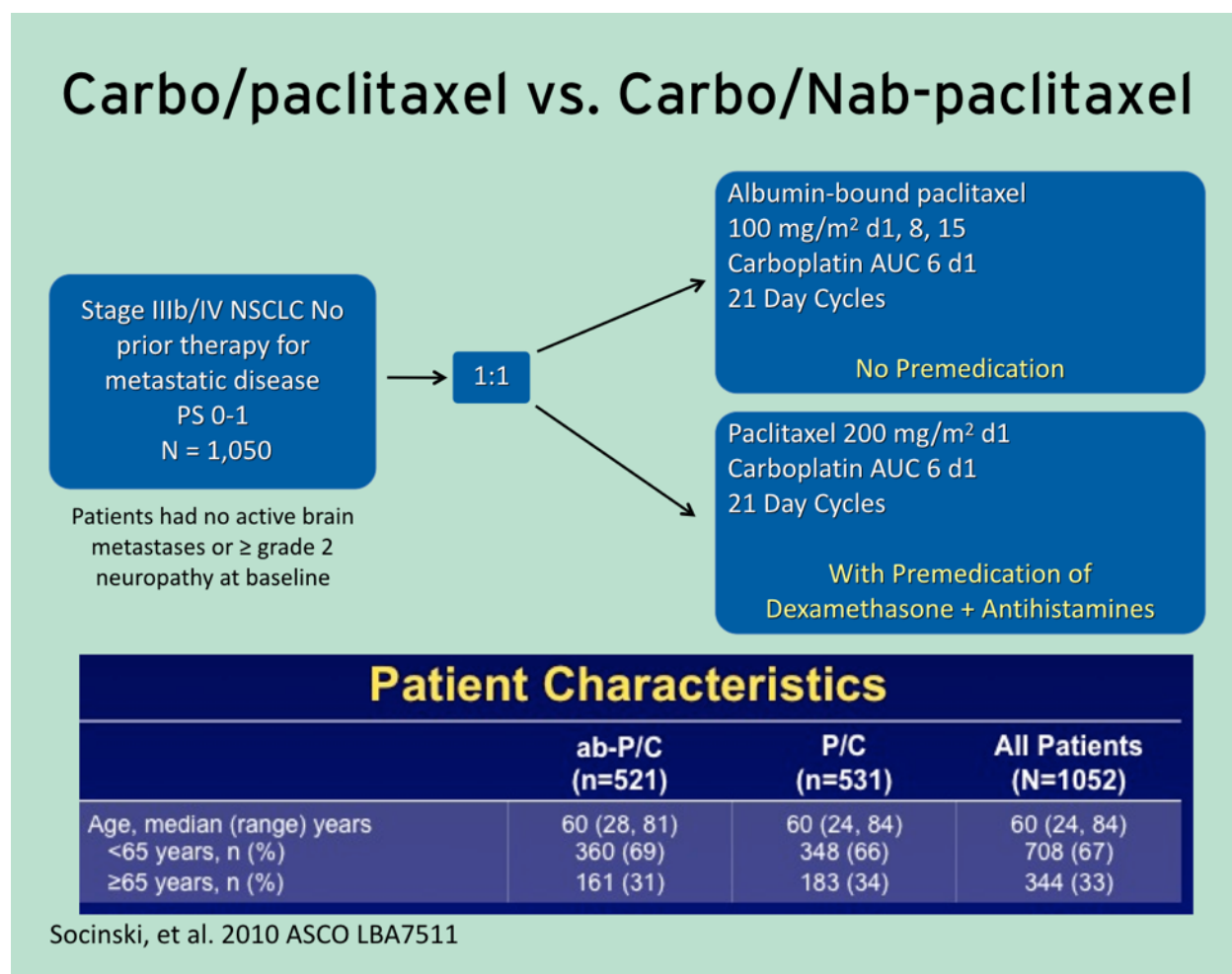


TRANSCRIPT & FIGURES

It is my privilege to speak to you today about elderly patients; consideration of which chemotherapeutic agents might be best. So we've seen a lot on CancerGRACE about the advent of targeted therapy and this theme that when you combine a target with a targeted therapy, like a lock and key model, you as a theme get a treatment that has less side effects, is more convenient because they're often oral, and tend to work better.

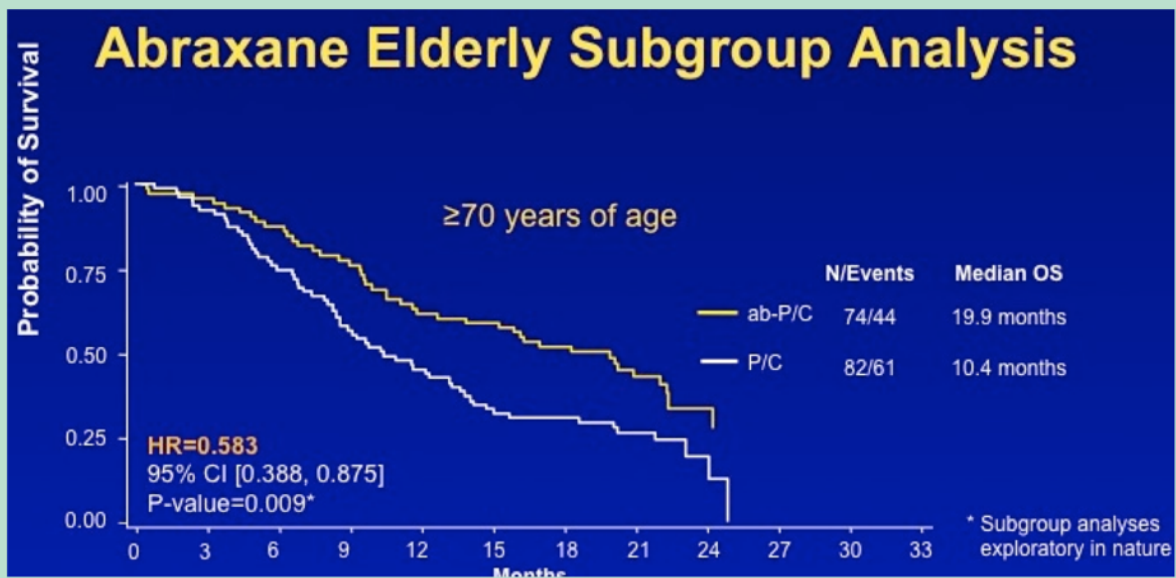


This of course has made lots of work for our medical students as we subdivide by histology, by driver mutations, and an even more complex systems view that probably starts to approach reality. But in the simplest way when thinking about targeted therapies such as erlotinib or gefitinib for EGFR mutants, or crizotinib for ALK or ROS1, and other emerging targeted therapies – as a theme these drugs are very effective and less toxic, and so to my mind, even though we don't normally speak about them as geriatric drugs, to me they're the epitome of geriatric drugs because of these themes.



In terms of traditional chemotherapy, there's really only one agent that I would consider to have any data for superior efficacy in the elderly. You're looking here at the design of a randomized phase III trial that randomized patients to carboplatin and regular cremophor solvent-dissolved paclitaxel, versus carboplatin and a newer nano albumin-bound formulation called Abraxane.

Overall Survival



Socinski et al, ASCO 2011, Abstr 7551

Patients were randomized one to one, you can see the basic results by age at the bottom of this slide. Why I'm showing this to you is that the only subgroup that had a major survival difference was the elderly. In patients of at least 70 years of age, there was a rather important improvement in survival, 19.9 versus 10.4 months – that is statistically significant. I would call that clinically meaningful but it is a retrospective subgroup analysis and so it requires confirmation in prospective studies. Two important studies are ongoing to look at this. One is looking at older patients with this regimen for their first treatment, and the other looking at such patients for their second treatment.

CDDP/pemetrexed vs. CDDP/Gem elderly data (Nonsquamous patients)

Toxicity	Age < 65 Years n = 815 (67.2%)		Age ≥ 65 Years n = 398 (32.8%)	
	Pem + Cis (n = 390)	Gem + Cis (n = 425)	Pem + Cis (n = 215)	Gem + Cis (n = 183)
Thrombocytopenia	11 (2.8)	34 (8.0)	11 (5.1)	32 (17.5)
Neutropenia	45 (11.5)	107 (25.2)	45 (20.9)	49 (26.8)
Anemia	23 (5.9)	43 (10.1)	7 (3.3)	19 (10.4)
Leukopenia	15 (3.8)	34 (8.0)	11 (5.1)	12 (6.6)
Diarrhea Without Colostomy	6 (1.5)	5 (1.2)	1 (0.5)	4 (2.2)
Fatigue	26 (6.7)	15 (3.5)	14 (6.5)	12 (6.6)
Febrile Neutropenia	2 (0.5)	12 (2.8)	6 (2.8)	8 (4.4)
Nausea	32 (8.2)	17 (4.0)	17 (7.9)	10 (5.5)
Vomiting	27 (6.9)	29 (6.8)	11 (5.1)	9 (4.9)

HR OS (all favor pem):

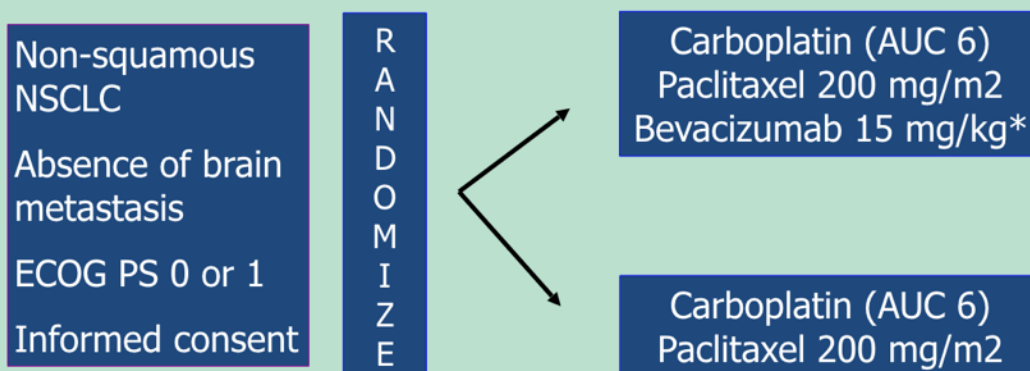
Subgroup <65: .89
Subgroup ≥65: .75

Subgroup <70: .83
Subgroup ≥70: .85

Gridelli et al, Clinical Lung Cancer, 13:5, 2012.

This was a randomized trial that compared for first treatment cisplatin and pemetrexed, versus cisplatin and gemcitabine. We've covered this trial a number of times on GRACE before in terms of looking at histology-specific differences in drugs and we've seen on GRACE before that pemetrexed is a particularly effective drug for patients with non-squamous histology, which mostly means adenocarcinoma, where it's less effective in patients with squamous histology. We've also seen that it tends to be one of our better tolerated chemotherapy drugs, and these results held in this definitive trial both for younger patients and for older patients. While I don't tend to use cisplatin in older patients (we'll get to that) I do think that pemetrexed is a particularly geriatric-friendly drug for patients with non-squamous histology.

Treatment Scheme of ECOG 4599



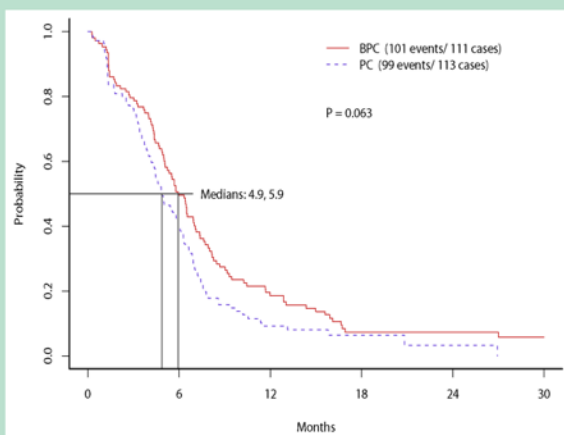
* Bevacizumab continued as monotherapy for CR/PR/SD after 6 cycles

Ramalingam, JCO 26:1, 2008

ECOG 4599, another trial we've covered multiple times over the years looked at the standard platinum doublet carboplatin and paclitaxel, with or without the addition of the VEGF inhibitor bevacizumab, otherwise known as Avastin.

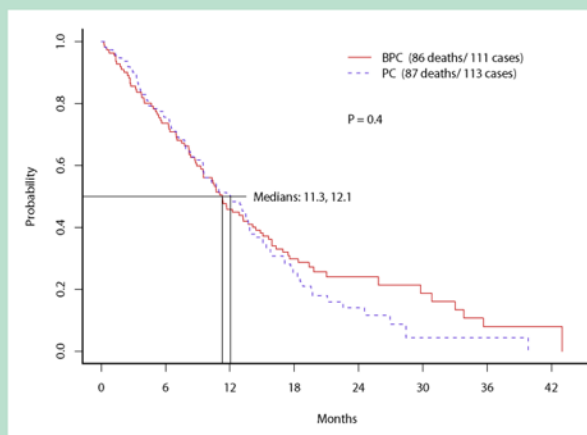
Efficacy of bevacizumab in Elderly in E4599 (carbo/paclitaxel +/- bev)

PFS



mPFS 4.5PC, 5.9m PCB, HR .76, p.063

OS



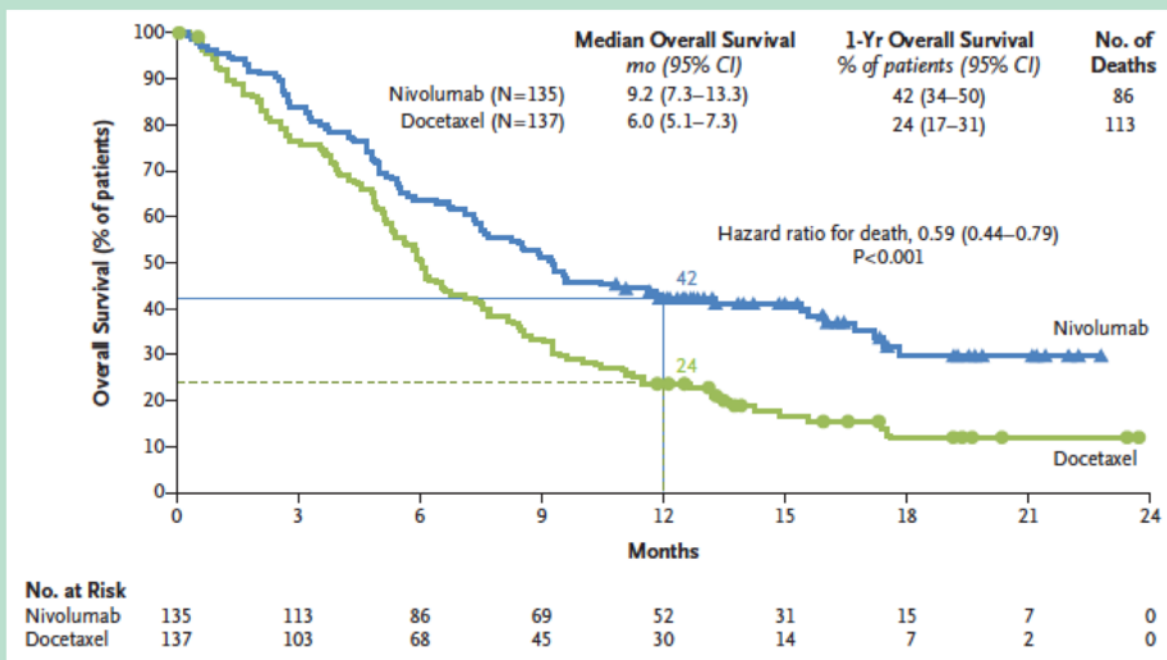
mOS 12.1 PC, 11.3 PCB, HR .87

Ramalingam, JCO 26:1, 2008

We know that trial showed a small but real survival advantage in unselected patients, but why I show it to you today is that treatment advantage really seems to slim down when we look at older patients. So in my practice I don't tend to use bevacizumab except for my really, really most fit older patients.

All the rage these days, of course, in thoracic oncology are the immunotherapeutic agents. These drugs as a theme are more effective in the second line than chemotherapy and less toxic – these make them good geriatric drugs so bear with me a moment.

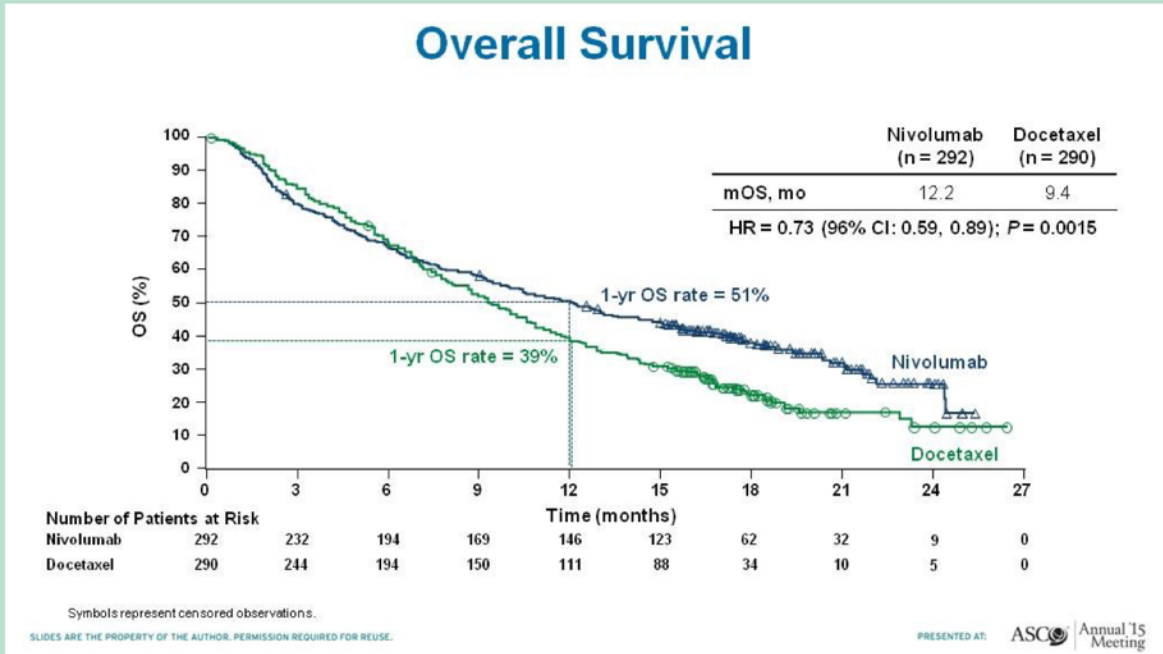
Nivolumab in SqCC Lung–2ND LINE



Brahmer, NEJM 2015

Here’s the data on nivolumab in squamous cell carcinoma, second line of therapy, compared to my second least favorite geriatric drug docetaxel. We can see here a dramatic improvement in survival, and perhaps equally important, a better tail to the curve – more patients living a very long time on the nivolumab.

Nivolumab in non-SqCC NSCLC 2ND LINE



Paz-Ares ASCO 2015

A similar effect shown here in non-squamous histology, and as far as to why this is making its way to a talk about geriatric oncology, here's the toxicity.

Toxicity of PD1

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	<i>number of patients with an event (percent)</i>			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

Brahmer,
NEJM
2015

It's very rare in looking at thoracic oncology trials to ever have this favorable of a rate of grade 3-4 or high-grade toxicity, even for placebo. So these drugs are more effective and less toxic – these are very geriatric-friendly drugs.

Bringing it back to chemotherapy, which is what unfortunately still the majority of patients get – I think it's worth taking a minute to talk about which of these drugs are particularly geriatric-friendly and which perhaps should be avoided for most older patients.

Specific Drugs in Elderly Lung CA

Drug	Excretion	Dose adjustment for renal impairment
Cisplatin	35-51% urine Significant portion remains in tissue at 180 days after administration	CrCl 60: 75% dose CrCl 45: 50% dose
Carboplatin	75% urine	Accounted for by AUC method
Paclitaxel	14% urine 71% feces	Not well studied. None recommended in package insert and likely not required for CrCl \geq 50
Docetaxel	6% urine 75% feces	Not required
Nab-paclitaxel	Mostly feces	Not required
Gemcitabine	> 90% renal	Required, but no specific guideline
Pemetrexed	70-90% renal	CrCl \geq 40: None required CrCl < 40: Unpredictable so no specific guidelines

Weiss, Expert Rev. Anticancer Ther. 12:1, 2012.

So cisplatin is my least favorite drug for older patients. Why? It's our most nausea- and vomiting-inducing drug, perhaps of any we use in oncology. It has a high rate of harming hearing and there is already age-related hearing decline, it's one of our worst drugs on the kidneys and kidney function does tend to naturally decline with age. There are plenty of other reasons to hate cisplatin as well, making it my least favorite geriatric drug.

In contrast, its little brother carboplatin I regard as a much more geriatric-friendly drug. It has much, much less for side effects, particularly on the kidneys and for patients who already have a little bit of age-related kidney

decline, the dosing formula for carboplatin, it's called the AUC formula, inherently accounts for this, so you just don't have to worry about it – you get the right exposure to the drug sort of automatically even if there is some preexisting decline in kidney function.

Paclitaxel I would call a middle-of-the-road geriatric drug, particularly I would call it more favorable when used on a weekly schedule. Docetaxel, as I mentioned, is my second least favorite geriatric drug – there's a lot of count suppression, a lot of fatigue. When I do use it for older patients, I tend to reduce the dose some from the standard dose. We've discussed nab-paclitaxel, otherwise known as Abraxane, because of the subgroup survival data suggesting it may be more effective in older patients. Pending the confirmatory ongoing studies, I think that this is a very geriatric-friendly drug. Gemcitabine I would call on the better side of geriatric drugs, it's mostly excreted by the kidneys so you need to pay attention if there is kidney decline, but it's a pretty geriatric-friendly drug – an effective drug with lower side effects. Pemetrexed or Alimta we've already talked about as a particularly geriatric-friendly drug, I would comment though that this drug is excreted mostly by the kidneys, and so if kidney function is not ideal, it's a drug that needs to be used with extreme caution or perhaps not at all.

I thank you for your kind attention.

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