Non Small Cell Lung Cancer (NSCLC) – Ramucirumab+Docetaxel

Low Value Regimen Rationale

- Ramucirumab is a VEGF inhibitor that is utilized in combination with docetaxel for subsequent line therapy in metastatic NSCLC.
- A randomized phase 3 trial - REVEL – comparing ramucirumab+docetaxel vs docetaxel demonstrated marginal PFS and OS benefit with the addition of ramucirumab to docetaxel.
- Although the phase 2 SCORPION trial included patients with prior immunotherapy or chemoimmunotherapy, it was a small number of patients that received ramucirumab+docetaxel and did not include a comparator arm. Therefore, the benefit of adding ramucirumab to docetaxel is difficult to discern.
- Several retrospective studies demonstrated similar OS for combination ramucirumab and docetaxel that studies have demonstrated for single agent docetaxel
- The REVEL and SCORPION trials, a large meta-analysis, and several retrospective studies have all shown significant increases in adverse events associated with combination ramucirumab and docetaxel
- Ramucirumab+docetaxel comes at the risk of financial toxicity at just under 100-fold greater cost of $47,800 compared to docetaxel at $510 for 90 days of treatment.
- The increased clinical and financial toxicity of ramucirumab+docetaxel outweighs marginal OS benefits when compared to single agent docetaxel

RECOMMENDED ALTERNATIVES

- For subsequent therapy metastatic NSCLC : single agent Docetaxel

Data Summary								
Study	**Experimental arm**	**Comparator arm**	**ORR**	**Disease Control Rate**	**PFS (mos.)**	**OS (mos.)**	**Adverse events Grade ≥ 3 (%)**	**Comment**
REVEL	Ramucirumab + docetaxel	Placebo + docetaxel	23% vs 14%	NA	4.5 vs 3.0	10.5 vs 9.1	Any AEs 98 vs 95 Anemia 21 vs 6 Febrile neutropenia 16 vs 10 Hypertension 6 vs 2 Bleeding/ hemorrhage 2 vs 2 VTE 2 vs 3	Marginal PFS and OS benefit with the addition of ramucirumab. Meta-analysis of 10 RCTs showed increased risk of serious adverse effects and negligible benefit with ramucirumab in metastatic solid tumors. This study did not include patients treated with prior immunotherapy or chemo-immunotherapy.
SCORPION	Ramucirumab + docetaxel	NA	34%	81%	6.5	17.5	Any AE 100% AE Grade 3 or higher 58% Most common > Grade 3 AEs: neutropenia (24%), anorexia (15%) hyponatremia (9%), pneumonitis (9%), febrile neutropenia (9%)	Phase 2 trial with small number of patients (N=32). Patients progressed on or after chemoimmunotherapy. Without comparator arm, it is difficult to determine the benefit of adding ramucirumab to docetaxel. The combination regimen was associated with significant adverse events.
Meta-analysis	Ramucirumab +/- chemotherapy Bevacizumab with Nab-paclitaxel	Placebo or chemotherapy	NA	NS	With exception of RELAY trial, gains in mPFS ranged from 0.3 months to 1.5 months	Gains in mOS ranged from 1.2 to 2.2	SAEs were greater in ramucirumab arm compared with control arm in all 10 trials RCTs (RR 1.13) Fatal AE were greater in ramucirumab arm compared with the control arm in 9 RCTs and equal to control arm in 1 RCT (RR 1.41)	Meta-analysis of 10 RCTs showed increased risk of serious adverse effects and negligible benefit with ramucirumab in metastatic solid tumors. QOL outcomes were reported in 7 RCTs, none showed improvement in QOL with ramucirumab.
German Retrospective	Ramucirumab + docetaxel	NA	33%	62%	3.9	7.5	AE Grade 3 or higher – neutropenia (15.6%), febrile neutropenia (3.9%), fatigue (6.5%), dysparonychia (5.2%), mucositis (3.9%), stomatitis (1.3%), ileus (1.3%)	Retrospective study that included 77 patients post chemoimmunotherapy. Although KRAS status had no impact on 1st line therapy, positive KRAS status was significantly associated with worse mPFS in 2nd line D+R. . Without comparator arm, it is difficult to determine the benefit of adding ramucirumab to docetaxel. The combination regimen was associated with significant adverse events.

Data Summary								
Study	**Experimental arm**	**Comparator arm**	**ORR**	**Disease Control Rate**	**PFS (mos.)**	**OS (mos.)**	**Adverse events Grade ≥ 3 (%)**	**Comment**
REACTIVE	Ramucirumab + docetaxel	NA	29%	70%	4.1	11.6	Not reported	Retrospective study that included 288 patients with previous chemoimmunotherapy. Without comparator arm, it is difficult to determine the benefit of adding ramucirumab to docetaxel. The combination regimen has been associated with significant adverse events. These are omitted in this analysis
US Retrospective	Taxane Combination Therapy	Taxane Monotherapy	NA	NA	NA	8.4 vs 9	Not reported	Retrospective study that included 400 patients with previous chemotherapy and immunotherapy. Taxane monotherapy consisted of docetaxel, paclitaxel, or nab-paclitaxel. Taxane combination therapy featured a taxane in combination with ramucirumab, carboplatin, carboplatin plus bevacizumab or gemcitabine. Although data was limited in this review, OS favored taxane monotherapy versus combination therapy.

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